A phase II trial of LEE011 in combination with everolimus in the treatment of advanced well differentiated neuroendocrine tumors of foregut origin.

PROTOCOL FACE PAGE FOR MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title of Study: A phase II trial of LEE011 in combination with everolimus in the treatment of advanced well differentiated neuroendocrine tumors of foregut origin.

Trial Phase: Phase II.

Patient Population: Advanced (unresectable or metastatic) well differentiated neuroendocrine tumors (WDNETs) of foregut origin (thymic, bronchopulmonary, gastric, duodenal, and pancreatic).

Trial Type: Interventional

Type of control: No treatment control

Route of administration: LEE011 (oral), everolimus (oral)

Trial blinding: Unblinded open-label

Groups: One cohort - foregut WDNETs

Number of trial subjects: 41 patients

Estimated duration of trial: 5 to 6 years

Study Design: This will be a multicenter, non-randomized, open-label phase II clinical trial.. This study will be conducted to determine the efficacy and safety of the combination of LEE011 and everolimus in subjects with advanced WDNETs of foregut origin (thymic, bronchopulmonary, gastric, duodenal, and pancreatic).

The first 10 patients enrolled on this study were treated with a starting dose of LEE011 300 mg once daily for 3 weeks on/1 week off and everolimus 2.5mg daily, based on the results of CLEE011X2106 in breast cancer. Given the toxicities noted in the WDNET patient population (see below), primarily with regards to cytopenias for these 10 patients treated on protocol, subsequent enrolled patients will receive the oral combination of LEE011 200 mg once daily and everolimus 5 mg daily, based on more recent data from CLEE011XUS29 (TRINITI-1) study in metastatic breast cancer. Subjects will continue treatment until meeting one of the criteria for removal from study.

If patients have a functional NET, they are permitted to continue on a somatostatin analog for hormonal symptom control.

The primary objective of this trial is to determine the progression free survival (PFS) in patients with WDNETs of foregut origin treated with LEE011 + everolimus using RECIST v1.1.

In this simon two stage design, a total of 41 patients will be enrolled; 21 patients will be enrolled in the first stage. If 10 or more patients are alive and progression free at 1 year, then we will enroll an additional 20 patients. If 23 or more out of 41 patients are alive and progression free at 1 year, then the combination is considered promising.

The secondary objectives include establishing the safety of LEE011 + everolimus in this patient population, objective response rate (ORR), event free survival (EFS), and OS. Correlative objectives include investigating the associations between biomarkers related to the Rb pathway and/or the pathogenesis of foregut WDNETs and clinical response to the combination of LEE011 + everolimus.

The study will be completed when all subjects have progressed or discontinued from the study for other reasons. The accrual time is estimated to be 1 to 2 years. The study is expected to take approximately 4 to 5 years to complete. The study duration is estimated at 5 to 6 years.

Status of Study on 12/08/2017: Ten patients have been enrolled to date and initiated therapy on protocol. Two patients were taken off study due to infectious complications. Seven patients were taken off study in the setting of either clinical or radiographic disease progression. Of the 10 patients, 7 patients underwent dose reductions (4 patients with 1 dose reduction, 3 patients with 2 dose reductions).

4/10 (40%) patients experienced grade 1 thrombocytopenia, 2/10 (20%) patients experienced grade 2 thrombocytopenia, and 2/10 (20%) patients experienced grade 3 thrombocytopenia. No patients experienced grade 1 neutropenia. 7/10 (70%) patients experienced grade 2 neutropenia and 2/10 (20%) patients experienced grade 3 neutropenia.

1/10 (10%) patients experienced grade 1 rash, 1/10 (10%) patients experienced grade 2 rash, and 1/10 (10%) patients experienced grade 3 rash – the rash was maculopapular and acne-like in nature.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

- The primary objective is to determine the PFS in patients with WDNETs of foregut origin treated with LEE011 + everolimus.
- The secondary objectives are to:
    - Establish the safety of LEE011 + everolimus in foregut WDNETs.
    - Determine the ORR during treatment of foregut WDNETs with LEE011 + everolimus.
    - Determine the event free survival during treatment of foregut WDNETs with LEE011 + everolimus.

- Determine OS during treatment of foregut WDNETs with LEE011 + everolimus.

- The exploratory objectives are to investigate the associations between biomarkers related to the Rb pathway and/or the pathogenesis of foregut WDNETs and clinical response to the combination of LEE011 + everolimus.

3.0 BACKGROUND AND RATIONALE

3.1 Overview of WDNETs

3.1.1 Epidemiology and clinical presentation of WDNETs

WDNETs are an uncommon and heterogeneous group of neoplasms that arise in a variety of locations, most commonly in the lung and gastrointestinal tract.[1] WDNETs are subdivided into two groups: carcinoid tumors and panNETs. Carcinoid tumors develop from the neuroendocrine tissues of the aerodigestive tract, and panNETs develop from the endocrine tissues of the pancreas (i.e. islets of Langerhans). This group of WDNETs is both morphologically and clinically distinct from high grade neuroendocrine carcinomas, tumors that are characterized by an extremely aggressive behavior and are treated along small cell lung cancer paradigms with platinum-based chemotherapy.[2] Epidemiological data from the last 30 years has demonstrated that the incidence of neuroendocrine tumors continues to rise, while there have been no significant changes in survival from this disease.[3, 4]

Although most WDNETs are slow growing, after the development of metastatic disease, most commonly to the liver, median survival is only a few years.[5] Metastatic disease is a common presentation for the majority of patients with WDNETs, especially those with non-functioning tumors given the absence of clinical symptoms that would warrant earlier clinical evaluation.[6] Asymptomatic patients diagnosed with WDNETs are often monitored initially, however with time, their disease will progress and these patients will require treatment. Typical indications for therapy are pain/symptoms due to tumor bulk, symptoms from hormone secretion, or progression of disease and increased tumor burden under observation.[6] Given the heterogeneous clinical presentations and complex spectrum of aggressiveness of WDNETs, their treatment is challenging, and requires multimodality management with surgeons, interventional radiologists, medical oncologists, endocrinologists, and gastroenterologists.

3.1.2 Treatment options for WDNETs

The primary site of WDNETs is important when considering medical therapy, as panNETs generally respond better to therapies in comparison to carcinoid tumors. Treatment options for WDNETs include somatostatin analogs (SSA), peptide receptor radiation therapy (PRRT), targeted agents, and cytotoxic therapy.

SSA (octreotide long-acting-release or octreotide LAR, lanreotide) act through a family of 5 G-protein couple receptors to exert many functions, including inhibition of endocrine and exocrine secretions and inhibition of tumor cell growth. For this reason, SSA is highly useful to treat

hormonally related NET symptoms.[7] In addition, it has been demonstrated in both the PROMID and CLARINET studies, that SSA have antiproliferative tumor effects and can offer cytostatic control of WDNETs.[8, 9] SSA generally serve as first-line therapy for WDNETs, however, once these tumors progress on SSA, there are few therapy options available, especially for extra-pancreatic WDNETs.

The recognition that WDNETs highly express somatostatin receptors is the molecular basis for the use of tumor targeting with radiolabeled somatostatin analogs (PRRT). Several radioisotopes linked to a somatostatin analog have been used, and include indium-111 (^{111}In-), yttrium-90 (^{90}Y-), and lutetium-177 (^{177}Lu); while many single-institution series as well as the multicenter MAURITIUS trial have demonstrated improved response in symptom control in both carcinoid tumors and in panNETs, the degree of activity and toxicity patients can expect from PRRT has not been adequately defined.[10-13]

Targeted agents have undergone investigation in WDNETs. Both sunitinib (small multitargeted tyrosine kinase inhibitor) and everolimus (mammalian targeted of rapamycin/mTOR inhibitor) are FDA approved for the treatment and panNETs and have been demonstrated to offer a PFS benefit. [14, 15] In carcinoid tumors, sunitinib has no proven benefit, while the RADIANT-4 trial has provided evidence for a PFS benefit of everolimus in the carcinoid cohort. Despite a PFS benefit of these targeted agents, objective response rates are low, and although side effects are manageable, they can be persistent.

Finally, cytotoxic therapy has been investigated in WDNETs, and while certain chemotherapy drugs (streptozocin, temozolomide, dacarbazine, platinum agents) can increase response rate in panNETs, these drugs are inactive in carcinoid tumors and do not represent treatment options.

It is well understood in the scientific community, and has been defined within the World Health Organization classification of endocrine and digestive tumors, that NETs that arise from different anatomic sites are biologically different.[16] More recent data suggests that embryologic origin (foregut, midgut, hindgut) can classify these tumors genetically and clinically with foregut tumors (thymic, bronchopulmonary, gastric, duodenal, and pancreatic) sharing very similar genetic and clinical characteristics (as opposed to the midgut and hindgut tumors which appear different).

3.1.3 Cyclin-dependent kinases in WDNETs

Recent investigation has suggested a role of the retinoblastoma (Rb) tumor suppressor pathway in NET development. The Rb1 tumor suppressor normally regulates and prevents entry of cells into the S-phase of the cell cycle.[17] Rb1 inactivation can result from either loss of Rb1 protein through gene mutations, or by alterations in the Rb1 pathway that increases Rb1 protein phosphorylation.[17] In fact, a majority of cancers have intact Rb1 protein despite genetic alterations in components of the Rb1 pathway.[17] One mechanism of Rb1 inactivation is through phosphorylation by cyclin-dependent kinases Cdk4 and Cdk6 (both which are activated by cyclin D1).[17] Tumors with intact Rb1 gene may have loss or downregulation of $p16^{INK4a}$, a Cdk inhibitor that specifically inhibits Cdk4 and Cdk6; this mechanism is thought to play a role in tumor development when the Rb1 gene is intact.[17, 18]Early mouse models demonstrated a role of the

G1 to S-phase transition in pancreatic endocrine cell proliferation.[18] Based on the initial pre-clinical data, further investigation of human tissue samples corroborated these findings, and inactivation of $p16^{INK4a}$ has been observed in a variety gastrointestinal NETs.[18] A study of 12 gastrinoma and nonfunctioning panNET specimens was notable for inactivating $p16^{INK4a}$ gene alterations in 91.7% of the specimens.[19] The $p16^{INK4a}$ gene was homozygously deleted in 3 of 8 gastrinomas and 2 of 4 nonfunctional panNETs; methylation of the gene was seen in 58.3% of the specimens.[19] A later study evaluating the CpG island methylator phenotype in 11 primary panNETs observed a large proportion of tumor-specific methylation or deletion in $p16^{INK4a}$ in nonfunctional panNETs, as well as lack of $p16^{INK4a}$ nuclear staining in almost half of the tumors without obvious $p16^{INK4a}$ alterations.[20] The findings from this study suggested that there is an unknown mechanism for loss of $p16^{INK4a}$ in panNETs.[20] More recent studies corroborated this data, demonstrating the presence of $p16^{INK4a}$ inactivation in panNETs.[21, 22] Taken together, these findings implicated a role for $p16^{INK4a}$ and the Rb tumor suppressor pathway in panNET development.

Recently, a study at MSK investigated abnormalities in the Rb1 pathway in panNETs.[17] In this study, panNETs from 92 patients underwent staining by immunohistochemistry (IHC) for markers of the Rb pathway. It was demonstrated that a majority of tumors expressed high amounts of Cdk4 or cyclin D1. Specifically, 100% of patients stained positive for RB1 by IHC, 58% of samples stained for Cdk4, 68% of samples stained for phospho-Rb1, and 68% of samples stained for Cyclin D1; in addition, there was a significant correlation between phospho-Rb1 and Cdk4 protein expression as well as cyclin D1 and Rb1 phosphorylation. In this study, genomic DNAs from 26 tumors were then subjected to copy number analysis to search for amplifications of Rb genes, and the copy numbers of Cdk4 or Cdk6 were increased in 19% of the tumors. Subsequently, the investigators observed that growth of the human panNET cell line QGP1 was inhibited in a xenograft mouse model by the Cdk4/6 inhibitor, PD 0332991, which reactivates the Rb pathway. This data suggests that patients with panNETs may strongly respond to Cdk4/6 inhibitors such as LEE011.

Looking specifically at carcinoid tumors, unpublished data from next-generation sequencing utilizing the institutional MSK-IMPACT platform (MSK IRB protocol #12-245) has identified CdkN2A/B alterations in a large proportion of sequenced patients. To date, we have observed CDKN2A/B alterations in approximately 20% of patients with WDNETs (including pancreatic and extra-pancreatic primary tumors) who have consented to MSK-IMPACT testing of their tissue. CdkN2A encodes tumor suppressor proteins that bind and inhibit Cdk4 and Cdk6. With CdkN2A/B loss, this inhibition does not occur, leading to dysregulation of the Cdk4/6-cyclin-Rb pathway and loss of cell cycle control. This data demonstrating CdkN2A/B loss in patients with carcinoid tumors suggests that Cdk4/6 inhibitors such as LEE011 may be beneficial in this patient population as well.

3.1.4 Rationale for combination cyclin-dependent kinase inhibition with everolimus in WDNETs

Everolimus, an inhibitor of mTOR, is approved for panNET treatment, and in comparison to placebo, doubles PFS from 5 to 11 months.[15] Its benefit in carcinoid tumors was tested in the RADIANT-2 trial where median PFS was 16.4 months versus 11.3 months.[23] However, the PFS did not achieve its primary endpoint of PFS based on adjudicated central radiologic review and the

difference was not statistically different. Many in the NET community felt strongly that there was a signal in RADIANT-2.

As a result, RADIANT-4 was conducted to test the hypothesis that mTOR inhibitors are active in WDNETs of the lung and gastrointestinal tract. RADIANT-4 has recently returned a positive trial with PFS of 11.0 months in the everolimus arm, versus 3.9 months in the placebo arm; in addition, tumor shrinkage was seen in 64% of patients receiving everolimus, in comparison to 26% of patients receiving placebo. Based on these recent results from RADIANT-4, everolimus is now the first targeted agent to show robust antitumor activity across a broad spectrum of WDNETs, including those arising from the pancreas, lung, and gastrointestinal tract.

Everolimus has unequivocally proven to be helpful in patients with WDNETs. Preclinical data (discussed below in section 3.2 of protocol) suggests that everolimus and LEE011 are synergistically active. In addition, there in an ongoing trial looking at the anti-tumor effects of LEE011 in this patient population (NCT02420691). Based on this foundation, we hypothesize that the combination of LEE011 and everolimus will prolong PFS in WDNETs.

3.2 Introduction to investigational treatments and other study treatments

3.2.1 Overview of LEE011

In the mammalian cell cycle, entry into S phase is achieved by CDK 4/6. LEE011 is an orally bioavailable, highly selective small molecule inhibitor of CDK4/6 that induces G1 arrest at sub-micromolar concentrations in a variety of pRb-positive cancer cells *in vitro*. LEE011 has proven efficacious when combined with other targeted therapies *in vitro* and *in vivo* in cancers driven by a variety of oncogenic signaling pathways. LEE011 may therefore be an effective anti-cancer agent in a variety of pRb-positive human neoplasms, especially in those that contain activated CDK4/6-pRb pathway. LEE011 is currently being developed in phase III clinical studies for the treatment of hormone receptor positive breast cancer patients; several other phase I or II clinical studies are being conducted.

3.2.1.1 Pharmacology of LEE011

3.2.1.1.1 *In vitro* pharmacology (Per LEE011 Investigators Brochure)

LEE011 inhibits the CDK4/CCND1 and CDK6/cyclin-D3 enzyme complexes with concentration resulting in 50% inhibition (IC50) values of 0.01 and 0.039 μM in biochemical assays, respectively. In Jeko-1 cells, the compound inhibits CDK4/6-dependent pRb phosphorylation with an average IC50 of 0.06 μM. Consistent with the observed inhibition of pRb phosphorylation, LEE011 also inhibited G1 to S phase cell cycle progression in Jeko-1 cells as judged by both the inhibition of bromodeoxyuridine (BrdU) uptake (IC50 of 0.1 μM) and fluorescence activated cell sorting (FACS) analysis (half-maximal increase in cells in G1 at 0.11 μM).

The effect of LEE011 on pRb phosphorylation, BrdU uptake and cell cycle progression has been assessed in more than 40 cell lines derived from hematological, esophageal, liposarcoma and breast cancers. In pRb+ cell lines, LEE011 inhibits pRb phosphorylation with a median IC50 value of

0.275 µM (range: 0.06 to 8.8 µM). Similarly, LEE011 interferes with G1 to S phase cell cycle progression in these cells as determined by either BrdU uptake or FACS analysis with a median IC50 value of 0.46 µM. In contrast, in lineage-matched pRb- cell lines no effect of LEE011 on either pRb phosphorylation or cell cycle progression is observed. Thus, LEE011 is able to impact cell cycle progression in cell lines derived from a variety of tumor types that harbor a diversity of genetic alterations in a manner dependent on intact pRb.

3.2.1.1.2 *In vivo* pharmacology (Per LEE011 Investigators Brochure)

LEE011 was well-tolerated in mice and rats with body weight loss not exceeding 12.5% at doses up to 250 mg/kg qd po or 150 mg/kg qd po, respectively, for up to 28 days. However, myelosuppression was observed and correlated with pRb phosphorylation inhibition.

Treatment with LEE011 resulted in tumor regression in the Jeko-1 MCL xenograft model at doses greater than or equal to 75 mg/kg, qd po. *In vivo* pharmacokinetics (PK)/pharmacodynamics (PD) studies demonstrated dose-related inhibition of pRb phosphorylation in tumors, with continuous dosing over at least 3-5 days being required to achieve optimal target inhibition. In male nude rats, a PK/PD/efficacy study indicated that plasma levels corresponding to approximately 0.5 - 4 µM over a 24 h dose interval are sufficient to obtain near complete inhibition of pRb phosphorylation and complete regression in the Jeko-1 MCL xenograft model.

LEE011 has demonstrated *in vivo* anti-tumor activity in subsets of tumor xenograft models. Consistent with the compound mechanism of action, efficacy was only observed in tumors expressing pRb. Tumor types where LEE011 has demonstrated robust anti-tumor activities include but are not limited to breast, melanoma, neuroblastoma, malignant rhabdoid, lung, pancreas and hematological malignancies.

In addition, LEE011 has shown anti-tumor activity when combined with targeted agents which inhibit signaling pathways known to regulate D-cyclin levels, including inhibitors of the RAF/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK), phosphoinositide 3-kinase (PIK3) and mammalian target of rapamycin (mTOR) pathways.

3.2.1.2 Synergy with everolimus and LEE011 (Per LEE011 Investigators Brochure)

LEE011, when combined with everolimus (RAD001), induced synergistic growth inhibitions in multiple tumor models, including cell lines derived from MCL, ER+ breast cancer, and MRTs (RD-2012-50383). The combination of LEE011 with the PI3K inhibitor, alpelisib (BYL719), showed similar synergistic effects in ER+ breast cancer, neuroblastoma and colorectal cancer cell lines (RD-2013-50144). Table 1 shows synergy scores which demonstrate that co-treatment of LEE011 and everolimus or alpelisib leads to synergistic growth inhibition.

Table 1: Synergy scores for LEE011 / everolimus combination in cancer cells

Cell Line	Type	Combination partner	Synergy Score*

T-47D	ER+/HER2- breast	everolimus (RAD001)	7.6
MCF-7	ER+/HER2- breast	everolimus (RAD001)	8.0
A-204	Rhabdoid	everolimus (RAD001)	7.8
G-401	Rhabdoid	everolimus (RAD001)	5.6
T-47D	ER+/HER2- breast	alpelisib (BYL719)	2.0
MCF-7	ER+/HER2- breast	alpelisib (BYL719)	7.6
MDA-MB-453	ER-/HER+ breast	alpelisib (BYL719)	3.2
HCT116	Colorectal	alpelisib (BYL719)	5.0
SIMA	Neuroblastoma	alpelisib (BYL719)	3.3

*Shown are synergy scores for the combination of LEE011 and everolimus or alpelisib in tumor cell lines. Synergy scores are described in Lehar et al (2009) with scores >2 representing real synergy. All 3 breast cancer and the neuroblastoma derived cell lines harbor activating mutations in the PIK3CA gene, both rhabdoid derived cell lines have bi-allelic inactivation of SMARCB1, and the neuroblastoma cell line displays high levels of N-Myc.

3.2.1.3 **Safety, pharmacology, and toxicology of LEE011** (Per LEE011 Investigators Brochure)

In vivo cardiac safety studies demonstrated a signal for QT prolongation with the potential to induce incidences of premature ventricular contractions (PVCs) at higher exposure levels.

The effects of LEE011 on the bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation) and testes (atrophy) are considered to be related to the pharmacological inhibition of cell replication in these tissues due to CDK4/6 inhibition. An increased number of ovarian corpora lutea was observed in a single female dog in the 4-week toxicity study at the highest dose tested (20 mg/kg/day) and this effect could also be related to the pharmacology of LEE011 (arrest of estrous cycle). The liver, bile system and gallbladder (proliferative changes, cholestasis, sand-like gallbladder calculi and inspissated bile) and the kidney (concurrent degeneration and regeneration of tubular epithelial cells) were identified as additional target organs of toxicity which are not likely related to the primary pharmacology of LEE011. Inflammatory changes in the lungs of dogs were considered secondary to aspiration of test-article and are indicative of the irritant potential of the formulated test-article in the respiratory tract. Correlating hematological and/or biochemistry changes were seen for the effects described in the bone marrow, lymphoid system and liver. Generally all changes demonstrated either reversibility or a clear tendency towards reversibility.

Nonclinical studies in pregnant animals have shown that LEE011 can harm an unborn fetus. Data from a rabbit embryofetal development study shows that LEE011 is teratogenic in the rabbit in the absence of maternal toxicity. In rabbits, LEE011 also demonstrates embryotoxicity and fetotoxicity. Reproductive studies have also demonstrated that LEE011 induced embryotoxicity and fetotoxicity in rats.

3.2.1.4 Nonclinical pharmacokinetics and metabolism of LEE011 (Per LEE011 Investigators Brochure)

LEE011 showed high clearance (CL) in the mouse, rat, dog and monkey. The volume of distribution was large across species and the terminal elimination half-life (T1/2) was moderate in rodents and monkey (~2 to 5 h) and longer in dog (18 h).

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

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

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

LEQ803 (N-demethylation) was a prominent metabolite found in mouse, rat, dog, monkey and human hepatocytes. This metabolite retains some pharmacologic activity and interacts with human Ether-a-go-go Related Gene (hERG) channels *in vitro*. In male rats, unchanged LEE011 (24.7% of [3H]AUC0-24h) and its metabolite M11 (26.3% of [3H]AUC0-24h) were the major components in plasma. In rats, LEE011 was eliminated mainly by metabolism with direct sulfation as the major pathway. Direct LEE011 secretion accounted for 18.2% of the total plasma clearance. In male dogs, metabolism was the major elimination route. The most prominent components in plasma were LEE011 (55.9% of [14C]AUC0-48h) and its metabolite LEQ803 (1.61% of [14C]AUC0-48h).

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

In vitro, LEE011 was a reversible inhibitor of cytochrome P450 (CYP) enzymes CYP1A2, CYP2E1 and CYP3A4 and a time-dependent inhibitor of CYP3A4. LEE011 may inhibit CYP3A4 under therapeutic conditions. No induction of CYP1A2, CYP2B6 or CYP3A4 was observed. The *in vitro* inhibitory potency of LEE011 observed for the transporters OATP1B1 (organic anion transporting polypeptide 1B1), BCRP (breast cancer resistance protein), OCT1 (organic cation transporter 1), OCT2, MATE1 (multidrug and toxin extrusion protein 1), MATE2K and BSEP (bile salt export pump) may translate into clinically relevant inhibition at therapeutic doses.

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

3.2.1.5 Clinical Experience with LEE011

LEE011 is currently being investigated in patients as a single agent in 3 phase I studies: CLEE011X1101, CLEE011X2101, CLEE011X2102; in 2 phase II studies: CLEE011X2201, CLEE011XUS03; and in combination in 15 studies: 12 phase Ib/II CLEE011X2105, CLEE011X2106, CLEE011X2107, CLEE011X2108, CLEE011A2115C, CLEE011X2110C, CMEK162X2114, CMEK162X2110, CLGX818X2102, CLGX818X2109, HDM201X2103C, PIM447X2104C and 3 randomized phase III studies: CLEE011A2301, CLEE011F2301 and CLEE011E2301. Four studies, were closed to enrolment: CLEE011A2201, a randomized phase II study; CLEE011A2112C, a phase I dose finding study; CLEE011X2102, a phase I study in malignant rhabdoid tumors and neuroblastomas; and CLEE011X2105, a phase Ib/II study in BRAF mutant melanoma. LEE011 is also being investigated in 4 clinical pharmacology studies: CLEE011A2102, CLEE011A2103, CLEE011A2109, and, CLEE011A2116. Three clinical pharmacology studies in healthy subjects have been completed: CLEE011A2101, CLEE011A2106 and CLEE011A2111.

To date, one study treatment related death occurred in study [CMEK162X2114] and one death suspected to be related occurred in study [CLEE011X2106].

Please refer to the LEE011 Investigator's Brochure for a summary of the current clinical experience in the above trials.

3.2.2 Overview of everolimus

Everolimus has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Everolimus is a derivative of rapamycin. It is a selective mTOR inhibitor, specifically targeting the mTOR-raptor (regulatory-associated protein of mTOR, Raptor) signal transduction complex 1 (mTORC1). Everolimus potently inhibits proliferation of endothelial cells and has antiangiogenic activity *in vivo*.[24-28].

Everolimus is approved in Europe and other global markets for cardiac and renal transplantation, and in the United States for the prevention of organ rejection of kidney transplantation. Everolimus is currently approved for advanced kidney cancer, subependymal giant cell astrocytoma, pancreatic neuroendocrine tumors, progressive, well-differentiated, non-functional neuroendocrine tumors of gastrointestinal or lung origin (that are unresectable, locally advanced or metastatic), and breast cancer (in combination with exemestane).

The following is a brief summary of the main characteristics of everolimus. More detailed information can be obtained from the Everolimus Prescribing Information.

3.2.2.1 Non-clinical experience

Everolimus inhibits the proliferation of a wide range of human tumor cell lines *in vitro* at IC50s ranging from sub/low nM to µM.

The antitumor efficacy of everolimus was compared to other compounds in a panel of six breast cancer xenograft models established after direct transplantation of patients' tumors onto nude mice [Report RD-2011-50492]; this panel included an ER+ model, HBCx-3 (XTS-181).[29] Everolimus given daily by oral gavage for 21 to 35 days at 20 mg/kg was well tolerated with no significant mean body weight loss. In all breast cancer models tested, tumor growth was significantly inhibited, and was particularly evident in the HBCx-3 (XTS-181) model with nine partial regressions in ten mice tested (-13.5% mean tumor volume regression, $p<0.001$).

Based on data generated using human liver microsomes and microsomes from cells expressing single human cytochrome P450s enzymes, CYP3A4 was identified as the major enzyme involved in the microsomal biotransformation of everolimus. Everolimus inhibited competitively the metabolism of the CYP3A4 substrate cyclosporine with a Ki value of 2.3 µmol/L (2204 ng/mL) under *in vitro* conditions.

Further details can be found in the Everolimus Investigator's Brochure.

3.2.2.2 Clinical experience

3.2.2.2.1 Everolimus pharmacokinetics

Everolimus is rapidly absorbed with a median tmax of one to two hours. The steady-state AUC0-τ is dose-proportional over the dose range between 5 to 70 mg when given weekly and 5 and 10 mg when given daily. Steady-state was achieved within two weeks with the daily dosing regimen. Cmax is dose-proportional between 5 and 10 mg for both the weekly and daily regimens.

In healthy subjects, high fat meals reduced systemic exposure to a 10 mg dose of everolimus (as measured by AUC) by 22% and the peak plasma concentration Cmax by 54%. Light fat meals reduced AUC by 32% and Cmax by 42%. Food had no apparent effect on the post absorption phase concentration-time profile ([Study RAD001C2120]). The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given everolimus 10 mg/day [DMPK R303044]. Plasma protein binding is similar in healthy patients and in subjects with moderate hepatic impairment (approximately 74%, [Study RAD001A2303]).

The major and nearly exclusive enzyme responsible for the metabolism of everolimus in man was CYP3A4 (DMPK(US)1998/005; DMPK(CH) R99-2448).[30] Other CYP isoenzymes either do not metabolize everolimus or do so at very low rates. Everolimus is a moderate inhibitor of P-glycoprotein-like mediated efflux systems, although the compound has a high intrinsic permeability when P-glycoprotein is inhibited.[31, 32][DMPK(CH) 1997/417] Following oral administration, everolimus is the main circulating component in human blood and contributes the majority of the overall pharmacologic activity (Study W107).

No specific excretion studies have been undertaken in cancer patients; however, data available from the transplantation setting found the drug to be mainly eliminated through the feces.

3.2.2.2.2 Everolimus monotherapy in WDNETs

Everolimus monotherapy in WDNETs has been evaluated in multicenter, randomized phase III studies.

RADIANT-3 was a randomized phase III double-blind placebo-controlled study of 410 patients with low or intermediate-grade, progressive and advanced panNETs.[15] Patients were randomized to receive everolimus plus best supportive care or placebo plus best supportive care. The results demonstrated significantly improved median PFS of 11.0 months with everolimus compared with 4.6 months with placebo. Response rate was 5% in the everolimus arm compared with 2% in the placebo arm.

A subsequent phase III study, RADIANT-2, evaluated the efficacy of everolimus plus octreotide LAR versus placebo plus octreotide LAR in 429 patients with functional carcinoid tumors.[23] The primary end point was PFS, and patients in the placebo arm were allowed to cross over to everolimus upon disease progression. By central review, median PFS was 16.4 months in the everolimus group versus 11.3 months in the placebo group but did not meet its statistical predefined end point. Therefore, the study was considered negative.

Given the findings of RADIANT-2, with suggestion that there may be a role for everolimus in the management of carcinoid tumors, RADIANT-4 was conducted. RADIANT-4 was a study of 302 patients with advanced, progressive, nonfunctional WDNETs of the lung and gastrointestinal tract. RADIANT-4 has recently returned a positive trial with PFS of 11.0 months in the everolimus arm, versus 3.9 months in the placebo arm; in addition, tumor shrinkage was seen in 64% of patients receiving everolimus, in comparison to 26% of patients receiving placebo. Based on these findings, everolimus is now the first targeted agent to show robust antitumor activity across a broad spectrum of WDNETs, including those arising from the pancreas, lung, and gastrointestinal tract.

3.2.2.2.3 Safety profile of everolimus

The following adverse events are considered to be class-effects of mTOR inhibitors: stomatitis/oral mucositis/ulcers, infections and infestations, rash and similar events, cytopenia, hemorrhages, non-infectious pneumonitis, hyperglycemia/new-onset diabetes mellitus, renal events, and thromboembolism. The more common metabolic side effects reported with mTOR inhibitors result from inhibitory effects on mTOR-regulated lipid and glucose pathways, while infections stem from the immunosuppressive properties of these agents. Virtually all of the side effects associated with mTOR inhibitors can be managed effectively with dose modification and/or supportive intervention.

Further details related to everolimus safety can be found in the Everolimus Investigator's Brochure, Everolimus Prescribing Information, and the Everolimus Package Insert.

3.2.2.3 Potential for drug interaction (LEE011 and everolimus)

In vitro experiments observed time-dependent inhibition of CYP3A4 by LEE011 with a KI value of 5 μM and a kinact value of 0.0245 min^{-1}; a clinical DDI confirmed these in vitro results. Everolimus is a sensitive CYP3A4 substrate . Therefore, a pharmacokinetic drug-drug interaction was possible with the combination of everolimus and LEE011.

As of March 2, 2015, 84 patients have been treated with the combination of LEE011 + everolimus + exemestane in a Phase Ib/II study(CLEE011X2106). Everolimus was administered at 2.5 mg (daily) concurrently with 200, 250 and 300 mg of LEE011 (daily, 3 weeks on/1 week off) with or without food. Additionally 350 mg of LEE011 was administered with 1 mg of everolimus without food or 2.5 mg everolimus with food and 200 mg of LEE011 was administered with 5 mg of everolimus with food. A fixed dose of 25 mg of exemestane (daily) was administered in each combination.

Preliminary PK data for Cmax and AUC0-24h for LEE011 and everolimus were available on Day 1 and after multiple doses on Day 15. Everolimus (2.5 mg daily) exposure (AUC0-24h) was increased in the presence of LEE011 (200-350 mg) to levels of 5 to 10 mg when compared to historical single agent data.[33-35][RAD001 IB] In general, mean steady state exposure for LEE011 and everolimus appeared to be lower in the presence of food at the same dose level; however individual Cmax and AUC0-24h values with food were within the range of values observed without food. Further evaluation of 2.5 mg of everolimus (daily) with 300 mg LEE011 (daily, 3 weeks on/1 week off) with food is ongoing.

Results from CLEE011X2106 were presented amongst 70 evaluable patients in 12/2015 at the 2015 San Antonio Breast Symposium.(Bardia 2015, Publication Number P6-13-01) In this cohort, grade 3/4 treatment-related adverse events were neutropenia (45.7%), leukopenia (8.6%), and thrombocytopenia (5.7%), with 2 patients (2.9%) discontinuing treatment due to adverse events. Six patients (8.6%) treated with LEE011 (300 mg) and everolimus (2.5 mg) experienced grade 3 dose-limiting toxicities: increased alanine aminotransferase/aspartate aminotransferase (2 patients, 2.9%), febrile neutropenia and hypophosphatemia (1 patient, 1.4%), oral mucositis (1 patient, 1.4%), rash and thrombocytopenia (1 patient, 1.4%), and thrombocytopenia with bleeding (1 patient, 1.4%).

In the more recent CLEE011XUS29 (TRINITI-1) study in breast cancer, the dose de-escalation cohort C has been included, where patients initiate therapy with a starting dose of LEE011 200 mg daily and everolimus 5 mg daily. To date, the dosing regimen has been better tolerated with regards to hematologic toxicities, and also allows for maximum exposure of everolimus. To date, five patients have been treated as part of cohort C in CLEE011XUS29 for a period of more than one month and no dose limiting toxicities have been observed.

3.2.2.4 Ongoing clinical experience with Treatment of WDNETs with LEE011 and everolimus

Our experience at MSKCC with treatment of WDNETs on this protocol (as of 12/08/2017) with LEE011 + everolimus with starting dose of LEE011 300mg once daily 3 weeks on/1 week off and everolimus 2.5mg daily are as follows. Ten patients have been enrolled to date and initiated therapy on protocol. Two patients were taken off study due to infectious complications; one patient had

recurrent urinary tract infections and elected to come off of study and the second patient had colitis in the setting of febrile neutropenia and was taken off of study. For both of these patients, the infectious complications occurred during the first cycle of treatment. Seven patients were taken off study in the setting of either clinical or radiographic disease progression. One patient continues on therapy at this time.

Of the 10 patients, 7 patients underwent dose reductions (4 patients with 1 dose reduction, 3 patients with 2 dose reductions).

4/10 (40%) patients experienced grade 1 thrombocytopenia, 2/10 (20%) patients experienced grade 2 thrombocytopenia, and 2/10 (20%) patients experienced grade 3 thrombocytopenia. No patients experienced grade 1 neutropenia. 7/10 (70%) patients experienced grade 2 neutropenia and 2/10 (20%) patients experienced grade 3 neutropenia.

1/10 (10%) patients experienced grade 1 rash, 1/10 (10%) patients experienced grade 2 rash, and 1/10 (10%) patients experienced grade 3 rash – the rash was maculopapular and acne-like in nature.

Given our results after enrollment of 10 patients on this study, based on the dose de-escalation cohort C of CLEE011XUS29, for any patients enrolled in the future, the decision has been made to initiate treatment with a starting dose of LEE011 200mg daily and everolimus 5 mg daily. The expectation is that with this dosing schema, we will allow for additional safety for patients with maximum exposure of everolimus, a known effective therapy for WDNETs. Additionally, we believe that a higher dose of everolimus (already an FDA approved drug in foregut WDNETs as discussed in this protocol) will allow for more promising efficacy.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a multicenter, non-randomized, phase II clinical trial. This study will be conducted to determine the efficacy and safety of the combination of LEE011 and everolimus in subjects with advanced WDNETs of foregut origin.

The primary objective of this trial is to determine the PFS in patients with WDNETs treated with the combination of LEE011 and everolimus using RECIST v1.1.

A total of 41 patients will be enrolled in this study. A simon two stage design will be employed.

4.2 Intervention

All subjects will receive the oral combination of LEE011 and everolimus, with dosing based on the Cohort C of of CLEE011XUS29 (TRINITI-1), currently enrolling for the treatment of patients with breast cancer. Subjects will receive LEE011 200 mg daily, in combination with everolimus 5 mg daily; in the setting of toxicity, everolimus dosing will be changed to 2.5 mg daily or 2.5 mg every other day. Subjects will continue treatment until meeting one of the criteria for removal from study.

Subjects will be evaluated by physical exam and routine blood tests every 2 weeks for cycles 1 and 2, and monthly for every cycle thereafter during the study period. CT or MRI will be performed during screening, and then at 12 week intervals. Evaluation of tumor responses will be performed according to RECIST v1.1.

Subjects who discontinue treatment for reasons other than disease progression will have posttreatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for OS until death or withdrawal of consent.

The study will be completed when all subjects have progressed or discontinued from the study for other reasons. The accrual time is estimated to be 1 to 2 years. The study is expected to take approximately 4 to 5 years to complete. The study duration is estimated at 5 to 6 years.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 LEE011 (LEE011)

LEE011 will be provided by Novartis. LEE011 will be administered orally at the dose of 200 mg daily.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

5.1.1 Description and composition of LEE011

The LEE011 drug product is planned for oral administration. The available clinical forms are capsules/tablets (50 mg, 200 mg). LEE011 will be administered as a flat-fixed dose, and not by body weight or surface area.

5.1.2 Storage condition of LEE011

Study treatments will be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the medication label. Medication labels will comply with the legal requirements of the United States and be printed in the local language.

The shelf-lives of the drug products are established based on ongoing stability studies and may be extended during the clinical study.

Please refer to the clinical labels for current shelf-life, in-use and storage conditions for the capsules/tablets.

5.2 Everolimus

Everolimus will be provided for study use and will be supplied by Novartis. Everolimus was administered orally at the dose of 2.5 mg daily, as established in LEE011X2106 for the first 10 patients enrolled to this study. For subsequently enrolled patients, given the toxcities observed in the WDNET population, everolimus will be administered orally at the dose of 5 mg daily, as established in CLEE011XUS29 (TRINITI-1), cohort C dose de-escalation.

Complete guidelines for the management and administration of everolimus can be found in the Everolimus Investigator's Brochure and Everolimus Package Insert.

5.3 Study drug compliance and accountability

Compliance should be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver. Records of study medication used, dosages administered, and intervals between visits and the completion of the study should be captured in the Pill Diary. This information must be captured in the source document at each patient visit.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

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

1. Patient has signed the Informed Consent prior to any screening procedures being performed and is able to comply with the protocol requirements.
2. Adults $\geq$ 18 years old.
3. Histologic or cytologic diagnosis of a WDNET, Ki67 ≤ 30%, unresectable, of foregut origin (thymic, bronchopulmonary, gastric, duodenal, and pancreatic) confirmed by the enrolling institution.
    - Note: If patients have a functional NET, they are permitted to continue on a somatostatin analog for hormonal symptom control.
4. MSK patient has tissue available from a previous biopsy for the evaluation of potential predictive biomarkers. If tissue is not available for MSK patient, a new tumor specimen will need to be obtained prior to the start of study treatment. If archived tissue is available, participating site patient will provide for the evaluation of potential predictive biomarkers. If tissue is not available for participating site patient, a new tumor specimen is optional prior to the start of study treatment.
5. Documented radiological evidence for disease progression (measurable or nonmeasurable) ≤12 months prior to enrollment.
6. Disease that is currently not amenable to surgical resection with curative intent as determined by the treating investigator
7. Measurable disease as defined by RECIST v1.1.
8. ECOG performance status 0 or 1 or KPS performance status 100 to 70.
9. Patient has adequate bone marrow and organ function as defined by the following laboratory values at screening:
    - Absolute neutrophil count $\geq 1.5 \times 10^9$/L

- Platelets ≥100 x 10^9/L
- Hemoglobin ≥9.0 g/dL
- INR ≤1.5
- Serum creatinine <1.5mg/dL or creatinine clearance ≥50 mL/min
- In the absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5 x ULN. If a patient has liver metastases, ALT and AST <5 x ULN
- Total bilirubin < ULN; or total bilirubin ≤3.0 x ULN or direct bilirubin ≤1.5 x ULN in patients with well-documented Gilbert's Syndrome

10. Negative serum pregnancy test done ≤14 days prior to registration, for women of childbearing potential only. A serum pregnancy test will be conducted ≤ 72 hours prior to treatment start as a pre-treatment parameter. All women of reproductive potential and their partners must agree to use adequate methods of birth control (e.g. latex condoms) throughout the study and for 30 days after the last dose of study drug.

    † A female of reproductive potential is a sexually mature female who: has not undergone a hysterectomy or bilateral oophorectomy; or has not been naturally postmenopausal for at least 24 consecutive months (i.e. has had menses at any time in the preceding 24 consecutive months).
11. Patient with standard 12-lead ECG with the following parameters at screening (defined as the mean of the triplicate ECGs):
    - QTcF interval at screening <450msec (using Fridericia's correction)
12. Must be able to swallow LEE011 and everolimus capsules/tablets.
13. Recovered from adverse events (to grade 1 or less toxicity according to CTCAE 4.0) due to agents administered previously.
    a. NOTE: Chemotherapy-induced alopecia and grade 2 neuropathy are acceptable.

6.2 Subject Exclusion Criteria

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

1. Patient has a known hypersensitivity to any of the excipients of LEE011 or everolimus.
2. Previous treatment with a CDK 4/6 inhibitor or an mTOR inhibitor.
3. Has had prior chemotherapy, targeted small molecule therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e. ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
    - Note: Subjects with ≤ Grade 2 neuropathy or chemotherapy-induced alopecia are an exception to this criterion and may qualify for the study.
4. Patient has a concurrent malignancy or malignancy within 3 years prior to starting study drug, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.
5. Patients with central nervous system (CNS) involvement unless they meet ALL of the following criteria:

- At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment
- Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme-inducing anti-epileptic medications for brain metastases

6. Patient 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).
7. Patient has a known history of HIV infection (testing not mandatory).
8. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol (e.g. chronic pancreatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.).
9. Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary
10. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality, including any of the following:
    - History of myocardial infarction (MI), angina pectoris, symptomatic pericarditis, or coronary artery bypass graft (CABG) within 6 months prior to study entry
    - Documented cardiomyopathy
    - Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
    - Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
        - Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
        - Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued or replaced by safe alternative medication (e.g. within 5 half-lives or 7 days prior to starting study drug)
        - Inability to determine the QTcF interval
    - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
11. Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to starting study drug (see Table 1 for details):
    - Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges, that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5

- Herbal preparations/medications, dietary supplements

12. Patient is currently receiving or has received systemic corticosteroids ≤2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.
    - The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular)
13. Participation in a prior investigational study within 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer
14. Patient who has received radiotherapy ≤4 weeks or limited field radiation for palliation ≤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) or in whom ≥25% of the bone marrow (Ellis, 1961) was irradiated.
15. 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).
16. Patient with a Child-Pugh score B or C (see Appendix D).
17. Patient has a history of non-compliance to medical regimen or inability to grant consent.
18. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception until the termination of gestation, confirmed by a positive hCG laboratory test.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by members of the patient's treatment team, the protocol investigator or research team at participating institutions. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants. The investigator will use information provided by the patient and/or medical record to confirm that the patient is eligible and contact the patient regarding study enrollment. All eligible patients, regardless of sex and race, will be approached for participation. The investigators are aware of the NIH policy concerning inclusion of women and minorities in clinical research populations.

Participation in the study is completely voluntary. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. Patients will not receive payment for their participation on this study. Patients are free to withdraw from the study without consequence at any time.

8.0 PRETREATMENT EVALUATION

The following must be completed within 28 days of starting LEE011 + everolimus:

1. CT scan of the chest, abdomen, and pelvis with contrast. If patient is unable to receive CT contrast, or the abdominal/pelvic target lesion is indeterminate on CT scan then MRI abdomen and pelvis with contrast plus CT chest without contrast may be perfromed.

Non-contrast CT chest, abdomen, and pelvis may be used if the target lesion(s) do not require contrast for accurate measurements.

2. 12-lead Electrocardiogram (EKG).
3. Signed informed consent for study participation.
4. History and physical examination, including height, weight, vital signs (temperature, pulse rate, respiration rate, blood pressure), and ECOG performance status.
5. Serum pregnancy test for all women of childbearing potential (within 72 hours prior to receiving first dose of study medication). If the test result is positive related to pregnancy, the patient will not be allowed to participate in this study.
6. CBC with differential and platelet count, serum chemistries (Na, K, Cl, CO2, BUN, creatinine, glucose, calcium, albumin, and total protein), liver function tests (AST, ALT, alkaline phosphatase, total bilirubin), coagulation panel (PT/INR and PTT), lipid panel, and urinalysis.
7. Serology for hepatitis B (HepBsAg, and HepBcAb) and hepatitis C antibody (negative test acceptable prior to screening period). HepB PCR will be performed if HepB core antibody or HepB surface antigen is reactive.
8. Transthoracic echocardiogram (TTE) or multigated acquisition (MUGA) scan.
9. Perform baseline tumor biopsy for MSK patients without archived tissue or obtain archived tissue for research purposes for MSK patients. Performing baseline tumor biopsy for participating site patients is optional. Obtain archived tissue for research purpoes for participating site patients if available.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Study drug preparation and dispensation

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

LEE011 will be supplied by Novartis or its designee in the form of 50mg and 200mg capsules/tablets as individual patient supply packaged in bottles. Storage conditions are described in the medication label.

Everolimus will be supplied for study use and will be supplied by Novartis as tablets for oral use.

LEE011 and everolimus will be administered as a flat-fixed dose and not by body weight or body surface area.

9.1.1 Study drug packaging and labeling

LEE011 capsules/tablets are packaged in high density polyethylene (HDPE) bottles with child resistant closures. Everolimus tablets are packaged in blister packs (4 blisters per pack per strength).

Medication labels will be in English. They will include storage conditions for the drug but no information about the patient. The study drug will be labeled and packaged under the responsibility of the Novartis drug supply management department. The medication will be supplied as open label supply in a way which allows the patient to take medication at home.

9.1.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels, the LEE011 Investigator's Brochure, and in the Everolimus Package Insert.

9.1.3 Study drug compliance and accountability

Patients will be instructed to return unused study drugs to the site at discontinuation or completion of treatment. The site personnel must ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed. Compliance should be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Pill Diary.

9.1.4 Disposal and destruction

The LEE011 and everolimus supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate, or if pre-arranged between Novartis and study site, destruction of used and unused LEE011 and everolimus will be performed at the study site if permitted by local regulations.

9.2 Dosing Instructions and Schedule

The dosing regimen to be used in this trial is outlined below in Table 2. For the first 10 patients enrolled on this study, the doses of LEE011 and everolimus were based on the final results of LEE011X2106. Given the toxicities observed in our first 10 WDNET patients, for subsequently e nrolled patients, the doses of LEE011 and everolimus are based on cohort C of CLEE011XUS29 (LEE011 200 mg daily and everolimus 5 mg daily. The investigator will instruct the patient to take the study drug as per protocol. Patients will be instructed to return unused study drugs to the investigator at the end of each cycle. The investigator will ensure that the appropriate dose of each study drug is administered at each visit and will provide the patient with the correct amount of drugs for subsequent dosing.

Table 2: Dosing regimen

Study treatments	Pharmaceutical Form	Dose	Route of Administration	Regimen/ Treatment Period
LEE 011	Capsule/Tablet	200 mg	Oral	Daily (continuous)
Everolimus	Tablet	5 mg	Oral	Daily (continuous)
Everolimus (first dose reduction)	Tablet	2.5 mg	Oral	Daily (continuous)
Everolimus (second dose reduction)	Tablet	2.5 mg	Oral	Every other day (continuous)

Day 1 is considered the first day of dosing. Each treatment cycle is 28 days. The study drugs will be administered as a flat-fixed dose, and not by body weight or by body surface area. LEE011 and everolimus will be taken orally, once a day, or every other day if the patient develops toxicity that requires a second dose reduction as per Table 2.. All trial treatments will be administered in an outpatient setting.

9.3 LEE011 and everolimus administration

Patients will take the LEE011 and everolimus combination at home. Patients will be asked to record in a diary the date and time that the study medication was taken on a Pill Diary.

LEE011 and everolimus must be taken as follows (also noted on the Pill Diary):

- Patients should be instructed to take the study drug combination of LEE011 and everolimus with a large glass of water (~250 ml) at approximately the same time each day.
- Patients should be instructed to swallow the LEE011 capsules/tablets and everolimus tablets whole and not to chew, crush, or open them.
- LEE011 and everolimus can be taken after eating a light, low fat meal.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting and/or diarrhea (or increase stool frequency) during a treatment cycle must be noted on the Pill Diary.
- 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 must avoid consumption of grapefruit, grapefruit hybrids, pummelos, star-fruit, Seville oranges, or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.
- No herbal or dietary supplements are permitted, due to potential interactions with LEE011; multivitamins are allowed.

9.4 Treatment duration

During the treatment period, the patient must follow the investigators instructions with regards to contraception, concomitant medications, and dosing regimen. There is no fixed treatment duration; patients may continue treatment with the LEE011 and everolimus combination until disease progression, unacceptable toxicity occurs that precludes any further treatment, and/or treatment is discontinued at the discretion of the investigator or by patient refusal (withdrawal of consent).

For details of the frequency of the visits and assessments during the treatment period, refer to the study calendar (Table 7).

9.5 Dose modifications

For patients who do not tolerate the protocol-specified dosing schedule, LEE011/everolimus adjustments are permitted in order to allow the patient to continue the study treatment. Any changes to the dose or interruption of dosing must be recorded on the Pill Diary. Patients who require a drug hold of more than 28 days will be discontinued from the study unless discussed and approved by the MSK PI. Once dose-reduced the dose may not be re-escalated.

Management of severe or intolerable adverse reactions (sections 9.5.1 to 9.5.7) requires temporary interruption, and/or discontinuation of LEE011 therapy and in the case of everolimus requires dose reduction, temporary interruption, and/or discontinuation of everolimus therapy.. Each patient is allowed a maximum of two dose reductions for everolimus. After this, the patient will be discontinued from the study treatment. For each patient, once a dose level reduction for everolimus has occurred for toxicity meeting the criteria for dose interruption and/or adjustment, the dose level cannot be re-escalated during subsequent treatment cycles. If a dose reduction is required, everolimusshould be reduced one dose level. Dose levels for everolimus are provided in Table 3.

A dose-dependent drug-drug interaction was observed between LEE011 and everolimus based on clinical PK analyses in a separate dose escalation trial, where everolimus exposure increased 2- to 4-fold in the presence of LEE011. The dose de-escalation modification of everolimus, which we are adopting given our experience in treating our first 10 patients enrolled to this study, allows for additional safety with maximum exposure of everolimus. After permanent discontinuation of either LEE011 or everolimus, patients should be discontinued from study treatment.

Table 3: Dose modification guidelines for LEE011 and everolimus

	LEE011	Everolimus
	Dose	**Dose**
Starting dose	200 mg	5 mg daily
First dose reduction	200 mg	2.5 mg daily

Second dose reduction	200 mg	2.5 mg every other day

Anticipated risks and safety considerations of the study drug combination

Preclinical and Phase I clinical data available from ongoing studies with LEE011 and everolimus suggest few overlapping toxicities for the proposed combinations. Special attention will be paid to blood counts (cytopenias), mucositis, liver function test abnormalities and QTc prolongation. Clinical data from the CLEE011X2101 study do not show marked accumulation in LEE011 with time, suggesting that it does not substantially inhibit its own metabolism or clearance.

Everolimus and LEE011 are *in vitro* inhibitors and substrates of CYP3A4, and the latter is also a time-dependent CYP3A4 inactivator. The available preclinical and clinical data therefore suggest the possibility of a drug interaction, specifically one that may increase exposure to everolimus. Based on simulation using Simcyp software (Simcyp Version 12, release 1), the projected increase in the AUC 0-6h of everolimus was 3.5-fold following the starting daily dose of 200 mg LEE011 co-administered with 2.5 mg of everolimus for 14 days. No significant effect on LEE011 metabolism was predicted when co-administered with everolimus. Appropriate eligibility criteria, dose modification guidelines and stopping rules are included in this protocol.

9.5.1 Dose modifications and management recommendations for hematologic adverse reactions (see Table 3 for dose reduction guide)

Toxicity	Grade	Dose Adjustment and Management Recommendations
Thrombocytopenia	Thrombocytopenia	
	Grade 1(≥75 x 10^9/L)	No dose adjustment required.
	Grade 2 (≥50 x 10^9/L – <75 x 10^9/L)	Dose interruption of LEE011 and everolimus until recovery to grade ≤1. CBC will be repeated weekly (± 3 day window) until toxicity has recovered to grade ≤1. Re-initiate study treatment at the same dose.
	Grade 3 (≥25 x 10^9/L - <50 x 10^9/L)	Dose interruption of LEE011 and everolimus until recovery to grade ≤1. CBC will be repeated weekly (± 3 day window) until toxicity has recovered to grade ≤1. Re-initiate study treatment at the same dose level. If toxicity recurs at grade 3: temporary dose interruption of LEE011 and everolimus until recovery to grade ≤1 and reduce everolimus to the next lower dose level. Maintain LEE011 at same dose.
	Grade 4(<25 x 10^9/L)	Dose interruption of LEE011 and everolimus until recovery to grade ≤1. CBC will be repeated weekly (± 3 day window) until toxicity has recovered to grade ≤1. Re-initiate study everolimus at the next lower dose level. Maintain LEE011 at the same dose. If toxicity recurs at grade 4: discontinue study treatment.
Neutropenia	Absolute neutrophil count (ANC)	
	Grade 1 (≥1.5 x 10^9/L)	No dose adjustment required.
	Grade 2 (≥1.0 - <1.5 x 10^9/L)	No dose adjustment required.
	Grade 3 (≥0.5 - <1.0 x 10^9/L)	Dose interruption of LEE011 and everolimus until recovery to ≥1.0 x 109/L. CBC will be repeated weekly (± 3 day window) until toxicity has recovered to grade ≤1.Re-initiate study treatment at the same dose level. If toxicity recurs at grade 3: temporary dose interruption of LEE011 and everolimus until recovery to ≥1.0 x 109/L. If resolved in ≤7 days, then maintain dose level. If resolved in >7 days, consider growth factors then reduce everolimus dose to the next lower dose level. Maintain LEE011 at same dose.

	Grade 4 (<0.5 x 10^9/L)	Dose interruption of LEE011 and everolimus until recovery to ≥1.0 x 109/L. CBC will be repeated weekly (± 3 day window) until toxicity has recovered to grade ≤1. Re-initiate everolimus at the next lower dose level (first dose reduction level). Maintain LEE011 at same dose If toxicity recurs at grade 4: temporary dose interruption of LEE011 and everolimus until recovery to ≥1.0 x 109/L and reduceeverolimus at the next lower dose level. Maintain LEE011 at same dose.
Febrile Neutropenia	Grade 3: ANC<1.0 x 10^9/L with [a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour] .	Dose interruption of both LEE011 and everolimus until improvement of ANC ≥1.0 x 10^9/L and no fever. CBC will be repeated weekly (± 3 day window) until toxicity has recovered to grade ≤1. Restart everolimus at the next lower dose level. Maintain LEE011 at the same dose. If febrile neutropenia recurs, discontinue study treatment. Colony Stimulating Factors should be considered in patients with fever and profound neutropenia (<1.0 x 10^9/L).
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue study treatment.
Anemia (Hemoglobin)	Grade 1: ≥10.0 – LLN g/dL	No dose adjustment required.
	Grade 2: ≥8.0 – <10.0 g/dL	No dose adjustment required.
	Grade 3: <8.0 g/dL	Dose interruption of LEE011 and everolimus until recovery to grade 1. CBC will be repeated weekly (± 3 day window) until toxicity has recovered to grade ≤1. Re-initiate study treatment at the same dose.
	Grade 4: Life-threatening consequences; urgent intervention indicated	Discontinue study treatment PRBC transfusion to be considered per NCCN guidelines.

9.5.2 LEE011/everolimus dose modification and management for QTcF prolongation (see Table 3 for dose reduction guide)

Adverse drug reaction	Severity	Dose adjustment and management recommendations
QTcF prolongation	For All Grades	Check the quality of the ECG and the QT value and repeat if needed. Perform analysis of serum electrolytes (K+, Ca++, Phosphorus, Mg++). If outside of normal range, hold LEE011 and everolimus, 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 study treatment Consider collecting a time matched PK sample; record date and time of last study drug intake.
	Grade 1 QTc 450-480 ms	No dose adjustment required.
	Grade 2 QTc 481-500 ms	Hold LEE011 and everolimus. Perform a repeat ECG one hour after the first QTcF of ≥481 ms. If QTcF <481 ms, restart LEE011 and everolimus 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 and everolimus at the same dose. No dose adjustment required for first occurrence. If QTcF ≥481 ms recurs, everolimus should be reduced by 1 dose level; continue with LEE011 at same dose. Repeat ECGs 7 days and 14 days after dose. Resumption of study treatment (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥481 ms.

	Grade 3 QTc ≥501 ms on at least two separate ECGs	Hold LEE011 and everolimus. Transmit ECG immediately and confirm prolongation/ abnormalities with central assessment. Perform a repeat ECG within one hour of the first QTcF of ≥501 ms. If QTcF remains ≥501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms. If QTcF returns to <481 ms, everolimus will be reduced by 1 dose level. Maintain LEE011 at same dose. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥501ms If QTcF of ≥501 ms recurs, discontinue study treatment. Perform frequent ECGs until the QTcF is <500 msec. Address electrolyte, calcium and magnesium abnormalities.
	Grade 4 QT/QTc ≥501 or >60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia	Discontinue study treatment. Transmit ECG immediately and confirm prolongation/ abnormalities with central assessment. Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms.

9.5.3 LEE011/everolimus dose modification and management for cardiac dysfunction (see Table 3 for dose reduction guide)

Adverse drug reaction	Severity	Dose adjustment and management recommendations
Cardiac - Left Ventricular Systolic Dysfunction	Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	Maintain dose level, and continue LEE011 and everolimus with caution. Repeat LVEF within 4 weeks or as clinically appropriate**.**
	Symptomatic, responsive to intervention, ejection fraction 20-39% or >20% drop from baseline	Hold LEE011 and everolimus until resolved, then reduce everolimus by one dose level. Maintain LEE011 at same dose. Referral to cardiologist mandatory for management of heart failure symptoms. LVEF measurement to be repeated, if not resolved within 28 days permanently discontinue LEE011 and everolimus if applicable.

9.5.4 LEE011/everolimus dose modification and management for hepatotoxicity (see Table 3 for dose reduction guide)

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 1 (> ULN – 1.5 x ULN) (confirmed 48 to 72hrs later)	If confirmed, maintain dose level with LFTs monitored bi-weekly until normalizes.
Grade 2 (>1.5 – 3.0 x ULN)	Dose interruption of LEE011 and everolimus. Liver enzymes and bilirubin tests will be repeated twice weekly (± 3 day window) until toxicity has recovered to grade ≤1. If resolved to ≤grade 1 in ≤21 days, then maintain dose level. If resolved to ≤grade 1 in >21 days or toxicity recurs, reduce everolimus by 1 dose level. Maintain LEE011 at same dose. Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption. If toxicity recurs after two dose reductions of everolimus, discontinue study treatment.
Grade 3 (>3.0 – 10.0 x ULN)	Dose interruption of LEE011 and everolimus. Liver enzymes and bilirubin tests will be repeated twice weekly (± 3 day window) until toxicity has recovered to grade ≤1. If resolved to ≤ Grade 1 in ≤21 days, lower 1 dose level of everolimus, maintain LEE011 at same dose. Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption. If resolved to ≤grade 1 in >21 days or toxicity recurs, discontinue study treatment.
Grade 4 (>10.0 x ULN)	Discontinue LEE011
Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤1 x ULN) due to hemolysis or Gilbert's Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert's Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.	

HEPATOTOXICITY (AST or ALT)	
AST or ALT without bilirubin elevation >2 x ULN	
Same grade as baseline or increase from baseline grade 0 to grade 1	No dose adjustment required with LFTs monitored per protocol if same grade as baseline or bi-weekly in case of increase from baseline grade 0 to 1.
Increase from baseline grade 0 or 1 to grade 2 (>3.0 – 5.0 x ULN)	Dose interruption of LEE011 and everolimus until recovery to ≤baseline. Liver enzymes and bilirubin tests will be repeated twice weekly (± 3 day window) until toxicity has recovered to grade ≤1. If resolved to ≤baseline in ≤21 days, then maintain dose level. If resolved to ≤baseline in >21 days or toxicity recurs, then reduce everolimus by 1 dose level. Maintain LEE011 at same dose. Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption. If toxicity recurs after two dose reductions of everolimus or recovery to ≤baseline grade is >28 days, discontinue study treatment.

Increase from baseline grade 0 or 1 to grade 3 (>5.0 – 20.0 x ULN)	Dose interruption of LEE011 and everolimus until resolved to ≤baseline grade, then lower 1 dose level of study treatment. Liver enzymes and bilirubin tests will be repeated twice weekly (± 3 day window) until toxicity has recovered to grade ≤1. Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption. If recovery to ≤baseline grade is >28 days, discontinue study treatment. If toxicity recurs after two dose reductions of everolimus or recovery to ≤ baseline grade is > 28 days, discontinue study treatment.
Increase from baseline grade 2 to grade 3 (>5.0 – 20.0 x ULN)	Dose interruption of LEE011 and everolimus until resolved to ≤baseline grade, then lower everolimus by 1 dose level. Maintain LEE011 at same dose Liver enzymes and bilirubin tests will be repeated twice weekly (± 3 day window) until toxicity has recovered to grade ≤1. Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption. If toxicity recurs after two dose reductions of everolimus or recovery to ≤baseline grade is >28 days, discontinue study treatment.
Grade 4 (>10.0 x ULN)	Discontinue study treatment.
AST or ALT and concurrent Bilirubin	
For patients with normal ALT and AST and total bilirubin at baseline: AST or ALT > 3 x ULN combined with total bilirubin > 2 x ULN without evidence of cholestasis or For patient with elevated AST or ALT or total bilirubin at baseline: baseline : [AST or ALT >2 x baseline AND >3.0x ULN] OR [AST or ALT 8.0 x ULN]- whichever is lower- **combined with** [total bilirubin 2 x baseline AND >2.0 x ULN]	Discontinue study treatment.
Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, and alcohol intake.	

Additional follow-up for hepatic toxicities

Hepatic toxicity monitoring includes assessment of the following liver function tests (LFTs): albumin, ALT, AST, total bilirubin, direct and indirect bilirubin alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), creatinine kinase, prothrombin time (PT)/(PTT), international normalized ratio (INR) and Gamma-glutamyl transpeptidase (GGT). For patients with Gilbert's Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only.

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

- Repeating liver enzyme and serum bilirubin tests approximately two times weekly. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or return to normal values.
- Obtaining a more detailed history of current symptoms.
- Obtaining a more detailed history of prior and/or concurrent diseases including history of any pre-existing liver conditions or risk factors.
- Obtaining a history of concomitant drug use (including non-prescription medications, herbal and dietary supplements), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; hepatotropic virus infections cytomegalovirus (CMV), Epstein-Barr virus (EBV), or herpes simplex virus (HSV); autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.
- Assessing cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure as possible etiologies for liver dysfunction.
- Obtaining a PK sample, as close as possible to last dose of study drug.
- Liver biopsy as clinically indicated to assess pathological change and degree of potential liver injury.

Increase in transaminases combined with total bilirubin (TBIL) increase may be indicative of drug-induced liver injury (DILI), and should be considered as clinically important events. The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT AND AST AND TBIL value at baseline: AST or ALT >3.0 x ULN combined with TBIL >2.0 x ULN.
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT >2 x baseline AND >3.0 x ULN] OR [AST or ALT >8.0 x ULN], whichever is lower, combined with [TBIL >2 x baseline AND >2.0 x ULN].

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as: Alkaline phosphatase (ALP) elevation >2.0 x ULN with R value <2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values [R value = ALT/ULN)/(ALP/ULN)]. It denotes the relative pattern of ALT and/or ALP elevation is due to cholesteric or hepatocellular liver injury or mixed type injury.

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as “medically significant”, thus meeting the definition of SAE, and reported as SAE using the term “potential drug-induced liver injury”. All events should be followed up with the outcome clearly documented.

9.5.5 Dose modification and management for everolimus specific toxicities (Refer to dose modification Table 3)

Adverse drug reaction	Severity	Dose adjustment and management recommendations
Stomatitis	**Grade 1** Minimal symptoms, normal diet	No dose adjustment required. Manage with non-alcoholic steroid mouthwash and salt water (0.9%) mouth wash four times a day.
	Grade 2 Symptomatic but can eat and swallow modified diet	Interrupt everolimus and LEE011 until recovery to grade 1. Re-initiate study treatment at the same dose. If stomatitis recurs, interrupt LEE011 and everolimus until recovery to grade 1. Re-initiate study treatment at a one dose lower. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl minobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).
	Grade 3 Symptomatic and unable to adequately aliment or hydrate orally	Interrupt everolimus and LEE011 until recovery to grade ≤1.Re-initiate study treatment of everolimus at a reduced dose. Maintain LEE011 at the same dose. If reoccurs, interrupt LEE011 and everolimus until recovery to grade ≤1.Re-initiate everolimus study treatment at second dose level. Maintain LEE011 at the same dose. Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).
	Grade 4 Symptoms associated with life-threatening consequences	Hold LEE011 and everolimus and provide appropriate medical therapy. If recovered to ≤grade 1 within 3 weeks, Re-initiate study treatment with everolimus at a reduced dose. Maintain LEE011 at same dose. If >3 weeks, then discontinue study treatment.
Serum creatinine	Grade 1	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2	Hold LEE011 and everolimus until resolved to grade ≤1, then re-initiate study treatment at the same dose level. If toxicity recurs at Grade 2, interrupt LEE011 and everolimus until recovery to grade ≤1, re-initiate and reduceeverolimus by one dose level. Maintain LEE011 at same dose.

	Grade 3	Hold LEE011 and everolimus until resolved to grade ≤1, then reduce everolimus by 1 dose level. Maintain LEE011 at the same dose. If toxicity recurs after two everolimus dose reductions, discontinue study treatment.
	Grade 4	Discontinue study treatment and manage appropriately.
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and closely monitor. Consider metformin for hyperglycemia.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor. For hyperglycemia, consider metformin and follow up with endocrinologist.
	Grade 3	Hold LEE011 and everolimus until resolved to grade ≤1, then reduce everolimusby 1 dose level. Maintain LEE011 at the same dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Hold LEE011 and everolimus until resolved to grade ≤1 then discontinue study treatment

9.5.6 Management of non-infection pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Dose Adjustment
Grade 1 Asymptomatic radiographic findings only	CT scans with lung windows Repeat at least every 8-12 weeks until return to within normal limits.	No specific therapy is required	Administer 100% of study treatment dose.
Grade 2 Symptomatic, not interfering with ADL	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 Saturation at rest Repeat at least every 8-12 weeks until return to within normal limits. Consider a bronchoscopy with biopsy and / or BAL	Symptomatic only. Consider corticosteroids if symptoms are troublesome.	Reduce everolimus dose by 1 dose level until recovery to ≤Grade 1.* Patient will continue at LEE011 at current dose.
Grade 3 Symptomatic, interfering with ADL; O2 indicated	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold everolimus until recovery to Grade ≤1. May restart everolimus treatment within 3 weeks at 1 lower dose level if evidence of clinical benefit. Patient will continue LEE011 at current dose.
Grade 4 Life threatening; ventilatory support indicated	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue study treatment.

*If patient is minimally symptomatic, everolimus can be continued at 5 mg daily at the discretion of the treating oncologist and after discussion with the principle investigator. Everolimus may also be completely interrupted if symptoms are troublesome.

9.5.7 Recommended actions to be taken for positive baseline hepatitis B test

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBs Ab	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HBc Ab	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of study drug. Monitor HBV-DNA approximately every 6 weeks.		No prophylaxis. Monitor HBV-DNA approximately every 4 weeks at the end of treatment and until EOT + 30 days.		No specific action.

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of study drug. For hepatitis B reactivation, definition and management guidelines see Table 4: Guidelines for management of hepatitis B.

Table 4: Guidelines for management of hepatitis B

Reactivation is Defined as:	Treatment
Increase of 1 log in HBV-DNA relative to baseline HBV- DNA value OR new appearance of measurable HBV-DNA **AND** ALT elevation x 5 ULN	Start appropriate antiviral therapy. **AND** Interrupt LEE011 and everolimus administration until resolution: ≤grade 1 ALT (or baseline ALT, if >grade 1) and ≤baseline HBV-DNA levels. If resolution occurs within ≤21 days study treatment should be re-started at one dose lower, if applicable. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of study drug. If resolution occurs >21 days patients should discontinue study treatment but continue both antiviral therapies at least 4 weeks after last dose of study treatment.

9.5.8 Guidance for all other adverse reactions

Consider performing an analysis of serum potassium, calcium, phosphorus, and magnesium for all adverse reactions, if indicated. If electrolyte values are outside of the normal range, interrupt LEE011/everolimus administration, correct electrolytes with supplements or appropriate therapy as soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes.

Table 5: LEE011/everolimus dose adjustment and management recommendation for all other adverse reactions (see Table 3 for dose reduction guide)

Grade/Severity	**Dose adjustment and management recommendations**
Grade 1	No dose adjustment- maximize AE management.
Grade 2	Dose interruption of LEE011/everolimus until recovery to Grade ≤1 (28 days allowed for toxicity to return to ≤ grade 1). Initiate appropriate medical therapy and monitor. Re-initiate study treatment at the same dose. If the same toxicity recurs at Grade 2, interrupt LEE011/everolimus until recovery to Grade ≤1. Re-initiate everolimus treatment at the next lower dose level. Maintain LEE011 at same dose.
Grade 3	Hold both everolimus and LEE011 until it resolves to Grade ≤ 1 (28 days allowed for toxicity to return to ≤ grade 1).. Initiate appropriate medical management and monitor. Re-initiate study treatment at the next lower everolimus dose level. Maintain LEE011 at same dose. If toxicity recurs at grade 3, discontinue study treatment.
Grade 4	Discontinue study treatment.
Additional recommendations: **Nausea**: Ensure adequate hydration or fluid repletion. Consider performing an analysis of serum potassium, calcium, phosphorus and magnesium, if indicated. If electrolyte values are below the lower limits of normal, interrupt LEE011, correct electrolytes with supplements as soon as possible, and repeat electrolyte testing until documented normalization. **Diarrhea**: At the first sign of loose stools (Grade 1), initiate loperamide. Patient should remain well hydrated. Fluids and electrolytes should be replaced as needed. Consider performing an analysis of serum potassium, calcium, phosphorus and magnesium, if indicated. If electrolyte values are below the lower limits of normal, interrupt LEE011, correct electrolytes with supplements as soon as possible, and repeat electrolyte testing until documented normalization.	

9.5.9 Dose Adjustments in Special Populations

9.5.9.1 Renal impairment

Insufficient data are available to provide a dosage recommendation for LEE011 in patients with renal impairment.

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

9.5.9.2 Elderly

Physicians should exercise caution in monitoring the effects of LEE011 in the elderly. Insufficient data are available to provide a dosage recommendation.

9.6 Concomitant medications

9.6.1 Permitted concomitant therapy for all treatment groups

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as packed red blood cells (PRBCs), pain medications, anti-emetics, short courses of steroids, chronic use of a low dose steroid for physiologic replacement, topical treatments for stomatitis and anti-diarrheal are allowed. The use of any other potential new concomitant medications may be discussed between the investigator and the MSK PI on a case by case basis.

The patient must be told to notify the treating physician about any new medications he/she takes after the start of the study drug combination. All medications (other than study drugs) and significant non-drug therapies (including vitamins, herbal medicines, physical therapy and blood transfusions) administered within 30 days of study entry and during the study must be listed on the Concomitant medications/Significant non-drug therapies eCRF.

Patients taking concomitant medication chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible.

Refer to the LEE011 and Everolimus Investigator's Brochures for concomitant medications.

Hematopoietic growth factors

The use of Transfusions or Hematopoietic growth factor support (e.g. erythropoietins, G-CSF and GM-CSF) should be according to ASCO guidelines.

Bisphosphonates and denosumab

Bisphosphonates and denosumab are generally allowed with the following comments:

- Bisphosphonate/denosumab therapy for the treatment of osteoporosis is permitted.
- Bisphosphonate/denosumab therapy for the prevention of skeletal related events for patients with existing bone metastases is permitted.
- If bisphosphonate therapy is to be started after the first dose of study drug, prior consultation and approval by Novartis is required and the reason for its use must be clearly documented.

Palliative radiotherapy

Palliative radiation is permitted while on study after discussion with sponsor. It should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow.

If palliative radiotherapy is initiated after the start of study treatment, the reason for its use must be clearly documented and progression as per RECIST v1.1 must be ruled out.

No dose modification of study treatment is needed during palliative radiotherapy.

9.6.2 Prohibited concomitant therapy

The following medications are prohibited during study treatment in the study (see Table 6). This list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions.

- Strong and moderate inhibitors or inducers of CYP3A4/5.
- Substrates of CYP3A4/5 with a narrow therapeutic index.
- Medications with a known risk for QT prolongation.
- Other investigational and anti-neoplastic therapies, including chemotherapy, immunotherapy, target therapy, biological response modifiers, or endocrine therapy.
- Hormone replacement therapy, topical estrogens (including any intra-vaginal preparations), megestrol acetate and selective estrogen-receptor modulators (e.g. raloxifene).
- Prolonged systemic corticosteroid treatment (≥2 weeks), except for topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intraarticular) should not be given. A short duration of systemic corticosteroids is allowed (e.g. chronic obstructive pulmonary disease, LFT abnormality).
- Herbal preparations/medications (except for vitamins) including, but not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications and dietary supplements at least 7 days prior to first dose of study treatment.

9.6.3 Permitted concomitant therapy requiring caution and/or action while on study

Permitted medications to be used with caution combined LEE011 and everolimus in this study are listed below (see Table 7). These medications should be excluded from patient use if possible. If they must be given based on the investigator's judgment, then use with caution and consider a LEE011 interruption if the concomitant medication is only needed for a short time:

- 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.
- Sensitive substrates of BCRP.

9.6.4 Drugs with QTc prolongation

As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential drug-drug interaction that increases the exposure of LEE011 or the exposure of the QT prolonging drug). A definitive list of drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or Torsades de Pointes (TdP) is available online at www.qtdrug.org.

Medications with a known risk for QT prolongation are prohibited during study treatment.

Table 6: List of prohibited medications during study drug treatment

Category	Drug Name
Strong CYP3A4/5 inhibitors	voriconazole, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, 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]	Terfenadine, alfentanil, apixaban (doses >2.5 mg only), aprepitant, astemizole, cisapride, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin, sirolimus, tacrolimus, terfenadine, thioridazine
Medications with a known risk for QT prolongation[4]	vavdetanib, amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl, mesoridazine, methadone, moxifloxacin, ondansetron (intravenous only), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, sevoflurane, sotalol, sparfloxacin, sulpiride, terfenadine, thioridazine, vandetanib, venlafaxine
Herbal preparations/ medications	Herbal preparations/medications are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.
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 study drug.
[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.qtdrugs.org (as of Apt 7, 2015)	

Table 7: List of medications to be used with caution during study drug treatment

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Amprenavir, atazanavir, casopitant, cimetidine, darunavir, diltiazem, fosamprenavir, lomitapide, netupitant, tofisopam, verapamil
Moderate CYP3A4/5 inducers	Bosentan, efavirenz, etravirine, genistein, lersivirine, modafinil, nafcillin, Talviraline
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine, almorexant, alpaviroc, apixaban (doses < 2.5 mg only), atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, darifenacin, darunavir, ebastine, eletriptan, eplerenone, felodipine, fluticasone, ivacaftor, lomitapide, lumefantrine, lurasidone, maraviroc, midazolam, perospirone, quetiapine, ridaforolimus, sildenafil, ticagrelor, tilidine, tolvaptan, triazolam, vardenafil, vicriviroc, voclosporin
Strong BSEP inhibitors	Bosentan, fusidate, glibenclamide, sulindac, troglitazone (TGZ-sulfate)
Medications that carry a possible risk for QT prolongation[2]	Alfuzosin, apomorphine, aripiprazole, atazanavir, atomoxetine, bedaquiline, clozapine, dexmedetomidine, dolasetron, eribulin, famotidine, felbamate, fingolimod, foscarnet, gatifloxacin, gemifloxacin, granisetron, iloperidone, isradipine, lithium, mirabegron, mirtazapine, moexipril, norfloxacin, ofloxacin, olanzapine, ondansetron (p.o. only at 4 mg or 8 mg), oxytocin, paliperidone, pasireotide, pipamperone, promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin, sertindole, telavancin, tetrabenazine, tizanidine, tolterodine, vardenafil, 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	Rosuvastatin, sulfasalazine

[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.qtdrugs.org (as of Apr 7, 2015)
[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

9.7 Biomarkers

The biomarker collections for this study are summarized in Table 8 below.

9.7.1 Potential predictive biomarkers

MSK patients must supply a tumor specimen that may be from a previous biopsy (archival tumor specimen) or from a newly obtained tumor specimen before beginning treatment with LEE011 and everolimus. Participating site patients can supply an archival tumor specimen if available. The most recent biopsy is preferred. The availability of tumor specimens must be confirmed **before** MSK patients receive treatment. Additionally, a pathology report must be submitted along with the patient's archival tumor block/slides for MSK patients and for applicable participating site patients.

While on protocol, all patients will also be given the opportunity to consent to an optional biopsy (regardless of disease response) for further evaluation of predictive biomarkers.

Baseline tumor samples (archival or newly obtained) will be tested for p-Akt, p-S6K, p-pRb and PTEN protein as well as Ki-67 by immunohistochemistry at each participating site as per institutional guidelines. The status of molecules (e.g., gene expression, mutations, amplifications, deletions and/or protein expression/activation etc.) that are involved in the D-cyclin-CDK4/6-INK4a-Rb and mTOR pathways, such as mutations of CCND1, PIK3CA, PTEN and CDK4; gene amplification of CCND1 and CDK4, deletion of CDKN2, as well as other cancer associated genes, will also be investigated in the tumor tissue from all patients (provided that acceptable assays exist), with the intention to identify potential predictive markers related to therapeutic responses or resistant disease. Other pathways that may interact with D-cyclin-CDK4/6-INK4a-Rb and/or mTOR, or thought to be important in cancer may also be assessed, depending on sample and assay availability. Tumor samples obtained while on protocol (through an optional biopsy after patient consent for any patient on protocol) will be tested for total pRb and p-pRB, Ki-67, p-Akt, and p-S6K expression by IHC. The results from these exploratory analyses will be correlated with clinical outcome to determine potential predictive biomarkers of LEE0011/everolimus response/resistance.

Biomarker analysis will be performed by each participating site for their respective patients.

Next-generation sequencing

Next-generation sequencing of tumor tissue may be considered for all patients on this protocol, however if next-generation sequencing is pursued, patients must be separately consented.

At MSK, patients will be offered the opportunity to participate in MSK IRB# 12-245 to have MSK-IMPACT testing performed through our institutional protocol. Similarly, each participating site will be asked to consent their patients to the appropriate institution protocol as per their site IRB guidelines. Participation within these next-generation sequencing is not mandatory for patients to participate in this study. Participating sites will be responsible for submitting available sequencing data to MSK as per institutional guidelines.

Table 8: Biomarker sample collection schedule

Sample	Tissue	Visit	Biomarker assay
FFPE or newly obtained tumor (required for MSK patients, optional for participating site patients without archived tissue)	Tumor	Screening	p-Akt, p-S6K, p-pRB, PTEN, Ki-67 by IHC DNA sequence of PIK3CA, CDK4, PTEN, CCND1 Copy number assessment (by next-generation sequencing)

			of CDK4, CCND1, CDKN2
Newly obtained on-therapy tumor samples (*optional*)	Tumor	On therapy or in follow-up after therapy	Total pRb and p-pRB, Ki-67, p-Akt, and p-S6K expression by IHC Other biomarkers related to Rb pathway and WDNET pathogenesis

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Assessment	Screening	Cycle 1		Cycle 2		Cycle 3	Cycle 4 onwards	End of treatment[8]	Follow-up
Day of cycle	-28 to -1	1[1]	15[1]	1[1]	15[1]	1[1]	1[1]	within 15 days of last dose	
Informed Consent	X								
Physical Examination	X	X	X	X	X	X	X	X	
Height and Weight	X							X	
Vital signs (ECOG, temp, pulse, respiration rate, blood pressure)	X	X	X	X	X	X	X	X	
Medical history	X								
EKG (12-Lead)	X[2]		X[2]	X[2]		As clinically indicated[2]			
ECHO/MUGA	X	As clinically indicated							
CBC with diff and platelet count	X	X	X	X	X	X	X	X	
Serum Chemistries[3]	X	X	X	X	X	X	X	X	
Liver Function Tests[3]	X	X	X	X	X	X	X	X	
Coagulation Panel (PT/INR and PTT)	X	X	X	X	X	X	X		
Lipid panel	X						X[4]		
Urinalysis/BUN	X	X	X	X	X	X	X	X	
HepBsAg, HepBcAb and Hepatitis C Antibody[5]	X								
Pregnancy test if female (Serum)	X[6]								
CT/MRI scan	X						X[7]		
Archival Tissue	X[8]								
Research Tumor Biopsy (optional)	X[8]	After initiating therapy for any patient on protocol							
Concomitant Medications	Continuous[8]								
Adverse Events	Continuous[8]								
LEE011 dosing		*Continuous*							

Everolimus dosing		*Continuous*							
Survival Follow-up									X[9]

1. All study assessments, with the exception of CT/MRI scans, must be performed as per the above schedule of events ± 3 days. CT/MRI scans must be performed as per the above schedule of events ± 7 days.
2. Triplicate 12-lead EKG (2 minutes apart) will be used and the combined QTcF values from these EKGs will be averaged to provide a single value for each time point.

   For patients with QTcF >481 ms at any time, interrupt study treatment and follow the procedures described in the "LEE011 Dose Modification section." If treatment is resumed, repeat EKGs 7 days and 14 days after dose resumption (and then as clinically indicated).
3. Serum chemistries must include the following: Na, K, Cl, CO2, BUN, creatinine, glucose, calcium, albumin, and total protein. Liver function tests must include the following: AST, ALT, alkaline phosphatase, total bilirubin.
4. Lipid panel must be performed every 4th cycle.
5. Hepatitis B PCR will be done if the Hepatitis B core antibody or Hepatitis B surface antigen is reactive.
6. Serum pregnancy test must be performed for all women of childbearing potential within 72 hours prior to receiving first dose of study medication. If the test result is positive related to pregnancy, the patient will not be allowed to participate in this study.
7. Disease assessments must be performed every 12 weeks ± 7 days or sooner if there is clinical evidence of disease progression. All patients who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up.
8. If archival tissue is not available, a baseline tumor biopsy must be done. Patients will also be given the opportunity to consent to an optional biopsy (regardless of disease response for any patient on protocol) for further evaluation of predictive biomarkers. This optional biopsy may be performed on therapy or in follow-up after therapy.
9. All patients who discontinue study treatment should be contacted for safety evaluations for 30 days after the last dose. Patients whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory values, should be followed at least once a week for 4 weeks and subsequently at 4-week intervals until resolution or stabilization of the event, whichever comes first.
10. All patients enrolled in the study will be followed for survival every 3 months with phone call until death, lost to follow-up, or withdrawal of consent, whichever occurs first.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Adverse Events (AE) Definition

Definition
An adverse event is defined as the appearance of (or worsening of) any unintended or undesirable symptom(s), sign(s) or medical condition(s) which may be associated with the use of the investigational study drug, whether considered related to the drug or not and presenting any time after formal written consent has been obtained.

An abnormal laboratory value or test result occurring after obtained consent is considered an adverse event only if it results in a clinically significant change in signs or symptoms, requires therapy, or results in a change in the study medication.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the subject and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the subject through the completion of final study procedures.
- AEs not previously observed in the subject that emerge during the protocol- specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).

The following are NOT considered AEs:

- Pre-existing condition: A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- Pre-planned or elective hospitalization: A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- Diagnostic Testing and Procedures: Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

11.2 Adverse Event Reporting

Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

After the end of treatment, subjects will be followed for 30 days for adverse event monitoring (serious adverse events and events of clinical interest will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new cancer therapy, whichever is earlier).

11.3 End of treatment visit, including premature withdrawal and study safety follow up

All patients who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up.

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

11.4 Possible Side Effects of LEE011 and everolimus combination

Likely

- Lowering of red blood cell counts which can lead to tiredness and weakness (anemia)
- Lowering of white blood cell counts which can increase the risk for infection
- Lowering of platelet counts which can lead to easy bruising and bleeding
- Inflammation of the mouth and lip
- Mouth and tongue ulcers
- Evidence of liver or kidney damage
- Nausea
- Diarrhea
- Fever
- Muscle aches and spasms
- Headaches
- Difficulty sleeping
- Shortness of breath
- Hair loss
- Itching

Less likely

- Rash
- Weakness/lack of energy
- Fatigue
- Vomiting
- Decreased appetite
- Change in taste
- Nosebleeds

- Headache
- Elevated blood sugar levels
- Constipation
- Shortness of breath
- Low potassium levels which may cause your muscles to feel weak, cramp or twitch
- Low phosphate levels which may cause your muscles to feel weak, cramp, or twitch
- Low calcium levels which may cause your muscles to feel weak, cramp, or twitch
- Elevated cholesterol
- Abnormal kidney function (increase in creatinine)
- Swelling
- Inflammation of the lung (pneumonitis)
- Hot flashes
- Low magnesium levels
- Weight loss
- High blood pressure
- Syncope
- Increased eye tearing
- Dry eye
- Change in taste
- Heartburn

Rare but serious

- Bleeding
- Low white blood cell count with a fever which can result in life-threatening infection (pneumonia, urinary tract infection)
- Skin infection (cellulitis)
- Difficulty breathing with low levels of oxygen in the blood
- Irregular heart rhythms (arrhythmia)
- Liver inflammation that could result in liver failure
- Inflammation of the colon (colitis)
- Disorders of the bone marrow (leukemia)
- Cardiac arrest
- Sudden cardiac death

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

For the purposes of this study, patients will be evaluated for response every 12 weeks, or as clinically indicated if interim toxicity occurs mandating cancer staging re-assessment. RECIST v1.1 criteria will be used.

CT scan with contrast of the chest, abdomen, and pelvis

CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

MRI scans

MRI of the abdomen and pelvis is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1-weighted images. However, there are no specific sequence recommendations.

Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- **Measurable Lesions -** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
    - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
    - 10 mm caliper measurement by clinical exam (when superficial)
    - Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- **Nonmeasurable Lesions -** Nonmeasurable lesions are defined as 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). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
- **Target Lesions -** All lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. 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.
- **Non-target Lesions -** It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”)

Response Criteria

Evaluation of Target Lesions

- **Complete Response -** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be “0” if there are target nodes).

- **Partial Response -** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease -** At least a 20% increase in the sum of 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 progression.)
- **Stable Disease -** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-target Lesions

- **Complete Response -** 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).
- **Non-complete response/Non-progressive disease -** Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease -** Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large,' an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST v1.1 guidelines.

Evaluation of Overall Response

Table 8 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 10: Evaluation of Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response	No	Complete response
Complete response	Not evaluable	No	Partial response

Table 10: Evaluation of Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Non-complete response / non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable[1]	No	Partial response
Stable disease	Non-progressive disease and not evaluable[1]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease

[1] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

13.0 CRITERIAFOR REMOVAL FROM STUDY

In the absence of serious toxicity or complications, all patients will continue treatment until evidence of disease progression. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Progression of disease.
- Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial.
- Unacceptable toxicity or any adverse event that precludes further participation in the trial.
- The investigator removes the patient from the trial in the best interests of the patient.
- Patient death.
- Study completion or discontinuation for any reason.
- Patient withdraws consent to continued participation in the trial or is lost to follow up.

Subjects who are permanently discontinued from receiving investigational product will return for end of study visit, unless consent is withdrawn, the subject is lost to follow-up or begins another treatment. All subjects will be followed for survival by phone every 3 months until death or withdrawal of consent.

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

14.0 BIOSTATISTICS

PFS: The primary endpoint will be PFS, using RECIST v1.1. An exact binomial single stage design will be employed.

The below statistics are generated based on the PFS results from the RADIANT-2 and RADIANT-3 trials (local PFS review; discussed in section 3 of protocol).

With a simon two stage design, we can show an improvement from 45% to 65% with a total of 41 patients with type I and II error rates of 10% each. In the first stage, we will enroll 21 patients and if 10 or more are alive and progression free at 1 year, we will enroll an additional 20 patients for a total of 41 patients. If at the end we have 23 or more out of 41 patients alive and progression free at 1 year then we would consider the study promising The accrual rate is approximately 2 patients per month. Patients lost to follow up without document progression prior to 1 year follow-up will be included as events for the primary endpoint of PFS.Secondary outcomes, including safety, ORR, EFS, and OS, as well as exploratory objectives, will also be summarized.

Safety and Tolerability Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment. Any significant vital signs and clinical laboratory test results will be listed and summarized. Any significant physical examination findings and clinical laboratory results will be listed.

Antitumor Activity (objective response rate - ORR)

Assessments of antitumor activity will be based on ORR using RECIST v1.1. The ORR is defined as the proportion of subjects with CR or PR based on RECIST criteria. The exact 95% CI of ORR will be estimated using the binomial distribution.

Event free survival (EFS)

EFS will be measured from the start of treatment with LEE011 + everolimus until the documentation of disease recurrence, progression, or death due to any cause, whichever occurs first. EFS will be evaluated using the Kaplan-Meier method.EFS will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who are still alive prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Subjects having no tumor assessments after the start of treatment with LEE011 + everolimus will have EFS censored on the first date of treatment with LEE011 + everolimus.

Overall survival (OS)

OS will be determined as the time from the start of treatment with LEE011 + everolimus until death. For subjects who are alive at the end of study or lost to follow-up, OS will be censored on the last date when subjects are known to be alive. The OS will be evaluated using the Kaplan-Meier method.

Exploratory objectives

Categorical biomarkers will be associated with response using Fisher's exact test and with PFS using the log-rank test while continuous markers will be associated with response using Wilcoxon rank sum test and Cox model for PFS.

Stopping rules

In order to reduce patient risk, the study design includes early termination of the trial in the event of excessive toxicities defined as treatment related toxicities leading to a treatment delay of more than 6 weeks as well as any delayed or irreversible grade 3 or 4 toxicities. The stopping rules are derived using repeated significance testing and are given in the table below.

Toxicity	# of toxicities needed to stop the study	Toxicity rate	Probability boundary is crossed
Excessive toxicity	2 within the first 6 patients 3 within the first 15 patients 4 within the first 30 patients 5 within 42 patients	0.05	0.1
		0.2	0.96

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

This research study does not require randomization.

16.0 DATA MANAGEMENT ISSUES

A MSK Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the MSK RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered remotely into electronic Case Report Forms (eCRFs) using the internet base system, Medidata Rave. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent, and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on theMSK Intranet at: http://mskweb5.mskcc.org/intranet/_assets/_tables/content/359689/Data_safety%20Monitoring07.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, and there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

All the patients will be required to sign an IRB-approved informed consent and will have all their questions fully addressed before enrolling in the study. During informed consent, it will be made clear to the patient that participation is voluntary. All the data will be confidential, maintained in a password protected electronic database and will comply with all HIPAA guidelines.

Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors) may review patients' records and pathology slides, as required.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in 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 (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last

investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

17.2.1 Reporting to Novartis (MSK ONLY)

Serious Adverse Events

The principal investigator has the obligation to report all serious adverse events to the FDA (if applicable), IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E) (if applicable).

Per Novartis guidelines, an adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- Results in persistent or significant disability/incapacity
- An adverse event that results in 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 (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

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

Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form along with the Novartis provided fax cover sheet to the Novartis Oncology Drug Safety and Epidemiology (DS&E) department by fax (fax: 877-778-9739) or email (email: clinicalsafetyop.phuseh@novartis.com) within 24 hours.

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

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from MSK for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions

(SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to Novartis by MSK within 24 hours of MSK learning of the event. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by MSK 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 using the Novartis provided fax cover sheet to the Novartis Oncology Drug Safety and Epidemiology (DS&E) department by fax (fax: 877-778-9739) or email (email: clinicalsafetyop.phuseh@novartis.com) within 24 hours.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix A: Pill Diary

Appendix B: Multicenter Addendum

Appendix C: SAE Report Form For Participating Sites

Appendix D: Child Pugh Classification

Appendix E: ECOG to KPS Conversion Table