**Title: LEE001 and Chemoembolization In Patients With Advanced Hepatocellular Carcinoma**

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**A Phase Ib/II Study of LEE011 and Chemoembolization In Patients With Advanced Hepatocellular Carcinoma**

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**Amendment #3 dated August 6, 2017**

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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PI Signature: _____

Date: _____

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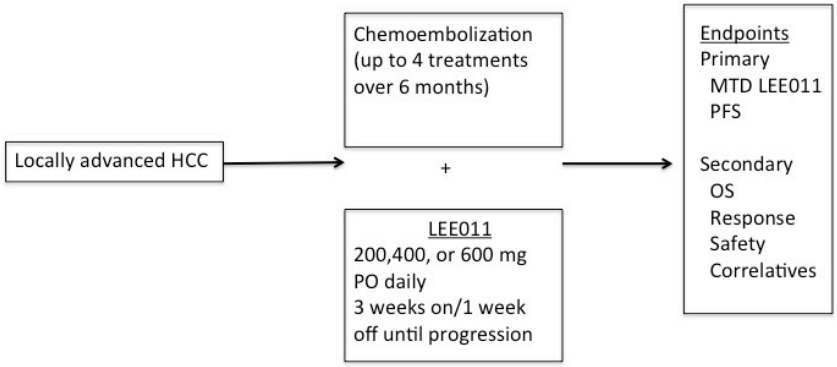
**LIST OF ABBREVIATIONS**

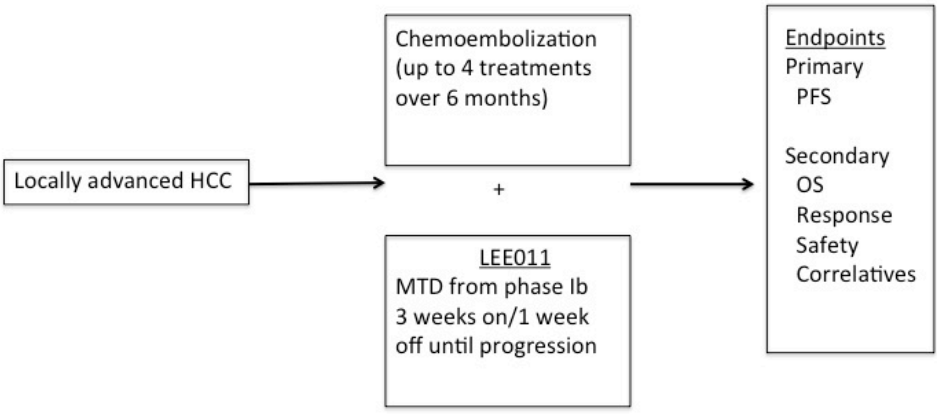
| | |
|---|---|
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| ALC | Absolute Lymphocyte Count |
| AST | Aspartate Aminotransferase |
| BUN | Blood Urea Nitrogen |
| CBC | Complete Blood Count |
| CMP | Comprehensive Metabolic Panel |
| CR | Complete Response |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | Dose Limiting Toxicity |
| DSMB | Data and Safety Monitoring Board |
| ECOG | Eastern Cooperative Oncology Group |
| H&P | History and Physical Exam |
| HRPP | Human Research Protections Program |
| IV | Intravenously |
| MTD | Maximum Tolerated Dose |
| NCI | National Cancer Institute |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| PBMCs | Peripheral Blood Mononuclear Cells |
| PD | Progressive Disease |
| PFS | Progression Free Survival |
| p.o | Per os |
| PR | Partial Response |
| SAE | Serious Adverse Event |
| SD | Stable Disease |
| WBC | White Blood Count |

## STUDY SCHEMA

### Phase Ib




### Phase II



**STUDY SUMMARY**

| | |
|---|---|
| Title | A Phase Ib/II Study of LEE011 and Chemoembolization In Patients With Advanced Hepatocellular Carcinoma (HCC) |
| Protocol Number | 052015-073 |
| Phase | Phase Ib/II |
| Methodology | Open label |
| Study Duration | Four Years (4) |
| Study Center(s) | Single institutional trial: UT Southwestern Medical Center (UTSW) and Parkland Health and Hospital System (PHHS) |
| Objectives | Primary objective:<br>1. To determine the maximum tolerated dose (MTD) of LEE011 in patients with locally advanced HCC treated with chemoembolization<br>2. To determine the progression free survival (PFS) of combination LEE011 and chemoembolization in patients with locally advanced HCC.<br><br>Secondary objectives:<br>1. To determine overall survival of LEE011 combined with chemoembolization and compared to historical controls.<br>2. To determine the safety and tolerability of LEE011 in combination with chemoembolization as measured by rates of adverse events according to the CTCAE v. 4.03.<br>3. To determine treatment response with pre- and intra-treatment biopsies and plasma/serum. |
| Number of Subjects | Phase Ib: 9-18<br>Phase II: 40 |
| Diagnosis and Main Inclusion Criteria | 1. Patients must have a histologically confirmed diagnosis of Hepatocellular carcinoma.<br>2. RB positivity as defined by RB expression (score of 0.5 or 1) with concurrent p16in4a loss (score of 0-2);<br>3. Patients must have HCC limited to the liver;<br>4. Absence of occlusive main portal vein thrombus, branch venous thrombus is allowed;<br>5. Patients with locally advanced HCC not eligible for curative therapies;<br>6. Age ≥ 18 years;<br>7. Child-Pugh Score A or B7 |
| Study Product(s), Dose, Route, Regimen | Phase Ib: LEE011 (200, 400, or 600mg) by mouth daily (3 weeks on/1 week off) in combination with chemoembolization<br>Phase II: LEE011 (MTD from phase Ib) by mouth daily (3 weeks on/1 week off) in combination with chemoembolization |
| Duration of administration | Study treatment will continue until disease progression, unacceptable toxicity, death or discontinuation from the study treatment for any other reason. |

| | |
|---|---|
| Statistical Methodology | Phase Ib: The primary endpoint of this aspect will be to determine the MTD of LEE011 following chemoembolization utilizing a standard 3+3 dose escalation (200, 400, 600 mg).<br>Phase II: The primary endpoint of the trial will be progression free survival (PFS) of HCC patients. PFS is defined to be the time from initiation of treatment to progression or death without evidence of progression. |

# 1.0 BACKGROUND AND RATIONALE

## 1.1 HEPATOCELLULAR DISEASE BACKGROUND

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and is responsible for more than 500,000 deaths annually. (1) Previously considered uncommon in Western countries, the incidence and mortality of HCC have increased three-fold in the United States over the past two decades. (2)

## 1.2 HEPATOCELLULAR CARCINOMA MANAGEMENT

Currently, the only potentially curative options available to patients with HCC are partial hepatectomy, liver transplantation, or ablative techniques, but only 15% of patients are likely to benefit from such options due to concomitant cirrhosis and donor organ shortages. (3) For patients who undergo transplantation, a 5-year survival of 70% is possible, provided they meet Milan criteria (one lesion less than 5 cm or up to three lesion less than 3 cm).

For patient with HCC limited to the liver that are not candidates for curative therapies, loco-regional therapies such as chemoembolization offer tumor control while minimizing systemic toxicity and are felt to be reasonable alternatives to systemic therapy according to the National Comprehensive Cancer Network guidelines. (4) Tumor directed hepatic artery chemoembolization is possible because normal liver receives blood flow from both the hepatic artery and the portal vein, whereas HCC receives almost all blood flow from the hepatic artery. By inserting an angiographic catheter into the branches of the hepatic artery supplying the tumor and injecting cytotoxic chemotherapeutic agents (eg. Doxorubicin and/or cisplatin) followed by injecting cytotoxic particles leading to cessation of blood flow in the hepatic artery branch, tumor necrosis may result from both exposure to cytotoxic agents as well as ischemia.

While there have been multiple randomized trials of chemoembolization that have failed to demonstrate a survival advantage in favor of chemoembolization, all these studies were conducted in the 1980s and 1990s. Since then, interventional radiology techniques have improved and two randomized trials reported in 2002 demonstrated a survival advantage for chemoembolization. Llovet and colleagues randomized 112 patients to chemoembolization, bland embolization, or best supportive care (BSC)

and reported a significant result in favor of chemoembolization. One and 2 year survival probabilities were 82% and 63% for chemoembolization; 63% and 27% for BSC, p=0.009. (5) In a single institution study from Hong Kong, Lo and colleagues randomized 80 patients to either BSC or cisplatin based chemoembolization. Survival for the chemoembolization arm (1 year, 57%, 3 years, 26%) was superior to the BSC arm (1 year, 32%; 3 years, 3%, p=0.002). A subsequent meta-analysis of randomized trials in HCC conducted between 1978 and 2002 with a combined total of 545 patients reported a significant improvement of 2 year survival in favor of chemoembolization, OR 0.42; 95% CI, 0.2-0.88. Multiple studies have demonstrated median progression free survival times ranging from 8-10 months. (6) Our institutional historical controls for chemoembolization demonstrate an 8.0 month median PFS. Chemoembolization has become the accepted standard of treatment option for local advanced HCC with no curative options. The NCCN, the American Association for the Study of Liver Diseases, and the Barcelona Clinic Liver Cancer Group, all recommend chemoembolization for the treatment of unresectable HCC. (7)

### 1.3 COMBINATION OF CHEMOEMBOLIZATION AND SYSTEMIC THERAPY IN ADVANCED HCC

Combining systemic therapy with standard of care chemoembolization has been studied in multiple clinical trials utilizing sorafenib and brivanib as systemic therapy with disappointing rates of efficacy although good tolerability. The largest clinical trial combining sorafenib with chemoembolization was the randomized phase II SPACE trial. A total of 307 patients were randomized to receive sorafenib or placebo continually; all patients received a first chemoembolization 3-7 days after the first dose of the studied drug, and subsequent chemoembolizations on defined time points. The primary endpoint of time to progression was not met following comparison with placebo. (8) Similar results were obtained when combining brivanib with chemoembolization in a randomized controlled phase III trial. (9) Currently despite a lack of significant long-term efficacy following chemoembolization alone there is no systemic therapy that when given in combination with chemoembolization that has demonstrated increased benefit.

### 1.4 ROLE OF CELL CYCLE RELATED GENES AND PROTEINS IN CANCER

In the mammalian cell cycle, entry into S phase is achieved by cyclin-dependent kinases 4 and 6 (CDK4/6). The cyclin D proteins act through the CDK4 and CDK6 protein kinases to promote G1 progression. CDK4 and CDK6, in turn, hyperphosphorlyate and activate the retinoblastoma protein (RB) to promote cell cycle entry and cellular proliferation (Figure 1). (10,11)

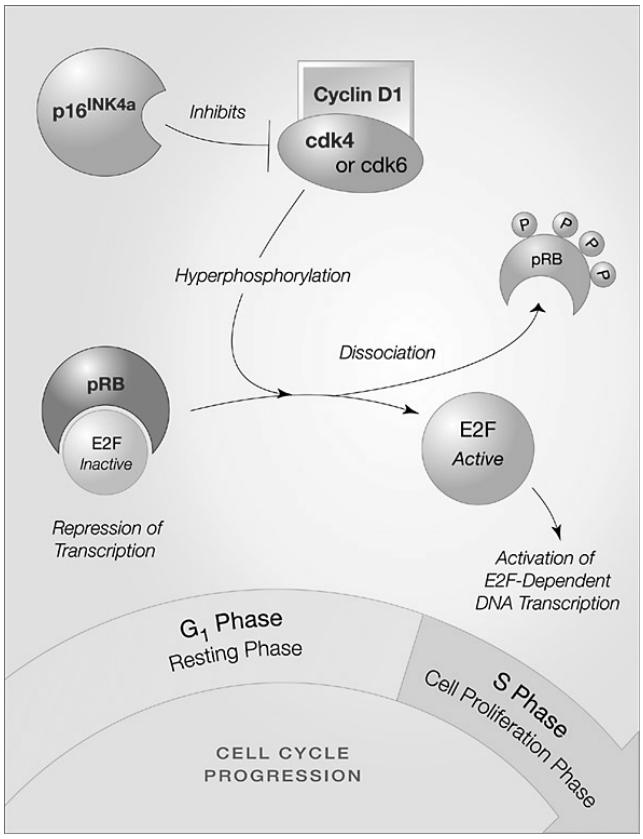



**Figure 1. The D-cyclin-CDK4/6-INK4a-pRb pathway**

Mitogenic signals converge at the level of cyclin D1 upregulation and CDK4/6 association, localization, and kinase activity. CDK4/6 phosphorylates and inactivates RB tumor suppressor proteins, leading to dissociation of E2F transcription factors and subsequent expression of genes required for the G1/S transition and cell cycle progression. (10,11)

D-cyclins are the positive regulators of these kinases, while the p16 protein encoded by the CDKN2A gene functions as their major inhibitor. Upon mitogen stimulation, signal transduction pathways including MAPK and PI3K increase cell proliferation by upregulating the expression of D-cyclins, which in turn activate the kinases. (10,11)

A wide range of human tumors, including HCC, harbor genetic alterations that increase the activity of CDK4/6 via deregulated signaling pathways. (12) Furthermore, copy number abnormalities that result in increased CDK4/6 activity are

among the most commonly described genetic lesions observed in diverse tumor types. Specifically, amplifications of the genes that encode cyclin D1 or CDK4/6, and homozygous deletions affecting the CDKN2A locus are particularly common. The CDKN2A locus is also subject to frequent epigenetic silencing in multiple cancer subtypes including HCC. Finally, RB is a tumor suppressor protein that is dysfunctional in multiple cancers. Direct analyses of primary HCC has revealed loss of RB expression in 10-15% of tumors, with genetic alterations observed in ~8% of cases. (12,13) Thus, the majority of HCC tumors represent a viable target for LEE011. (12)

### 1.5 PROLIFERATION FOLLOWING CHEMOEMBOLIZATION IN HEPATOCELLULAR CARCINOMA

There are multiple pre-clinical and clinical studies suggesting that hepatic artery embolization leads to increased HCC tumoral cell proliferation. Kim et al reported a case series in which explanted livers from transplanted patients undergoing chemoembolization 3 to 4 weeks prior to transplant had an elevated Ki67 proliferative index compared to non-treated controls.The increase in proliferative index within intratumoral endothelial and tumor cells was likely secondary to a post-embolization ischemic necrosis. (14) Farris et al also demonstrated a statistically significant difference in proliferation, again measured by the Ki67 proliferative index, between patients undergoing chemoembolization and control patients. (15)

### 1.6 CD4/6 INHIBITION AND REDUCTION OF PROLIFERATION IN PRE-CLINICAL HEPATOCELLULAR TUMOR MODELS AND EARLY STAGE CLINICAL TRIALS IN HCC

Our group previously demonstrated that inhibition of CDK4/CDK6 potently suppressed proliferation in HCC tumor models. For example, in a hepatoma xenograft model there was substantial suppression of proliferation following CDK4/6 inhibition (Figure 2). Similarly, in necrotic mouse livers following CCL4 administration, CDK4/6 inhibition had a profound impact on aberrant proliferation (Figure 3). These, and additional preclinical data served as the basis for a small single arm Phase II trial in advanced HCC using the CD4/6 inhibitior, palbociclib. This study used Rb and p16ink4 staining of tumor tissue as inclusion criteria. The immunohistochemical stains were developed and optimized by Dr. Agnieszka Witkiewicz, who assisted in developing this study This study treated 23 HCC patients who had failed on previous sorafenib therapy due to either intolerability or disease progression with palbociclib. The safety profile was largely consistent with CDK4/6 inhibition, the most common adverse event was bone marrow suppression. Grade 3 and 4 adverse events included the following: thrombocytopenia, 43%; neutropenia, 43%;leucopenia, 30%. (16) There was no evidence of liver related toxicity, including elevated AST and/or or AST and/or total bilirubin, following palbociclib administration in these patients with underlying cirrhosis. (Littman SJ, Gastrointestinal Cancers Symposium 2015, abstract 277)

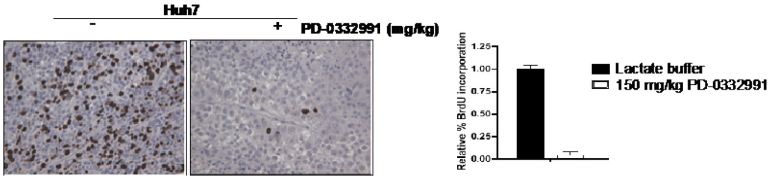



**Fig 2.** Huh7 xenografts were treated with the vehicle control or the CDK4/6 inhibitor (PD-0332991) by gavage. Mice were sacrificed and tumor proliferation was determined by BrdU incorporation

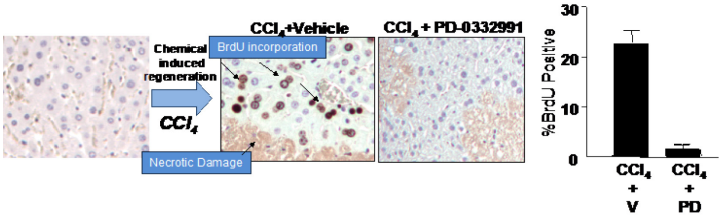



**Fig 3.** Mice were treated with $CCl_4$ to induce liver damage and CDK4/6 inhibitor by gavage. Mice were sacrificed and hepatoic proliferation in the presence of necrotic damage was determined by BrdU incorporation.

## 1.7 INTRODUCTION OF INVESTIGATIONAL TREATMENT(S) AND OTHER STUDY TREATMENT(S)

### 1.7.1 Overview of LEE011

LEE011 is an orally bioavailable and highly selective small molecule inhibitor of the CDK4/cyclin-D1 and CDK6-cyclin-D3 enzyme complexes with IC50s of 0.01 and 0.039 mM in biochemical assays, respectively. In preclinical models, LEE011 has potent cytostatic activity that is dependent on the presence of RB.

The pharmacokinetics (PK) of LEE011 was investigated in mouse, rat, dog, and monkey. The absorption of LEE011 after oral administration was moderate for rats (48-84%). Oral bioavailability ranged from 10% and 65% across animal species. Time to maximum plasma drug concentration (Tmax) was between 2 and 4 hours. Terminal half-life (T1/2) of LEE011 was moderate in rodents and monkeys (2-7 hours), and was longer in dogs (18 hours). LEE011 is moderately bound to plasma proteins in all animal species with unbound fractions in plasma ranging from 20-32%. [3H]LEE011 and metabolites were extensively distributed to tissues in male rates, but there was no uptake into the brain.

In vitro metabolism studies showed that oxidative metabolism of LEE011 is dominated by CYP3A4 with a minor contribution of about 20% by flavin-containing monoxygenase 3. In rate ADME studies, LEE011 was predominantly excreted in the bile as metabolites, with limited excretion of unchanged drug in urine. The bulk of the administered dose (87%) was excreted within 24 hours. LEQ803 is a prominent metabolite in rat, monkey, and human hepatocytes, and the only metabolite in dog hepatocytes.

LEQ803 is weakly pharmacologically active; however, it interacts with hERG channels in vitro.

LEE011 is a time-dependent CYP3A4 inhibitor and a reversible inhibitor of CYP1A2 at higher concentrations. LEE011 is a low affinity substrate of P-glycoprotein. LEE011 inhibits MDR1 mitoxantrone-resistant protein and human bile salt export pump, but not rat or dog BSEP. Overall, the elimination of LEE011 may potentially be affected by co-administered drugs that inhibit or induce CYP3A4. LEE011 may inhibit substrates of CYP3A4, CYP1A2, and BSEP, if sufficiently high concentrations are achieved in vivo.

In GLP toxicology studies, LEE011 and LEQ803 exposure generally increased in a dose proportional manner in rates and dogs. Gender-different pharmacokinetics were observed in rats with higher exposure to LEE011 and LEQ803 in males as compared to females; however no gender differences were identified in dogs.

### 1.7.2 Non-clinical Toxicokinetics

Four week oral GLP toxicity studies with LEE011 (succinate salt) have been performed in the rat and dog.

#### 1.7.2.1 Rat

Rats received qd oral doses of 25, 75 and 150 mg/kg/day in 0.5% methylcellulose aqueous solution (low dose) and suspension (mid and high dose). Maximum plasma concentrations of LEE011 and LEQ803 were reached between 0.5 and 7 hours after dosing. In general, plasma AUC0-24h of LEE011 and its metabolite LEQ803 increased with increasing dose in a roughly proportional manner following single and multiple administrations of LEE011. This was less evident for the metabolite LEQ803 in the male rats. Following multiple administrations of LEE011 for 30 days no distinct increase in exposure was observed on day 30 when compared with Day 1. Overall, irrespective of the study days and gender, the exposure to the metabolite LEQ803 was substantially lower than LEE011 (3.9 to 18.2% for Day 1 and 3.2 to 10.9% for Day 30). Gender-dependent toxicokinetics were identified, with higher exposure to LEE011 in males as compared to females (Cmax: 2.4 to 4.0-fold and AUC0-24h: 3.2 to 7.0-fold) and higher exposure in males for the metabolite LEQ803 (Cmax: 3.9 to 14.0-fold and AUC0-24h: 6.2 to 17.8-fold), over the dosing regimen and study days.

#### 1.7.2.2 Dog

Dogs received once daily oral doses of LEE011 of 5, 10 and 20 mg/kg/day per gavage administered in 0.5% methylcellulose aqueous solution. The time to maximum plasma concentration (Tmax) generally occurred between 0.5 and 3 h post-dose for

LEE011 and LEQ803, irrespective of gender. In general, plasma AUC0-24h of LEE011 and its metabolite LEQ803 increased with increasing dose in a roughly proportional manner following single and multiple administrations of LEE011. Following multiple administrations of LEE011 a slight increase of the exposure was observed on Day 29 for LEE011 (1.2 to 1.9-fold) and for LEQ803 (1.3 to 1.9-fold) when compared to Day 1 (single administration). The exposure to the metabolite LEQ803 was found to be lower than for LEE011 (6.0 to 8.5% for Day 1 and 5.6 to 9.5% for Day 29) following single and multiple administrations, regardless of the study day and gender. Generally, there was no apparent gender difference (based on AUC) over the dosing regimen or study day

### 1.7.3 Overall Assessment of Non-clinical Studies

LEE011 was profiled in a safety pharmacology receptor/enzyme panel and showed activity against PDE4D ($IC_{50}$ 0.88 µM and 0.39 µM). LEE011 did not induce vasculitis or cardiovascular toxicity in the toxicology studies performed so far (up to 4 weeks). The impact of PDE4D inhibition in the clinic may include nausea and emesis. Rat safety pharmacology studies did not reveal any effects on CNS or respiratory functions. In the *in vitro* manual patch clamp assay, LEE011 had an $IC_{50}$ of 53 µM and LEQ803, a metabolite of LEE011 that represents 6 to 10% of the parent drug in dogs, had an $IC_{50}$ of 4.5 µM. In the dog telemetry study, prolongation of the average QT and QTc was observed with the potential to induce incidences of PVCs at higher exposure levels. LEE011 and LEQ803 likely contributed to the QT prolonging effects seen *in vivo*. Cardiac (ECG) monitoring in patients should be performed.

Oral single dose toxicity studies were performed in dogs only. Oral multiple dose toxicity studies were performed in rats and dogs (up to 4 weeks).

In the 4-week toxicity studies, LEE011 was tolerated up to 150 mg/kg in rats and up to 20 mg/kg in dogs without mortality. Reversibility was assessed up to 4 weeks.

In rats and dogs effects on bone marrow, lymphoid tissue (thymus, spleen, lymph nodes, gut- associated lymphoid tissues), hepatobiliary system, testes, adrenals and lungs were observed. In addition, in dogs, effects on intestinal mucosa, skin, bone/ribs and ovaries were also reported.

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) can be regarded as 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 at the highest dose tested (20 mg/kg/day) and this effect could also be related to the pharmacology

(arrest of estrous cycle). The hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) was identified as an additional target organ of toxicity which is not likely related to the primary pharmacology of LEE011. Inflammatory changes in the lung 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.

In rats, the changes seen in the bone marrow and hematology demonstrated a clear tendency towards reversibility. All other findings fully reversed. In dogs, the changes seen in testes and lungs demonstrated a clear trend towards reversibility and all the other changes were fully reversible. It can be expected that after a prolonged recovery time incompletely recovered findings would have totally reversed in both species.

It is advised to monitor carefully hematological and hepatobiliary parameters, as well as gastrointestinal effects in patients treated with LEE011.

*In vitro*, LEE011 did not show an indication for mutagenic potential.

*In vitro*, LEE011 did not show a phototoxic potential.

In conclusion, multiple biological effects were observed in toxicology studies up to 4 weeks duration in rats and dogs. The observed toxicities can be considered clinically manageable. The critical nature of many of these effects and the potentially severe consequences for patients, however, warrant careful monitoring.

LEE011 was moderately absorbed (48 to 84%) and rapidly absorbed after oral administration in rats, with $T_{max}$ ranging from 2 to 4 hr. Oral bioavailability ranged from 10 to 65% across animal species. The T1/2 of LEE011 was moderate in rodents and monkeys (3 to 5 h), and was comparatively longer (18 h) in dogs. LEE011 exhibited moderate binding to plasma proteins (human fu = 30%). LEE011 and its metabolites were extensively distributed into the organs and tissues of rats including the choroid, ciliary body, and meninges. The highest radioactivity concentrations were found in tissues such as the pituitary gland, pineal gland, spleen, kidney, and adrenal medulla, with remarkably high exposure in the thyroid gland. Distribution of LEE011 and/or its metabolites into melanin-containing structures was seen in pigmented rats. No radioactivity was detected in the brain after i.v. or p.o. dosing.

Oxidative metabolism of LEE011 was dominated by CYP3A4 with a minor contribution of about 20% by FMO3. LEE011 is a low-affinity substrate of P-gp. LEE011 is a time- dependent CYP3A4 inhibitor and a reversible

inhibitor of CYP1A2. LEE011 was found to inhibit the MXR and human BSEP, but not the rat or dog BSEP. LEQ803 (*N*-demethylation) is a prominent metabolite found in rat, monkey and human hepatocytes, and the only metabolite formed in dog hepatocytes. This metabolite was found to interact with hERG channels *in vitro*.

In rat ADME studies, LEE011 was predominantly excreted in the bile. The elimination of unchanged drug was limited. A minor proportion of the administered dose is excreted in urine. The bulk of the administered dose (87.3%) was excreted within 24 hr.

### 1.7.4 Clinical Safety of LEE011

Please see investigator's brochure for up to date details on LEE011. As of June 15, 2015, 157 patients have been treated with LEE011 in the first-in human phase I study (CLEE011X2101). Patients with advanced solid tumors or lymphomas were treated with increasing doses of LEE011 orally, once daily for 21 days followed by a 1-week rest (28-day cycle).

Evaluation of safety, tolerability, and PK from patients with advanced solid tumors and lymphoma in the FIH study was used to define the MTD and recommended dose for future development. The MTD was determined as 900 mg/day on a 3-weeks-on/1-week-off schedule. The recommended dose for further studies based on the expansion cohort is 600 mg/day with a 3 weeks on/1 week off schedule, which has an acceptable safety profile, lower risk for QTcF prolongation, adequate exposures, and preliminary evidence of clinical activity. The most common hematologic and non-hematologic adverse events are in Tables 2-1 and 2-2.

**Table 2-1 Hematologic AEs in study CLEE011X2101**

| Adverse Event, n (%) | | LEE011, 600 mg/day, 3 week on/1 week off schedule (n=67) |
|---|---|---|
| Neutropenia | All<br>Grade 3/4 | 22 (33%)<br>15 (22) |
| Leukopenia | All<br>Grade 3/4 | 14 (21)<br>7 (10) |
| Thrombocytopenia | All<br>Grade 3/4 | 13 (19)<br>7 (10) |
| Anemia | All<br>Grade 3/4 | 16 (24)<br>2 (3) |
| Lymphopenia | All<br>Grade 3/4 | 10 (15)<br>8 (12) |

**Table 2-2 Non-hematologic AEs in study CLEE011X2101**

| Adverse Event, n (%) | | LEE011, 600 mg/day, 3 weekon/1 week off schedule (n=67) |
|---|---|---|
| Fatigue | All<br>Grade 3/4 | 20 (30)<br>0 |
| Nausea | All<br>Grade 3/4 | 32 (48)<br>1 (2) |
| Vomiting | All<br>Grade 3/4 | 19 (28)<br>0 |
| Diarrhea | All<br>Grade 3/4 | 19 (28)<br>2 (3) |
| QT prolongation | All<br>Grade 3/4 | 10 (15)<br>0 |

#### 1.7.4.1 Clinical Pharmacokinetics of LEE011

LEE011 is rapidly absorbed with median $T_{max}$ ranging from 2-5 hours in both adult and pediatric patients. Plasma concentrations increased approximately 2- to 3-fold from C1D1 to C1D18 due to accumulation, with steady state being reached by approximately day 8. Mean effective $T_{1/2}$ was 32.6 hours in study CLEE011X2101. At steady state (C1D18/21), plasma exposure increases in LEE011 were slightly higher than dose proportional over the dose range 50-1200mg.

## 1.8 STUDY RATIONALE

Combination therapy consisting of chemoembolization and LEE011 is attractive for patients with advanced HCC for the following reasons:

- Based on the previously mentioned SPACE and brivanib trials there are no currently paired chemotherapy agents with chemoembolization demonstrating efficacy. The lack of significant long-term efficacy with chemoembolization alone coupled with significant post-procedure progression is an unmet need in the treatment of locally advanced HCC, the largest subset of HCC patients;
- Following chemoembolization there is significant pre-clinical and clinical data demonstrating a proliferative affect both intra- and peri-tumoral. Inhibition of CDK4 and CDK6 is associated with a reduction in proliferation both in *in vitro* and *in vivo* models;
- Previous administration of a CDK4/6 inhibitor in patients with metastatic HCC has demonstrated efficacy with limited toxicity in early phase trials.

It is our hypothesis that combination therapy with LEE011 and chemoembolization in patients with locally advanced HCC not amenable to curative therapies will provide greater efficacy than chemoembolization alone with a tolerable safety profile.

## 2.0 STUDY OBJECTIVES

### 2.1 PRIMARY OBJECTIVE

2.1.1 To determine the maximum tolerated dose (MTD) of LEE011 in patients with locally advanced HCC treated with chemoemolization. (Phase Ib)

2.1.2 To determine the progression free survival (PFS) of combination LEE011 and chemoembolization in patients with locally advanced HCC. PFS will be calculated from the date of enrollment on the study to appearance of new metastatic lesions or objective tumor progression using RECIST version 1.1 guidelines and be compared with historical controls. (Phase II)

### 2.2 SECONDARY OBJECTIVES

2.2.1 To determine overall survival of LEE011 combined with chemoembolization and compare to historical controls;

2.2.2 To determine the safety and tolerability of LEE in combination with chemoembolization as measured by rates of adverse events according to the CTCAE v. 4.03;

2.2.3 To determine treatment response with pre- and intra-treatment biopsies and plasma/serum. Correlative studies will be performed on the collected tissue and blood samples to determine if predictive markers of response can be generated.

## 3.0 STUDY DESIGN

This is a single arm, open-label, single-institution phase Ib/II therapeutic trial of chemoembolization in combination with LEE011 in patients with locally advanced HCC. This study will enroll patientsat the UT Southwestern Medical Center and its affiliated hospitals and clinics, and Parkland Health and Hospital System.
Immunohistochemistry testing: Prior to initiation on treatment, all patients will sign an informed consent form. Only patients with protocol defined RB-positivity will be eligible for treatment. Eligible patients should have RB expression defined as a score of 0.5 or 1 with concurrent P16in4a loss of expression defined as a score of 0-2. TACE treatment can be initiated prior to confirmation of RB status provided an informed consent is signed.
Tissue, either from archival formalin fixed paraffin embedded samples or a new biopsy of a target lesion will be needed. RB-proficiency is determined by tumor biopsy demonstrating RB normal and p16in4a low by immunohistochemistry. RB staining is scored on an absent (no nuclear staining), weak (nuclear staining less than observed in endothelial cells and stromal cells surrounding the tumor), positive (nuclear staining at or above surrounding tissue) (0, 0.5, 1 respectively). P16ink4a is a routine clinical stain, wherein high expression is indicative of RB loss (ie. the markers are inversely correlated). Staining is scored using absent, weak, positive, and strong (0, 1, 2, 3, respectively). This determination will be made

by the study pathologist who has extensive experience with these markers in the context of HCC and breast cancer clinical studies.

## 3.1 ENDPOINTS

Phase Ib:

The primary endpoint of the phase Ib trial will be determination of the maximum tolerated dose of LEE011 administered following chemoembolization (section 6.6).

Phase II:

The primary endpoint of the phase II trial will be progression free survival (PFS) of HCC patients.

Statistics and sample size justification:

PFS is defined to be the time from initiation of treatment to progression or death without evidence of progression. For cases without documentation of progression, follow-up will be censored at the date of last disease assessment without progression, unless death occurs within 4 months following the date of last progression-free, in which case death will be counted as an event. The historical median PFS for TACE alone is 8-10 months. Our institutional median PFS for TACE based on similar chemoembolization procedures as outlined below is 8.0 months. This study will target a hazard ratio of 1.45 with an 80% power and a one-sided significance level of 10%. Assuming a 24-month accrual and an 18-month follow-up period the study requires 40 patients initiating LEE011 treatment with the median PFS for TACE alone is 8 months. PFS will be estimated using the Kaplan-Meier method, and Greenwood's formula will be used to calculate the standard error of the corresponding Kaplan-Meier estimate and 95% confidence interval. Survival curves will be estimated using Kaplan-Meier methodology.

Secondary endpoints of efficacy are to evaluate OS. The same statistical methods used for the analysis of PFS will be used for the analysis of OS.

Other secondary objectives will include description of toxicity of the therapy regimen. These data will be analyzed separately. The safety analyses will be performed on all patients who receive any dose of therapy. Adverse events will be described using the NCI CTCAE v. 4.03 criteria (ctep.cancer.gov/forms.CTCAEv4.pdf). Frequency and severity of adverse events according to the NCI CTCAE v. 4.03 body system and severity criteria will be described. In addition, frequency of Grade 3 or 4 adverse events will be described separately. Causality will also be noted. Adverse events will be recorded for up to 30 days following discontinuation of LEE011 or followed until resolution, whichever comes first. Response rate and toxicity rate will be estimated

using an exact binomial method along with the 95% confidence interval.

Laboratory assessments will also be described according to the NCI CTCAE v.4.03 criteria, with separate descriptions for Grade 3 or 4 laboratory abnormalities. Clinically significant laboratory abnormalities will be described as well. Serious adverse events will be summarized, including a causality assessment.

The number of treatment cycles and doses administered will be summarized using descriptive statistics. Treatment delays will be summarized using counts and percentages.

Patients' disposition will be summarized in the following manner:

- The number and percentage of patients selected, included, completed, withdrawn and lost to follow-up will be summarized using descriptive statistics.
- Major protocol deviations will be summarized.
- The reason for withdrawal (adverse events, lack of efficacy, major protocol deviation, non-medical reason, recovery or remission) will be summarized.

For pathology-, laboratory- and imaging-correlative studies, Cox regression analysis will be conducted to investigate the association between PFS and parameters from correlative studies.

## 4.0 STUDY POPULATION

This study will include patients with locally advanced HCC not amenable to curative treatments who have no evidence of metastatic disease. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study. The study population will be the same for phase Ib and II.

## 5.0 SUBJECT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered and enrolled to the study. Study treatment may not begin until a subject is registered (See Section 14.3).

### 5.1 INCLUSION CRITERIA

5.1.1 Histologically confirmed diagnosis of hepatocellular carcinoma (mixed HCC/cholangiocarcinoma is allowed).

5.1.2 **RB positivity as defined by RB expression (score of 0.5 or 1) with concurrent p16in4a loss (score of 0-2);**

5.1.3 Patients must have HCC limited to the liver. There must be no definitive

clinical or radiographic evidence of extrahepatic HCC. Portal lymphadenopathy is permitted as lymphadenopathy is commonly associated with cirrhosis unrelated to malignancy;

5.1.4 Absence of occlusive main portal vein thrombus, branch venous thrombus is allowed;

5.1.5 Patients with locally advanced HCC not eligible for curative therapies;

5.1.6 Age ≥ 18 years;

5.1.7 Child-Pugh Score A or B7;

5.1.8 ECOG Performance score of 0-2;

5.1.9 Anticipated life expectancy greater than 6 months;

5.1.10 Following baseline laboratory values should be met:

**5.1.10.1** Total bilirubin ≤ 2.0 x ULN or direct bilirubin ≤1.5 x ULN in patients with well-documented Gilbert's Syndrome;

**5.1.10.2** INR ≤ 1.7;

**5.1.10.3** Hgb ≥ 9.0 g/dl;

**5.1.10.4** Alkaline Phosphatase, AST, ALT <5 times ULN;

**5.1.10.5** Platelet count ≥ 75,000/$mm^3$;

**5.1.10.6** Serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 50 mL/min;

**5.1.10.7** Absolute neutrophil ≥ 1,500 cells/$mm^3$;

**5.1.10.8** Potassium, total calcium (corrected for serum albumin), magnesium, and phosphorus within normal limits for the institution or corrected to within normal limits with supplements;

5.1.11 Women of childbearing potential must have a negative pregnancy test;

5.1.12 Prior therapy is allowed provided the following are met: at least 4 weeks since prior locoregional therapy including surgical resection, radiotherapy, or

ablation. Provided target lesion has increased in size by 25% or more or the target lesion was not treated with locoregional therapy;

## 5.2 EXCLUSION CRITERIA

5.2.1 Patient who received any CDK4/6 inhibitor;

5.2.2 Patient who has received previous systemic therapy or TACE for HCC;

5.2.3 Clinically significant, uncontrolled heart disease and/or recent events including any of the following:

**5.2.3.1** History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting,

**5.2.3.2** coronary angioplasty, or stenting) or symptomatic pericarditis within 12 months prior to screening;

**5.2.3.3** History of documented congestive heart failure (New York Heart Association functional classification III-IV);

**5.2.3.4** Documented cardiomyopathy;

**5.2.3.5** Patient has a left ventricular ejection fraction <50% as determined by MUGA scan or ECHO at screening;

**5.2.3.6** History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrthymias, or conduction abnormality within 12 months of screening;

**5.2.3.7** Bradycardia (heart rate <50 at rest), by ECG or pulse, at screening;

**5.2.3.8** Congenital long QT syndrome or family history of long QT syndrome;

**5.2.3.9** Systolic Blood Pressure (SBP) >160 or <90 mm Hg;

5.2.4 On screening inability to determine the QTcF interval on the ECG (i.e.: Unreadable or Not Interpretable) or QTcF > 450 msec (using Fridericia's correction). All as determined by screening ECG (mean of triplicate ECGs);

5.2.5 Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to treatment (see appendix 1 for details):

5.2.5.1 Known strong inducers or inhibitors of CYP3A4/5 or bile salt pump efflux, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges;

5.2.5.2 That have a known risk to prolong the QT interval or induce Torsades de Pointes;

5.2.5.3 Herbal preparations/medications, dietary supplements;

5.2.5.4 That have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5;

5.2.6 Tumor involvement > 50% of the liver;

5.2.7 Patient has a known history of HIV infection (testing is not required);

5.2.8 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 study or compromise

compliance with the protocol (e.g. chronic pancreatitis, active untreated or uncontrolled fungal, bacterial, or viral infections, etc.);

5.2.9 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);

5.2.10 Patient is currently receiving warfarin or other Coumadin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH) or fondaparinux is allowed;

5.2.11 Participation in a prior investigational study within 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer;

5.2.12 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) and/or in whom ≥ 30-25% of the bone marrow was irradiated;

5.2.13 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);

5.2.14 Patient has not recovered from all toxicities related to prior anticancer therapies to NCI-CTCAE version 4.03 Grade <1 (Exception to this criterion: patients with any grade of alopecia are allowed to enter the study);

5.2.15 Patient has a known hypersensitivity to any of the excipients of LEE011;

5.2.16 Prior ablative, radiation, resection, or transplant therapies less than 4 weeks before study registration;

5.2.17 Active gastrointestinal bleeding;

5.2.18 Allergy to iodine or gadolinium contrast that cannot be safely controlled with premedication;

5.2.19 Concurrent malignancy or malignancy within 3 years of study entry, with the exception of adequately treated basal or squamous cell carcinoma, non-melanomatous skin cancer or treated cervical cancer;

5.2.20 Contraindication to angiography or chemoembolization medications;

5.2.21 Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after contraception and until the termination of gestation, confirmed by a positive hCG laboratory test;

5.2.22 Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective

methods of contraception throughout the study and for 8 weeks after study drug discontinuation. Highly effected contraception methods include:

**5.2.22.1** Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

**5.2.22.2** Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

**5.2.22.3** Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.

**5.2.22.4** Combination of any of the two following (a+b or a+c or b+c)

A. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception;

B. Placement of an intrauterine device (IUD) or intrauterine system (IUS);

C. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository in case of use of oral contraception, women should have been stable on the same pill before taking study treatment.

Note: Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

5.2.23 Sexually active males, unless they use a condom during intercourse while taking the drug, and for 21 days after stopping treatment of LEE011 -- should not father a child in this period. A condom is required to be used also by vasectomized male in order to prevent delivery of the drug via seminal fluid.

**5.2.24** Any physical condition that can prevent ability to tolerate oral therapy

# 6.0 TREATMENT

## 6.1 OVERVIEW

Study subjects will sign an informed consent prior to initiation of screening processes. Following this, patients will undergo an image guided biopsy of liver tumor and the tissue will be collected and sent to: 1) The Pathology Department for histological confirmation of HCC and RB status through previously validated RB/p16ink4a staining; and 2) the pathology laboratory for correlative studies detailed in Section 11. If the patient has archival formalin fixed paraffin embedded tissue, no additional baseline biopsy will be required.

## 6.2 STUDY TREATMENT

For this study, the term “investigational drug” refers to Novartis study drug LEE011. The procedure, chemoembolization, is standard of care for locally, advanced, non-metastatic HCC. Study treatment in this study refers to the combination of chemoembolization and LEE011.

LEE011 will be supplied by Novartis or its designee as 200 mg hard gelatin capsules as individual patient supply packaged in bottles. Storage conditions are described in the medication label. Chemoembolization will be performed in usual standard of care practice by the interventional radiology division at UT Southwestern Medical Center as described in section 6.12 .
All dosages prescribed and dispensed to the patient, and all dose changes during the study will be recorded in the drug accountability records.

### 6.2.1 Description and Composition

The LEE011 drug product is planned for oral administration. The available clinical forms are 10 mg, 50 mg and 200 mg hard gelatin capsules. The capsules only contain the drug substance; there are no excipients.

### 6.2.2 Storage Condition

The shelf life of the drug product is established based on ongoing stability studies and may be extended during the clinical study. The capsules are stored in HDPE bottles and the powder in bottle product is stored in amber glass bottles. Storage for the capsules and for the powder in bottle product is “Do not store above 25 °C, protect from moisture”.

### 6.2.3 Hazards and Precautions

LEE011 is a potent investigational new drug that has not been fully evaluated. Exercise appropriate hygiene and clinical practice precautions.

## 6.3 LEE011 ADMINISTRATION SCHEDULE AND DOSE ADJUSTMENTS

LEE011will be given orally once a day on days 1-21 of a 28 day cycle (3 weeks on / 1 week off). Days 22-28 will be a "rest" from LEE011.

Table 6.1 Dose and Treatment Schedule

| Study Treatment | Pharmaceutical form and route of administration | Total Dose | Frequency and/or Regimen |
|---|---|---|---|
| LEE011 | 200 mg capsules by mouth | 200,400, or 600 mg | Once Daily on Days 1-21 of a 28 day cycle. Rest Days 22-28 |

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

The investigators will instruct the patient to take the study drug as per protocol. Patients must be instructed to return unused study drugs to the site at discontinuation or completion of treatment. The site personnel will ensure that dosing compliance is being performed by reviewing patient dosing diaries at each the end/start of a new treatment cycle.

## 6.4 LEE011 DOSING

LEE011 must be taken as follows:

- Patients should be instructed to take the LEE011 capsules with a large glass of water (~250 mL or 8 oz.) at the same time each day;
- LEE011 can be taken without regard to meals; however dietary habits around the time of dosing should be as consistent as possible throughout the study;
- Patients should be instructed to swallow the LEE011 capsules whole and not to chew, crush or open them;
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose;
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day;
- Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medication, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.

## 6.5 TREATMENT DURATION

Patients will receive trial treatment until one of the following criteria applies:

- disease progression,
- unacceptable toxicity or toxicity that results in treatment interruption of >4 weeks,
- patient experiences DLT

- patient decides to withdraw from study, starts a new therapy or is lost to follow up
- discontinuation from the study treatment for any other reason.
- PI or study sponsor discretion

Patients who come off therapy will be followed for survival regardless of cause of treatment discontinuation."

## 6.6 DOSE LIMITING TOXICITIES-PHASE IB COMPONENT

The phase Ib component of the study will consist of 3+3 dose escalation rule with the dose of LEE011 escalating up to 600mg daily to determine the maximum tolerated dose (MTD) that will be used during the phase II component. The dose levels for the phase Ib aspect will be 200 mg, 400 mg, or 600 mg daily.

Only the first cycle of therapy (one cycle equals to one month) will be used to determine dose limiting toxicity (DLT). However, if two total grade 5 adverse events or 2 Grade 4 adverse events (lasting ≥ 7days); occur at any time while the patient is still receiving study treatment that are either: definitely, probably, or possibly related to either LEE011 or TACE the study will be terminated to enrollment.

Only patients started on the first dose of LEE011 will be included in the evaluation of DLT. If a patient has a DLT that patient will not receive further LEE011. Patients following initial chemoembolization who never receive LEE011 will not be included in the MTD analysis and will be replaced. The patients will be followed for thirty days following the initial chemoembolization for safety assessment. Patients will be enrolled into the next highest drug cohort only after 3 or 6 patients have completed the first cycle of therapy. Once the MTD is determined, patients at the MTD dose will continue with LEE011 and represent the first three patients accrued to the phase II aspect.

Due to observed (TACE related, non DLT) toxicity on cohort 1 specific criteria for cohort 1 has been developed after discussion with the FDA. Cohort 1 has been expanded to 6 patients. Decision for dose escalation will be made using the following criteria:

- No or one DLT: the next three patients will be assigned to next higher dose level (400 mg of LEE011).
- At least two toxicities: the MTD is exceeded and the phase I component of the trial will be stopped with no continuation into the phase II component.

For Cohort 2 and 3 the following traditional 3+3 dose escalation rules will be used:

- If a dose limiting toxicity (DLT) is observed in 1 out of 3 patients at a given dose level, up to 3 additional patients will be enrolled and treated at that dose level.
- If 2 out of 3-6 patients at that dose level have DLTs, the dose will be decreased to the previous dose level, and up to 3 additional patients will be enrolled at that dose level for a total of 6 patients.
- When up to 3 additional patients are added to a given dose level, if 0-1 of 6 patients has a DLT then the dose will be increased to the next dose level.
- Additional dose levels may be explored per investigator discretion to define the safety profile of the treatment.

The recommended Phase II dose (RP2D) will be the highest cohort level in which one or fewer subjects of 6 develops a first cycle DLT.

The Data and Safety Monitoring Committee as described below will regularly review all serious adverse events and any local adverse events, which are unanticipated problems. The study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for grading of all adverse events related to treatment.

**Table 6.2: Dose-limiting toxicity: phase Ib component**
The following will be considered a DLT if they occur within the first cycle of therapy with LEE011 and are determined to be possibly, probably or definitely related to LEE011

| |
|---|
| Grade 4 neutropenia lasting more than 7 consecutive days |
| Grade 3 or 4 febrile neutropenia |
| ≥ Grade 3 vomiting ≥ 48 hours despite optimal anti-emetic therapy |
| ≥ Grade 3 diarrhea ≥ 48 hours despite optimal anti-diarrhea therapy |
| Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or Troponin ≥ grade 3 |
| Grade 4 serum alkaline phosphatase > 7 days |
| ≥ Grade 3 serum creatinine |
| ≥ Grade 3 adverse event for any non-hematologic toxicity unless otherwise specified as below (excluding alopecia, fatigue< 5 days, laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant). |

| THROMBOCYTOPENIA | |
|---|---|
| **Toxicity/Grade** | **Dose Limiting Toxicity and Management Recommendations** |
| Grade 3<br>( ≥ 25 x $10^9$/L - <50 x $10^9$/L) without clinically significant bleeding | Dose interruption until recovery to grade ≤2.<br><br>Re-initiate LEE011 at the same dose level.<br><br>• If toxicity recurs at grade 3: dose limiting toxicity |
| Grade 3<br>( ≥ 25 x $10^9$/L - <50 x $10^9$/L) with clinically significant bleeding | Dose limiting toxicity |
| Grade 4<br>(<25 x $10^9$/L) | Dose limiting toxicity |

| HEPATOTOXICITY (BILIRUBIN, ALT, AST) | |
|---|---|
| **TOTAL BILIRUBIN without ALT/AST increase above baseline value** | |
| **Toxicity/Grade** | **Dose Limiting Toxicity and Management Recommendations** |
| Same grade as baseline or increase from baseline grade 0 to grade 1 | Maintain dose level with LFTs monitored every other-week |
| Increase from baseline grade 0 or 1 to grade 2 (1.5-3.0 x ULN) or from baseline grade 2 to grade 3 (>3.0 -10 x ULN) | Dose interruption of LEE011<br><br>If resolved to ≤ grade 1 in ≤ 21 days, then maintain dose level<br><br>If resolved to ≤ grade 1 in > 21 days or toxicity recurs, then dose limiting toxicity |
| Increase from baseline grade 0 or 1 to grade 3 (>3.0-10 xULN) | Dose limiting toxicity |
| Grade 4 (> 10.0 x ULN) | Dose limiting toxicity |

Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤ 1 x ULN) due to hemolysis or Gilbert Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs.

For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.

**HEPATOTOXICITY (BILIRUBIN, ALT, AST)**

**AST or ALT without bilirubin elevation > 2 x ULN**

| AST or ALT Toxicity/Grade | Dose Limiting Toxicity and Management Recommendations |
|---|---|
| Same grade as baseline or increase from baseline grade 0 to grade 1 (confirmed 48 to 72 hrs later) | No dose adjustment required with LFTs monitored per protocol if same grade as baseline or bi-weekly in case of increase from baseline grade 0 to 1 |
| Increase from baseline grade 0 or 1 to grade 2 (> 3.0 – 5.0 x ULN) or from baseline grade 2 to grade 3 (> 5.0 – 20.0 x ULN) | Dose interruption of LEE011<br><br>If resolved to ≤ baseline value in ≤ 21 days, then maintain dose level<br><br>If resolved to ≤ baseline value in > 21 days or toxicity recurs, then dose limiting toxicity |
| Increase from baseline grade 0 or 1 to grade 3 (> 5.0 – 20.0 x ULN) | Dose limiting toxicity |
| Grade 4 (> 20.0 x ULN) | Dose limiting toxicity |

| **AST or ALT and concurrent Bilirubin** | |
|---|---|
| AST or ALT ≥ grade 2 (> 3 x ULN) in patients with normal values at baseline and total bilirubin > 2 x ULN<br>or AST or ALT ≥ grade 3 (> 5 x ULN) in patients with grade | Dose limiting toxicity |
| 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. | |

| **QTC** | |
|---|---|
| **Toxicity/Grade** | **Dose Limiting Toxicity and Management Recommendations** |
| For all grades | • Check the quality of the ECG<br>• Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If below the lower limit of normal, interrupt LEE011 administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal<br>• Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval<br>• Check compliance with correct dose and administration of LEE011 |
| 2<br>QTc 481-500 ms | Interrupt LEE011<br><br>Perform a repeat ECG one hour after the first QTcF of ≥481ms<br><br>If QTcF < 481 ms, restart LEE011 at the same dose. No dose adjustment for the first occurrence<br><br>If QTcF remains ≥481 ms, restart LEE011 at the same dose level. No dose adjustments required for the first occurrence<br><br>If QTcF ≥481 ms recurs, dose limiting toxicity<br><br>Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patient who has therapy interrupted due to QTcF ≥481 ms |
| 3<br>QTc ≥ 501 ms on at least two separate ECGs | **Interrupt LEE011**<br>• Consider consulting a local cardiologist |

| | |
|---|---|
| | • **Perform a repeat ECG one hour after the first QTcF of ≥501 ms**<br>• If QTcF remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 481 ms.<br>• If QTcF returns to < 481 ms, LEE011 should be reduced by 1 dose level. (please refer to the dosing schedule table)<br>**Repeat ECGs 7 days and 14 days after dose resumption for any patient who has therapy interrupted due to QTcF ≥501 ms**<br>• If QTcF of ≥ 501 ms recurs, discontinue LEE011- Dose limiting toxicity |
| 4<br>QT/QTc ≥ 501 **or** > 60 ms change from baseline<br><br>**And**<br><br>Torsades de pointes **or** polymorphic ventricular tachycardia, **or** signs/symptoms of serious arrhythmia | Dose limiting toxicity |

## 6.7 LEE011 DOSE MODIFICATION GUIDELINE- PHASE IB CYCLE 2+ AND PHASE II COMPONENTS

Management of severe or intolerable adverse reactions requires temporary dose reduction and/or interruption of LEE011 therapy. Refer to Table 6.3 for guidance. Dose increases once LEE011 has been reduced are not allowed.

**Table 6.3 Dose Modification Guidelines**

| Dose Level | LEE011 | |
|---|---|---|
| | Dose | Number of capsules & strength |
| **Highest dose (0)** | 600 mg | 3 x 200 mg capsules |
| **First dose reduction (-1)** | 400 mg | 2 x 200 mg capsules |
| **Second dose reduction (-2)** | 200 mg | 1 x 200 mg capsules |
| **Third dose reduction (-3)** | Discontinue Treatment of LEE011 | |

Recommendations for dose reduction, interruption, of discontinuation of LEE011 in the management of adverse reactions are summarized in Table 6-4, Table 6-5, Table 6-6, and Table 6-7. *Clinical judgment and discretion of the treating physician should guide the management plan of each patient based on individual benefit and risk assessment.*

**Table 6-4 LEE011 Dose Adjustment and Management Recommendations for HEMATOLOGICAL ADVERSE REACTIONS**

| THROMBOCYTOPENIA | |
|---|---|
| **Toxicity/Grade** | **Dose Adjustment and Management Recommendations** |
| Grade 1<br>( ≥ 75 x $10^9$/L) | No dose adjustment required. |
| Grade 2<br>( ≥ 50 x $10^9$/L - <75 x $10^9$/L) | No dose adjustment required. |
| Grade 3<br>( ≥ 25 x $10^9$/L - <50 x $10^9$/L) | Dose interruption until recovery to grade ≤2.<br><br>Re-initiate LEE011 at the same dose level.If toxicity recurs at grade 3: discontinue LEE011 |
| Grade 4<br>(<25 x $10^9$/L) | Discontinue LEE011. |

| Toxicity/Grade | Dose Adjustment and Management Recommendations |
|---|---|
| **Absolute neutrophil count (ANC)** | |
| Grade 1<br>(≥1.5 x $10^9$/L) | No dose adjustment required. |
| Grade 2<br>(≥1.0 - <1.5 x $10^9$/L) | No dose adjustment required. |
| Grade 3<br>(≥0.5 - <1.0 x $10^9$/L) | Dose interruption until recovery to ≥1.0 x $10^9$/L.<br>Re-initiate LEE011 at the same dose level.<br>• If toxicity recurs at grade 3: temporary dose interruption until recovery to ≥1.0 x $10^9$/L and reduce LEE011 dose to the next lower dose level. |
| Grade 4<br>(<0.5 x $10^9$/L) | Dose interruption until recovery to<br>≥ 1.0 x $10^9$/L.<br>Re-initiate LEE011 at the next lower dose level.<br>• If toxicity recurs at grade 4: temporary dose interruption until recovery to ≥ 1.0 x $10^9$/L and reduce LEE011 at the next lower dose level. |
| **Febrile Neutropenia** | |
| Grade 3<br>ANC <1.0 x $10^9$/L with [a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour] | Dose interruption until improvement of ANC ≥ 1.0 x 109/L and no fever.<br>Restart at the next lower dose level.<br>• If febrile neutropenia recurs, discontinue LEE011. |
| Grade 4<br>Life-threatening consequences; urgent intervention indicated | Discontinue LEE011. |
| **Anemia (Hemoglobin)** | |
| Grade 1<br>(≥ 10.0 g/dL) | No dose adjustment required. |
| Grade 2<br>( ≥ 8.0 – <10.0 g/dL) | No dose adjustment required. |
| Grade 3<br>(<8.0 g/dL) | Dose interruption until recovery to grade ≤ 2.<br>Re-initiate LEE011 at the same dose. |

| | |
|---|---|
| Grade 4<br>Life-threatening consequences; urgent intervention indicated | Discontinue LEE011. |

**Table 6-5 LEE011 Dose Adjustment and Management Recommendations for HEPATIC ADVERSE REACTIONS**

| **HEPATOTOXICITY (BILIRUBIN, ALT, AST)** | |
|---|---|
| **TOTAL BILIRUBIN without ALT/AST increase above baseline value** | |
| **Grade** | **Dose Adjustment and Management Recommendations** |
| Same grade as baseline or increase from baseline grade 0 to grade 1 | Maintain dose level with LFTs monitored every other-week |
| Increase from baseline grade 0 or 1 to grade 2 (1.5-3.0 x ULN) or from baseline grade 2 to grade 3 (>3.0 -10 x ULN) | Dose interruption of LEE011<br><br>If resolved to ≤ grade 1 in ≤ 21 days, then maintain dose level<br><br>If resolved to ≤ grade 1 in > 21 days or toxicity recurs, discontinue LEE011 |

| | |
|---|---|
| Increase from baseline grade 0 or 1 to grade 3 (>3.0-10 xULN) | Discontinue LEE011 |
| 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 Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs.<br><br>For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated. | |

| **HEPATOTOXICITY (BILIRUBIN, ALT, AST)** | |
|---|---|
| **AST or ALT without bilirubin elevation > 2 x ULN** | |
| **AST or ALT Toxicity/Grade** | **Dose Adjustment and Management Recommendations** |
| Same grade as baseline or increase from baseline grade 0 to grade 1 (confirmed 48 to 72 hrs later) | No dose adjustment required with LFTs monitored per protocol if same grade as baseline or bi-weekly in case of increase from baseline grade 0 to 1 |

| | |
|---|---|
| Increase from baseline grade 0 or 1 to grade 2 (> 3.0 – 5.0 x ULN)<br>or<br>from baseline grade 2 to grade 3 (> 5.0 – 20.0 x ULN) | Dose interruption of LEE011<br><br>If resolved to ≤ baseline value in ≤ 21 days, then maintain dose level<br><br>If resolved to ≤ baseline value in > 21 days or toxicity recurs, discontinue LEE011 |
| Increase from baseline grade 0 or 1 to grade 3 (> 5.0 – 20.0 x ULN) | Discontinue LEE011 |
| Grade 4 (> 20.0 x ULN) | Discontinue LEE011 |
| **AST or ALT and concurrent Bilirubin** | |
| AST or ALT ≥ grade 2 (> 3 x ULN) in patients with normal values at baseline and total bilirubin > 2 x ULN<br>o<br>r<br>AST or ALT ≥ grade 3 (> 5 x ULN) in patients with grade 1 or 2 at baseline, and total bilirubin > 2 x ULN | Discontinue LEE011 |
| 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. | |

**Table 6-6 LEE011 dose modification guidance in case of QT PROLONGATION**

The ECG are done based on scheduled assessment as detailed in table 7.1.

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

| | |
|---|---|
| | • If QTcF returns to < 481 ms, LEE011 should be reduced by<br>1 dose level. (please refer to the dosing schedule table)<br><br>**Repeat ECGs 7 days and 14 days after dose resumption for any patient who has therapy interrupted due to QTcF ≥501 ms**<br><br>• If QTcF of ≥ 501 ms recurs, discontinue LEE011 |
| 4<br>QT/QTc ≥ 501 **or** > 60 ms change from baseline<br><br>**And**<br><br>Torsades de pointes **or** polymorphic ventricular tachycardia, **or** signs/symptoms of serious arrhythmia | Discontinue LEE011 |

**Table 6-7 LEE011 Dose Adjustment and Management Recommendations for ALL OTHER ADVERSE REACTIONS**

| Grade | Dose Adjustment and Management Recommendations |
|---|---|
| 1 | No dose adjustment recommended. Initiate appropriate medical therapy and monitor. |
| 2 | Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor.<br><br>Re-initiate LEE011 at the same dose.<br><br>• If the same toxicity recurs at grade 2, interrupt LEE011 until recovery to grade ≤1. Re-initiate LEE011 at the next lower dose level. |

| | |
|---|---|
| 3 | Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor.<br><br>Re-initiate LEE011 at the next lower dose level.<br><br>• If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤1 and reduce LEE011 dose the next lower dose level.<br>• If toxicity recurs at grade 3, discontinue LEE011. |
| 4 | Discontinue LEE011 and treat with appropriate medical therapy. |

## 6.8 ADJUSTMENT OF STARTING DOSE IN SPECIAL POPULATIONS

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 > 1.5 or creatinine clearance < 50 mL/min). Patients who experience serum creatinine impairment of grade 3 or higher during the treatment period should discontinue treatment and should be followed for safety assessments.

## 6.9 CONCOMITANT MEDICATIONS

Permitted Concomitant Therapy

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed.

The patient must be told to notify the investigational site about any new medications s/he takes after the start of the study treatment. All medications (other than study drugs) and significant non-drug therapies (including vitamins, 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 section of the patient record.

Bisphosphonates and Denosumab

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

Hematopoietic Growth Factors

Hematopoietic growth factors may be used according to ASCO guidelines.

Palliative Radiotherapy

Palliative radiation is permitted if done solely for bone pain relief. It should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow Refer to the LEE011 (LEE011) Investigator's Brochure, Appendix table 1, and Appendix table 2 for information on possible interactions with other drugs.

Permitted Concomitant Therapy Requiring Caution

Medications to be used with caution during LEE011 in this study are listed below (**see Table 2**). This list is not comprehensive and is only meant to be used as a guide. Concurrent use of CYP1A2 substrates is not expected to lead to clinically important drug-drug interactions, therefore their use is not regulated. These medications should be excluded from patient use if possible. If they must be given, then use with caution and consider a LEE011 interruption if the concomitant medication is only needed for a short time (**See Appendix Table 1**):

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

Prohibited Concomitant Therapy

The following medications are prohibited during study treatment in the study **(see Appendix Table 2).** This list is not comprehensive and is only meant to be used as a guide:

- Strong inhibitors or inducers of CYP3A4/5;
- Substrates of CYP3A4/5 with a narrow therapeutic index;
- Medications that carry a known risk for QT prolongation;
- Herbal medications/preparations, herbal dietary supplements;
- Other investigational and antineoplastic therapies not part of the study;
- Herbal medications include, but are not limited to: St. John's Wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications and dietary supplements at least 7 days prior to first dose of study treatment.

## 6.10 DRUG SUPPLY AND STORAGE

Study drug must be received by the designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only designated personnel have access. Upon receipt, the study drug should be stored according to the instructions specified on the drug labels and in the Investigators Brochure. Medication labels will comply with the legal requirements of each country and be printed in the local language.

## 6.11 STUDY DRUG COMPLIANCE AND ACCOUNTABILITY

### 6.11.1 **Compliance**

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient via patient drug diary. Records of the study medication used, dosages administered, and intervals between visits and completion of the study will be captured in the Drug Accountability Form.

### 6.11.2 **Accountability**

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log at the study close-out visit, and as appropriate during the course of the study.

## 6.12 DRUG ELUTING BEAD-CHEMOEMBOLIZATION

Chemoembolization is considered standard of care for locally advanced, non-metastatic HCC.

### 6.12.1 **DC Bead description**

a) DC bead comprise a range of hydrogel microspheres that are biocompatible, hydrophilic, non resorbable, precisely calibrated and capable of loading doxorubicin. DC bead is produced from polyvinyl alcohol and are available in the following size ranges:

| Nominal bead size | Label color | Upon loading with doxorubicin, DC bead undergo a slight decrease in size, up to 20% when loading at 25 mg/ml |
|---|---|---|
| 100-300 um | Yellow | |
| 300-500 um | Blue | |
| 500-700 um | Red | |
| 700-900 um | Green | |

b) How supplied:

- 10 ml glass vial
- Each vial contains approximately 2 ml of DC bead in non-pyrogenic, sterile, physiological buffered saline. Total volume of saline and DC bead is approximately 8 ml.
- The vial is stopper sealed by an aluminum cap equipped with a color-coded lid
- Each vial is intended for single patient use only. Do not resterilize. Discard any unused material

C) Contraindications-DC bead

- Patients intolerant to vascular occlusion procedures
- Vascular anatomy that precludes catheter placement or emboli injection
- Presence or likely onset of vasospasm

- Presence of likely onset of hemorrhage
- Presence of severe atheromatous disease
- Presence of feeding arteries smaller than distal branches from which they emerge
- Presence of patent extra-to-intracranial anastomoses or shunts
- Presence of collateral vessel pathways potentially endangering normal territories during embolization
- Presence of end arteries leading directly to cranial nerves
- Presence of arteries supplying the lesion not large enough to accept DC bead
- Vascular resistance peripheral to the feeding arteries precluding passage of DC bead into the lesion
- Do not use DC bead for embolization of large diameter arteriovenous shunts

### 6.12.2 DRUG LOADING INSTRUCTIONS

DC bead is suitable for loading doxorubicin-HCL only. Liposomal formulations of doxorubicin are not suitable for loading into DC bead.

To obtain final loading of 50 mg per 2 ml vial of DC bead;

I. Reconstitute a vial containing 50 mg of doxorubicin with 2 ml of sterile water for injection. Mix well to obtain a clear red solution (25 mg/ml).
II. Remove as much saline as possible from vial of DC bead using a syringe with a small gauge needle.
III. Using a syringe and needle add the 2 ml of reconstituted doxorubicin solution directly to the vial of DC bead.
IV. Agitate the DC bead/doxorubicin solution occasionally to encourage mixing until the DC bead is red. Although the solution retains a red color, doxorubicin will be loaded.
V. Loading will take a minimum of 20 minutes for the smallest size DC bead and up to 120 minutes for the larges DC bead.
VI. Prior to use, transfer the DC bead loaded with doxorubicin to a syringe and add 1 to 4 times the volume of the non-ionic contrast media, Omnipaque 350. Invert the syringe gently to obtain an even suspension of DC bead. A dose of up to 37.5 doxorubicin per ml DC bead can be loaded.
VII. The maximum recommended total dose of doxorubicin per procedure is 150 mg.

### 6.12.3 PATIENT PRE-PROCEDURAL PREPARATION

a) IV normal saline
b) Pre-medications
    a. Versed and Fentanyl titrated for moderate sedation

### 6.12.4 CHEMOEMBOLIZATION PROCEDURAL PREPARATION

a) The patient is prepped and draped in a sterile fashion.
b) Carefully evaluate the vascular network associated with the lesion with high resolution imaging prior to beginning the embolization procedure.

c) DC beads are available in a range of sizes, but only 100 to 500 um particles should be utilized. Care should also be taken to choose the appropriate size of DC bead athat bases matches the vascular target or vessel size.
d) Choose a delivery catheter based on the size of the target vessel. DC bead can tolerate temporary compression of 20% to 30% in order to facilitate passage through the delivery catheter.
e) Introduce the delivery catheter into the target vessel according to standard techniques. Position the catheter tip as close as possible to the treatment site to avoid inadvertent occlusion of normal vessels.
f) DC are not radio-opaque. It is recommended to monitor the embolization under fluoroscopic visualization by adding the desired amount of contrast medium to the suspension fluid.
    a. Take care to ensure proper suspension of the DC bead in the contrast medium to enhance distribution during injection.
    b. Draw the DC bead into a syringe needle of a size greater than or equal to 19 gauge.
    c. At a rate no faster than 1ml/minute, slowly inject DC bead into the delivery catheter under fluoroscopic visualization while observing the contrast flow rate. Exercise conservative judgment in determining the embolization endpoint.
g) Upon completion of the treatment, remove the catheter while maintaining gentle suction so as not to dislodge the DC bead still within the catheter lumen.
h) Discard any unused DC bead loaded with doxorubicin.

### 6.12.5 POST-CHEMOEMBOLIZATION PROCEDURE ORDERS AND CARE

a) Admit patients overnight for observation.
b) Hydration with IV normal saline
c) Patient controlled analgesia for pain control.

### 6.12.6 POST-PROCEDURE CARE

a) Post-arteriography bedrest with monitoring of vital signs and pulses.
b) Patient can be discharged as soon as they demonstrate adequate oral intake or liquids, no longer require parenteral narcotics or antiemetics.
c) Fevers <103 degrees F are normal during the first week following treatment and do not require cultures.
d) Following institutional guidelines, patients will be seen in the HCC multidisciplinary clinic 7-10 days following chemoembolization and will have the following evaluations completed:

- Physical examination
- Comprehensive metabolic panel
- Complete blood count without differential
- Prothrombin time/INR

At this time the decision will be made to initiate LEE011 treatment.

LEE011 ADMINISTRATION WITH CHEMOEMBOLIZATION

Subjects are to be evaluated from toxicity with:

- Physical Examination (PE)
- Comprehensive Metabolic Panel (CMP)
- CBC
- ECG's

LEE011 will be initiated at the earliest of 7 days following embolization chemoembolization provided the following criteria are met:

- Serum bilirubin elevation < 2.0 x ULN. If serum bilirubin ≥ 2.0 x ULN then subjects will be assessed weekly and LEE011 will be initiated once bilirubin < 2.0 x ULN.

- Resolution of Grade < 3 non-hematologic toxicity (other than bilirubin criteria above). If non-hematologic toxicity ≥ Grade 3 then subjects will be assessed weekly and LEE011 will be initiated once < Grade 2;

- Hematological toxicity of ≤ Grade 2. If hematologic toxicity ≥ Grade 3 then subjects will be assessed weekly and LEE011 will be initiated once ≤ Grade 2.

  If baseline AST, ALT and alkaline phosphate are elevated post chemoembolization decrease to baseline grade is necessary to continue/initiate LEE011;

- ECOG performance status ≤ 2;

- Serum AST, ALT, and/or Alkaline Phosphate < 5 x ULN.

*If criteria is not met, subjects will be reevaluated in 5-7 day intervals. If study subjects are unable to meet the above LEE011 starting criteria following initial chemoembolization treatment within 28 days after treatment, they will be removed from the study.*

6.12.7 **Subsequent Chemoembolizations**

To proceed with subsequent chemoembolization, study subjects must meet the following criteria:

≤ Grade 2 hematologic toxicity with the exception of:

- serum creatinine ≤ 1.5 mg/dl;
- serum bilirubin ≤ 3.0 mg/dl.

Repeat Chemoembolization (for either ipsilateral or contralateral disease) if indicated, should be performed at least 4 weeks apart. Up to 4 chemoembolizations can be performed in 6 months of the first chemoembolization. Additional chemoembolizations, if clinically indicated can occur after the first 6 months

## 7.0 VISIT SCHEDULE AND ASSESSMENTS

Table 7.1, lists all of the assessments and indicates with an "X", the visits and when they are performed. For the phase Ib component only the first cycle will be utilized for determination of dose limiting toxicities. All data obtained from these assessments must be supported by the proper source documentation and placed in the patient's chart.

### 7.1 TABLE OF ASSESSMENTS

| Treatment Days | Screening Phase[1] | | Treatment Phase: Chemoembolization | Treatment Phase: LEE011 | | | | | | Post Treatment Follow-up | | | Survival Phase |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 – Day -1 | Day -7 – Day -1 | 7-14 days Following chemoembolization | Cycle 1 | | Cycle 2 | | C3 | C4+ | End of Treatment or Early Withdrawal (Within 15 Days of Last LEE011 Dose) | Safety Follow-Up (Within 30 Days of Last LEE011 Dose) | Efficacy Follow-Up | Survival Follow-Up Every 12 weeks |
| | | | | Day 1[2,13] | Day 15 | Day 1 | Day 15 | Day 1 | Day 1 | | | | |
| Visit Assessments | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | |
| Eligibility Checklist - Inclusion / Exclusion | X | | | | | | | | | | | | |
| Med History | X | | | | | | | | | | | | |
| Dx and Extent of Cancer (Staging) | X | | | | | | | | | | | | |
| Physical Exam | | X | X | X | X | X | X | X | X | X | X | | |
| ECOG Status | | X | X | X | X | X | X | X | X | X | X | | |
| Height | X | | | | | | | | | | | | |
| Weight | | X | | X | X | X | X | X | X | X | X | | |
| Vital Signs | | X | X | X | X | X | X | X | X | X | X | | |
| CBC | | X | X | X | X | X | X | X | X | X | X | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chemistry (CMP) | | X | X | X | X | X | X | X | X | X | X | | |
| Cholesterol/Lipid Panel | | X | | X | X | X | X | X | X | X | X | | |
| PT/INR | | X | X | X | X | X | X | X | X | X | X | | |
| Serum Pregnancy Test (WOCBP Only) | | X | | | | | | | X | X | | | |
| Urinalysis | | X | | | | | | | | X | X | | |
| Tumor Assessments with RECIST 1.1[5] | X | | | ←---------- Every 8 weeks[5] ----------→ | | | | | | | | X[5] | |
| ECHO/MUGA | X | | | | | | | | | | | | |
| ECG (12 – Lead) | | X[3] | | X | X | X | X[3] | X | X | X | X | | |
| Adverse Events[6] | X | X | | X | X | X | | X | X | X | X | | |
| Conmeds[6] | X | X | | X | X | X | | X | X | X | X | | |
| Biomarker Tissue Collection (Biopsy)[7] | X[7] | | | | | X[7] | | | | | | | |
| Biomarker Blood Collection[8] | | X | | X | | X | | X | X | X | | | |
| LEE011 Study Drug (Oral)[9] | | | | X | | X | | X | X | | | | |
| Patient Dosing Diary for LEE011[9] | | | | X | | X | | X | X | | | | |
| Chemoembolization (TACE)[10] | | | | X | | X | | X | X | | | | |
| Discontinuation[11] | | | | | | | | | | | X | | |
| Survival Follow-Up[12] | | | | | | | | | | | | | X |

1. Screening assessments, apart from those listed above, must occur within 28 days of registration as per Table 7.1;
2. Vital Signs, ECOG Performance Status, Physical Exam, ECG, CBC, CMP, PT/INR, Lipid Panel, Serum Pregnancy Test (WOCBP Only), and Urinalysis should be performed within 7 days of the first treatment day (Cycle 1, Day 1). If there are any dose modifications or halting of drug in the phase II aspect, weekly hematology, comprehensive metabolic panels, and PT/INR laboratory investigations will be performed until the grade of adverse event leading to the modification or cessation is stable or a grade reduction occurs. In addition, following each chemoembolization the following will be done every other week for two cycles after each chemoembolization: physical examination, CMP, CBC, and PT/INR.
3. In order for an accurate evaluation of baseline QTc, a total of three (triplicate) 12-lead ECGs will be performed after resting in a supine position for 5-10 min, with a 2 minute interval between each ECG (triplicate ECG's at screening only). Subsequent ECG's will be performed after resting in a supine position for 5-10 min, on Day 1, C1D15, and C2D15 of each treatment cycle (single ECG's )prior to chemoembolization and LEE011;

4. For all treatment visits there is a general +/- 3 day window on assessments to take into account scheduling over public holidays, if not specifically specified otherwise;
5. Baseline scans can be completed within 28 days prior to registration. After baseline, radiological assessments (CT –chest/abdomen/pelvis or MRI – abdomen/pelvis) must be performed as outline in Table 7.1 (Every 8 weeks during the treatment phase). CT Chest must be performed at baseline. CT Chest during treatment will be performed if clinically indicated. A visit window of +/- 7 days is allowed. Once the patient has been discontinued from the study and enters the efficacy phase, radiological assessments (CT or MRI) will continue on the every 8 weeks schedule until progression or for the first 12 months, whichever comes first. After a year, radiological (CT or MRI) assessments will be performed every 12 weeks until progression.
6. AE/Conmeds will be assessed from consent until up to 30 days last dose of LEE001 or until resolution, whichever comes first. Conmeds will recorded up to30 day prior to consent;
7. The biopsy performed during screening is for HCC diagnosis and RB positive status and must be performed for the subject to be eligible for the study. However, initial TACE can be performed following agreement of informed consent while RB proficiency is being determined. If patient is not RB proficient patient will be removed from the study as a screen failed and offered other treatment. If the patient has archival formalin fixed paraffin embedded tissue no additional baseline biopsy will be done. The post treatment biopsy is optional and for research purposes only (phase 2 only). If the subject consented to the research biopsy during the consent process, it will be performed during the $8^{th}$ and $9^{th}$ week of after initiating treatment of LEE011 and at least one chemoembolization. NOTE: LEE011 should be held for 24-48 hours prior to and after the second biopsy. These held doses will not be made up and noted on the patient's diary.
8. Biomarker blood collection is also an optional research procedure and the patient must have consented to the additional blood collection to participate (phase II only). Blood will be collected according to the schedule in table 7.1;
9. Patients will be treated with LEE011 (3 weeks on / 1 week off of a 28 day cycle) until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to any other reason. The patient will complete a subject dosing log in order to ensure drug compliance. The patient will be provided a new dosing diary at each new treatment cycle and reviewed at the end of each cycle for compliance.
10. Patients will be treated with chemoembolization with up to 4 total chemoembolizations within the first 6 months from the initial chemoembolization.
11. Patients who discontinue treatment for reasons other than disease progression, death, start of new anti-neoplastic therapies, lost to follow-up, or withdrawal of consent to efficacy follow-up, then tumor assessments and patient reported outcomes must continue to be performed every 8 weeks during the first 12 months and every 12 weeks thereafter until the start of new anti-cancer therapy, disease progression, death, lost to follow-up, or withdrawn consent to efficacy follow-up;
12. All patients will be followed for survival status every 12 weeks regardless of treatment discontinuation until death, lost to follow-up, or withdrawal of consent to survival follow-up. Survival follow-up assessment may be made by a phone call to the patient or designated PHI, EPIC medical record review, or certified mail. At least 3 documented attempts should be made to contact the patient before the patient is considered lost to follow-up.
13. The follow-up visit after chemoembolization can be used as day 1 visit of each cycle if the decision is made to continue with LEE011 treatments.

## 7.2 SCREENING PHASE

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. ***Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained***.

All screening procedures must be performed within 28 days prior to registration, unless otherwise stated. The screening procedures include the following: (See Table 7.1 above for the list of assessments to be performed.)

### 7.2.1 Informed Consent

Patients must provide a signed inform consent form prior to any study specific evaluations including screening. Eligibility will be determined according to the inclusion/exclusion criteria as described in Section 5. A list of procedures to be performed at time of screening is summarized in Table 7.1. Patients must meet all eligibility criteria to be considered for enrollment in the study.

### 7.2.2 Eligibility Checklist (Inclusion/Exclusion)

In order to determine and confirm the eligibility of the patient, once all screening procedures are completed, an eligibility checklist must be completed by the research team prior to chemoembolization.

### 7.2.3 Patient Demographics and other Baseline Characteristics

The data that will be collected on patient characteristics at screening includes:

- Demographic (name, date of birth, age), sex, race/ethnicity;
- Diagnosis, RB status, and extent of cancer (staging) – tissue biopsy (required);
- Pertinent Medical History;
- Prior cancer treatment;
- All medications taken within 30 days before first treatment. If there are any changes, medications are to be updated on a continual basis.

Furthermore the following assessments will be performed:

- Vital Signs (BP, HR, T, RR);
- Adverse Events / Conmeds
- Height and Weight;
- Physical Examination (PE);
- ECOG Performance Status (PS);
- Laboratory Evaluations (chemistry, CBC, PT/INR, Lipid Panel, and UA)
- ECG (in Triplicate – baseline only)
- ECHO or MUGA;

- Radiological Assessments (RECIST 1.1) (CT - chest/abdomen/pelvis or MRI – abdomen/pelvis). Chest CT will be performed at baseline only. During the treatment phase, a Chest CT will be performed as clinically indicated;
- Pregnancy Test (Women of Child-bearing Potential Only).

#### 7.2.4 Pre-Treatment - Biomarker Tissue Biopsy (Required)

After signing the treatment and biopsy informed consent, the screening biopsy, confirming HCC diagnosis, staging, and (RB+) result, must be complete within 28 days prior to registration unless the patient has archival formalin fixed paraffin embedded tissue to determine RB status. This biopsy is required to confirm patient eligibility. However, initial TACE procedure can be initiated prior to determination of RB status provided informed consent is signed and biopsy tissue is available for analysis.

#### 7.2.5 Biomarker / DNA Blood Collection (Optional – Phase II only)

After signing the optional biomarker / DNA consent for future biomarker and DNA blood, samples will be collected at baseline, during treatment, and at the end of treatment or early-term visit. This procedure is for research and will not be used to make medical decisions regarding the patient's treatment.

### 7.3 TREATMENT PHASE

#### 7.3.1 Study Treatment

Patients will be treated with chemoembolization once every 4 weeks (or every 28 Days), for a total of up to 4 chemoembolizations within the first 6 months.

In addition, patients will be treated with 200, 400, or 600 mg LEE011 once daily by mouth (3 Weeks on / 1 Week off in a 28 day cycle) until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to any other reason. For details of assessment, refer to Table 7.1.

#### 7.3.2 Post-Treatment – Biomarker Tissue Biopsy (Optional – Phase II only)

The post treatment biopsy is optional and the patient must have consented to this second procedure during the initial consenting process. The second biopsy, for research purposes only, will be performed between Weeks 8 and 9 post initial treatment of LEE011. To qualify for the second biopsy, patients must have taken LEE011 for 21 consecutive days (21 days on treatment / 7 days off in a 28 day cycle) and had at least one chemoembolization.

#### 7.3.3 Additional Treatment Phase Assessments will be performed:

- Vital Signs (BP, HR, T, RR);
- Adverse Events / Conmeds
- Weight;

- Physical Examination (PE);
- ECOG Performance Status (PS);
- Laboratory Evaluations (chemistry, CBC, PT/INR, and Lipid Panel);
- ECG;
- Radiological Assessments (RECIST 1.1) (CT - chest/abdomen/pelvis or MRI – abdomen/pelvis). During the treatment phase, a Chest CT will be performed as clinically indicated;

## 7.4 POST – TREATMENT FOLLOW-UP PHASE

### 7.4.1 End of Treatment and Early Withdrawal Visit

Patients who completely discontinue study treatment should be scheduled for an End of Treatment (EOT) visit within 15 days following the last dose date of LEE011, at which time all of the assessments listed for the EOT visit will be performed. For details of the assessment, see Table 7-1.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for AE evaluations during the 30 days following the last dose date of LEE011.

#### 7.4.1.1 Criteria for Early Withdrawal

Patients may voluntarily withdraw from the study treatment or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study treatment if any of the following occur:

- Adverse event
- Lost to follow-up
- Physician decision
- Progressive disease
- Protocol deviation
- Study terminated by the sponsor
- Technical problems

### 7.4.2 Safety Follow-Up

All patients will be followed up for safety up to 30 days after last dose of study drug (LEE011) treatment. Patients whose treatment is interrupted or permanently discontinued due to an AE, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first.

### 7.4.3 Efficacy Follow-Up

Patients who discontinue treatment for reasons other than disease progression, death, start of new anti-neoplastic therapies, lost to follow-up, or withdrawal of consent -- Tumor Assessments and scans (CT or MRI) (See Section 8) must continue to be performed every 8 weeks during the first 12

months, then thereafter, every 3 months (every 12 Weeks) until the start of new anti-cancer therapy, disease progression, death, lost to follow-up, or withdrawn of consent.

## 7.5 SURVIVAL PHASE

### 7.5.1 Survival Follow-Up

All patients will be followed for survival status every 12 weeks, starting from the Safety Follow-Up visit, regardless of treatment discontinuation, until death, lost to follow-up, or withdrawal of consent to survival follow-up.

Survival follow-up assessment may be made by a phone call to the patient or designated PHI, EPIC medical record review, or certified mail. At least 3 documented attempts should be made to contact the patient before the patient is considered lost to follow-up.

# 8.0 MEASUREMENT OF EFFECT

For the purposes of this study, patients will be evaluated for progression every 8 weeks for the first 12 months, then every 12 weeks (3 months) thereafter following the initial chemoembolization. Imaging will consist of a CT or MRI abdomen with liver protocol. The same imaging modality used at baseline will be used for further scans unless documented by primary investigator. CT Chest or additional imaging will be at the discretion of the investigator based on clinical suspicion of additional progressive disease.

## 8.1 ANTITUMOR EFFECT- SOLID TUMORS

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

### 8.1.1 Disease Parameters

Measurable Disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (CT, MRI, x-ray) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). A “high-resolution” CT scan is one in which images are recorded at least every 5 mm.

Non-Measurable Disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions,

lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target Lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-Target Lesions. All other lesions (or sites of disease) that are not target lesions, as defined in the section above, will be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are required when feasible, since a patient may have progressive disease on the basis of larger non-target lesions. The presence or absence of each non-target lesion should be noted throughout follow-up.

### 8.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

### 8.1.3 Response Criteria

#### 8.1.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

#### 8.1.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

#### 8.1.3.3 Evaluation of Best Overall Response

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

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Response for this Category Also Requires: |
|---|---|---|---|---|
| CR | CR | No | CR | ≥4 wks. confirmation |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks. confirmation |
| PR | Non-PD | No | PR | |
| SD | Non-PD | No | SD | documented at least once ≥4 wks. from baseline |
| PD | Any | Yes or No | PD | |

| | | | | |
|---|---|---|---|---|
| Any | PD* | Yes or No | PD | no prior SD, PR or CR |
| Any | Any | Yes | PD | |

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

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

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

#### 8.1.4 Duration of Response

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

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

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

#### 8.1.5 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

### 8.2 SAFETY/TOLERABILITY

Analyses will be performed for all subjects having received at least one dose of study drug. The study will use the CTCAE version 4.03 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events (Appendix #/letter).

## 9.0 ADVERSE EVENTS

### 9.1 LEE001 TREATMENT RELATED EVENTS

The following grade 3 and 4 AEs are suspected to be related to LEE011 treatment for reporting purposes:

- Anemia, febrile neutropenia, leukopenia, lymphopenia, neutropenia, thrombocytopenia;
- Electrocardiogram QT prolonged, hypertension;
- Diarrhea, nausea, vomiting, stomatitis, mucositis; abdominal pain;
- Pneumonia
- Asthenia/fatigue; decreased appetite
- Hepatocellular injury; Hepatic function abnormalities (elevated transaminases); elevated creatinine
- Rash;
- Hyponatremia

## 9.2 CHEMOEMBOLIZATION TREATMENT RELATED EVENTS

The following events are considered to be expected for reporting purposes following chemoembolization:

- Abdominal pain;
- Fever;
- Fatigue;
- Nausea;
- Elevated liver enzymes;
- Infection;
- Cholecystitis;
- Hemorrhage;
- Thromboembolic events;
- Alopecia;
- Hyperpigmentation;
- Mucositis;
- Hepatocellular injury; hepatic function abnormalities (elevated transaminases)

## 9.3 ADVERSE EVENT MONITORING

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;

- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

9.3.1 **Definition**

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild;
- Grade 2: Moderate;
- Grade 3: Severe or medically significant but not immediately life threatening;
- Grade 4: Life threatening consequences;
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death;
- Immediately life-threatening;
- Results in inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect;
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets any of the above

criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

Refer to the UTSW IRB website at http://www.utsouthwestern.net/intranet/research/research-administration/irb/study-management/adverse-events.html to determine when a serious adverse event requires reporting to the IRB.

9.3.2 Unanticipated Problems:

The term “unanticipated problem” is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets each of the following criteria:

- Unexpected (in terms of nature, severity or frequency);

***AND***

- Definitely, probably, or possibly related to participation in the research;

***AND***

- Serious or a possible unexpected problem in that the research places subjects or others at greater risk of harm than was previously known or recognized. Note: Any serious adverse event would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

9.3.3 Reporting

Local unanticipated problems require expedited reporting, and are submitted to the UTSW IRB through the UTSW eIRB and to the SCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation

available should be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix IV of the SCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB in not required).*

All local serious adverse events which occur on research subjects on protocols for which the SCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. Hardcopies or electronic versions of the FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator.

If the event occurs on a multi-institutional clinical trial coordinated by the Cancer Center, the Disease Oriented Team (DOT) Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all serious adverse events within upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Written reports to:

Muhammad Shaalan Beg, MD
c/o
QA Coordinator
5323 Harry Hines Blvd, NB2.418
Dallas, Texas 75390
Phone: 214-648-5919
Fax: 214-648-1875
Email: silvia.pilarski@utsouthwestern.edu

UTSW SCC Data Safety Monitoring Committee Coordinator
Email: SCCDSMC@utsouthwestern.edu
Fax: 214-648-5949 or deliver to BLB.306

UTSW Institutional Review Board (IRB)
Submit via eIRB with a copy of the final sponsor report as attached supporting documentation.

1. **SAEs**
   Local serious adverse events (SAEs) for studies where SCC DSMC is the DSMC of record require reporting to the DSMC coordinator within 2 working days of PI awareness, or as described in the protocol.

2. **Unanticipated Problems**

   Local unanticipated problems require reporting to the UTSW IRB within 2 working days of PI awareness of the event.

   Unanticipated problems, including those that occur as non-local events, require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

   For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

## 9.4 STOPPING RULES

There is no interim analysis planned.

Simmons Cancer Center Data and Safety Monitoring Board (DSMB) will oversee this study and will determine if early stoppage of the trial is needed due to unacceptable rates of drug related serious adverse events.

To assess for aggregate severe hepatobiliary toxicity and severe events that occur at any time during the study, if 2 total grade 5 or 2 grade 4 adverse events (lasting ≥ 7 days) occur while at patient is receiving study treatment and the adverse events are attributed to either being definitely, probably, or possible related to the study treatment then the study will terminate with no further patients entered.

## 9.5 STEPS TO DETERMINE IF AN ADVERSE EVENT REQUIRES EXPEDITED REPORTING

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v. 4.03).

Step 2: Grade the adverse event using the NCI CTCAE v. 4.03.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is unlikely related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

## 10.0 SAFETY AND TOLERABILITY ASSESSMENTS

Safety will be monitored by assessing physical examinations, ECOG performance status, height and weight, vital signs, ECG, patient reported outcomes, laboratory assessments including hematology, chemistry, cholesterol and lipid panel, PT, INR, and urine as well as collecting adverse events at every visit. For details on AE collection and reporting, refer to Section 9.

### 10.1 PHYSICAL EXAMINATION, VITAL SIGNS, HEIGHT AND WEIGHT

A total body examination, vital signs, height and weight should be performed according to the visit schedule as outline in Table 7.1.

### 10.2 ECOG PERFORMANCE STATUS (PS)

The performance status will be assessed according to the ECOG performance status scale following the schedule in Table 7.1. See Appendix A.

### 10.3 LABORATORY ASSESSMENTS

Hematology, chemistry, coagulation, urinalysis, and cholesterol panels are to be performed according to the visit schedule outlined in Table 7.1 and 10.1.

**Table: 10.1: Clinical Laboratory Parameters Collection Plan**

| Test Category | Test Name |
|---|---|
| Hematology | Hemoglobin, Platelets, white blood cells with differential (neutrophils, lymphocytes, basophils, eosinophils, monocytes) |
| Chemistry | Albumin, alkaline phosphatase, ALT, AST, creatinine, potassium, sodium, glucose, direct bilirubin, |

| | |
|---|---|
| | total bilirubin, total protein, magnesium, phosphorus |
| Cholesterol and Lipid Panel | Total cholesterol, LDL, HDL, triglycerides |
| Coagulation | PT, INR |
| Urinalysis | Glucose, protein, bilirubin, red blood cells, white blood cells, crystals, and bacteria. |

## 11.0 CORRELATIVES STUDIES

Pathology Correlative Studies

A major obstacle to molecularly targeted chemotherapeutic agents has been obtaining relevant tumor tissue to measure the agents' biologic effects on target molecules or cellular pathways within the tumor. The utilization of sequential tumor biopsies to obtain tissue following treatment is well established in breast and colorectal carcinoma. (17) However, sequential tumor biopsies of liver tumors are less established due to a fear of procedural complications. The fear of bleeding events following liver biopsy of HCC appears unfounded and based on anecdotal evidence. A large, multi-institutional trial where patients with advanced chronic Hepatitis C underwent sequential liver biopsies demonstrated 16 cases (0.6%) of bleeding following 2740 liver biopsies. There were no deaths from peri-procedural bleeding and a platelet count under 60000 was identified as a risk factor. (18) Two large published series of core needle biopsy of HCC as a diagnostic measure report bleeding events in less than 1% of patients with no reported mortalities. In both series capsular location of HCC was associated with increased incidence of bleeding event. (19, 20) In this study all patients will potentially undergo up to two image-guided (either CT or Ultrasound) core needle biopsy of a single site of HCC at baseline (for clinical care) and between eight and nine weeks after the initiation of LEE011 (research only). The biopsy between eight and nine weeks following LEE011 initiation is not mandatory to initiate or continue with therapy and is subject to a separate informed consent. The baseline biopsy is needed to confirm HCC and RB positivity as an eligibility criterion. If archival formalin fixed paraffin embedded tissue is available for RB status analysis, a pre-treatment biopsy will not be required.To increase patient safety the following conditions must be met prior to liver biopsy:

- Platelet count ≥ 70,000
- INR ≤ 1.8
- Target lesion not subcapsular in nature as determined by the participating interventional radiology team
- LEE011 will be discontinued for a period of 24-48 hours prior to biopsy

There is no evidence that an image-guided liver biopsy following TACE increases risk of bleeding or tumor seeding. Due to the consideration that TACE is not considered a curative procedure and viable tumor tissue remains after an initial biopsy it is anticipated that enough tumor tissue will be available for the planned studies. (21)

The patient will sign the informed consent for participation in research liver biopsy prior to the procedure. The liver biopsy will be performed by radiologists and the ancillary staff of Department of Radiology following the standard clinical protocol, which includes obtaining a separate informed consent for the procedure itself. The core samples will be provided to the Department of Pathology for histological and RB status confirmation in addition to the pathology laboratory. If a core biopsy is performed as a part of the patient's clinical care, extra cores will be obtained for surgical oncology laboratory, in addition to the cores necessary for clinical care. All cores will be obtained through the same needle to avoid the need of additional punctures and to minimize associated risks.

Tumor tissue will be used for several specific purposes. Pre-treatment biopsies will be used to evaluate potential markers of durable response, in addition to staining for p16inkin4a and RB. This will include the analysis of phospho-RB, Cyclin D1, Cyclin E1, Cyclin E2, and p27Kip1 by immunohistochemistry. These proteins have been functionally associated with the response to CDK4/6 inhibitors. We will also assess baseline features of tumor proliferation by Ki67 and phospho-histone H3 staining and cleaved caspase 3 as a marker of tumor cell death. In parallel, if there is sufficient material we will employ RNA sequencing to delineate baseline features of tumor tissue. The molecular features of the tumor from RNA sequencing will be analyzed for association with PFS and other clinical features of disease to explore markers of response. We will use the post-treatment biopsies to determine the effect of LEE011 on tumor markers discussed above and by RNA sequencing. These studies will enable us to evaluate whether LEE011 is acting upon its targets in the tumor and to infer response markers with clinical outcome.

Plasma and serum samples (2 x 5 mL red tops and 2 x 6mL lavender tops) will also be collected at baseline and at the beginning of every cycle following initiation of LEE011. The blood samples will be used to measure circulating tumor DNA or other features of tumor burden that can be correlated with disease response. Storage and processing of the blood samples will be at the discretion of the pathology laboratory.

## 12.0 STATISTICAL CONSIDERATIONS

### 12.1 STUDY DESIGN/STUDY ENDPOINTS

The study is an open-label, non-randomized single-arm, single institution phase Ib/II therapeutic clinical trial. The study population will be patients with advanced hepatocellular carcinoma.

The phase Ib component of the study will consist of a traditional 3+3 dose escalation rule with 3 or 6 patients in each cohort, the process for dose escalation is outline in section 6.4.

The primary endpoint of the phase II component will be progression free survival (PFS) of

HCC patients. PFS is defined to be the time from initiation of treatment to progression or death without evidence of progression. For cases without documentation of progression, follow-up will be censored at the date of last disease assessment without progression, unless death occurs within 4 months following the date of last progression-free, in which case death will be counted as an event. The historical median PFS for TACE alone is 8-10 months. Our institutional median PFS following the TACE protocol outlined is 8.0 months. This study will target a hazard ratio of 0.69 with an 80% power and a one-sided significance level of 10%. Assuming a 24-month accrual and an 18-month follow-up period the study requires 38 patients initiating LEE011 treatment with the median PFS for TACE alone is 8 months, and 40 patients with the median PFS for TACE alone is 10 months. PFS will be estimated using the Kaplan-Meier method, and Greenwood's formula will be used to calculate the standard error of the corresponding Kaplan-Meier estimate and 95% confidence interval. Survival curves will be estimated using Kaplan-Meier methodology. Forty total patients will be enrolled in the phase II aspect of the trial. This includes only patients who undergo chemoembolization and initiate LEE011 therapy.

Secondary endpoints of efficacy are to evaluate OS. The statistical methods used for the analysis of PFS will be used for the analysis of OS.

Other secondary objectives will include description of toxicity of the therapy regimen. These data will be analyzed separately. The safety analyses will be performed on all patients who receive any dose of therapy. Adverse events will be described using the NCI CTCAE v 4.03 criteria (ctep.cancer.gov/forms.CTCAEv4.pdf). Frequency and severity of adverse events according to the NCI CTCAE v# body system and severity criteria will be described. In addition, frequency of Grade 3 or 4 adverse events will be described separately. Causality will also be noted. Adverse events will be recorded for up to 1 year following discontinuation from study. Response rate and toxicity rate will be estimated using an exact binomial method along with the 95% confidence interval.

Laboratory assessments will also be described according to the NCI CTCAE v. 4.03 criteria, with separate descriptions for Grade 3 or 4 laboratory abnormalities. Clinically significant laboratory abnormalities will be described as well. Serious adverse events will be summarized, including a causality assessment.
The number of treatment cycles and doses administered will be summarized using descriptive statistics. Treatment delays will be summarized using counts and percentages.

Patients' disposition will be summarized in the following manner:

- The number and percentage of patients selected, included, completed, withdrawn and lost to follow-up will be summarized using descriptive statistics;
- Major protocol deviations will be summarized;
- The reason for withdrawal (adverse events, lack of efficacy, major protocol deviation, non-medical reason, recovery or remission) will be summarized.

For pathology-, laboratory- and imaging-correlative studies, Cox regression analysis will be

conducted to investigate the association between PFS and parameters from correlative studies.

Approximately 175-200 patients with HCC are seen annually at UT Southwestern Medical Center with 80-90 chemoembolizations performed. We anticipate no potential problems meeting the accrual deadlines with the proposed trial. In addition, there are no competing trials either nationally or at UT Southwestern for this patient population that would potential limit accrual.

## 13.0 STUDY MANAGEMENT

### 13.1 CONFLICT OF INTEREST

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

### 13.2 INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL AND CONSENT

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

## 14.0 RECRUITMENT AND REGISTRATION PROCEDURES

### 14.1 RECRUITMENT PLAN

The study will be open to all patients seen at the UT Southwestern Medical Center (including Parkland Health & Hospital System, University Hospital-Clements and

Zale, and the Harold C. Simmons Cancer Center) who meet the eligibility criteria outlined in Section 5.0.

In addition, a description of the study and the enrollment criteria will placed on the UT Southwestern Medical Center website to maximize patient recruitment. Patients will be identified from surgical, hepatology, gastroenterology, radiology and medical oncology clinics for treatment of their disease. After a discussion of the patient's disease and a formulation of the initial treatment plan, the physician-investigator will describe the study to the patient. The protocol will be discussed in a private clinic room or office. Details including the risks and obligations of the subjects will be explained. For non-English speaking patients, an independent translator will be available to communicate the details of the protocol. A research coordinator will be available either in the clinic or by phone to answer any additional questions.

Upon completion of the informed consent form and confirmation of protocol eligibility, the Clinical Research Office (CRO) at the Harold C. Simmons Cancer Center will be notified of the new enrollment. All patients will be entered into the Velos Clinical Trials Management System for ongoing monitoring. All data collected will be entered into the password protected REDCap electronic data capture system.

The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation to access with regard to race or gender. Patients will be required to read, agree to and sign an IRB-approved informed consent form prior to registration on this trial. The registration procedure will be conducted as described above. Patients will not receive payment for their participation on this study.

### 14.2 STUDY SUBJECT IDENTIFICATION NUMBER

All subjects will be assigned a study number that is not linked to their personal identifiers to prevent loss of confidentiality. The number will be the Site Number, 01, 02, etc. followed by a sequential number starting with number 001. For example, the first subject enrolled from site # 01 will be assigned study subject number 01-001; the next will be 01-002, and so forth. For this protocol, current sites are: 01 – UTSW and 02 – PHHS. Any additional sites added to this protocol will be numbered sequentially…03, 04, etc. This number will be assigned by the UTSW - Clinical Research Manager or QA Coordinator or delegate upon confirmation of subject eligibility during the subject registration process.

### 14.3 SUBJECT REGISTRATION

Following completion of baseline assessments and confirmation of subject eligibility, patients will be assigned a subject identification number by the UTSW - CRM or delegate and registered into Velos, the UTSW Clinical Trial Management System (CTMS). Subject registration will be confirmed (within

24 hours) once the following documents have been received by the UTSW-CRM or delegate.

- Signed copy of the Informed Consent signature page;
- Inclusion/Exclusion worksheet signed by the coordinator and treating physician;

All subjects must be registered with the UTSW - CRM before enrollment to study. To register a subject, email the above supporting documents to the UTSW – QA Coordinatorsilvia.pilarski@utsouthwestern.edu or call 214-648-5919, Monday through Friday, 8:00a.m. - 4:00p.m. CST.

## 15.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Inclusion of Women and Minorities: Patients of all races, both male and female, will be accepted into the protocol.

Exclusion of Lactating or Pregnant Women: Children have been excluded from this study. Hepatocellular carcinoma is an adult cancer. Thus, the relevance of this drug to the pediatric population has not been established. Lactating and pregnant women are also excluded because of potential anti-proliferative effects of therapy that may be harmful to the developing fetus or nursing infant.

Benefits: It is possible that this treatment will result in shrinkage of hepatocellular carcinoma or in a stabilization of an otherwise progressing disease. It is not known, of course, whether these or any other favorable events will occur. It is not known whether this treatment will affect overall survival of the patients.

Costs: The patient will be responsible for the costs of standard medical care, including, all hospitalizations, even for complications of treatment. LEE011 will be supplied to patients without costs from Novartis Pharmaceuticals. Patients will not be responsible for the costs of tissue or serum procurement (including image guided biopsies) obtained for research purposes.

Incentives: No incentives will be offered to patients/subjects for participation in this study.

Alternatives: For patients with advanced hepatocellular carcinoma, alternative treatments may include other chemotherapy regimens or loco-regional therapies including transarterial chemoembolization and radiofrequency ablation. At present, no specific treatment approach is considered standard of care for the disease. Patients may be eligible for other investigational studies.

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

## 16.0 DATA AND SAFETY MONITORING PLAN

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT, which includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

Study PI or designated Co-investigator and the research coordinator will attend the weekly Phase I research meeting during the dose escalation phase. Toxicity and dose escalation reviews will be performed in real-time by the Phase I DOT and DSMC. As the study transitions to the Phase II stage, toxicity will be reviewed at the GI DOT research meetings and by DSMC. These reviews will be documented by distributing reports of the findings to the members of the GI DOT and investigators.

The UTSW Simmons Cancer Center (SCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and unanticipated problems in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles. Safety is monitored in real-time as serious adverse events and adverse events, which are unanticipated problems, are submitted to the DSMC and IRB with attributions.

## 17.0 ADHERENCE TO THE PROTOCOL

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

### 17.1 EMERGENCY MODIFICATIONS

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

### 17.2 OTHER PROTOCOL DEVIATIONS/VIOLATIONS

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

If {non-Research Office} managed study, please maintain the following language in your protocol:

**Protocol Deviations:** Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

**Protocol Violations:** Study personnel should report violations within two (2) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

## 17.3 AMENDMENTS TO THE PROTOCOL

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

## 17.4 RECORD RETENTION

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

## 17.5 OBLIGATIONS OF INVESTIGATORS

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the

Principal Investigator and will require his/her final signature to verify the accuracy of the data.

## 18.0 REFERENCES


1. Parkin DM, Bray F, Ferlay J, et al. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001; 94(2):153-6.

2. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009; 27(9):1485-91.

3. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999; 340(10):745-50.

4. Benson AB, D'Angelica MI, Abrams TA, et al. Hepatobiliary Cancers. NCCN Guidelines 2.2015.

5. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359(9319):1734-9.

6. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002; 35(5):1164-71.

7. Bruix J, Sherman M, American Association for the Study of Liver D: Management of hepatocellular carcinoma: an update. Hepatology 53:1020-2, 2011

8. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin eluting beads (DEBOX) for intermediate stage hepatocellular carcinoma: Phase II, randomized double-blind SPACE trial. J Clin Onc 2012; 30 (supple4;abstr LBA 154).

9. Kudo M, Han G, Finn RS, et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase III trial. Hepatology 2014;60:1697-1707.

10. Ortega S, Malumbres M, Baracid M. Cyclin D-dependent kinases, INK4 inhibitors and cancer. Biochimica et Biophysica Acta-Reviews on Cancer 2002;1602:73-87.

11. Asghar U, Witkiewicz AK, Turner NC, Knudsen ES. The history and future of targeting cyclin-dependent kinases in cancer therapy. Nat Rev Drug Discov. 2015 Feb;14(2):130-46.

12. Rivadeneira DB, Mayhew CN, Thangavel C, Sotillo E, Reed CA, Graña X, Knudsen ES. Proliferative suppression by CDK4/6 inhibition: complex function of the retinoblastoma pathway in liver tissue and hepatoma cells.Gastroenterology. 2010 May;138(5):1920-30.

13. Borg A, Zhang QX, Alm P, et al. The retinoblastoms gene in breast cancer: allele loss is not correlated with loss of gene protein expression Cancer Res1992;52:2991-4.

14. Kim YB, Park YN, Park C. Increased proliferation activities of vascular endothelial cells and tumor cells in residual hepatocellular carcinoma following transcatheter arterial embolization. Histopathology 200;38:160-166.

15. Farris AB 3rd, Dursun N, Dhanasekaran R, et al. Tumoral and angiogenesis factors in hepatocellular carcinoma after locoregional therapy. Pathol Res Pract 2012 208: 15-21.

16. Littman SJ, Brus C, Burkhart A. A phase II study of PD-0332991 in adults patients with advanced hepatocellular carcinoma. J Clin Onc 2015 (suppl 3, abstract 277).

17. Dowlati A, Haaga J, Remick SC, et al. Sequential tumor biopsies in early phase clinical trial of anticancer agents for pharmacodynamic evaluation. Cancer Res 2001;7(10);2971-6.

18. Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Am J Gastro doi:10.1016lj.cgh.2010.03.025.

19. Giorgio A, Tarantino L, de Stefano, et al. Complications after interventional sonography of focal liver lesions: a 22-year single-center experience. J Ultrasound Med 2003;22:193-205.

20. Caturelli E, Solmi L, Anti M, et al. Ultrasound guided fine needle biopsy of early hepatocellular carcinoma complicating liver cirrhosis: a multicentre study. Gut 2004;53:1356-62.

## 19.0 APPENDICES

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or LEE011.

The following lists are not comprehensive and are only meant to be used as a guide. The lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: 29 Oct 2012), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction Table (http://medicine.iupui.edu/clinpharm/ddis/main-table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (http://www.druginteractioninfo.org/). For current lists of medications that may cause QT prolongation and/or torsades de pointes (TdP), refer to the CredibleMeds® website (https://crediblemeds.org/). Please contact the medical monitor with any questions.

Appendix Table 1: List of medications to be used with caution during study drug treatment

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

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

[2] Source: www.crediblemeds.org

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

Appendix Table 2: List of prohibited medications during study drug treatment

| Category | Drug Name |
|---|---|
| Strong CYP3A4/5 inhibitors | Boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, voriconazole |
| Strong CYP3A4/5 inducers | Avasimibe[2,3], carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[3] |
| CYP3A4/5 substrates with NTI[1] | Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine |
| Medications with a known risk for QT prolongation[4] | Amiodarone, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, flecainide, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, moxifloxacin, pentamidine, pimozide, probucol, procainamide, quinidine, sotalol, sparfloxacin, terfenadine, thioridazine, vavdetanib |
| Herbal preparations/ medications | Herbal preparations/medications are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, 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.crediblemeds.org

**Appendix A: ECOG Performance Status**

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

**Appendix B: Child-Pugh Score**

| Measure | 1 point | 2 points | 3 points |
|---|---|---|---|
| Total bilirubin (mg/dl) | <2.0 | 2.0-3.0 | >3.0 |
| Serum albumin (g/l) | >3.5 | 2.8-3.5 | <3.5 |
| INR | <1.7 | 1.7-2.2 | >2.2 |
| Ascites | None | Mild (based on clinical findings) | Severe (based on clinical findings) |
| Hepatic Encephalopathy | None | Controlled Medically | Refractory |

5-6 points Child-Pugh A
7-9 points Child-Pugh B
10-15 points Child-Pugh C

**Appendix C: NYHA Classification**

| Class | Patient Symptoms |
|---|---|
| I | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath). |
| II | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea. |
| III | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. |
| IV | Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased |