Lombardi
COMPREHENSIVE
CANCER CENTER

A Phase I/II Study of LEE011 plus Everolimus in Patients with Metastatic Pancreatic Adenocarcinoma Refractory to Chemotherapy

Georgetown Protocol #:	2016-0232
Clinicaltrials.gov #:	NCT02985125
Initial Concept Approval Date:	Version 1.0, July 15, 2015
Initial Protocol Version Date:	Version 1.0, October 15, 2015
Amended:	Version 2.1, June 10, 2016 Version 2.2, July 17, 2017 Version 2.3, July 16, 2018

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Funding Sources:

1) Novartis, Inc
2) Conquer Cancer Foundation (Young Investigator Award)

Summary of Changes

The full protocol was first approved by the Georgetown Scientific Review Committee (CRC) on 02/17/2016, and by the IRB on 08/03/2016. Version 2.2 07/17/2017 was the first major update since IRB approval, and the changes made are summarized below. Version 2.3 06/22/2018 is the second update in order to update protocol safety changes for LEE011 (ribociclib). (Please note, minor formatting, spelling and grammatical corrections, and pagination updates are not detailed below).

Version 2.3, 07/XX/2018

1) This protocol will be open at other sites. As a result, the full list of sub-investigators has been removed, as it would be overly cumbersome.
    a. In addition, language in the protocol has been re-added throughout the protocol regarding oversight of the trial at other sites
2) Dose adjustments for QTc prolongation have been added.
3) Additional drugs have been added to the list of prohibited drugs and drugs to be used with caution.
4) INR inclusion criteria was changed to ≤ 1.5 from < 1.5.
5) Tumor biopsies are mandatory UNLESS the patient has been evaluated for a biopsy in consultation with radiology in good faith, and there is a determination that an attempt at a biopsy would cause undue risk to the patient.
6) Corticosteroids should not be given during the study except for topical applications, inhaled sprays, eye drops, or local injections. A short duration (< 5 days) of systemic corticosteroids less than or equal to the potency of 4 mg dexamethasone daily is allowed (e.g. for chronic obstructive pulmonary disease, or an anti-emetic).
7) Address of Dr. Knudsen (moved to Roswell Park Comprehensive Cancer Center) has been updated.
8) The patient Drug Diary (Appendix A) was modified to clarify timing of each oral agent separately, and to clarify that the LEE-011 should only be taken 21 out of 28 days
9) The pregnancy language in the Protocol and the Informed Consent Form has been clarified:
    a. In the protocol, the details of eligible patients, with regards to avoidance of pregnancy have been clarified (Section 3.2)
    b. The time frame for avoiding pregnancy after coming off of the study medications needs to only be 21 days, per Novartis standards
    c. The section on avoidance of pregnancy has been enhanced and clarified for patients

Version 2.2, 07/17/2017

1) The study was originally designed as a multi-institutional trial. However, we were unable to obtain support for a multi-institutional study, and thus, this will be a single institutional trial, at Georgetown only.
    a. Correspondingly, all external coinvestigators have been removed
    b. The list of internal (Georgetown) sub-investigators has been updated
    c. Dr. Erik Knudsen is a key scientific collaborator, and thus is now listed as a study Co-chair
    d. Because this is a single-site study, the sections on “Trial Coordination” have been removed entirely
    e. We have also updated the accrual timeline to allow for enrollment over 24-29 months
2) The collection of samples for correlative studies has been updated and clarified:
    a. Section 4.4.5 includes a clarification on collection of blood samples for ctDNA
    b. Section 8.1.1 includes a clarification that 2 cores will be collected for FFPE, and 2

cores will be frozen in tubes in liquid nitrogen. A lab manual has been updated (Version 2.5 05/12/2017) to reflect this as well

3) The first patient enrolled experienced Grade 3 anemia during Cycle 1, which brought to light the fact that there was a lack of clarification of the timing of treatment holds and dose modifications in Section 6. Thus, clarification was added to Section 6.7.1.2 regarding treatment holds and dose modifications for myelosuppression.
4) The second patient enrolled in the trial had to go off study due to a Grade 3 allergic reaction to one or both of the study medications, manifest as a diffuse rash. In discussion with Novartis, the rash is not typical of the rash that can be observed with everolimus, and a rash with LEE011 is very rare. Furthermore, in the Phase I trial of everolimus and LEE011, there was no indication of an increased risk of a rash. Thus, it has been our determination that this patient had a true "allergic" reaction, that was not dose dependent. Therefore, the section on the definition of a DLT was modified to add a Grade 3 or 4 allergic reaction as ***an exception*** to a DLT.
    a. In compliance with the protocol version when the patient was enrolled, the rash was determined to be a DLT, and the cohort was expanded to six patients.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

4E-BP1	Eukaryotic initiation factor 4E-binding protein 1
5-FU	5-fluorouracil
ACE	Angiotensin-converting enzyme
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
β-hCG	β-human chorionic gonadotropin
BCS	Biopharmaceutics Classification System
BrdU	Bromodeoxyuridine
BUN	Blood urea nitrogen
CBC	Complete blood count
CDK	Cyclin-dependent kinase
CDKN2A	Cyclin-dependent kinase inhibitor 2A (gene)
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DSMB	Data and safety monitoring review board
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
FOLFIRINOX	5-fluorouracil, irinotecan, oxaliplatin
GEM	Gemcitabine
GGT	Gamma-glutamyl transpeptidase
HIF-1	Hypoxia-inducible factor 1
HIV	Human immunodeficiency virus
HR	Hazard ratio
IHC	Immunohistochemistry
IND	Investigational new drug
INR	International normalized ratio
IV	Intravenously
LCCC	Lombardi Comprehensive Cancer Center
LD	Longest diameter
LFT	Liver profile
LLN	Lower limit of normal
MCL	Mantle cell lymphoma
MEF	Mouse embryonic fibroblast
MRI	Magnetic resonance imaging
mOS	Median overall survival
mPAC	Metastatic pancreatic adenocarcinoma
mPFS	Median progression-free survival
mTOR	Mammalian target of rapamycin
mTORC1	Mammalian target of rapamycin complex 1

NGS	Next-generation Sequencing
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progression of disease
PFS	Progression-free survival
$PFS_{8\ weeks}$	Progression-free survival rate at 8 weeks
PgP	P-glycoprotein
PI	Principal investigator
PK	Pharmacokinetics
PO	By mouth
PR	Partial response
PS	Performance Status
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	Once daily
RB	Retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase II Dose
RR	Response rate
S6K1	S6 ribosomal protein kinase
SAE	Significant adverse event
SD	Stable disease
SRS	Stereotactic radiosurgery
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor

STUDY SYNOPSIS

Title	A Phase I/II Study of LEE011 Plus Everolimus in Patients with Metastatic Pancreatic Adenocarcinoma Refractory to Chemotherapy
Short Title	LEE011 plus Everolimus in Refractory Pancreatic Cancer
Protocol Number	2016-0232
Clinicaltrials.gov number:	NCT02985125
Phase	Phase I/II
Investigational Agents	1) LEE011 (ribociclib), an oral CDK4/6 inhibitor (Novartis) 2) Everolimus (Afinitor®), an oral mTOR inhibitor (Novartis)
Indication	Metastatic pancreatic adenocarcinoma (mPAC) refractory to gemcitabine (GEM)- and 5-fluorouracil (5-FU)-based chemotherapy
Concept and Scientific Rationale	Pancreatic adenocarcinoma has an overall poor prognosis, with an estimated five-year survival rate around 7.2%[(1)]. Approximately 53% of patients have metastatic disease at diagnosis, and their prognosis is even more dismal with an estimated five-year survival rate around 2.3%[(1)]. In the past, single-agent gemcitabine (GEM) was the preferred treatment option for advanced pancreatic cancer as it was shown to have a survival benefit compared to single-agent 5-FU, although the median progression-free survival (mPFS) was only 2.3 months compared to 0.9 months (P=0.0002)[(2)]. The two largest first-line trials in metastatic pancreatic adenocarcinoma (mPAC) that demonstrated a survival benefit over single-agent GEM used FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and 5-FU)[(3)] and GEM plus *nab*-paclitaxel[(4)]. Conroy *et al*. showed an improved disease control rate (DCR, the proportion of patients with a complete response (CR), partial response (PR), or stable disease (SD)) of 70.2% and mPFS of 6.4 months using FOLFIRINOX compared to 50.9% and 3.3 months using GEM (both P<0.001)[(3)]. Using *nab*-paclitaxel plus GEM, Von Hoff *et al*. also demonstrated an improved DCR (48% versus 33%, P<0.001) and mPFS, 5.5 versus 3.7 months (P<0.001), when compared to single-agent GEM[(4)]. Recently, we have seen patients who have had progression of disease on both lines of therapy and retain an adequate performance status for further treatment. Previous studies of third-line therapy in mPAC are limited but reveal stable disease in 25-31% of patients with no partial or complete responses (31% of patients in the GVAX/CRS-207 combination vaccine study had stable disease but only 52% of these patients were treated in the third-line setting)[(5, 6)]. Therefore, novel therapeutic options are needed both for pancreatic cancer in general as well as for this subset of patients with refractory mPAC. We propose a therapeutic approach using agents that directly target the signaling pathways responsible for tumorigenesis. LEE011 (ribociclib, Novartis) is an oral small-molecule inhibitor of cyclin-dependent kinase 4 (CDK4) and cyclin-dependent kinase 6 (CDK6). CDK4/6 acts by phosphorylating and inactivating the retinoblastoma protein (RB), allowing E2F family transcription factors to accelerate cell cycle progression from G1 to S phase[(7)]. Pancreatic cancer is frequently associated with an alteration in the *CDKN2A* gene resulting in the loss of the p16INK4a protein that naturally inhibits CDK4/6[(8)]. LEE011 as a single agent has not

	shown significant activity, likely due to aberrant induction of Cyclin D and E1[9]. The addition of an inhibitor of the mammalian target of rapamycin (mTOR) blocked this pathway and halted tumor cell proliferation when studied in pancreatic cancer cells xenograft models[9, 10]. The combination of everolimus (Afinitor®, Novartis), an mTOR inhibitor, with LEE011 is currently under evaluation in a Phase Ib/II clinical trial of LEE011, everolimus, and exemestane in patients with locally advanced or metastatic hormone-receptor positive, HER2-negative breast cancer (CLEE011X2106). We aim to study the combination of LEE011 and everolimus as third-line therapy in patients with mPAC refractory to 5-FU- and GEM-based chemotherapy. Hypothesis: We hypothesize that the combination of LEE-011 and everolimus will improve the progression-free survival rate at 8 weeks from a historical baseline of 25% to a hypothesized rate of 50%.
Study Duration	24 – 29 months
Objectives	Primary Objective of the Phase I Portion: To determine the Recommended Phase II dose (RP2D) of LEE011 in the combination with everolimus in patients with mPAC refractory to 5-FU- and GEM-based chemotherapy Primary Objective of the Phase II Portion: To determine the progression-free survival (PFS) rate at 8 weeks (PFS_{8weeks}) to assess the clinical efficacy of the combination of LEE011 and everolimus in patients with mPAC refractory to 5-FU- and GEM-based chemotherapy Secondary Objectives: To determine, in patients with refractory mPAC treat with LEE011 and everolimus: ▪ Median progression-free survival (mPFS) ▪ Median overall survival (mOS) ▪ Best overall response rate (ORR) ▪ Change in serum tumor markers (CA 19-9 or CEA) ▪ Safety and tolerability Exploratory Objectives: 1) To correlate the $PFS_{8\ weeks}$ to correlative scientific markers, including the analysis of tumor biopsies and blood-based markers, including RB, pRB, p16, cyclin D1, Ki67, MCM7, and pS6 levels by immunohistochemistry 2) To screen for use a targeted sequencing approach for genetic lesions observed in pancreatic cancer that includes KRAS, SMAD4, TP53, CDKN2A as well as other commonly mutated cancer genes. 3) To assess blood for the analysis of circulating tumor DNA as a surrogate marker of disease burden. KRAS and other mutations will be used as the determinants of tumor selective DNA
Number of Subjects	A minimum of 12 and a maximum of 44 evaluable patients
Diagnosis and Main Inclusion and Exclusion Criteria	Key Inclusion Criteria 1) Histologically confirmed metastatic adenocarcinoma of the pancreas with measurable disease per RECIST 1.1 2) Patient must consent to two mandatory biopsies and have tumor amenable to biopsy

	- Tumor biopsies are mandatory UNLESS the patient has been evaluated for a biopsy in consultation with radiology in good faith, and there is a determination that an attempt at a biopsy would cause undue risk to the patient. 3) Documented progression of disease on at least one 5-FU-based regimen and at least one GEM-based regimen for metastatic disease (progression during or within 3 months of the completion of adjuvant therapy is acceptable) 4) Age ≥ 18 years 5) ECOG performance status 0 or 1 6) Signed informed consent form 7) Adequate hepatic, bone marrow, and renal function as defined below in the body of the protocol <u>Key Exclusion Criteria</u> 1) Patients previously exposed to, intolerant of, or ineligible for CDK inhibitors, mTOR inhibitors, and/or their combination 2) Prior anti-tumor therapy within 3 weeks of Cycle 1 Day 1 (anti-tumor therapy defined as, but is not limited to, anti-cancer agents (cytotoxic chemotherapy, immunotherapy, and biologic therapy), radiotherapy, and investigational agents), the "wash-out period" 3) Patients with known CNS metastases (that do not meet inclusion criteria, detailed below) 4) Active severe infection, or known chronic infection with HIV or hepatitis B virus 5) Cardiovascular disease problems including unstable angina, therapy for life-threatening ventricular arrhythmia, or myocardial infarction, stroke within the last 6 months, or a diagnosis of congestive heart failure 6) Patient has a concurrent malignancy or malignancy within 3 years prior to starting study drug, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer. 7) Women who are pregnant or breastfeeding 8) Patient is currently receiving or has received systemic corticosteroids ≤2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.
Study Design	This study is a multi-institutional single-arm, open-label, Phase I/II trial of the combination of LEE011 and everolimus in refractory mPAC. <u>Phase I Portion</u> The Phase I portion of the study will be used to determine the R2PD for LEE011 for the Phase II portion of the study. Patients will be evaluated every 2 weeks for the first 8 weeks and then every 4 weeks thereafter. The dose of everolimus will remain constant at 2.5 mg by mouth daily every day, and LEE011 will be given daily days 1-21 out of a 28 day cycle with the dose determined by the patient cohort. A standard

3+3 design will be employed in which patients are enrolled in cohorts of 3 patients each (see figure 1):

- 3 patients are enrolled at dose level 1.
  - If 0 patients experience a DLT, 3 patients are enrolled at dose level 2.
  - If 1 patient experiences a DLT, 3 additional patients are enrolled at dose level 1. If 1 of 6 patients at dose level 1 experiences a DLT, 3 patients are enrolled at dose level 2.
  - If ≥ 2 patients experience a DLT, 3 patients are enrolled at dose level -1.
- If 0-1 of 3 patients at dose level 2 experience a DLT, then 3 additional patients are enrolled at dose level 2.
  - If 0-1 of 6 patients at dose level 2 experience a DLT, dose level 2 is the RP2D.
- If ≥ 2 of 3 patients at dose level 2 experience a DLT, 3 additional patients may be enrolled (to achieve 6 patients total) at dose level 1.
  - If 0-1 of 6 patients at dose level 1 experience a DLT, dose level 1 is the RP2D.
  - If ≥ 2 of 6 patients at dose level 1 experience a DLT, 3 patients are enrolled at dose level -1.
- If 0-1 of 3 patients at dose level -1 experience a DLT, 3 additional patients are enrolled at dose level -1.
  - If 0-1 of 6 patients at dose level -1 experience a DLT, dose level -1 is the RP2D .
  - If ≥ 2 of 3 or 6 patients at dose level -1 experience a DLT, 3 patients are enrolled at dose level -2.
- If 0-1 of 3 patients at dose level -2 experience a DLT, 3 additional patients are enrolled at dose level -2.
  - If 0-1 of 6 patients at dose level -2 experience a DLT, dose level -2 is the RP2D.
  - If ≥ 2 of 3 or 6 patients at dose level -2 experience a DLT, the study is terminated.

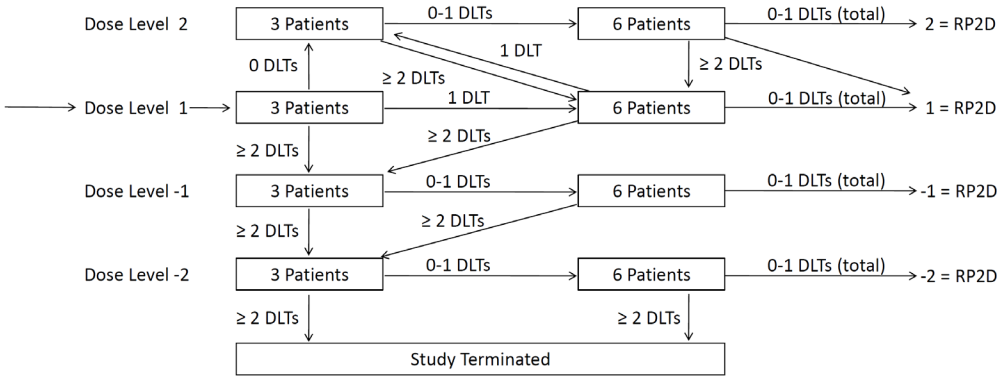
There will be no intra-patient dose escalation or de-escalation.

Patients enrolled in the Phase I portion of the trial who have received the recommended Phase II dose of LEE011 will be counted towards the Phase II efficacy analysis.

Table 1. Dose Escalation Schema

Dose Level	LEE011 (PO Days 1-21 out of a 28 Day Cycle)
2	300 mg
1	250 mg
-1	200 mg
-2	150 mg

Figure 1. Phase I Schema



Phase II Portion

Stage 1 – Initial Stage

The first stage of the Phase II portion of the study will be performed to establish a minimum level of clinical efficacy to warrant the enrollment of more patients in the second stage of the study. Using a Simon's Minimax two-stage design, 11 patients will be enrolled and will undergo baseline imaging and a pre-treatment biopsy. The patients will then be started on treatment with LEE011 at the RP2D by mouth daily for the first 21 days out of a 28 day cycle in combination with everolimus 2.5 mg by mouth daily continuously.

- LEE011 at the RP2D by mouth once daily Days 1-21
- Everolimus 2.5 mg by mouth once daily Days 1-28 (continuously)

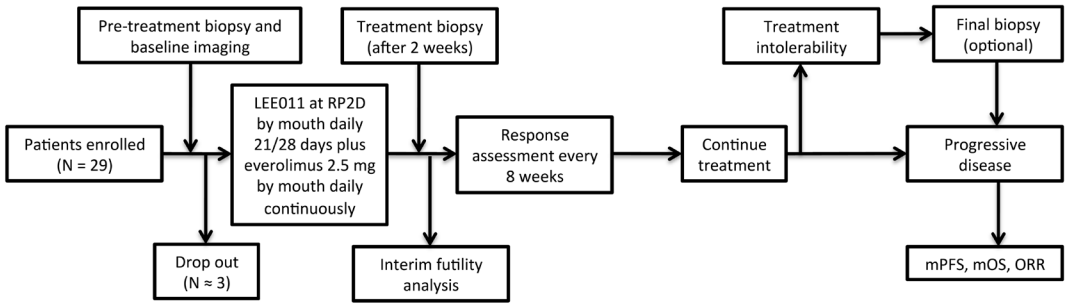
Patients will be evaluated, including laboratory testing at screening, on Cycle 1 Day 1, and every 2 weeks until the first response assessment at 8 weeks, then every 4 weeks thereafter. Response assessment will occur every 8 weeks regardless of treatment cycle. If at the first response assessment there is no evidence of progression of disease (PD), as determined by RECIST v1.1 criteria, and the patient is tolerating therapy, then the patient may be seen only every 4 weeks, unless clinically indicated. Patients will continue to remain on study as long as there is no evidence of PD (according to RECIST v1.1 criteria) and the therapy is adequately tolerated.

Patients will have a tumor biopsy prior to treatment, a second biopsy at 2 weeks on treatment, and an optional final biopsy at the time of progression of disease (PD).

3.6.1.2 Stage 2 – Final Stage

After all 11 patients from the initial stage have undergone their 8 week response assessment, an interim analysis will be conducted to determine how many had a PR, CR, SD, or PD. The study will be stopped prematurely if 2 or fewer patients obtain a PR, CR, or SD at 8 weeks. If 3 or more patients obtain a PR, CR, or SD at 8 weeks, then 15 additional patients will be enrolled on the study for a total of 26 patients. Assuming a dropout rate of 10% in this refractory patient population, up to 3 additional patients may replace patients whose come off study prior to being evaluable for the primary endpoint (for reasons other than disease progression). Thus, up to 29 patients may be screened for the Phase II portion of this study.

Figure 2: Phase II Schema



Multi-Institutional Trial Coordination

Personnel

At each site, personnel dedicated to this protocol will be:

- A site PI
- A research coordinator/data manager

In addition, at Lombardi-Georgetown, there will be a dedicated "multi-institutional" research coordinator who will play the primary role in coordinating the trial between Lombardi-Georgetown and additional sites. This coordinator will be the main point of contact for Dr. Pishvaian and the other site PIs for any study related concerns, and to screen each patient being considered for enrollment (Including "remote" screening for the patients being screened at other sites). This coordinator will also be the point of contact for the data managers for data entry questions. Finally, this coordinator will play a major role in regulatory coordination of the study, specifically by: 1) reviewing and confirming all study-related adverse events; 2) submitting all SAE reports to the Georgetown IRB; and (the research coordinators at the other sites will prepare SAE reports for patients treated at their respective sites, but the "multi-institutional" coordinator will submit the final report); 3) gathering and preparing all primary source data for review/audit.

Patient Enrollment

Enrollment at the sites will be competitive. If a patient is being screened for enrollment, the local research coordinator must send a secure/encrypted email within 24 hours containing the patient's name, to the local PI, to Dr. Pishvaian, and to the multi-institutional coordinator. If a patient is successfully screened, the local research coordinator must send all supporting documentation to the multi-institutional research coordinator (by email or fax). Patients should not start therapy until both Dr. Pishvaian and the multi-institutional coordinator have reviewed the patient's records and confirmed that the patient is indeed eligible for enrollment.

Data Collection and Management

Patient data will be entered into the online accessible database. This database is housed at Lombardi-Georgetown, but is accessible anywhere there is Internet access. The data manager and research coordinator at each site will attend an online training session so that they may learn how to enroll data into the database. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within one week of each patient visit.

Conference Calls

A monthly conference call will be held between Lombardi-Georgetown and the other sites meeting will be held to review patient enrollment, toxicity, and response assessment.

	Trial Auditing The multi-institutional coordinator will arrange all primary source documents for the patients to be audited. This will include collecting copies of the primary source data for any patients treated at other sites.
Statistical Design, Feasibility, and Trial Duration	This is a multi-institutional single arm, open label Phase I/II study to evaluate the PFS_{8weeks} of the combination of LEE-011 plus everolimus, in patients with metastatic pancreatic cancer refractory to 5-fluorouracil (5-FU) and gemcitabine-based chemotherapy. Previous studies of third-line therapy in mPAC are limited but reveal stable disease in 25-31% of patients with no partial or complete responses (31% of patients in the GVAX/CRS-207 combination vaccine study had stable disease but only 52% of these patients were treated in the third-line setting)[5, 6]. It is hoped that the combination of LEE-011 plus everolimus can increase the PFS_{8weeks} to at least 50%, though early stopping rules are in place for lack of efficacy. All patients meeting the eligibility criteria and who have signed a consent form, have begun treatment, are not lost to follow-up, and are not taken off study for reasons other than progression or death before 8 weeks will be considered evaluable for the assessment of the DCR. Between 12 and 24 patients will be enrolled in the Phase I portion of the study, depending on whether DLTs occur and dose de-escalation is required. The 6 patients treated at the RP2D will be included in the Phase II portion of the study. We anticipate the combination will be well tolerated such that all of the patients in the Phase I portion are likely to be evaluable for the Phase II efficacy analysis. 26 evaluable patients will be enrolled in the Phase II portion of the study (though the potential drop-out rate is 10%), which will provide a 90% power to detect an improvement in the DCR from 25% (based on historical control) to 50%, assuming a 1-sided significance level of 0.1 and an accrual rate of 2 patients per month. A Simon's optimal two-stage design will be used to test the null hypothesis that the DCR P<=0.25 versus the alternative that P>=0.5. For the first stage, 11 patients will be entered to the study. The trial will be terminated if 2 or fewer patients achieve a PR, CR, or SD at 8 weeks. If at least 3 patients in the first stage achieve a PR, CR, or SD at 8 weeks, the trial goes on to the second stage. A total of 26 patients will be enrolled. If the total number of patients who achieve a PR, CR, or SD at 8 weeks is less than or equal to 9, the combination therapy will be rejected. If however, 10 or more patients achieve a PR, CR, or SD at 8 weeks the combination therapy will be considered for further analysis. With 26 evaluable patients in the Phase II portion, combined with a minimum of 12 to a maximum of 18 patients enrolled strictly in the Phase I portion of the trial, there will be up to 44 patients enrolled. At an expected accrual rate of 3 patients per month, the expected accrual duration will be approximately 15 months. Descriptive statistics will be used to summarize patients' demographics, toxicity, and quality of life. The PFS_{8weeks} will be estimated from the observed data with 95% exact binomial confidence interval. The nonparametric Kaplan-Meier method will be used to estimate the survival function and calculate the PFS and OS. The ORR will be estimated from the observed data with 95% exact binomial confidence intervals.

1.0 BACKGROUND AND JUSTIFICATION

1.1 Cyclin Dependent Kinases

[redacted]

1.2 Cell Cycle Inhibition in Pancreatic Caner

The activity of CDK4/6 is frequently deregulated in pancreatic cancer due to the loss of *CDKN2A* via either homozygous deletion or epigenetic silencing. The signature driver of pancreatic cancer (KRAS) drives cells into senescence through activation of CDKN2A. Thus, there is a potent hypothetical rationale for pharmaceutically mimicking the function of CDKN2A based on a plethora of published data. Most recently, in the sequencing of over 109 cases, we discovered amplification of CCND1 and CDK4 also occurs in pancreatic adenocarcinoma (Figure 2), while the loss of RB is rare[8]. Therefore from a genetic perspective one would anticipate that pancreatic cancers could respond efficiently to CDK4/6 inhibition.

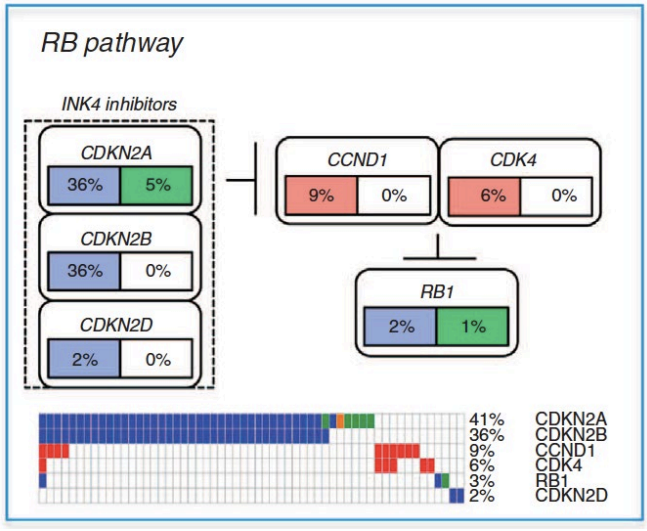


Figure 3. The RB-pathway in Pancreatic Cancer. 109 dissected pancreatic cancers were subjected to whole exome sequencing. Frequent loss of *CDKN2A/2B* was observed, and amplification of *CCND1* and *CDK4* was found in select cases. *RB1* loss that compromises the action of CDK4/6 inhibitors was observed in ~3% of cases. (Blue boxes denote homozygous deletion, green boxes denote mutation, and red boxes denote amplification). Data and figure from Witkiewicz, et al.[8]

In patient-derived patient derived xenografts we found that CDK4/6 inhibition was highly effective at limiting tumor growth, and had a profound impact on proliferative index (Figures 3 and 4). This finding was also recapitulated in the analysis of primary tumor explants (Figures 5 and 6). Both of these patient-derived models recapitulate the histology and tumor microenvironment of pancreatic cancer. Interestingly, we did identify a single case (out of 15 tested) that failed to response to CDK4/6 inhibition. We could show that the basis for the lack of response is loss of RB; therefore select biomarkers can be deployed to define rare tumors which fail to respond (Figure 6). Overall, these data suggest that the vast majority of primary pancreatic cancers would have the capacity to response to CDK4/6 inhibition.

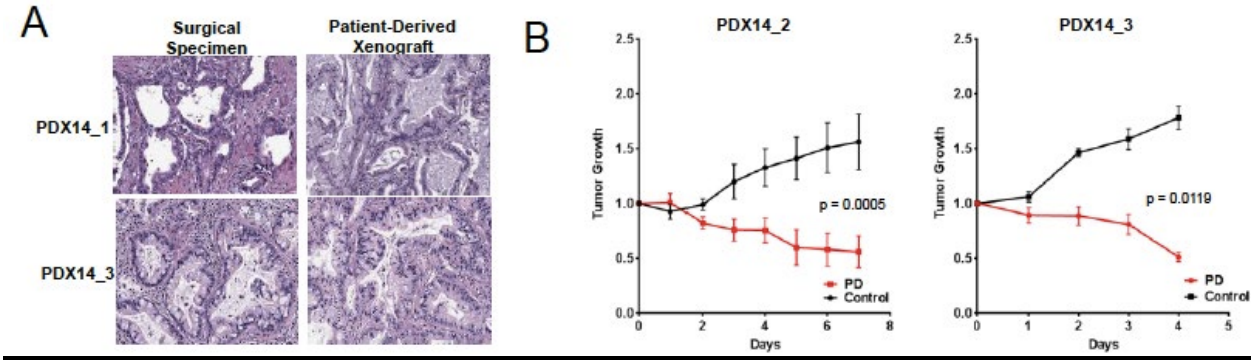


Figure 4. Potent Impact of CDK4/6 Inhibition in Patient-derived Xenografts: (A) Three patient derived xenograft models were employed that maintained the tissue architecture consistent with the primary tumor. **(B)** Xenograft models were treated with CDK4/6 inhibitor by oral gavage daily. Tumor volume was determined by daily measuring and lead to a substantial impact on tumor size.

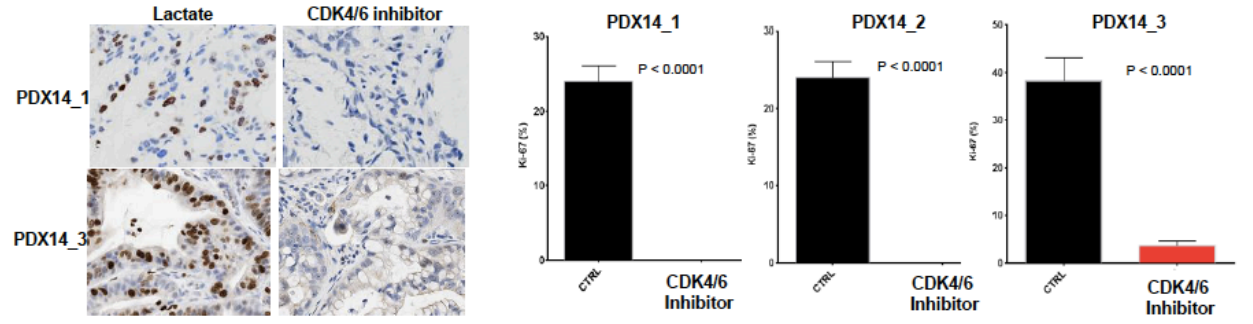


Figure 5. Potent Impact of CDK4/6 Inhibition in Patient-derived Xenografts: Xenograft models were treated with CDK4/6 inhibitor by oral gavage daily. At sacrifice tissue were stained with Ki67. Data show significant cytostatic activity across the models employed.

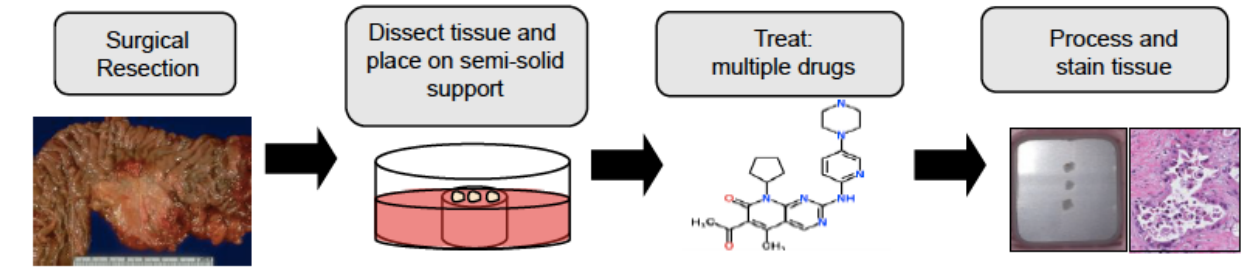


Figure 6. Schematic of the Explant Approach: Surgical tissue is cultured *ex vivo* and treated with specific drugs. Samples are processed and stained for specific markers. In this fashion the model recapitulates serial biopsying of primary tumor during treatment.

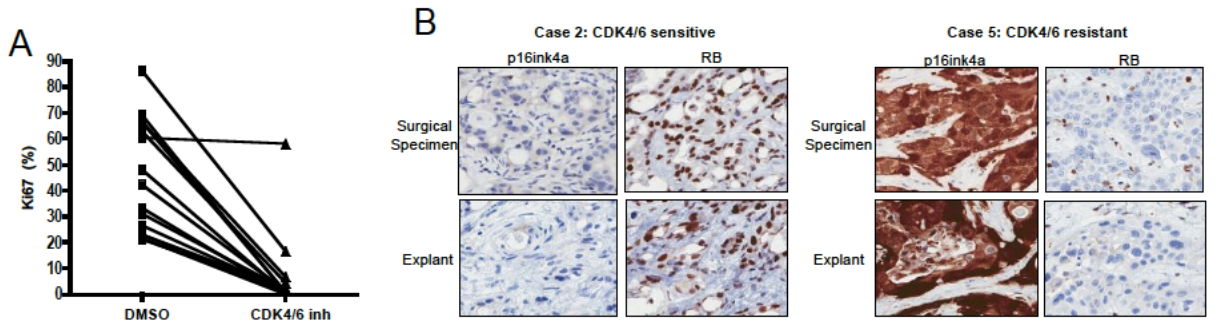


Figure 7. Response of 15 cases to CDK4/6 Inhibition: (A) Surgical tissues from 15 different patients were exposed *ex vivo* to CDK4/6 inhibition and impact on Ki67 was determined. >95% of cases could respond. **(B)** Staining for RB and p16ink4a demonstrated that the vast majority of cases have low p16ink4a levels and robust nuclear RB staining. The one case that failed to respond had very high p16ink4a and loss of nuclear RB in the tumor compartment.

In the context of this clinical trial the disease will be advanced and perhaps more indicative of aggressive models of disease. In evaluation of such models, our group and others found that while some models respond very effectively, others can develop resistance to CDK4/6 inhibition in spite of loss of *CDKN2A* (Figure 7). We explored the mechanism and found that there is deregulation of parallel pathways that facilitate the bypass which involves signaling to other CDK/Cyclins and involves the mTOR pathway[9, 10]. In drug screening, our group and others found that mTOR inhibitors were particularly potent cooperative agents with CDK4/6 inhibitors across all models[9, 10] and served to broaden the efficacy of CDK4/6 inhibition into resistant models (Figure 8).

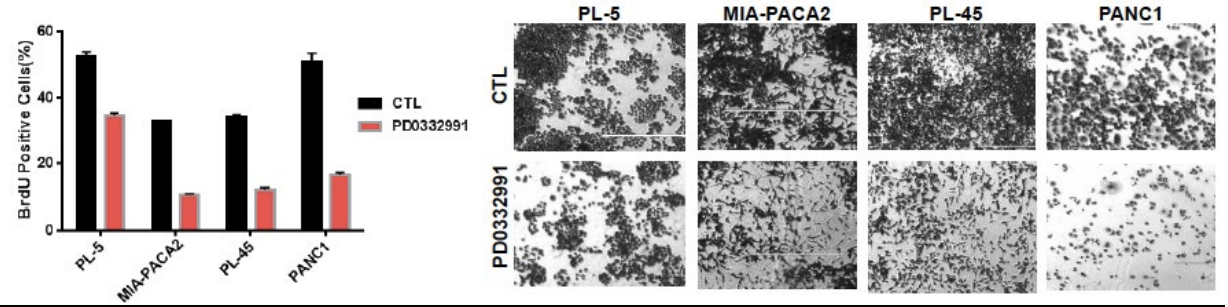


Figure 8. Established Pancreatic Lines have Limited Response to CDK4/6 Inhibition: Bromodeoxyuridine (BrdU) incorporation was determined in the presence of CDK4/6 inhibition, demonstrating substantial residual cell cycle progression. These cells were further able to proliferate in spite of treatment as determined by crystal violet staining.

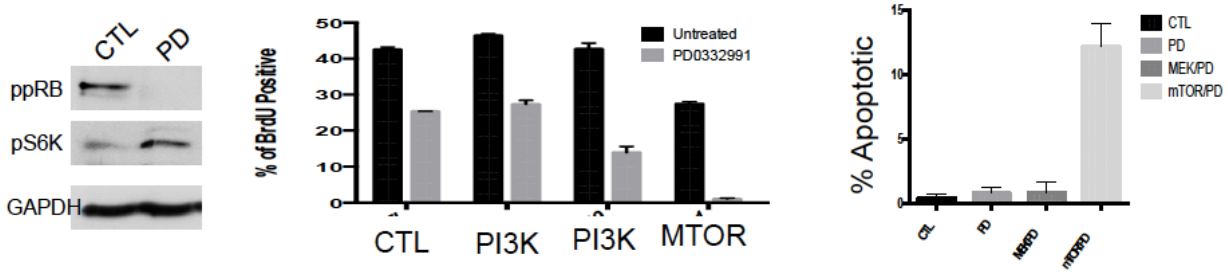


Figure 9. MTOR Inhibitors are Synergistic with CDK4/6 Inhibition in Pancreatic Cancer Models.

Treatment with CDK4/6 inhibitors can lead to an accumulation or maintenance of mTOR activity as measured by phosphorylated S6 kinase. While phosphatidylinositol 3-kinase (PI3K) inhibitors have modest effects, mTOR inhibitors are synergistic for the suppression of proliferation and lead to active cell killing. In contrast, MEK inhibitors suppress proliferation but do not induce apoptosis in these models. Identical results were observed by independent groups using different cell lines and xenograft models[9, 10].

Together the genetic rationale, the findings in patient-derived models, and aggressive established models of metastatic disease suggest that CDK4/6 inhibitors in combination with mTOR inhibitors can have a highly significant impact on a broad range of pancreatic cancers. The use of combination approaches is particularly important since resistance to CDK4/6 inhibition as a single agent can develop in pancreatic adenocarcinoma models, and by all accounts mTOR inhibitors are particularly effective at countering the acquisition of resistance and actively leading to the death of cell treated with CDK4/6 inhibitors[9, 10].

1.3 LEE011 (Investigator's Brochure[24])

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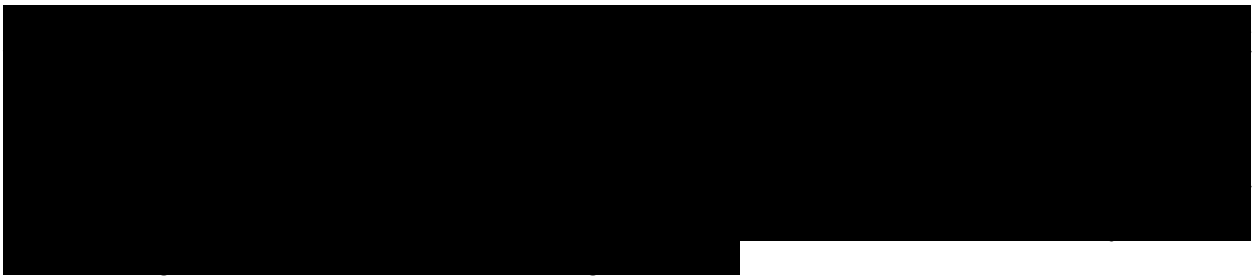

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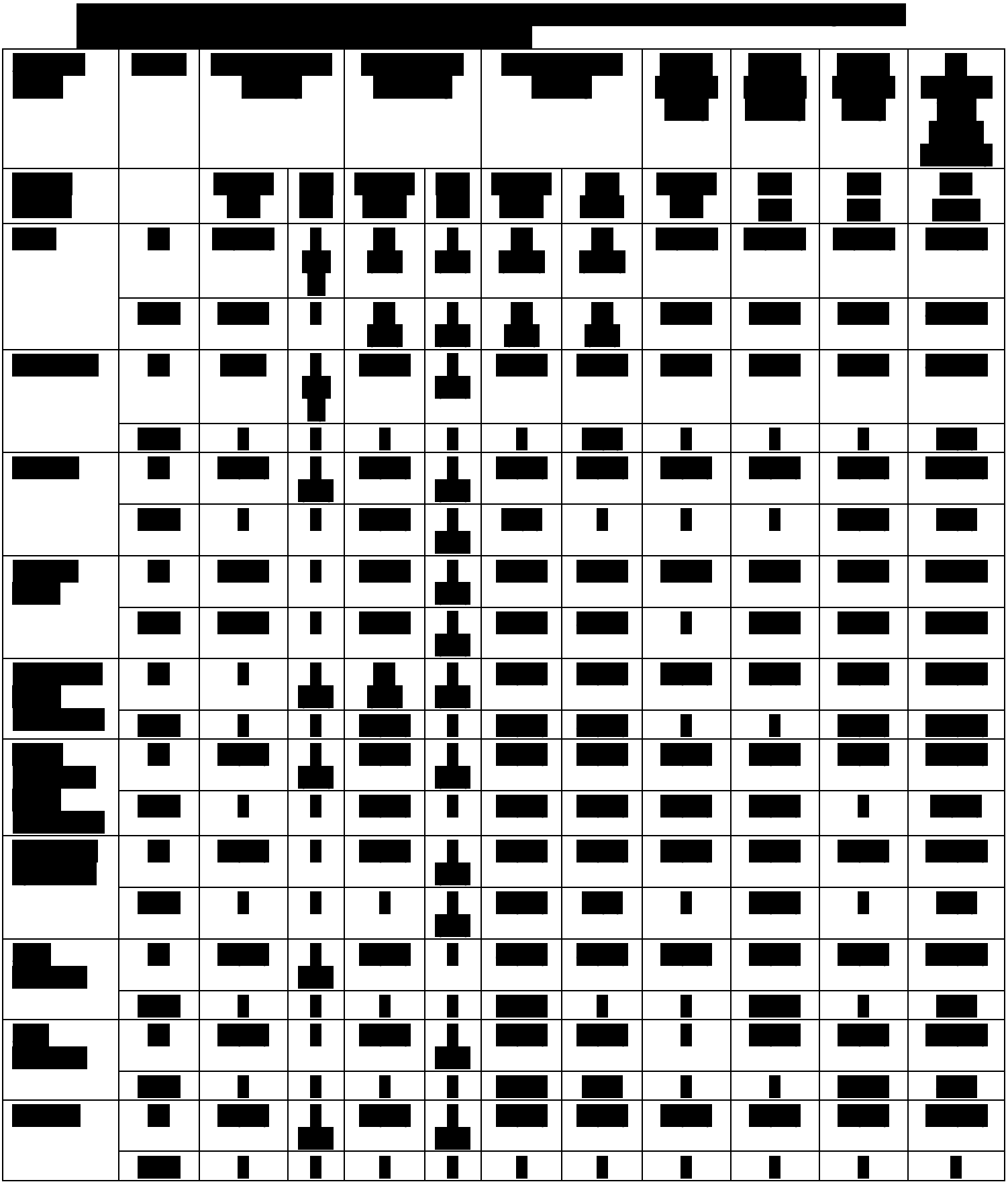

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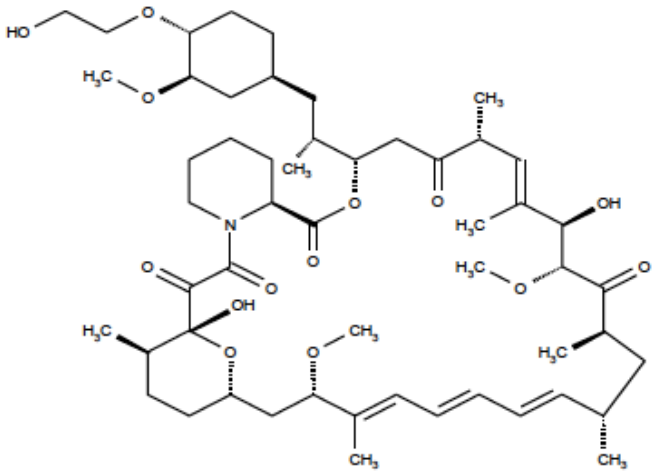
1.4 Everolimus (Afinitor® Package Insert[29])

1.4.1 Chemical Structure of Everolimus

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase downstream of the phosphoinositide 3-kinase (PI3K)/AKT pathway. Its chemical name is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.04,9]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone. The molecular formula is $C_{53}H_{83}NO_{14}$ and the molecular weight is 958.2 grams per mole. The tablets also contain anhydrous lactose, butylated hydroxytoluene, crospovidone, hypromellose, lactose monohydrate, and magnesium stearate as inactive ingredients.

Figure 11: Molecular Structure of Everolimus



1.4.2 Everolimus Mechanism of Action

Everolimus inhibits mTOR kinase activity by binding to FKBP-12 intracellularly forming a complex with mTOR complex 1 (mTORC1). This inhibition has been demonstrated to decrease cell proliferation and angiogenesis through decreased expression of hypoxia-inducible factor 1 (HIF-1) and vascular endothelial growth factor (VEGF). It also reduces protein synthesis by decreasing activity of S6 ribosomal protein kinase (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1).

1.4.3 Everolimus Pharmacokinetics

Peak serum concentrations are observed within 1-2 hours and are proportional to dosing between 5 and 10 mg daily. Above 20 mg the maximum concentration is less than dose-proportional, but the AUC demonstrates a maintenance of dose-proportionality up to 70 mg. Steady-state concentration is reached in 2 weeks. Fatty meals may reduce serum concentrations, and it is recommended that patients take the medication consistently either with or without food. Blood-to-plasma ratio is 17-73%, with about 20% confined to plasma, and 74% plasma protein binding.

Everolimus is a potent competitive inhibitor of CYP3A4, a mixed inhibitor of CYP2D6, and a substrate of PgP. Thus, avoidance of co-administration with strong CYP3A4/PgP inhibitors and dose-reduction with moderate CYP3A4/PgP inhibitors is recommended. 80% of the drug is excreted in the feces and 5% in the urine, with a mean half-life of elimination of about 30 hours. Clearance of everolimus does not vary based on creatinine clearance (as low as 25 mL/min) and no dose adjustment is recommended; however, no clinical studies were conducted in patients with decreased renal function. There are notable increases in serum concentration of everolimus in patients with impaired liver function, with relative increases in AUC by 1.8-, 3.2-, and 3.6-fold in patients with Child-Pugh classes A, B, and C respectively. Recommended dose adjustments include decreasing to 7.5 mg daily, 5 mg daily, and 2.5 mg daily in Child-Pugh classes A, B, and C respectively, with further dose reductions for tolerability. Use in Child-Pugh class C is only recommended if the benefits outweigh the risks of administration.

QTc prolongation was not seen in a trial of 59 healthy subjects given doses up to 50 mg in a single dose, and carcinogenesis was not observed in animal studies. Animal studies do suggest that everolimus may impair male and female fertility.

After administration of AFINITOR tablets in patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses ranging from 5 mg to

70 mg. Following single doses, C_{max} is dose-proportional with daily dosing between 5 mg and 10 mg. With single doses of 20 mg and higher, the increase in C_{max} is less than dose-proportional, however AUC shows dose-proportionality over the 5 mg to 70 mg dose range. Steady-state was achieved within 2 weeks following once-daily dosing.

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given everolimus 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself.

In vitro, everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan.

No specific elimination studies have been undertaken in cancer patients. Following the administration of a 3 mg single dose of radiolabeled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces. The mean elimination half-life of everolimus is approximately 30 hours.

1.4.4 Everolimus Drug Approval

Everolimus (Afinitor®) is currently approved by the Food and Drug Administration (FDA) for multiple indications: postmenopausal advanced hormone-receptor positive, HER2-negative breast cancer in combination with exemestane after failure with letrozole or anastrozole, pancreatic neuroendocrine tumors (PNET) that are unresectable, locally advanced, or metastatic, advanced renal cell carcinoma (RCC) after failure with sutininib or sorafenib, renal angiomyolipoma and tuberous sclerosis complex (TSC) not requiring immediate surgery, and TSC with subependymal giant cell astrocytoma (SEGA) that is unresectable. Everolimus (Zortress®) is also approved for organ rejection prophylaxis in kidney and liver transplant patients.

1.5 Pancreatic Cancer

Cancer of the pancreas is the fourth leading cause of cancer death in the United States, with an estimated 48,960 new diagnoses and 40,560 deaths attributable to the disease in 2015[30]. Presently, surgical resection offers the only chance of cure. However only 15 to 20 percent of patients have resectable disease at initial diagnosis; the majority have either locally advanced or metastatic cancer. Of those who are surgical candidates, most will have disease relapse after curative surgery. Reported five-year survival rates following pancreaticoduodenectomy for node-negative and node-positive disease are 25 to 30, and 10 percent, respectively[31, 32]. For those who are unresectable at diagnosis, the outcomes are even poorer. Median survival is 12-15 months for patients with locally advanced unresectable disease, and only 8-11 months for those who present with metastases[2-4, 33-36]. Thus, better medical intervention is desperately needed.

1.5.1 First Line Therapy in Pancreatic Cancer

Only recently have there been improvements in systemic therapy for advanced pancreatic cancer. Originally, gemcitabine became the standard front line therapy after a head to head comparison

with 5-fluorouracil (5-FU) showed gemcitabine to be superior[2]. Gemcitabine and 5-FU were found to yield an 18 percent versus 2 percent one-year survival and a 24 percent versus 4.8 percent improvement in clinical benefit response, respectively. For over 10 years, no clinically meaningful improvement in survival was achieved for any regimen compared to gemcitabine alone. Finally in 2011, the combination of 5-FU, oxaliplatin, and irinotecan (FOLFIRINOX) was compared against gemcitabine in a phase III trial with promising results, and FOLFIRINOX is considered the standard first-line treatment option in patients with a good performance status (PS 0-1)[3]. The median overall survival (mOS) was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group. The mPFS was 6.4 months in the FOLFIRINOX group as compared with 3.3 months in the gemcitabine group. The objective response rate was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group (P<0.001). More adverse events were noted in the FOLFIRINOX group including 5.4% of patients in this group who had febrile neutropenia. More recently, in a 2013 Phase III trial, the combination of gemcitabine and *nab*-paclitaxel was also demonstrated to be superior over gemcitabine alone[4]. The median overall survival of gemcitabine and *nab*-paclitaxel was 8.5 months, which was statistically superior to the 6.7 month survival seen with single agent gemcitabine. The mPFS was 5.5 months in the gemcitabine plus *nab*-paclitaxel group as compared with 3.7 months in the gemcitabine group. The objective response rate was 23% in the gemcitabine plus *nab*-paclitaxel group versus 7% in the gemcitabine group (P<0.001). More adverse events were noted in the gemcitabine plus *nab*-paclitaxel group including 3% of patients in this group who had febrile neutropenia. This trial has effectively established gemcitabine plus *nab*-paclitaxel as another definitive first-line treatment option for patients with metastatic pancreatic cancer. These two trials now form the standard for comparison for first line treatment for metastatic pancreatic cancer, and it should be noted that, based on these data, patients on the study proposed herein who are receiving first line therapy will be expected to remain on first line therapy for an average of ~6 months.

1.5.2 Second Line Therapy in Pancreatic Cancer

Research into second line therapy for pancreatic cancers is yet to reveal an obvious choice that shows efficacy above and beyond its comparators. Second line trials have demonstrated response rates of 2.5 to 24% and mOS rates of 4 to 6 months[37-55]. The best mOS rate from combination therapy for second line treatment is typically around six months (range 3-9 months). Promising data came from the results of the CONKO-003 trial[37]. Patients who had progressed on gemcitabine were randomized to 5-FU plus oxaliplatin vs. best supportive care (which could include 5–FU alone). Patients treated with a combination of 5-FU and oxaliplatin had a mOS of ~11 months as measured from the start of gemcitabine therapy. Additionally, Conroy, *et al* reported the mOS in patients receiving second-line therapy in the FOLFIRINOX vs. gemcitabine trial[3]. In both arms, the mOS for second line therapy was 4.4 months. There are no prospective trials of FOLFORINOX in patients whose disease had progressed on first line treatment, but a single-institution retrospective study of 27 patients treated with second-line FOLFIRINOX showed an ORR of 19 percent, and 12 others had stable disease (44%), and the median time to tumor progression was 5.4 months[38]. Finally, the recently presented NAPOLI-1 Phase III trial demonstrated an improvement in overall survival of the combination of MM-398 plus 5-FU over 5-FU alone and it is anticipated this trial will lead to the first approved agent in the second line setting for metastatic pancreatic cancer[55]. In the NAPOLI-1 trial, the median PFS for MM-398 plus 5FU was 3.1 months vs. 1.5 months for 5-FU alone.

1.5.3 Third Line Therapy in Pancreatic Cancer

Previous studies of third-line therapy in mPAC are limited but reveal stable disease in 25-31% of patients with no partial or complete responses (31% of patients in the GVAX/CRS-207 combination vaccine study had stable disease but only 52% of these patients were treated in the third-line setting)[5, 6].

2.0 STUDY OBJECTIVES

2.1 Primary Objective:

2.1.1 Primary Objective of the Phase I Portion: To determine the Recommended Phase II dose (RP2D) of LEE011 in the combination with everolimus in patients with mPAC refractory to 5-FU- and GEM-based chemotherapy

2.1.2 Primary Objective of the Phase II Portion: To determine the progression-free survival (PFS) rate at 8 weeks ($PFS_{8\ weeks}$) to assess the clinical efficacy of the combination of LEE011 and everolimus in patients with mPAC refractory to 5-FU- and GEM-based chemotherapy

2.2 Secondary Objectives

2.2.1 To determine the mPFS of patients treated with the combination of LEE011 and everolimus in patients with mPAC refractory to chemotherapy

2.2.2 To determine the mOS of patients treated with the combination of LEE011 and everolimus in patients with mPAC refractory to chemotherapy

2.2.3 To determine the best ORR, the largest percent decrease in tumor size from baseline as measured by expert radiologists using RECIST v1.1 criteria, defined as the proportion of patients with a CR or PR, of the combination of LEE011 and everolimus in patients with mPAC refractory to chemotherapy

2.2.4 To determine the safety and tolerability of the combination of LEE011 and everolimus in patients with mPAC refractory to chemotherapy

2.3 Exploratory Objectives:

2.3.1 To correlate the $PFS_{8\ weeks}$ to correlative scientific markers, including the analysis of tumor biopsies and blood-based markers, including RB, pRB, p16, cyclin D1, Ki67, MCM7, and pS6 levels by immunohistochemistry

2.3.2 To screen for use a targeted sequencing approach for genetic lesions observed in pancreatic cancer that includes KRAS, SMAD4, TP53, CDKN2A as well as other commonly mutated cancer genes

2.3.3 To assess blood for the analysis of circulating tumor DNA as a surrogate marker of disease burden. KRAS and other mutations will be used as the determinants of tumor selective DNA

2.4 Primary Endpoint:

PFS at 8 weeks in a patient with refractory mPAC treated with LEE011 and everolimus, defined as positive if a patient does not have evidence of PD at 8 weeks as measured by expert radiologists using RECIST v1.1 criteria

2.5 Secondary Endpoints:

2.5.1 PFS in a patient with refractory mPAC treated with LEE011 and everolimus, defined as the time from Cycle 1, Day 1 to PD (as measured by expert radiologists using RECIST v1.1 criteria), death from any cause, or last follow-up, as determined by the investigator

2.5.2 Overall survival (OS) in a patient with refractory mPAC treated with LEE011 and everolimus, defined as the time from Cycle 1, Day 1 to death from any cause or last follow-up

2.5.3 Best response in a patient, defined as the largest percent decrease in tumor size from baseline and categorized as a CR, PR, or SD by imaging studies, measured by expert radiologists using RECIST v1.1 criteria

2.5.4 Adverse events in a patient with refractory mPAC treated with LEE011 and everolimus, defined as the number of grade 3 and 4 toxicities according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE v4.03) that occur after Cycle 1, Day 1

2.6 Exploratory Endpoints:

2.6.1 Measurements of tumor cell proliferation, apoptosis, and RB-related gene expression by immunohistochemistry (IHC) in the pre-treatment and on-treatment biopsies:

2.6.1.1 RB, defined as positive if any tumor cells have RB nuclear staining

2.6.1.2 pRB, defined as positive if any tumor cells have phosphorylated-RB nuclear staining

2.6.1.3 p16, defined as positive if there is positive nuclear staining in 5% or more of tumor cells

2.6.1.4 Cyclin D1, defined as positive if any tumor cells have cyclin D1 nuclear staining

2.6.1.5 Ki67, defined as a percentage of positively stained cells (nuclear staining and mitotic figures) among the total number of malignant cells viewed in at least 3 randomly-selected high-power (x40 objective) fields

2.6.1.6 MCM7, defined as a percentage of positively stained cells (nuclei) among the total number of malignant cells viewed in at least 3 randomly-selected high-power (x40 objective) fields

2.6.1.7 pS6, defined using a histoscore of intensity and percent of tumor cells staining

2.6.2 Frequency of mutations (including, for example, *KRAS*, *CDKN2A*, *SMAD4*, and *TP53*) in the initial biopsy specimen from targeted NGS analyses from pre-treatment and on-treatment biopsy specimens

2.6.3 Frequency of mutations (including, for example, *KRAS*, *CDKN2A*, *SMAD4*, and *TP53*) from ctDNA as measured by quantitative PCR collected as detected in 5mL of serial blood samples collected every 8 weeks

2.7 Indication:

Patients with mPAC who have progressed on 5-FU- and GEM-based chemotherapy

3.0 SUBJECT POPULATION

3.1 Subject Population, Number of Subjects and Feasibility

(See Appendix C for Study Eligibility Checklist)

3.1.1 Subject Population

Patients with metastatic pancreatic adenocarcinoma whose disease has progressed on at least one 5-FU-based regimen and at least one GEM-based regimen for metastatic disease (progression during or within 3 months of the completion of adjuvant therapy is acceptable), and who have biopsiable disease, and who have an adequate performance status (PS), bone marrow, hepatic, and renal function

3.1.2 Number of Subjects

26 evaluable patients for the Phase II portion

3.1.3 Feasibility

Patients will be enrolled from the Lombardi Comprehensive Cancer Center (LCCC) at Georgetown University, and from partner institutions involved in this protocol. Only patients with mPAC will be eligible for enrollment. At our centers, over 300 new cases of pancreatic cancer are seen annually, at least one-half are metastatic, and around 25% of these patients would be eligible for further treatment after progression on 5-FU- and gemcitabine-based chemotherapy regimens. Therefore, around 18 patients would be eligible for enrollment in this trial each year. Based on this, we expect to accrue 1.5 patients per month, completing accrual in about 29 months.

3.2 Inclusion Criteria

1. Histologically confirmed mPAC (mixed histology is acceptable as long as the predominant histology is pancreatic adenocarcinoma)
2. Patient must consent to two mandatory biopsies and have tumor amenable to biopsy
    - Tumor biopsies are mandatory UNLESS the patient has been evaluated for a biopsy in consultation with radiology in good faith, and there is a determination that an attempt at a biopsy would cause undue risk to the patient.
3. Measurable disease by RECIST v1.1 criteria (tumor ≥ 1 cm in longest diameter on axial image on CT or MRI and/or lymph node(s) ≥ 1.5 cm in short axis on CT or MRI) on baseline imaging
4. Documented progression of disease on at least one 5-FU-based regimen and at least one GEM-based regimen for metastatic disease (progression during or within 3 months of the completion of adjuvant therapy is acceptable)
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1 (see Table 2)
6. Age ≥ 18 years
7. Subjects with no brain metastases or a history of previously treated brain metastases who have been treated by surgery or stereotactic radiosurgery (SRS) at least 4 weeks prior to enrollment and have a baseline MRI that shows no evidence of active intracranial disease
8. Patients with available standard 12-lead ECG with the following parameters at screening (defined as the mean of the triplicate ECGs):
    - QTcF interval at screening <450msec
    - Resting heart rate 50-90bpm

9. Bone marrow function: absolute neutrophil count (ANC) ≥ 1,500/mm^3; Platelets ≥100 × $10^{9/}$L; hemoglobin ≥ 9.0 g/dL
    - Patients may have a transfusion of red blood cells to meet the hemoglobin requirement
10. Renal function: serum creatinine ≤ 1.5 × upper normal limit of institution's normal range or creatinine clearance ≥ 50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal
11. Hepatic function: AST and ALT ≤ 3.0 × the upper normal limit of institution's normal range. Total bilirubin ≤ 1.5 × the upper normal limit of institution's normal range. For subjects with liver metastases, AST and ALT < 5 × the upper normal limit of institution's normal range, and total bilirubin >1.5 - 3.0 x the upper normal limit of institution's normal range are acceptable as long as there is no persistent nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.
12. Partial Thromboplastin Time (PTT) must be ≤ 1.5 × upper normal limit of institution's normal range and INR (International Normalized Ratio) ≤ 1.5. Subjects on anticoagulant (such as warfarin) will be permitted to enroll as long s the INR is in the acceptable therapeutic range as determined by the investigator.
13. Potassium, total calcium (corrected for serum albumin), magnesium, sodium and phosphorus within normal limits for the institution or corrected to within normal limits with supplements before first dose of study medication
14. Patients must have fully recovered from all effects of surgery. Patients must have had at least two weeks after minor surgery and four weeks after major surgery before starting therapy. Minor procedures requiring “Twilight” sedation such as endoscopies or mediport placement may only require a 24-hour waiting period, but this must be discussed with an investigator.
15. Patients and their partners must avoid pregnancy during the trial, and for 21 days after stopping the study medications
    - Avoidance of pregnancy may include total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Eligible female patients may have undergone surgical bilateral oophorectomy with or without hysterectomy, total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, patients are eligible only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Eligible male patients and male partners of patients must also agree to avoid pregnancy during the trial, and for 21 days after stopping the study medications
    - Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to initiation of treatment and/or postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential
16. Patient is capable of swallowing pills whole
17. Patient is capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by the Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures

Table 4. 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, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

3.3 Exclusion Criteria

1. Patients previously exposed to, intolerant of, or ineligible for CDK inhibitors, mTOR inhibitors, and/or their combination
2. Prior anti-tumor therapy within 3 weeks of Cycle 1 Day 1 (anti-tumor therapy defined as, but is not limited to, anti-cancer agents (cytotoxic chemotherapy, immunotherapy, and biologic therapy), radiotherapy, and investigational agents), the "wash-out period"
3. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.).
4. Women who are pregnant or breastfeeding
5. Concurrent use of CYP3A4 inhibiting or activating medications
6. Concurrent use of an ACE inhibitor (increased risk of angioedema with ACE inhibitors administered in combination with everolimus, seen in approximately 6.8% of patients)
7. Psychiatric illness or social situation that would limit compliance with study requirements
8. Patient has a concurrent malignancy or malignancy within 3 years prior to starting study drug, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.
9. Patients with central nervous system (CNS) involvement unless they meet ALL of the following criteria:
    - At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment
    - Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme-inducing anti-epileptic medications for brain metastases.
10. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
11. Patient has a known history of HIV infection or chronic, active Hepatitis B (testing not mandatory).

12. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.).
13. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormalities, including any of the following:
    - History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 6 months prior to screening
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Documented cardiomyopathy
    - Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) at screening
    - Clinically significant cardiac arrhythmias (e.g. ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g. bifascicular block, Mobitz type II and third-degree AV block)
    - Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
    - Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia.
        - Concomitant use of medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued (within 5 half-lives or 7 days prior to starting study drug) or replaced by safe alternative medication
        - Inability to determine the QT interval on screening (QTcF, using Fridericia's correction)
        - Systolic blood pressure (SBP) >160 mmHg or <90 mmHg at screening
14. Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to starting study drug (see Table 4 for details):
    - Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges
    - That have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5
    - Herbal preparations/medications, dietary supplements.
15. Patient is currently receiving or has received systemic corticosteroids ≤2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.
    - Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).

3.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at Screening up to the Final Visit must be recorded in source documents and the case report forms (CRFs). The reason for use, date(s) of administration (including start and end dates), and dosage information (including dose and frequency) must be recorded. Any change in concomitant therapy during the study period must be similarly recorded. Questions regarding prior or concomitant therapy should be directed to one of the investigators.

3.4.1 Prior Anti-cancer Therapy

For purposes of this protocol, anti-tumor treatment may be defined as, but is not limited to, anti-cancer agents (cytotoxic chemotherapy, immunotherapy, or biologic therapy), radiotherapy, and investigational agents. An investigational agent is any drug or therapy not currently approved for use in humans.

3.4.2 Prior Surgery

Patients must have fully recovered from all effects of surgery. Patients must have had at least two weeks after minor surgery and four weeks after major surgery before starting therapy. Minor procedures requiring "Twilight" sedation such as endoscopies or mediport placement may only require a 24 hour waiting period, but this must be discussed with an investigator.

3.4.3 Supportive Care

Subjects should receive best supportive care and treatment of symptoms during the study as appropriate, including transfusion of blood and blood products, oxygen therapy, nutritional support, intravenous fluids, and treatment with appropriate medications (antibiotics, antiemetics, antidiarrheals, and analgesics, etc.). Medications which are given for supportive care, such as appetite stimulation, may be given concurrently.

3.4.3.1 Bisphosphonates and denosumab

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

3.4.3.2 Hematopoietic growth factors

Hematopoietic growth factors may be used according to ASCO guidelines.

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

3.4.3.4 Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to lead to induction of CYP3A enzymes, thereby potentially increasing the risk of reducing LEE011 drug exposure to subtherapeutic levels. Systemic corticosteroid treatment should not be given during the study, except for:

- Topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular);

A short duration (< 5 days) of systemic corticosteroids $\leq$ to the anti-inflammatory potency of 4 mg dexamethasone (e.g. for chronic obstructive pulmonary disease, or as an antiemetic)

3.4.4 Drugs with QT prolongation

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

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

3.4.5 Permitted concomitant therapy requiring caution

Medications to be used with caution during LEE011 and everolimus in this study are listed below (see Table 3). This list is not comprehensive and is only meant to be used as a guide. These medications should be excluded from patient use if possible. If they must be given, then use with caution and consider a LEE011 and everolimus interruption if the concomitant medication is only needed for a short time.

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

Table 5. List of Medications to be Used with Caution During Study Drug Treatment

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Aprepitant, amprenavir, asafoetida resin (Ferula asafoetida) cimetidine, crizotinib, diltiazem, faldaprevir, imatinib, isavuconazole, netupitant, nilotinib, tofisopam, Schisandra sphenanthera (nan wu wei zi), verapamil
Moderate CYP3A4/5 inducers	Bosentan, dabrafenib, efavirenz, etravirine, genistein,lopinavir[5], modafinil, nafcillin, telotristat
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine, aprepitant, atorvastatin, avanafil, bosutinib,brotizolam, budesonide, buspirone, cobimetinib, darifenacin, dasatininb, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutnib, isavuconazole, ivabradine, ivacaftor, , levomethadyl (LAAM), lomitapide, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, sildenafil, simeprevir, simvastatin, ticagrelor, tilidine, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin
BSEP inhibitors	Alectinib, atorvastatin, bromocriptine, candesartan, clobetasol, clofaziminie, dabigatran, dipyridamole, glyburide, grazoprevir, ledipasvir, mifepristone,pioglitazone, reserpine,rifamycin, simeprevir, telmisartan,timcodar, troglitazone, valinomycin, velpatasvir
Medications that carry a possible risk for QT prolongation[2]	Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine , asenapine, atomoxetine, bedaquiline, bendamustine, bortezomib, bosutinib, buprenorphine, cabozantinib, capecitabine, ceritinib, clomipramine, crizotinib,clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, efavirenz, eliglustat, epirubicin, eribulin mesylate, ezogabine(retigabine), famotidine, felbamate, fingolimod, flupentixol, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, ketanserin, lapatinib, lenvatinib, leuprolide, lithium, melperone, midostaurin, mifepristone, mirabegron, mirtazapine, moexipril/HCTZ, necitumumab, nicardipine, nilotinib, norfloxacin, nortriptyline, nusinersen, ofloxacin, osimertinib, oxytocin, paliperidone, palonosetron, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, perphenazine, pilsicainide, pimavanserin, pipamperone, promethazine, prothipendyl, rilpivirine, risperidone, romidepsin, sertindole, sorafenib, sunitinib, tamoxifen, tipiracil/trifluridine, tizanidine, tolterodine, toremifene,trimipramine, tropisetron, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone
MATE1/2 substrates[3]	Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topotecan, varenicline
OCT1/2 substrates[4]	Amantadine, 6-beta-hydroxycortisol, carboplatin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, oxyplatin, oxybutynin, phenformin, picoplatin, pilsicainide, pindolol, ranitidine, sorafenib, tropisetron, trospium, umeclidinium, and zidovudine
BCRP substrates	Daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, tenofovir, topotecan, venetoclax

[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] The list provided is as of January 2018. Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.

[3] MATE1 and MATE2 share considerable substrate specificity.

[4] OCT1 and OCT2 share considerable substrate specificity.

[5] Lopinavir is prohibited when combined with ritonavir

Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University "Clinically Relevant" Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

3.4.6 Prohibited concomitant therapy

The following medications are prohibited during study treatment in the study (see Table 4). 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
- Other investigational and antineoplastic therapies not part of the study

• Herbal medications/preparations, dietary supplements (except for vitamins) including, but not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications and dietary supplements at least 7 days prior to first dose of study treatment.

Table 6. List of Prohibited Medications During Study Drug Treatment

Category	Drug Name
Strong CYP3A4/5 inhibitors	Atazanavir/ritonavir, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir,ombitasvir/paritaprevir/dasabuvir/ritonavir (VIEKIRA PAK), posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycinvoriconazole
Strong CYP3A4/5 inducers	carbamazepine[3], enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin[3], rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[2,3]
CYP3A4/5 substrates with NTI[1]	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus
Medications with a known risk for QT prolongation[4]	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacine, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sulpiride, sultopride, terlipressin, terodiline, thioridazine, vandetanib
Herbal preparations/ medications	Herbal preparations/medications known as strong inducers or inhibitors of CYP3A4/5 or those with a known risk of QT prolongation 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, all SERMS (including raloxifene), 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) or drugs which have <2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood.

[2] Herbal product

[3] P-gp inducer

[4] The list provided is as of January 2018.Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.

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

Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University "Clinically Relevant" Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

4.0 TRIAL DESIGN AND DETAILED STUDY PROCEDURES

4.1 Treatment Plan Overview

We propose a single arm, open-label Phase I/II study to evaluate the clinical activity of the combination of LEE011, a novel inhibitor of cyclin dependent kinases 4 and 6 (CDK4/6), and the mTOR inhibitor everolimus in patients with mPAC refractory to chemotherapy. We will also analyze the pharmacodynamics effects of this combination on tumor cells through serial biopsies.

4.1.1 Phase I Portion (Dose Escalation Procedures)

During the Phase I Portion of the study, patients will receive everolimus 2.5 mg once daily days 1-28 continuously and a dose of LEE011 by mouth once daily days 1-21 according to their dose level (see below):

- 3 patients are enrolled at dose level 1.
  - If 0 patients experience a DLT, 3 patients are enrolled at dose level 2.
  - If 1 patient experiences a DLT, 3 additional patients are enrolled at dose level 1. If 1 of 6 patients at dose level 1 experiences a DLT, 3 patients are enrolled at dose level 2.
  - If ≥ 2 patients experience a DLT, 3 patients are enrolled at dose level -1.
- If 0-1 of 3 patients at dose level 2 experience a DLT, then 3 additional patients are enrolled at dose level 2.
  - If 0-1 of 6 patients at dose level 2 experience a DLT, dose level 2 is the RP2D.
- If ≥ 2 of 3 patients at dose level 2 experience a DLT, 3 additional patients may be enrolled (to achieve 6 patients total) at dose level 1.
  - If 0-1 of 6 patients at dose level 1 experience a DLT, dose level 1 is the RP2D.
  - If ≥ 2 of 6 patients at dose level 1 experience a DLT, 3 patients are enrolled at dose level -1.
- If 0-1 of 3 patients at dose level -1 experience a DLT, 3 additional patients are enrolled at dose level -1.
  - If 0-1 of 6 patients at dose level -1 experience a DLT, dose level -1 is the RP2D .
  - If ≥ 2 of 3 or 6 patients at dose level -1 experience a DLT, 3 patients are enrolled at dose level -2.
- If 0-1 of 3 patients at dose level -2 experience a DLT, 3 additional patients are enrolled at dose level -2.
  - If 0-1 of 6 patients at dose level -2 experience a DLT, dose level -2 is the RP2D.
  - If ≥ 2 of 3 or 6 patients at dose level -2 experience a DLT, the study is terminated.

There will be no intrapatient dose de-escalation.

4.1.2 Phase II Portion, Stage 1 – Initial Stage

The first stage of the study will be performed to establish a minimum level of clinical efficacy to warrant the enrollment of more patients in the second stage of the study. 11 patients will be enrolled and will undergo baseline imaging and a pre-treatment biopsy. The patients will then be started on treatment with at the RP2D by mouth daily for the first 21 days out of a 28 day cycle in combination with everolimus 2.5 mg by mouth daily continuously.

- LEE011 at the RP2D by mouth once daily days 1-21
- Everolimus 2.5 mg by mouth once daily days 1-28 (continuously)

Patients will be evaluated, including laboratory testing, every 2 weeks until the first restaging analysis. Restaging will occur every 8 weeks regardless of treatment cycle. If at first restaging there is no evidence of PD, as determined by RECIST v1.1 criteria, and the patient is tolerating therapy, then patients may be seen only on Day 1 of future cycles, unless clinically indicated.

Patients will continue to remain on study as long as there is no evidence of PD (according to RECIST v1.1 criteria) and the therapy is adequately tolerated.

Patients will have a tumor biopsy prior to treatment, a second biopsy at 2 weeks on treatment, and an optional final biopsy at the time of PD.

4.1.3 Phase II Portion, Stage 2 – Final Stage

After all 11 patients from the initial stage have undergone their 8 week response assessment, an interim analysis will be conducted to determine how many had a PR, CR, SD, or PD. The study will be stopped early if 2 or fewer patients obtain a PR, CR, or SD at 8 weeks. If 3 or more patients obtain a PR, CR, or SD at 8 weeks, then 15 additional patients will be enrolled on the study for a total of 26 patients. Up to 3 additional patients may be screened and may be used to replace up to 3 patients in the initial 26 patients, provided those initial patients undergo screening but do not start study treatment within 3 weeks of screening. Thus, up to 29 patients may be screened for the Phase II portion of this study.

Figure 12 (Figure 1 Repeated): Phase I Schema

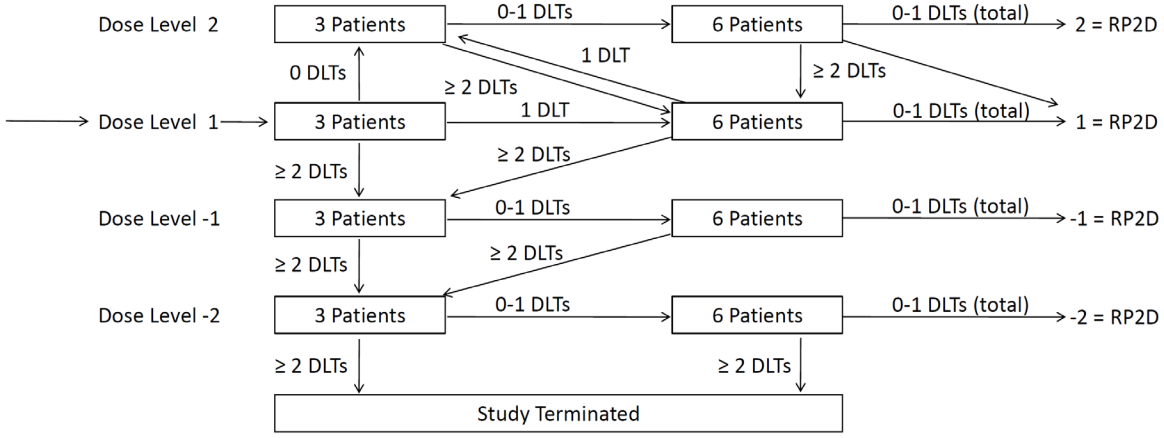
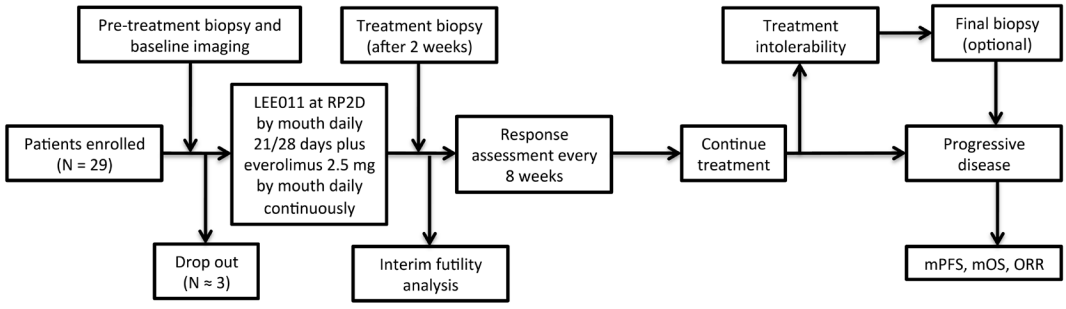


Figure 13 (Figure 2 Repeated): Phase II Schema



4.2 Detailed Study Plan

4.2.1 Screening

Study activities are detailed in Table 5, and a study activity checklist in Table 6. Screening will occur within 21 days prior to administration of the first doses of LEE011 and everolimus on Cycle 1 Day 1. Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken. For procedures

performed at screening and repeated, the later procedure performed prior to dosing, will serve as a baseline for clinical assessment. A complete history and physical will be obtained at the screening visit. Additionally, labs will be reviewed/ordered during the screening visit, prior to the initiation of therapy.

Patients who pass screening will again undergo a full evaluation on Cycle 1 Day 1, including a physical examination, vital signs, performance status, chemistry, hematology, medication review, and adverse event evaluation. If any abnormality is identified at subject assessment on Cycle 1 Day 1, prior to initiating therapy, the patient will be deemed a screen failure and will not start treatment.

For patients being considered for enrollment outside of Georgetown-Lombardi, all primary source documentation should be sent to the multi-institutional coordinator and the Study Chair, Dr. Pishvaian for review and approval. Patients must be approved for accrual prior to starting study medications. Faxed records should be sent to 202-687-3821, with an email to the multi-institutional coordinator and Dr. Pishvaian to confirm receipt of those records.

The screening procedures include the following listed below.

4.2.1.1 Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken.

4.2.1.2 Medical History

The following information will be collected during the Screening Period:

1) Complete medical history, including documentation of any clinically significant medical conditions
2) History of tobacco and alcohol use
3) Presence and severity of any symptoms/conditions associated with metastatic pancreatic cancer
4) Detailed oncology history, including:
    a. Date of primary cancer diagnosis
    b. Pathology (histology or cytology) of primary tumor
    c. Metastasis information (including the location)
    d. Surgical history
    e. Anti-cancer and radiation treatments administered (including dates and type of modality)
5) At each visit, the subject's medical history will be reviewed and any changes from baseline will be recorded in the case report form (CRF). On C1D1 any changes observed from the screening assessments, prior to dosing, will be recorded in the subject's medical history. All medications (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the Screening Visit and continuing up through the date of the off study visit.

4.2.1.3 Demographics

Age, gender, race and ethnicity will be recorded.

4.2.1.4 Review subject eligibility criteria

4.2.1.5 Review previous and concomitant medications

4.2.1.6 Physical exam including vital signs, height, and weight

A complete physical examination will be performed at the Screening Visit. Body weight will be recorded during every physical exam. The subject will wear lightweight clothing and no shoes during weighing. Height will be measured at the Screening Visit only; the subject will not wear shoes.

4.2.1.7 Vital sign determinations
Vital sign determinations of heart rate, blood pressure and body temperature will be obtained at the Screening Visit. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

4.2.1.8 Performance Status
Performance status will be evaluated prior to study entry according to Table 2.

4.2.1.9 Hematology
Hematology samples (CBC) will be collected and assessed using a certified laboratory. The Investigator will review, initial and date all laboratory results. Any laboratory value outside the reference range stated in the inclusion criteria will preclude the patient from study participation.

4.2.1.10 Serum chemistries
Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT, AST, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, total bilirubin, phosphorous, and magnesium. Any laboratory value outside the reference range stated in the inclusion criteria will preclude the patient from study participation.

4.2.1.11 Pregnancy Test
For female subjects of childbearing potential, a serum pregnancy test will be performed at the Screening Visit within 14 days of C1D1 and a urine pregnancy test will be done at the C1D1 visit prior to the first dose of study drug. Subjects considered not of childbearing potential must be documented as being surgically sterile or post-menopausal (for at least 1 year). The test results must be reviewed and determined to be negative prior to dosing. If the urine pregnancy test is positive at C1D1, it should be confirmed by a serum pregnancy test. The test may be repeated at the discretion of the investigator at any time during the study. Should a female study subject become pregnant or suspect she is pregnant while participating in this study, she should inform the treating Investigator immediately.

4.2.1.12 Tumor assessment
Only patients with metastatic pancreatic cancer not eligible for resection will be considered for entry. Subjects must have measurable disease, defined as at least 1 unidimensionally measurable lesion as defined by RECIST 1.1. Imaging for screening will be reviewed to prepare for tumor biopsies and molecular assessment.

4.3 Tumor Biopsies
Upon signing consent, patients will undergo a fresh tumor core biopsy by interventional radiologists. Tumor biopsies are mandatory UNLESS the patient has been evaluated for a biopsy in consultation with radiology in good faith, and there is a determination that an attempt at a biopsy would cause undue risk to the patient. Tumor samples will be sent to Dr. Erik Knudsen at:

Roswell Park Comprehensive Cancer Center
c/o Dr. Erik S. Knudsen
Elm & Carlton Streets
Buffalo, NY 14263

4.3.1 Patient Study Number Assignment and Sample Labeling

An additional scientific objective is to assess the pharmacodynamic effects of LEE011 and everolimus on tumor tissue and to correlate those effects to PFS. Thus, for all patients, we will require 2 core biopsies of a primary pancreatic tumor or metastatic lesion, and a third core biopsy will be optional:

- A fresh core biopsy prior to treatment (within 3 weeks of Cycle 1 Day 1)
- A repeat core biopsy on Cycle 1 Day 15 (± 3 days), preferably on the same tumor site if possible
- An optional final core biopsy after PD or off study, preferably on the same tumor site if possible

The first (pre-treatment) biopsy should be performed as soon as possible after consent is signed. For this reason, patients will be screened for accessibility of tumor tissue. Specifically, our radiologists will review the most recent images for each patient prior to enrollment. Only patients who, in their best estimation, have a tumor deposit(s), that are easily accessible by ultrasound or CT guidance in order to obtain serial core needle biopsies, will be eligible for study.

Patients will undergo core biopsies, as per standard protocol in the Department of Radiology. An 18-20 gauge needle will be used. At least three 1-2 cM core biopsies should be obtained with each biopsy. All samples should be labeled with the date, protocol number, protocol assigned patient number, and biopsy number (1 – pre-treatment; 2 – on-treatment; 3 – after PD or off study). The samples will be immediately placed in formalin and then embedded in paraffin.

Samples collected must be shipped at room temperature to Dr. Knudsen at:

Roswell Park Comprehensive Cancer Center
c/o Dr. Erik S. Knudsen
Elm & Carlton Streets
Buffalo, NY 14263

Of note, patients who are on chronic anticoagulation will be required to hold anticoagulation prior to the biopsies being performed. Patients on warfarin must hold treatment for 5 days, but will be on low-molecular weight heparin (LMWH), 1mg/kg subcutaneously twice a day. The LMWH will continue until the last biopsy is complete. Patients may then resume warfarin the day after the last biopsy. Additionally, patients on LMWH will hold (*i.e.*, not receive) the dose of LMWH the morning of the procedure, but will resume the LMWH the evening of the day of the biopsy.

Throughout the study, the following labelling procedures will be followed

4.3.1.1 Patient Study Number Assignment

Patients will be de-identified and labelled with a 5 digit study label (X-XXX-X):

- The first number will be the site from which the patient was enrolled (single digit)
  - 1 = Georgetown
  - 2 = Additional Sites as Added
- The second number will be the site-assigned patient number (three digit)
- The third number will indicate the collection timing
  - 1 = Pre-treatment
  - 2 = On treatment

4.3.1.2 Labeling of Serial Blood Samples

Serial blood samples will be labeled in a similar fashion, except that the collection timing will labelled by week number (e.g. week 0 = pretreatment; week 8; week 16)

4.4 Detailed Patient Assessments

Subject assessments (physical examinations, vital signs, performance status, chemistry, hematology, medication review, and adverse event evaluations) will be conducted at screening, Cycle 1 Day 1, every 2 weeks thereafter until the first response assessment at 8 weeks, and then every 4 weeks thereafter. Study visits and the on-treatment tumor biopsy may be performed 3 days before or after the scheduled date due to unforeseen or unavoidable circumstances, and attempts should be made to schedule visits to line up with the start of a new cycle (within the constraints of the above parameters). Study drugs will be dispensed at the last visit prior to the start of the next 28 day cycle. The radiologic first response assessment at 8 weeks, and subsequent radiologic response assessments every 8 weeks thereafter, may be performed up to 7 days before or after the scheduled date due to unforeseen or unavoidable circumstances. Details are provided in Table 5, and a checklist highlighting the important events for screening through the completion of the trial is provided below, as Table 6.

4.4.1 Physical Examinations

A complete physical examination will be performed at the screening visit, on Cycle 1 Day 1, then every 2 weeks up to the first response assessment at 8 weeks, then every 4 weeks thereafter. Any significant physical examination findings after the administration of the first doses of LEE011 and everolimus will be recorded as adverse events. Body weight will be recorded during every physical exam. The subject will wear lightweight clothing and no shoes during weighing. Weight will be measured on the same scale at each visit. Height will be measured at the screening visit only; the subject will not wear shoes.

4.4.2 Medical History

At each visit, the subject's medical history will be reviewed and any changes from baseline will be recorded as an adverse event. On Day 1, any changes observed from the screening assessments, prior to dosing, will be recorded in the subject's medical history. All medications (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the screening visit and continuing up through the date of the final visit.

4.4.3 Vital Signs

Vital sign determinations of body temperature (in degrees Celsius), heart rate, respiratory rate, blood pressure and pain (using a 0-10 Numeric Ranking Scale) will be obtained at the screening visit, on each day the subject is seen by the treating physician, and at the final visit. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

4.4.4 Clinical Laboratory Tests

All subjects will undergo the laboratory assessments outlined in Table 5.

1) A complete blood count (CBC) with differential will be collected at the screening visit, on Cycle 1 Day 1, Cycle 1 Day 15, then every 2 weeks until the first response assessment, at the first response assessment at 8 weeks, then every 4 weeks thereafter.
2) Serum chemistries (total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, magnesium, and phosphorous) will be collected at the screening visit, on Cycle 1 Day 1, Cycle 1 Day 15, then every 2 weeks until the first response assessment, at the first response assessment at 8 weeks, then every 4 weeks thereafter.
3) PT/PTT/INR will be collected at the screening visit, on Cycle 1 Day 15, and at final visit if the patient agrees to the optional third biopsy
4) Additionally, a tumor marker (serum CA19-9 or CEA level) and research blood samples for ctDNA will be sampled on Cycle 1 Day 1 and every 8 weeks thereafter.

Laboratory samples for this study will be assessed using the certified laboratory at the investigators' institutions, or at a clinical laboratory such as Quest or LabCorp and these data will

be used for all data analysis. The Principal Investigator or sub-investigator will review, initial and date all laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 8.

4.4.5 Collection and Processing of ctDNA

For collection of ctDNA on Cycle 1 Day and every 8 weeks thereafter, 4 mL of patient blood will be collected via venipuncture (venipuncture is preferred, however if an indwelling catheter must be used, 3 catheter volumes of blood must be collected and discarded prior to collection of the sample) into 2 evacuated Streck tubes. Immediately after collection, the tubes will be inverted 8 to 10 times to ensure good mixing of blood and placed in an ice bath. The date and time of collection for each sample will be recorded. The complete process of centrifugation, transfer to polypropylene tubes and freezing should be accomplished within 60 minutes from blood draw. The processing of samples should be performed as described below:

1. Immediately invert the collection tubes 8 to 10 times and placed in an ice bath.
2. Centrifuge the sample at 1,200 *g* for 10 minutes at 4°C to separate the plasma.
3. Isolate supernatants in sterile 1.5 mL Eppendorf tubes and centrifuge at 1,600 *g* for 10 minutes at 4°C
4. Transfer supernatants (plasma) using plastic pipettes into screw-capped polypropylene tubes labeled with the patient number, the protocol number, and the study week.
5. Store samples at –20°C or colder and ship on dry ice to Dr. Knudsen to:

Roswell Park Comprehensive Cancer Center
c/o Dr. Erik S. Knudsen
Elm & Carlton Streets
Buffalo, NY 14263

4.4.6 Cardiac Evaluation

All subjects will undergo a baseline ECG prior to enrollment. An ECG will also be performed on Cycle 1 Day 15. ECGs will be reviewed by the investigator and confirmed by a cardiologist. Standard triplicate 12-Lead ECG (2 minutes apart) is recommended in all visits; the combined QTcF values from these triplicate ECGs will be averaged to provide a single value for each time point. For patients with QTcF ≥481 ms at any time, interrupt study treatment and follow the procedures described in Table 9. If treatment is resumed, repeat ECGs 7 days and 14 days after dose resumption (and then as clinically indicated). During subsequent cycles, a predose ECG will be performed for every cycle starting at cycle 6, and predose and 2-4 postdose starting at cycle 9 and every 3rd cycle thereafter.

4.4.7 Adverse Event Evaluation

The Principal Investigator or sub-investigators will assess adverse events, laboratory data and vital signs throughout the study. Adverse events will be assessed by NCI CTCAE Version 4.03. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events not considered "probably related" to study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. All adverse events will be followed to a satisfactory conclusion.

4.4.8 Imaging and Response Evaluation

Patients will undergo a baseline tumor evaluation with imaging studies within 3 weeks prior to Cycle 1 Day 1. Imaging studies should include a diagnostic CT scan of the chest, abdomen, and pelvis with PO and IV contrast (unless medically contraindicated). If a patient has an allergy to IV contrast, appropriate pre-medication can be given to prevent a contrast reaction. Patients may undergo other modalities such as an MRI instead of a CT scan at the treating physician's discretion if appropriate (such as severe allergy to CT contrast, extremity tumors, bone metastases requiring bone scans, etc.).

Response evaluation will occur every 8 weeks (regardless of treatment cycle) and at the final visit, if not performed within the last 4 weeks. Tumor response and/or disease progression will be assessed by the modality(ies) used prior to treatment. Patients will continue to remain on study as long as there is no evidence of PD and the therapy is adequately tolerated.

4.4.9 Removal of Subjects from Therapy or Assessment

4.4.9.1 Reasons for Removal of Subjects from Therapy or Assessment

Each subject has the right to withdraw from study treatment at any time. In addition, the investigator may discontinue a subject from the study treatment at any time for any reason if the investigator considers it necessary, including the occurrence of an adverse event or noncompliance with the protocol. Each subject will be withdrawn from the study if any of the following occur:

1) The subject experiences either clinical or radiographic progressive disease.
2) The subject requires radiotherapy or alternate antineoplastic agents during the study period.
3) The investigator believes it is in the best interest of the subject.
4) Clinically significant deterioration of the subject's medical status as determined by the investigator.
5) Subject becomes pregnant or begins breastfeeding during the treatment portion of the study.
6) The subject or subject's legally acceptable representative decides to withdraw consent for any reason.
7) Any other medical reason that the study investigator deems appropriate.

4.4.9.2 Discontinuation of Individual Subjects

When a subject discontinuation from the study (without reaching a protocol-defined endpoint) is planned, the investigator will notify the PI as soon as possible (provided, in each case, subject care and safety are not compromised). When a subject discontinues the study, a final visit will be conducted (preferably prior to the initiation of another anticancer therapy). However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the investigator's best clinical judgment. At the final visit, the reason(s) for the discontinuation from the study will be recorded and a physical examination, body weight, vital signs measurement, laboratory analyses, performance status, tumor assessment, collection of unused study drug and an assessment of adverse events will be performed as soon as possible after discontinuation from the study. All subjects will have one final visit, which does not need to be performed for subjects who have had a visit greater than 30 days after discontinuation of the study drugs. If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, personnel will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved. In the event that a positive result is obtained on a pregnancy test for a subject during the study, the administration of study drug to that subject must be discontinued immediately.

4.4.9.3 Discontinuation of Entire Study

The investigators may terminate this study provided that written notice is submitted at a reasonable time in advance of the intended termination. The following procedures for discontinuation will be followed:

1) If the investigators have decided to prematurely discontinue the study, the investigators will promptly notify in writing the IRB of the decision and give detailed reasons for the discontinuation.
2) The PI must promptly notify enrolled subjects of the premature discontinuation and administer appropriate treatments such as replacement of protocol therapy by other appropriate regimens.

4.4.10 Longitudinal Outcomes Assessment

Subsequent therapies will be administered at the discretion of the treating physician. Patients will be followed after progression until death (or up to 24 months) to assess overall survival. Information pertaining to survival and post-treatment therapy will be collected approximately every 12 weeks (Month 3, 6, 9, 12, 15 and 18) beginning after the final visit, for a period up to 24 months.

4.4.11 Multi-Institution Study Coordination

4.4.11.1 Personnel

At each site, personnel dedicated to this protocol will be:

- A study PI
- A research coordinator/data manager

This coordinator will be the main point of contact for Dr. Pishvaian and the other PIs for any study related concerns, and to screen each patient being considered for enrollment. This coordinator will also be the point of contact for the data managers for data entry questions. Finally, this coordinator will play a major role in regulatory coordination of the study, specifically by: 1) reviewing and confirming all study-related adverse events; 2) submitting all SAE reports to the Georgetown IRB; and 3) gathering and preparing all primary source data for review/audit.

In addition, at Lombardi-Georgetown, there will be a dedicated “multi-institutional” research coordinator who will play the primary role in coordinating the trial between Lombardi-Georgetown and additional sites. This coordinator will be the main point of contact for Dr. Pishvaian and the other site PIs for any study related concerns, and to screen each patient being considered for enrollment (Including “remote” screening for the patients being screened at other sites). This coordinator will also be the point of contact for the data managers for data entry questions. Finally, this coordinator will play a major role in regulatory coordination of the study, specifically by: 1) reviewing and confirming all study-related adverse events; 2) submitting all SAE reports to the Georgetown IRB (the research coordinators at the other sites will prepare SAE reports for patients treated at their respective sites, but the “multi-institutional” coordinator will submit the final report); 3) gathering and preparing all primary source data for review/audit.

4.4.11.2 Patient Enrollment

Enrollment at the sites will be competitive. If a patient is being screened for enrollment, the local research coordinator must send a secure/encrypted email within 24 hours containing the patient’s name, to the local PI, to Dr. Pishvaian, and to the multi-institutional coordinator. If a patient is successfully screened, the local research coordinator must send all supporting documentation to the multi-institutional research coordinator (by email or fax). Patients should not start therapy until both Dr. Pishvaian and the multi-institutional coordinator have reviewed the patient’s records and confirmed that the patient is indeed eligible for enrollment.

4.4.11.32 Data Collection and Management

Patient data will be entered into the online accessible database. This database is housed at Lombardi-Georgetown, but is accessible anywhere there is Internet access. The data manager and research coordinator will attend an online training session so that they may learn how to enroll data into the database. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within one week of each patient visit.

4.4.11.4 3 Conference Calls/Meetings

A monthly meeting will be held to review patient enrollment, toxicity, and response assessment. A monthly conference call will be held between Lombardi-Georgetown and the other sites to review patient enrollment, toxicity, and response assessment.

4.4.11.54 Trial Auditing

The coordinator will arrange all primary source documents for the patients to be audited. This will include collecting copies of the primary source data.

4.4.12 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects.

Table 7. Study Activities

	Screening Visit	Cycle 1, Day 1	Cycle 1, Day 15	Every 2 Weeks thereafter until 1st Response Assessment	Cycle 2, Day 1	First Response Assessment (at 8 Weeks)	Every 4 Weeks after 1st Response Assessment	Every 8 Weeks after 1st Response	Off Study	Follow-up Assessments[G]
Informed consent	X									
Demographics	X									
Medical history	X	X	X	X	X	X	X	X	X	
Concurrent meds	X	X	X	X	X	X	X	X	X	
β-hCG	X[A]	X[A]								
Vital signs	X	X	X	X	X	X	X	X	X	
Height	X									
Weight	X	X	X	X	X	X	X	X	X	
History and physical	X	X	X	X	X	X	X	X	X	
Performance status	X	X	X	X	X	X	X	X	X	
Adverse event evaluation	X	X	X	X	X	X	X	X	X	
CBC w/ diff.	X	X	X	X	X	X	X	X	X	
Serum chemistry[B]	X	X	X	X	X	X	X	X	X	
Tumor markers[C]	X	X			X	X		X	X	
Radiologic evaluation and tumor measurements[D]	X					X		X	X[H]	
PT/PTT	X[E]		X[E]							
Tumor biopsy	X		X							
Research serum sample for ctDNA	X	X					X		X[I]	
Electrocardiogram (EKG)[F]	X									
Dispense study medications		X			X	X	X	X		
Survival		X	X	X	X	X	X	X	X	X

[A]Urine or serum pregnancy test (women of childbearing potential)

[B]Albumin, alkaline phos., total bili., bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium, phosphorus, magnesium

[C]Tumor marker (CA 19-9 or CEA)

[D]Screening scans should be within 3 weeks of starting treatment

[E]For biopsy

[F]Electrocardiograms should be done in triplicate, reviewed by the investigator, and confirmed by cardiology

[G]Up to 24 months

[H]Unless performed within 4 weeks of the off study date

[I]Optional

Table 8. Study Activities Checklist

Screening

Subject assessment	_____
Eligibility criteria met	_____
Informed consent	_____
Demographics	_____
Medical History	_____
Concurrent medications	_____
ECG	_____
Pregnancy test (if appropriate)	_____
Vital signs	_____
Height	_____
Weight	_____
History and physical	_____
Performance status	_____
CBC with differential	_____
Serum chemistries	_____
PT/PTT/INR	_____
Radiologic Assessment	_____
Tumor amenable to biopsy	_____
Pre-treatment biopsy	_____

Cycle 1, Day 1

Subject assessment	_____
Concurrent medications	_____
Pregnancy test (if appropriate)	_____
Vital signs	_____
Weight	_____
History and physical	_____
Performance status	_____
Adverse event evaluation	_____
CBC with differential	_____
Serum chemistries	_____
Serum Tumor Marker	_____
Research serum sample for ctDNA	_____
Dispense study drugs	_____

Cycle 1, Day 15

Subject assessment	_____
Concurrent medications	_____
ECG	_____
Vital signs	_____
Weight	_____
History and physical	_____
Performance status	_____
Adverse event evaluation	_____
CBC with differential	_____
Serum chemistries	_____
PT/PTT/INR	_____
On-treatment tumor biopsy	_____

Cycle 2, Day 1

Subject assessment _____
Concurrent medications _____
ECG _____
Vital signs _____
Weight _____
History and physical _____
Performance status _____
Adverse event evaluation _____
CBC with differential _____
Serum chemistries _____
PT/PTT/INR _____
Serum Tumor Marker _____
Dispense study drugs _____

Every 2 weeks until first response assessment

Subject assessment _____
Concurrent medications _____
Vital signs _____
Weight _____
History and physical _____
Performance status _____
Adverse event evaluation _____
CBC with differential _____
Serum chemistries _____

First response assessment (at 8 weeks on treatment)

Subject assessment _____
Concurrent medications _____
Vital signs _____
Weight _____
History and physical _____
Performance status _____
Adverse event evaluation _____
CBC with differential _____
Serum chemistries _____
Serum Tumor Marker _____
Radiologic Assessment _____
Research serum sample for ctDNA _____
Dispense study drugs _____

Every 4 weeks after first response assessment

Subject assessment _____
Concurrent medications _____
Vital signs _____
Weight _____
History and physical _____
Performance status _____
Adverse event evaluation _____
CBC with differential _____
Serum chemistries _____
Dispense study drugs _____

Every 8 weeks after first response assessment

Subject assessment _____
Concurrent medications _____
Vital signs _____
Weight _____
History and physical _____
Performance status _____
Adverse event evaluation _____
CBC with differential _____
Serum chemistries _____
Serum Tumor Marker _____
Radiologic Assessment _____
Research serum sample for ctDNA _____
Dispense study drugs _____

Upon disease progression or off study

Subject assessment _____
Concurrent medications _____
Vital signs _____
Weight _____
History and physical _____
Performance status _____
Adverse event evaluation _____
CBC with differential _____
Serum chemistries _____
Serum Tumor Marker _____
Radiologic Assessment _____
Research serum sample for ctDNA _____
Tumor biopsy (optional) _____

Follow-up assessment(s)

Subject assessment (may be done via phone)_____
Vital status data collection _____

5.0 DOSAGES AND DISPENSATION OF DRUGS

5.1 Dispensation of Study Drug and Treatments Administered

The study drugs are defined as LEE011 and everolimus. Patients will receive both drugs by mouth. Patients will receive sufficient quantities of LEE011 and everolimus for 1 cycle of administration on Day 1 of each cycle. Patients will receive bottles of LEE011 and everolimus and will be provided with drug diaries (see Appendix A) to record the date and time they took the drugs. LEE011 should specifically be taken WITH FOOD. Everolimus can be taken with or without food. LEE011 and everolimus should be taken with a large glass of water (~250 mL) at the same time each day and should be swallowed whole without crushing, chewing, or opening the pills. If vomiting occurs, no re-dosing of the patient is allowed prior to the next scheduled dose. If doses are not taken within 6 hours of the intended time, the dose should be skipped and not replaced or made up on a subsequent day. Patients will be instructed to store LEE011 and everolimus at room temperature. Subjects should return bottles of LEE011 and everolimus (empty, partially filled, or full) and their diaries (See Appendix A) prior to each cycle and at the final visit.

5.2 Packaging and Labeling of LEE011 and Everolimus

Film coated tablets of LEE011 will be packaged in bottles containing 200 mg and 50 mg tablets (75 tablets per bottle), and patients will be supplied with sufficient tablets for one cycle, plus enough for one extra day (see Table 7).

Table 9. Dispensation of LEE011 by Dose Level

Dose Level	Dose	200 mg Tablets Dispensed	50 mg Tablets Dispensed
2	300 mg	22	44
1	250 mg	22	22
-1	200 mg	22	0
-2	150 mg	0	66

Everolimus will be packaged in bottles containing 2.5 mg tablets with sufficient tablets in the bottle for once cycle, plus enough for one extra day (29 pills). Each bottle will be labeled with an open-label white single panel or booklet label that will include, but is not limited to, the following information:

1) Protocol number
2) Drug identification
3) Number of capsules
4) Storage conditions
5) Dosing instructions
6) Blank spaces to write the subject's identification number, initials and date dispensed

Each bottle label must remain affixed to the bottle.

5.3 Storage and Disposition of LEE011 and Everolimus

LEE011 is not to be stored at temperatures above 25°C and should be protected from moisture. Everolimus is to be stored at 25°C (excursions permitted between 15-30°C) and should be protected from light and moisture. All clinical supplies must be stored in a secure place until they are dispensed for subject use or are returned to the Georgetown Pharmacy. Investigational products are for investigational use only, and are to be used only within the context of this study. The clinical supplies supplied for this study must be maintained under adequate security and stored under conditions specified on the label. Destruction of used and unused study drug will be performed.

5.4 Treatment Compliance

Subjects will be instructed to return all bottles of LEE011 and everolimus (empty, partially filled or full) to the study personnel prior to each cycle and at the final visit. The study personnel will

document the bottles of study drug returned and the number of capsules per bottle, according to institutional policy. If the number of capsules taken and the number of capsules returned do not add up to the number of capsules dispensed, an explanation will be provided. Unless otherwise directed by the principal investigator, a subject will be considered compliant with study drug, if 85% of the assigned dose is taken during a cycle.

5.5 Drug Accountability

The investigator or designee will verify that LEE011 and everolimus supplies are received intact and in the correct amounts. A signed and dated Proof of Receipt (POR) or similar document will support documentation of the receipt of supplies. An accurate running inventory of LEE011 and everolimus will be maintained, and will include the lot number, POR number(s), the bottle numbers, and the date study drug was dispensed for each subject. Upon completion or termination of the study, all original containers (empty or containing unused study drug) will be returned to the manufacturer or destruction of used and unused study drug will be performed. Labels must remain attached to the containers. The investigator or his/her designated representative agrees not to supply study medication to any persons not enrolled in the study or not named as a sub-investigator. Personnel will record the lot number(s) and doses of LEE011 and everolimus given to each subject.

5.6 Selection of Doses in the Study (LEE011 Investigator's Brochure{Novartis, 2015 #16})

6.0 SAFETY VARIABLES AND TOXICITY ASSESSMENT

The Principal Investigator or sub-investigators will assess adverse events, laboratory data and vital signs throughout the study. Adverse events will be assessed by NCI CTCAE Version 4.03. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

6.1 Adverse Event Assessment

The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events not considered "probably related" to study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by personnel, or reported spontaneously by the subject will be recorded. All adverse events will be followed to a satisfactory conclusion.

6.2 Study Monitoring

6.2.1 Data Safety Monitoring Committee at Georgetown

The Georgetown Lombardi Comprehensive Cancer Center will be responsible for the data and safety monitoring of this trial. As this study is an investigator initiated Phase I/II study utilizing FDA-approved on label, and off label therapies, it is considered a high risk study which requires real-time monitoring by the PI and study team and quarterly reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

The Study Chair and the other investigators will review the data including safety monitoring at their monthly teleconferences with participating sites.

All Severe Adverse Events (SAEs) are required to be reported to the Georgetown IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 3 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC AD for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at G-LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the AD for Clinical Research.

Of note, the DSMC will also review the safety data of the patients enrolled outside of Georgetown University. The multi-institutional coordinator will be tasked with the job of collecting all primary source documentation for patients enrolled outside of Georgetown University. In addition, the data managers at each site will be entering data into the Georgetown database, so that all data will be available for the DSMC at Georgetown to review. Faxed records should be sent to 202-687-2399, with an email to the multi-institutional coordinator and Dr. Pishvaian to confirm receipt of those records.

6.2.2 Study Monitoring with Novartis

The Study Chair and when available, the responsible research coordinator will hold a phone conference with Novartis monthly to discuss trial management, safety concerns, response assessment and correlative studies. More frequent conferences may be held as necessary.

6.3 Adverse Event and Toxicity Definitions

6.3.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product. Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.3.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to the DSMC as a serious adverse event (SAE) within 24 hours of the study personnel being made aware of the serious adverse event.

1) **Death of Subject** An event that results in the death of a subject.
2) **Life-Threatening** An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
3) **Hospitalization or**
4) **Prolongation of Hospitalization** An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
5) **Congenital Anomaly** An anomaly detected at or after birth, or any anomaly that results in fetal loss.

6) **Persistent or Significant Disability/Incapacity** An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
7) **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
8) **Spontaneous Abortion** Miscarriage experienced by study subject.
9) **Elective Abortion** Elective abortion performed on study subject.

6.3.3 Adverse Event Severity

The study investigator will rate the severity of each adverse event according to the NCI CTCAE Version 4.03. For adverse events not captured by the NCI CTCAE Version 4.03, the following should be used:

1) **Grade 1 (Mild)** The adverse event is transient and easily tolerated by the subject.
2) **Grade 2 (Moderate)** The adverse event causes the subject discomfort and interrupts the subject's usual activities.
3) **Grade 3/4 (Severe or Life Threatening)** The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.
4) **Grade 5 (Death)** The adverse event resulted in death of the subject.

6.3.4 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

1) **Definitely Related** An adverse has a clear temporal relationship to study drug and/or recurs on re-challenge and an Other cause of event is extremely unlikely.
2) **Probably Related** An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an Other cause of event is unlikely or significantly less likely.
3) **Possibly Related** An adverse event has a strong temporal relationship to the study drug and an Other cause of event is equally or less likely compared to the potential relationship to study drug.
4) **Probably Not Related** An adverse event has little or no temporal relationship to the study drug and/or a more likely Other cause of event exists.
5) **Not Related** An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely Other cause of event).

If an investigator's opinion of possibly, probably not, or not related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signed the study-specific informed consent.

6.5 Adverse Event Reporting

In the event of a serious adverse event, whether related to study drug, study procedure such as a biopsy, or even if not directly related to any study intervention, the investigator will notify the IRB within 72 hours of being made aware of the serious adverse event. Furthermore, all serious adverse events, in addition to being reported to the FDA by the investigator, must be reported by facsimile within 24 hours to Novartis DS&E at 877-778-9739. Forms can be obtained from, and returned to e-mail: usdrugsafety.operations@novartis.com.

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to Novartis within 24 hours.

SAEs brought to the attention of the investigator at any time after cessation of LEE011 or everolimus and considered by the investigator to be related or possibly related to LEE011 or everolimus must be reported to Novartis if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged.

For patients enrolled outside of Georgetown University, serious adverse events will also be reported, and all supporting documentation sent (faxed or emailed) to the multi-institutional coordinator and to the Study Chair, Dr. Pishvaian, as well as to Novartis (as above) within 24 hours. Faxed records should be sent to 202-687-3821, with an email to the multi-institutional coordinator and Dr. Pishvaian to confirm receipt of those records.

6.6 Pregnancy

In the event of a positive pregnancy test result, study drugs will be immediately discontinued. The investigator must report the positive pregnancy test within 72 hours of the study personnel becoming aware of the pregnancy to the IRB and to Novartis. Patients should also notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within five days after the treatment period. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected, and the status of the mother and child should be reported to the IRB and to Novartis after delivery. Pregnancy in a study subject is not considered an adverse event but does require discontinuation of the subject from the study. However, the medical outcome of an elective or a spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to the IRB and to Novartis within 72 hours of study personnel becoming aware of the event. Male subjects should also notify the investigators if the subject's partner should become pregnant during the study, this should also be reported within 72 hours of study personnel awareness.

6.7 Toxicity Management and Dose Adjustments

6.7.1 Dose Reduction and Delays

6.7.1.1 Known toxicities of LEE011 and/or everolimus defined as dose-limiting toxicities (DLTs)

For the Phase I portion of the trial, toxicities will be defined as DLTs if they are included below (as defined by CTCAE v.4.03) AND they occur during the first 4 weeks of therapy AND are deemed related to the study regimen as assessed by the investigator:

Table 10. Criteria for Defining DLTs Related to LEE011 or everolimus

Toxicity	DLT (per CTCAE v. 4.03)
Hematology	≥ Grade 4 neutropenia (ANC < 500/μL) lasting ≥ 7 consecutive days
	≥ Grade 4 thrombocytopenia
	Grade 3 thrombocytopenia with clinically significant bleeding
	Grade 3 or 4 febrile neutropenia
ECG QT interval	QTc interval ≥ 501 ms on at least 2 separate ECGs
Cardiac	≥ Grade 3 cardiac toxicity, clinical signs of cardiac disease such as unstable angina, myocardial infarction, or troponin ≥ Grade 3
Gastrointestinal	≥ Grade 3 vomiting ≥ 48 hours despite optimal anti-emetic therapy
	≥ Grade 3 diarrhea ≥ 48 hours despite optimal anti-diarrheal therapy
	(Optimal therapy for vomiting and diarrhea should be based on institutional guidelines with consideration of the prohibited medications listed in these protocol guidelines).
Hepatobiliary	≥ Grade 2 total bilirubin > 7 consecutive days
	≥ Grade 3 total bilirubin
	≥ Grade 2 ALT with a ≥ Grade 2 bilirubin elevation of any duration in the absence of liver metastases
	≥ Grade 3 ALT for > 4 consecutive days
	Grade 4 ALT or AST
	Grade 4 serum alkaline phosphatase > 7 consecutive days
Renal	≥ Grade 3 serum creatinine
Stomatitis	≥ Grade 3 – everolimus is associated with stomatitis. Per the Afinitor® package insert, topical treatments are recommended, but alcohol-, hydrogen peroxide-, iodine-, or thyme- containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed.
Pneumonitis	Non-infectious pneumonitis – everolimus is associated with pneumonitis. The use of corticosteroids is suggested for Grade 1-2 pneumonitis, recommended for Grade 3 pneumonitis, and Grade 4 pneumonitis should result in the cessation of everolimus.
Non-hematologic, non-hepatic adverse events	≥ Grade 3 except for the following exceptions:
Exceptions to DLT criteria	Grade 3 or 4 Allergic Reaction
	Grade 3 alopecia
	< 5 days of Grade 3 fatigue
	Grade 3 fever or infection without neutropenia < 5 days duration
	Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant

6.7.1.2 Dose reduction and delays due to toxicities related to known toxicities of LEE011 or everolimus

If a subject experiences a DLT, as defined above in Table 10, the subject will complete the planned activities of the cycle as scheduled (*i.e.*, CT scans and lab tests will be performed per standard of care). The following are guidelines for dose delay and discontinuation of the study drugs:

1) All treatment drugs should be discontinued/delayed concurrently until the toxicity resolves to Grade 1 or lower or to baseline if Grade 2 at the time of study entry.

a. Of note, LEE011 is known to be associated with myelosuppression. Thus, for Grade 2 or 3 neutropenia, anemia, or thrombocytopenia which do NOT meet the definition of a DLT as detailed in Table 10, then treatment will continue without modification.
    i. Patients who experience Grade 2 or 3 neutropenia, anemia, or thrombocytopenia, while continuing treatment without modification for that cycle, will be followed with weekly CBCs to track the recovery (or worsening) of the myelosuppression
    ii. Dose modifications for Grade 2 or 3 neutropenia, anemia, or thrombocytopenia as detailed in Table 11 below will then be instituted FOR SUBSEQUENT CYCLES of therapy
        1. Thus, for example, a patient who experiences Grade 3 thrombocytopenia without bleeding at Cycle 1, Day 15 will continue treatment without modification. CBCs will be checked weekly
            a. If the thrombocytopenia worsens to Grade 4, for example Cycle 1, Day 22, then treatment will be held, and dose reductions will be instituted starting Cycle 2
            b. If the thrombocytopenia does NOT worsen through Cycle 1, then treatment hold and dose modifications will be followed for Cycle 2, as per Table 11 below
    iii. For clarity, for any hematologic toxicity that meets the definition of a DLT (even in the Phase II portion), treatment will be held, and doses modified as per Table 11, even within a cycle.

2) Subjects may delay retreatment for up to 3 weeks to allow the toxicity to resolve.

In the Phase II portion of the study, dose adjustments will be followed, as per Table 11. One dose adjustment is allowed, as delineated in Table 11.

Table 11. Dose Modifications for Toxicities Related to LEE011 or everolimus

Hematologic	
Thrombocytopenia	
Grade 1 (≥ 75 x 10^9/L)	No dose adjustment required
Grade 2 (≥ 50 x 10^9/L – < 75 x 10^9/L)	Hold LEE011 and everolimus until recovery ≤ Grade 1, re-initiate at same dose
Grade 3 (≥ 25 x 10^9/L – < 50 x 10^9/L)	Hold LEE011 and everolimus until recovery ≤ Grade 1, re-initiate at same dose If recurs at Grade 3: Hold LEE011 and everolimus until recovery ≤ Grade 1, re-initiate LEE011 at one dose level lower, everolimus 2.5 mg
Grade 4 (< 25 x 10^9/L)	Hold LEE011 and everolimus until recovery ≤ Grade 1, re-initiate LEE011 at one dose level lower, everolimus 2.5 mg If recurs at Grade 4: Discontinue all therapy (off study)
Neutropenia (Absolute neutrophil count, ANC)	
Grade 1 (≥ 1.5 x 10^9/L)	No dose adjustment required
Grade 2 (≥ 1.0 – < 1.5 x 10^9/L)	No dose adjustment required
Grade 3 (≥ 0.5 – < 1.0 x 10^9/L)	Hold LEE011 and everolimus until recovery ≥ 1.0 x 10^9/L, re-initiate at same dose If recurs at Grade 3: Hold LEE011 and everolimus until recovery ≥ 1.0 x 10^9/L If resolved ≤ 7 days, re-initiate at same dose If resolved > 7 days, re-initiate LEE011 at one dose level lower, everolimus 2.5 mg
Grade 4 (≥ 1.5 x 10^9/L)	Hold LEE011 and everolimus until recovery ≥ 1.0 x 10^9/L, re-initiate LEE011 at one dose level lower, everolimus 2.5 mg If recurs at Grade 4: Discontinue all therapy (off study)
Febrile neutropenia	
Grade 3 (ANC < 1.0 x 10^9/L with a single temperature > 38.3 °C (101 °F) or a sustained temperature of ≥ 38.3 °C (101 °F) for more than 1 hour	Hold LEE011 and everolimus until recovery ≥ 1.0 x 10^9/L and afebrile, re-initiate LEE011 at one dose level lower, everolimus 2.5 mg If recurs: Discontinue all therapy (off study)
Grade 4 (life-threatening consequences, urgent intervention indicated)	Discontinue all therapy (off study)

Anemia (hemoglobin)	
Grade 1 (≥ 10.0 – LLN g/dL)	No dose adjustment required
Grade 2 (≥ 8.0 – < 10.0 g/dL)	No dose adjustment required
Grade 3 (< 8.0 g/dL)	Hold LEE011 and everolimus until recovery to ≤ Grade 2, re-initiate at same dose
Grade 4 (life-threatening consequences, urgent intervention indicated)	Discontinue all therapy (off study)
<u>Hepatotoxicity</u>	
Total bilirubin elevation without AST/ALT increase above baseline value	
Grade 1 (> ULN – 1.5 x ULN) confirmed on repeat 48-72 hours later	Maintain dose level with LFTs monitored bi-weekly
Grade 2 (> 1.5 – 3.0 x ULN)	Hold LEE011 and everolimus If resolved to ≤ Grade 1 in ≤ 21 days, then re-initiate at same dose If resolved to ≤ Grade 1 in > 21 days or toxicity recurs, Re-initiate LEE011 at one dose level lower, everolimus 2.5 mg Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks following re-initiation If recurs at reduced dose level, discontinue all therapy (off study)
Grade 3 (> 3.0 – 10.0 x ULN)	Hold LEE011 and everolimus If resolved to ≤ Grade 1 in ≤ 21 days, Re-initiate LEE011 at one dose level lower, everolimus 2.5 mg Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks following re-initiation If resolved to ≤ Grade 1 in > 21 days or toxicity recurs, discontinue all therapy (off study)
Grade 4 (> 10.0 x ULN)	Discontinue all therapy (off study)
AST or ALT elevation without bilirubin elevation > 2 x ULN	
Same grade as baseline or increase from baseline Grade 0 to Grade 1 confirmed 48-72 hours 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)	Hold LEE011 and everolimus If resolved to ≤ baseline value in ≤ 21 days, then re-initiate at same dose If resolved to ≤ baseline value in > 21 days or toxicity recurs, Re-initiate LEE011 at one dose level lower, everolimus 2.5 mg Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks following re-initiation If recurs at reduced dose level or recovery to ≤ baseline value in > 28 days, Discontinue all therapy (off study)
Increase from baseline Grade 0 or 1 to Grade 3 (> 5.0 – 20.0 x ULN)	Hold LEE011 and everolimus If resolved to ≤ baseline value in ≤ 28 days, Re-initiate LEE011 at one dose level lower, everolimus 2.5 mg Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks following re-initiation If recurs at reduced dose level or recovery to ≤ baseline value in > 28 days, Discontinue all therapy (off study)
Increase from baseline Grade 2 to Grade 3 (> 5.0 – 20.0 x ULN)	Hold LEE011 and everolimus If resolved to ≤ baseline value in ≤ 28 days, Re-initiate LEE011 at one dose level lower, everolimus 2.5 mg Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks following re-initiation If recurs at reduced dose level or recovery to ≤ baseline value in > 28 days, Discontinue all therapy (off study)
Grade 4 (> 20.0 x ULN)	Discontinue all therapy (off study)
AST or ALT and concurrent bilirubin elevation	
Normal ALT or AST or total bilirubin at baseline: AST or ALT ≥ Grade 2 with total bilirubin > 2 x ULN without evidence of cholestasis OR Elevated AST or ALT or total bilirubin at baseline: baseline: [AST	Discontinue all therapy (off study)

or ALT >2 x baseline AND > 3.0 x ULN] OR [AST or ALT 8.0 x ULN]-whichever is lower-combined with [total bilirubin 2x baseline AND > 2.0 x ULN]	
QT Prolongation	
For All Grades	1. Check the quality of the ECG and the QT value, repeat if needed 2. Check serum electrolytes (potassium, calcium, phosphorus, and magnesium), if abnormal: hold LEE011 and everolimus, correct with supplements as soon as possible and repeat electrolytes until within normal range, then re-initiate at same dose 3. Review concomitant medications for propensity to prolong the QT interval and CYP3A4 inhibitors 4. Check compliance with correct dose and administration of LEE011
QTcF 450-480 ms	Perform steps 1-4 as directed in "For All Grades." No dose adjustment required
QTcF 481-500 ms	Hold LEE011 and everolimus. Perform steps 1-4 as directed in "For All Grades." Repeat ECG one hour after the first QTcF of ≥ 481 ms. • Repeat ECG as clinically indicated until the QTcF returns to < 481 ms, restart LEE011with dose reduced by 1 dose level. Refer to Table 1 for dosing schedule. • If QTcF ≥ 481 ms recurs, LEE011 should be reduced again by 1 dose level. • Repeat ECGs 7 and 14 days after dose resumption and as clinically indicated
QTcF ≥ 501 ms on at least 2 separate ECGs	Hold LEE011 and everolimus. Perform steps 1-4 as directed in "For All Grades." Transmit ECG immediately and confirm prolongation/abnormalities with central assessment (if applicable). Perform a repeat ECG within one hour of the first QTcF of ≥ 501 ms. If QTcF remains ≥ 501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to < 481 ms. • If QTcF returns to < 481 ms, LEE011 will be reduced by 1 dose level. Refer to Table 1 for dosing schedule. • If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in "For All Grades," discontinue LEE011. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 ms If QTcF of ≥ 501 ms recurs, discontinue LEE011.
QT/QTcF ≥ 501 ms or > 60 ms increase from baseline AND Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia	Discontinue all therapy (off study). Perform steps 1-4 as directed in "For All Grades." Obtain local cardiologist consultation (or qualified specialist), repeat cardiac monitoring as indicated until QTcF returns to < 481 ms
Non-infectious Pneumonitis	
Grade 1-2	Consider steroids, hold LEE011 and everolimus until below Grade 1, re-initiate at same dose
Grade 3	Trial of steroids, hold LEE011 and everolimus until below Grade 1 If recurs, discontinue all therapy (off study)
Grade 4	Discontinue all therapy (off study)
All Other Adverse Reactions	
Grade 1	No dose adjustment recommended, initiate appropriate medical therapy and monitor
Grade 2	Hold LEE011 and everolimus until ≤ Grade 1, treat with appropriate medical therapy and monitor, re-initiate at same dose If recurs at Grade 2, hold LEE011 and everolimus until ≤ Grade 1, Re-initiate LEE011 at one dose level lower, everolimus 2.5 mg
Grade 3	Hold LEE011 and everolimus until ≤ Grade 1, treat with appropriate medical therapy and monitor, re-initiate LEE011 at one dose level lower, everolimus 2.5 mg If recurs at Grade 3, discontinue all therapy (off study)
Grade 4	Discontinue all therapy (off study), treat with appropriate medical therapy

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.

7.0 EFFICACY ASSESMENT

7.1 Efficacy Variables

Tumor response and/or disease progression will be assessed by a CT scan (or other appropriate modalities such by way of MRI consistent with the modality used prior to treatment) utilizing RECIST v1.1 criteria. Assessments will be performed within 3 weeks before screening every 8 weeks thereafter, and at the final visit, if not performed within the last four weeks. If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery. The primary *clinical efficacy* endpoint is $PFS_{8\ weeks}$ as determined by RECIST v1.1 criteria. Analyses of these endpoints are described in Section 13.

7.2 RECIST v1.1 Criteria for Tumor Response

Changes in the measurable lesions over the course of therapy will be evaluated using the RECIST v1.1 criteria.

7.2.1 Definition of Lesions

7.2.1.1 Measurable Disease

The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

7.2.1.2 Measurable Lesions

Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with CT scan.

7.2.1.3 Non-measurable Lesions

All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with a CT scan), bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions and also abdominal masses that are suspicious though may or may not be confirmed and followed by imaging techniques.

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

7.2.2 Methods of Measurement

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. For accurate objective response evaluation, ultrasound should not be used to measure tumor lesions. However, ultrasound is a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

7.2.3 Baseline Documentation of "Target" and "Non-Target" Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) 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. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.2.4 Definitions of Tumor Response-Measurable Disease

7.2.4.1 Complete Response (CR)

The disappearance of all known disease, determined by two observations not less than 4 weeks apart. There can be no appearance of new lesions.

7.2.4.2 Partial Response (PR)

A 30% or more decrease in the sum of the LD of target lesions that have been measured to determine the effect of therapy by two observations not less than 4 weeks apart. There can be no appearance of new lesions or progression of any lesion.

7.2.4.3 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, the appearance of one or more new lesions and/or an unequivocal progression of non-target lesions.

7.2.4.4 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.

7.3 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.

Table 12. Response Evaluation. 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.

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	
PR	Non-PD	No	PR	>4 wks. confirmation
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: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

7.4 Definition of Disease Progression

Disease progression will be defined as:

1) Radiologic progression of disease by RECIST v1.1 criteria.
2) Clinical progression as determined by the investigator, which may be characterized as, but is not limited to:
    a. Increase of at least 2 points in ECOG performance status attributable to cancer progression.
    b. Requirement for palliative radiation, chemotherapy or surgery.
3) Death from disease progression

8.0 CORRELATIVE RESEARCH AND TUMOR BIOPSIES

8.1 Pharmacodynamic Assessment of the Efficacy of LEE011 and Everolimus

8.1.1 Introduction

The primary objective of this trial is to determine the efficacy of LEE011 and everolimus in patients with refractory mPAC. However, an important secondary endpoint is to assess the pharmacodynamic effects of the combination treatment on cell cycle, the retinoblastoma pathways and MTOR pathways, and to correlate those effects to the PFS. Thus, for all patients, we will require at least 2 serial biopsies.

- A fresh biopsy prior to treatment
- A repeat biopsy on the Cycle 1 Day 15
- An optional final biopsy after PD or off study

The first (pre-treatment) biopsy should be performed as soon as possible after consent is signed. For this reason, patients will be screened for accessibility of tumor tissue. Specifically, our radiologists will review the most recent images for each patient prior to enrollment. Only patients who, in their best estimation, have a tumor deposit(s), that are easily accessible by ultrasound or CT guidance in order to obtain serial core needle biopsies, will be eligible for study

With regards to the timing of the second biopsy, the pharmacokinetics of both LEE011 and everolimus suggest that the LEE011 reaches steady state by Day 8, and the everolimus by 2 weeks. Thus, the second biopsy was requested at a time point wherein both agents have achieved steady state, but before the week off of LEE011.

Patients will undergo core biopsies, as per standard protocol in the Department of Radiology. An 18-20 gauge needle will be used. At least four 1-2 cM core biopsies should be obtained with each biopsy. All samples should be labeled with the date, protocol number, protocol assigned patient number, and biopsy number (1 – pre-treatment; 2 – on-treatment; 3 – after PD or off study).

2 cores should be placed in screw-top tubes and frozen in liquid nitrogen.
The other 2 cores should be immediately placed in formalin and then embedded in paraffin.

Throughout the study, the following labeling procedures will be followed

8.1.1.1 Patient Study Number Assignment

Patients will be de-identified and labeled with a 5 digit study label (X-XXX-X):

- The first number will be the site from which the patient was enrolled (single digit)
  - 1 = Georgetown
- The second number will be the site-assigned patient number (three digit)
- The third number will indicate the collection timing
  - 1 = Pre-treatment
  - 2 = On treatment

8.1.1.2 Labeling of Serial Blood Samples

Serial blood samples will be labeled in a similar fashion, except that the collection timing will labeled by week number (e.g. week 0 = pretreatment; week 8; week 16)

8.1.1.3 Sample Shipment

Samples collected must be shipped at room temperature to Dr. Erik Knudsen at:

Roswell Park Comprehensive Cancer Center
c/o Dr. Erik S. Knudsen
Elm & Carlton Streets
Buffalo, NY 14263

8.1.2 Assessment of Pharmacodynamic Effects of LEE011 and Everolimus

A formalin-fixed, paraffin embedded core sample from the pre-treatment and on-treatment tumor biopsies will be used to make slides to stain for the following markers by IHC with the indicated cutpoints:

a. RB, defined as negative if tumor cells are devoid of nuclear staining, while lymphocytes and stromal cells have positive nuclear staining.
b. pRB (phosphorylated Ser780), defined using a histoscore of intensity and percent of tumor cell nuclei staining.
c. p16 levels are defined using established clinical staining criteria (0-3+)
d. Cyclin D1, defined using intensity and predominant localization (nuclear/cytoplasmic)
e. Ki67, defined as a percentage of positively stained nuclei in the tumor compartment
f. MCM7, defined as a percentage of positively stained cells nuclei in the tumor compartment
g. pS6 (Ser235/236) defined using a histoscore of intensity and percent of tumor cells staining

LEE011 directly suppresses the phosphorylation of RB which provides an assessment of on-target activity. Ki67 and MCM7 are markers of proliferation and are expected to diminish with treatment associated with response. RB, Cyclin D1, and p16 could be predictive markers of response, and the absence of RB and high-levels of p16 are associated with resistance. Phosphorylation of s6 protein is mediated by MTOR and provides a marker for the efficacy of MTOR inhibition by everolimus.

8.2 Mutational Analysis of Tumor Samples

Pre-treatment biopsy samples will be used for targeted next generation sequencing using a panel that includes 196 genes commonly altered in cancer with a specific emphasis on genes that are altered in pancreatic cancer. This platform will allow >500x coverage across the genes and provide both single nucleotide variant and copy number information. Each common gene mutation will be evaluated for association with PFS. The presence of a *CDKN2A* mutation or deletion will be correlated with PFS, given the hypothesis that derangement in this pathway results in p16 loss, creating a therapeutic target of CDK4/6 (naturally inhibited by p16).

8.3 Analysis of ctDNA

ctDNA will be collected from patient serum at Cycle 1 Day 1 and every 8 weeks thereafter. Mutations identified by the targeted sequencing will be evaluated in the circulating DNA specimens using PCR (predominantly focused around KRAS, TP53, or CDKN2A mutations). We will correlate changes in the ctDNA abundance with PFS and tumor marker levels. The data will determine if ctDNA may be a possible surrogate marker for disease burden.

8.4 Tissue Prioritization

We anticipate that the biopsies will provide sufficient tissue for all the studies to be performed above. One good core of tissue should be sufficient for all the IHC stains, and one good core should be sufficient for the NGS. However, should there be insufficient tissue, the priority will be as follows:

- The IHC will take priority, with the specific priority order following the order of markers listed above (a through g)
- The NGS will be the second priority. For the NGS, there is no “priority” order of the genes analyzed, as the entire panel will be run at once.

9.0 STATISTICAL CONSIDERATIONS

9.1 Objectives:

9.1.1 Primary Objective of the Phase I Portion:

To determine the Recommended Phase II dose (RP2D) of LEE011 in the combination with everolimus in patients with mPAC refractory to 5-FU- and GEM-based chemotherapy

9.1.2 Primary Objective of the Phase II Portion:

To determine the progression-free survival (PFS) rate at 8 weeks ($PFS_{8\ weeks}$) to assess the clinical efficacy of the combination of LEE011 and everolimus in patients with mPAC refractory to 5-FU- and GEM-based chemotherapy

9.1.3 Secondary Objectives

9.1.3.1 To determine the mPFS of patients treated with the combination of LEE011 and everolimus in patients with mPAC refractory to chemotherapy

9.1.3.2 To determine the mOS of patients treated with the combination of LEE011 and everolimus in patients with mPAC refractory to chemotherapy

9.1.3.3 To determine the best ORR, the largest percent decrease in tumor size from baseline as measured by expert radiologists using RECIST v1.1 criteria, defined as the proportion of patients with a CR or PR, of the combination of LEE011 and everolimus in patients with mPAC refractory to chemotherapy

9.1.3.4 To determine the safety and tolerability of the combination of LEE011 and everolimus in patients with mPAC refractory to chemotherapy

9.1.4 Exploratory Objectives

9.1.4.1 To correlate the $PFS_{8\ weeks}$ to correlative scientific markers, including the analysis of tumor biopsies and blood-based markers, including RB, pRB, p16, cyclin D1, Ki67, MCM7, and pS6 levels by immunohistochemistry

9.1.4.2 To screen for use a targeted sequencing approach for genetic lesions observed in pancreatic cancer that includes KRAS, SMAD4, TP53, CDKN2A as well as other commonly mutated cancer genes

9.1.4.1 To assess blood for the analysis of circulating tumor DNA as a surrogate marker of disease burden. KRAS and other mutations will be used as the determinants of tumor selective DNA

9.2 Study Design

This study is a single-arm, open-label, Phase I/II trial of the combination of LEE011 and everolimus in refractory mPAC. The Phase I portion of the trial will be conducted in a 3+3 design, enrolling patients in cohorts of 3 patients each. If 0-1 DLTs occur in a cohort of 3 patients, the cohort will be expanded to 6 patients. If 0-1 DLTs occur in the group of 6 patients, the RP2D will be that dose level. Otherwise, 3 patients will be enrolled at the next lowest dose level and the process continued until the RP2D is determined (0-1 DLTs within the 6 patients at that dose level) or the study is terminated (if there are 2 or more DLTs at Dose Level -3).

The Phase II study will be conducted using a Simon's Minimax two-stage design. In the initial stage 11 patients will be enrolled, and if at least 3 patients are progression-free at 8 weeks, then an additional 15 patients will be enrolled in the second stage for a total of 26 patients on study. If 2 or fewer patients are progression-free at 8 weeks, then the study will be terminated for futility. 3 additional patients will be screened and may be used to replace up to 3 of the 26 patients,

provided those initial patients undergo screening but do not start study treatment within 3 weeks of screening. Thus, a total of 29 patients are expected to be screened for the Phase II portion of this study.

9.3 Sample Size Considerations

Using a Simon Minimax 2-stage design with a null hypothesis of 25% and an alternative hypothesis of 50% (or greater) a total of 26 evaluable patients are needed (assuming 90% power and alpha=0.1 (one-sided)).

For the Phase I portion, there may be as few as 12, and as many as 18 patients enrolled strictly in the Phase I portion (and not treated at the RP2D of LEE011, thus not counted towards the Phase II portion of the study). Thus, as many as 44 patients may be accrued for this trial. Anticipating an accrual rate of 3 patients per month, the trial is expected to complete accrual in approximately 15 months.

9.4 Endpoints

9.4.1 Primary Endpoint

PFS at 8 weeks is a complete response (CR), partial response (PR), or stable disease (SD) by imaging study (CT or MRI), evaluated by expert radiologists using RECIST v1.1 criteria, at the 8 week response assessment. Each patient will be categorized as either success/failure for being progression free at 8 weeks.

9.4.2 Secondary Endpoints

9.4.2.1 PFS is the time from Cycle 1, Day 1 to PD, death from any cause, or last follow-up, as determined by the investigator. If a patient dies on study they will be censored at the time of death for the purposes of the PFS endpoint.

9.4.2.2 OS is the time from Cycle 1, Day 1 to death from any cause or last follow-up.

9.4.2.3 Best response is the largest percent decrease in tumor size from baseline and is categorized as a CR, PR, or SD by imaging studies, evaluated by expert radiologists using RECIST v1.1 criteria.

9.4.2.4 The number of grade 3 and 4 toxicities according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; Version 4.0) that occur after Cycle 1, Day 1 will be recorded at each study visit.

9.4.2.5 Pharmacodynamic effects of therapy will be evaluated by comparison of expression levels obtained by IHC in the pre-treatment biopsy and the on-treatment biopsy of:
9.4.2.5.1 RB, defined as positive if any tumor cells have RB nuclear staining

9.4.2.5.2 pRB, defined as positive if any tumor cells have phosphorylated-RB nuclear staining

9.4.2.5.3 p16, defined as positive if nuclear staining in 5% or more of tumor cells

9.4.2.5.4 Cyclin D1, defined as positive if any tumor cells have cyclin D1 nuclear staining

9.4.2.5.5 Ki67, defined as a percentage of positively stained cells (nuclear staining and mitotic figures) among the total number of malignant cells viewed in at least 3 randomly-selected high-power (x40 objective) fields

9.4.2.5.6 MCM7, defined as a percentage of positively stained cells (nuclei) among the total number of malignant cells viewed in at least 3 randomly-selected high-power (x40 objective) fields

9.4.2.5.7 pS6 (Ser235/236) defined using a histoscore of intensity and percent of tumor cells staining

9.4.2.6 Frequency of mutations from targeted NGS analyses from pre-treatment biopsy specimens will be ranked.

9.4.2.7 ctDNA will be collected via serial blood samples with frequency as described above and quantitatively measured, defined as the number of mutant fragments in 5 mL by quantitative PCR.

9.5 Analysis Plan

9.5.1 Analytic plan for primary objective

The null hypothesis is that the PFS rate at 8 weeks is 25% (based on historical controls wherein third-line therapy in mPAC revealed stable disease in 25-31% of patients[5,6].) versus an alternative hypothesis that the rate is 50% or higher. The plan is to use a Simon's Minimax two-stage design with 11 patients enrolled during the first stage. If 3 or more (out of 11) patients are progression free the trial will continue with an additional 15 patients being enrolled during the second stage (for a total of 26 patients). If 10 or more patients are progression free at 8 weeks the trial will declare that the intervention has met the pre-specified criteria for success.

9.5.2 Analytic plan for secondary objectives

9.5.2.1 Survival and response endpoints:
9.5.2.1.1 The nonparametric Kaplan-Meier method will be used to estimate median PFS.

9.5.2.1.2 The nonparametric Kaplan-Meier method will be used to estimate median OS.

9.5.2.1.3 We plan to determine the ORR within a ± 20% range based on our sample size.

9.5.2.2 Adverse event data will be compiled and tabulated using descriptive statistics.

9.5.2.3 Pharmacodynamic analyses are exploratory, but we hypothesize that proliferation indices (Ki67 and MCM7) will be decreased in the on-treatment sample compared to the pre-treatment sample and could correlate with PFS. Similarly, expected decreases in levels of pRB, cyclin D1, p16, and increases in RB could correlate with PFS. Cox proportional hazard regression models will be fit to determine whether these secondary endpoints are associated with PFS.

9.5.2.4 NGS analysis is also exploratory in nature. Using results from these analyses will examine whether median PFS is different with patients with mutations in *CDKN2A* compared to those without these mutations.

9.5.2.5 ctDNA studies are exploratory and overall trends in serial measurements may support a response (or lack of response) signal to treatment and could be correlated with PFS as a surrogate marker of disease burden.

9.5.2 Safety Assessments

9.5.2.1 Safety Assessments
The safety of LEE011 and everolimus will be assessed by evaluating study drug exposure, adverse events, serious adverse events, oncology-related events, all deaths, as well as changes in laboratory determinations and vital sign parameters.

9.5.2.2 Duration of Study Drug

A summarization of the number of days and/or cycles subjects were exposed to study drug will be provided.

9.5.2.3 Adverse Events

Analyses of adverse events (and serious adverse events) will include only "treatment-emergent" events, *i.e*., those that have an onset on or after the day of the first dose of study drug. Analyses will not include those that have an onset greater than 30 days after the last dose of study drug. Treatment emergent adverse events will be summarized by system organ class and preferred term according to the MedDRA adverse event coding dictionary. The percentage of subjects experiencing an adverse event at a given severity, NCI CTCAE toxicity grade, and relationship to study drug will be provided.

9.5.2.4 Deaths

The number of subject deaths will be summarized (1) for deaths occurring while the subject was still receiving study drug in this study, (2) for deaths occurring off treatment within 30 days after the last dose of study drug, and (3) for all deaths in this study regardless of the number of days after the last dose of study drug. The relatedness of the deaths to the study drugs will also be provided.

10.0 ETHICAL CONSIDERATIONS

10.1 Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB. IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to the study site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to the IRB. During the conduct of the study, the investigator should promptly provide written reports to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects.

10.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical Principals that have their origin in the Declaration of Helsinki.

10.3 Subject Information and Consent

Prior to the initiation of any screening or study-specific procedures, the investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. A separate informed consent is also required from subjects who provide blood for genetic testing or fresh biopsy tissue samples for analyses. Each informed consent will be reviewed, signed and dated by the subject and the person who administered the informed consent. A copy of each informed consent will be given to the subject and each original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Tissue sample collection for analysis will only be performed if the subject has voluntarily consented to participate after the nature of the testing has been explained and the subject has had the opportunity to ask questions. If the subject does not consent to the tissue sample collection, it will not impact the subject's participation in the study.

10.4 Ethical Consideration for Enrollment

Only patients with advanced cancer, for whom no curative therapy exists, will be considered for enrollment. The only treatment options for these patients are enrollment in a Phase I clinical trial, or treatment off protocol, with a non-standard therapy. As described above, the combination of LEE011 and everolimus is a rational and promising combination for such patients

10.5 Protection of Patient Confidentiality

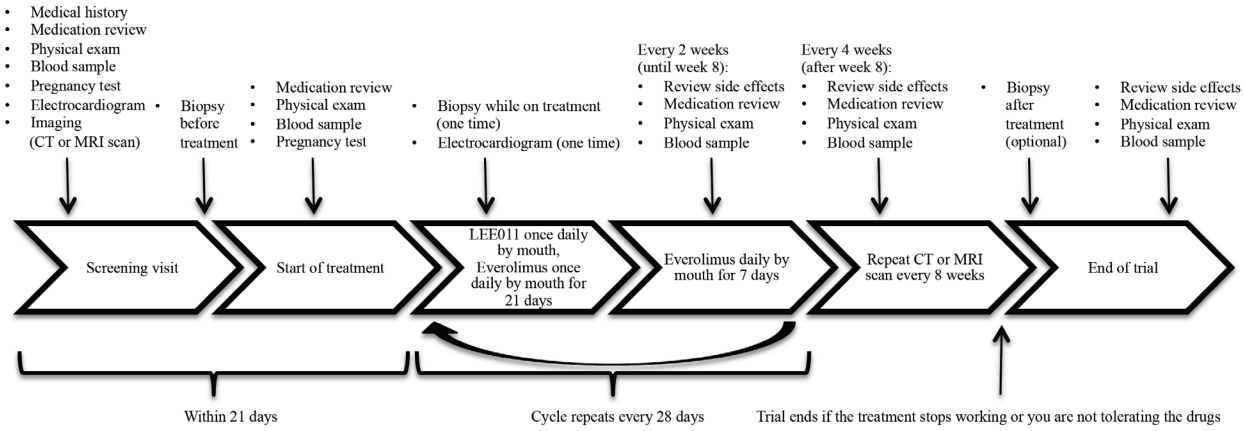
All patient records, questionnaires, and tissue specimens will be de-identified using a letter and number assigned to their case at the time of enrollment on study. No record or specimen will contain information which could identify the patient. The key which connects patient identifiable information with this assigned number will be held by the Principal investigator. For computer records, the key will be protected by a double password protection system. Any paper records will be contained in a locked cabinet within a locked office to ensure patient’s privacy is protected.

APPENDIX A – PATIENT DRUG DIARY

Cycle Number: _____ Day 1 Date: ___/____/_____

Day 1 LEE011 time: ____:____ Everolimus time: ____:____	Day 2 LEE011 time: ____:____ Everolimus time: ____:____	Day 3 LEE011 time: ____:____ Everolimus time: ____:____	Day 4 LEE011 time: ____:____ Everolimus time: ____:____	Day 5 LEE011 time: ____:____ Everolimus time: ____:____	Day 6 LEE011 time: ____:____ Everolimus time: ____:____	Day 7 LEE011 time: ____:____ Everolimus time: ____:____
Day 8 LEE011 time: ____:____ Everolimus time: ____:____	Day 9 LEE011 time: ____:____ Everolimus time: ____:____	Day 10 LEE011 time: ____:____ Everolimus time: ____:____	Day 11 LEE011 time: ____:____ Everolimus time: ____:____	Day 12 LEE011 time: ____:____ Everolimus time: ____:____	Day 13 LEE011 time: ____:____ Everolimus time: ____:____	Day 14 LEE011 time: ____:____ Everolimus time: ____:____
Day 15 LEE011 time: ____:____ Everolimus time: ____:____	Day 16 LEE011 time: ____:____ Everolimus time: ____:____	Day 17 LEE011 time: ____:____ Everolimus time: ____:____	Day 18 LEE011 time: ____:____ Everolimus time: ____:____	Day 19 LEE011 time: ____:____ Everolimus time: ____:____	Day 20 LEE011 time: ____:____ Everolimus time: ____:____	Day 21 LEE011 time: ____:____ Everolimus time: ____:____
Day 22 Everolimus time: ____:____	Day 23 Everolimus time: ____:____	Day 24 Everolimus time: ____:____	Day 25 Everolimus time: ____:____	Day 26 Everolimus time: ____:____	Day 27 Everolimus time: ____:____	Day 28 Everolimus time: ____:____

APPENDIX B – PATIENT TRIAL EVENTS



APPENDIX C: STUDY ELIGIBILITY CHECKLIST

A Phase I/II Study of LEE011 plus Everolimus in Patients with Metastatic Pancreatic Adenocarcinoma Refractory to Chemotherapy

Patient Initials: _____ Study ID: _____
Instructions: This form should be completed by the research staff before registering the patient into the trial.
Completed form can be faxed to 202-687-3821 or scanned/emailed to pishvaim@georgetown.edu.

☐Georgetown University Medical Center ☐ Other site: _____

INCLUSION CRITERIA (ALL ITEMS MUST BE CHECKED YES)

YES | NO

☐ | ☐ Histologically proven pancreatic adenocarcinoma with radiographically measurable disease

☐ | ☐ Documented progression of disease on at least one 5-FU-based regimen and at least one GEM-based regimen for metastatic disease (progression during or within 3 months of the completion of adjuvant therapy is acceptable)

☐ | ☐ Biopsy accessible tumor deposits (as can best be determined by imaging) - A patient's biopsied lesion must be at least 1cm in diameter (in at least one dimension)

☐ | ☐ Age ≥ 18 years

☐ | ☐ ECOG performance status 0 or 1 (see Table 2 below)

☐ | ☐ Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to initiation of treatment and/or postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential.

☐ | ☐ Subject is capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by the Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures

☐ | ☐ Patients must have fully recovered from all effects of surgery. Patients must have had at least two weeks after minor surgery and four weeks after major surgery before starting therapy. Minor procedures requiring "Twilight" sedation such as endoscopies or mediport placement may only require a 24-hour waiting period, but this must be discussed with an investigator.

☐ | ☐ Subjects with no brain metastases or a history of previously treated brain metastases who have been treated by surgery or stereotactic radiosurgery (SRS) at least 4 weeks prior to enrollment and have a baseline MRI that shows no evidence of active intracranial disease

☐ | ☐ Patients with available standard 12-lead ECG with the following parameters at screening (defined as the mean of the triplicate ECGs):
- QTcF interval at screening <450msec
- Resting heart rate 50-90bpm

LAB VALUES (ALL MUST BE CHECKED YES)

YES | NO

☐ | ☐ Absolute neutrophil count (ANC) ≥ 1,500/mm^3

☐ | ☐ Platelets ≥ 100,000/mm^3

☐ | ☐ Hemoglobin ≥ 9.0 g/dL

☐ | ☐ Serum creatinine ≤ 1.5 X the upper limit of normal of the institution's normal range OR creatinine clearance ≥ 50 mL/min/1.73 m^2 for subjects with creatinine level above the upper limit of normal

☐ | ☐ Hepatic function: AST and ALT $\leq$ 3.0 $\times$ the upper normal limit of institution's normal range. Total bilirubin $\leq$ 1.5 $\times$ the upper normal limit of institution's normal range. For subjects with liver metastases, AST and ALT < 5 $\times$ the upper normal limit of institution's normal range, and total bilirubin >1.5 - 3.0 x the upper normal limit of institution's normal range are acceptable as long as there is no persistent nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.

☐ | ☐ Potassium, total calcium (corrected for serum albumin), magnesium, sodium and phosphorus within normal limits for the institution or corrected to within normal limits with supplements before first dose of study medication

☐ | ☐ Prothrombin Time and Partial Thromboplastin Time (PTT) ≤ 2 X the upper limit of the institution's normal range

☐ | ☐ INR (International Normalized Ratio) < 2, subjects on anticoagulation will be permitted as long as the INR is in an acceptable therapeutic range as determined by the investigator

EXCLUSION CRITERIA (ELIGIBLE PATIENTS MUST ALL BE CHECKED NO)

☐ | ☐ Prior anti-tumor therapy within 3 weeks of Cycle 1 Day 1 (anti-tumor therapy defined as, but is not limited to, anti-cancer agents (cytotoxic chemotherapy, immunotherapy, and biologic therapy), radiotherapy, and investigational agents), the "wash-out period"

☐ | ☐ Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.).

☐ | ☐ Concurrent use of CYP3A4 inhibiting or activating medications; or concurrent use of an ACE inhibitor (increased risk of angioedema with ACE inhibitors administered in combination with everolimus, seen in approximately 6.8% of patients)

☐ | ☐ Patient has a concurrent malignancy or malignancy within 3 years prior to starting study drug, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.

☐ | ☐ Active severe infection or known chronic infection with HIV or hepatitis B virus

☐ | ☐ Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).

☐ | ☐ Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormalities, as detailed in full exclusion criteria in Section 3.3

☐ | ☐ Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to starting study drug (see Table 4 for details):
- Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges
- That have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5
- Herbal preparations/medications, dietary supplements.

OR Patient is currently receiving or has received systemic corticosteroids $\leq$2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.

☐ | ☐ Woman who is pregnant or breast feeding

Table 4 (repeated): ECOG Performance Status Scale

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, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

APPENDIX D: PATIENT REGISTRATION FORM

A Phase I/II Study of LEE011 plus Everolimus in Patients with Metastatic Pancreatic Adenocarcinoma Refractory to Chemotherapy

Patient Initials: _____ Study ID: _____
Instructions: This form should be completed by the research staff before registering the patient into the trial.
Completed form can be faxed to 202-687-3821 or scanned/emailed to pishvaim@georgetown.edu.

☐Georgetown University Medical Center ☐ Other site: _____

1. Date Informed Consent signed: ____/____/_____

2. Start date for treatment: ____/____/_____

3. Prior therapies (date initiated/type):

4. Please fax the following documentation:
   - ☐ Pathology Report
   - ☐ Physicians Note validating:
     - ▪Previous treatments
   - ☐ CT showing RECIST criteria
   - ☐ Laboratory Results
   - ☐ Past Medical History

ON-STUDY CARD

MRN: _____
DOB: ____/____/_____
Zip Code: _____
Race: ☐ African American
☐ Asian
☐ Caucasian
☐ Hispanic
☐ Native American
☐ Pacific Islander
☐ Other
☐ Unknown
Gender: ☐ Male ☐ Female ☐ Unknown
Treating Physician: _____
RN: _____

Ethnicity: ☐ Hispanic or Latino
☐ Not Hispanic or Latino
☐ Unknown
Consent Approval Date:
____/____/_____
Screen Failure: ☐ Yes ☐ No
Screening Date: ____/____/_____
On Study Date: ____/____/_____
Protocol Waiver: ☐ Yes ☐ No
Reason: _____
Registration Site: _____

First Treatment Date: ____/____/_____

APPENDIX E: REFERENCES

1. Table 22.8, Cancer of the pancreas (invasive). SEER Cancer Statistics Review; 1975-2011.
2. Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6):2403-13.
3. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817-25.
4. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691-703.
5. Sprinzl MF, Wytopil SM, Dahmen A, Kanzler S, Galle PR, Moehler M. Docetaxel as salvage therapy in highly pretreated and drug resistant gastrointestinal carcinomas. Clin Med Oncol. 2008;2:555-61.
6. Le DT, Wang-Gillam A, Picozzi V, Greten TF, Crocenzi T, Springett G, et al. Safety and survival with GVAX pancreas prime and Listeria Monocytogenes-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. J Clin Oncol. 2015;33(12):1325-33.
7. Lange CA, Yee D. Killing the second messenger: targeting loss of cell cycle control in endocrine-resistant breast cancer. Endocr Relat Cancer. 2011;18(4):C19-24.
8. Witkiewicz AK, McMillan EA, Balaji U, Baek G, Lin WC, Mansour J, et al. Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets. Nat Commun. 2015;6:6744.
9. Franco J, Witkiewicz AK, Knudsen ES. CDK4/6 inhibitors have potent activity in combination with pathway selective therapeutic agents in models of pancreatic cancer. Oncotarget. 2014;5(15):6512-25.
10. Heilmann AM, Perera RM, Ecker V, Nicolay BN, Bardeesy N, Benes CH, et al. CDK4/6 and IGF1 receptor inhibitors synergize to suppress the growth of p16INK4A-deficient pancreatic cancers. Cancer Res. 2014;74(14):3947-58.
11. Shapiro GI. Cyclin-dependent kinase pathways as targets for cancer treatment. J Clin Oncol. 2006;24(11):1770-83.
12. Joo M, Kang YK, Kim MR, Lee HK, Jang JJ. Cyclin D1 overexpression in hepatocellular carcinoma. Liver. 2001;21(2):89-95.
13. Lu ZL, Luo DZ, Wen JM. Expression and significance of tumor-related genes in HCC. World J Gastroenterol. 2005;11(25):3850-4.
14. Pascale RM, Simile MM, De Miglio MR, Muroni MR, Calvisi DF, Asara G, et al. Cell cycle deregulation in liver lesions of rats with and without genetic predisposition to hepatocarcinogenesis. Hepatology. 2002;35(6):1341-50.
15. Zhang YJ, Jiang W, Chen CJ, Lee CS, Kahn SM, Santella RM, et al. Amplification and overexpression of cyclin D1 in human hepatocellular carcinoma. Biochem Biophys Res Commun. 1993;196(2):1010-6.
16. Ito Y, Matsuura N, Sakon M, Miyoshi E, Noda K, Takeda T, et al. Expression and prognostic roles of the G1-S modulators in hepatocellular carcinoma: p27 independently predicts the recurrence. Hepatology. 1999;30(1):90-9.
17. Masaki T, Shiratori Y, Rengifo W, Igarashi K, Yamagata M, Kurokohchi K, et al. Cyclins and cyclin-dependent kinases: comparative study of hepatocellular carcinoma versus cirrhosis. Hepatology. 2003;37(3):534-43.
18. Grady WM, Willis JE, Trobridge P, Romero-Gallo J, Munoz N, Olechnowicz J, et al. Proliferation and Cdk4 expression in microsatellite unstable colon cancers with TGFBR2 mutations. Int J Cancer. 2006;118(3):600-8.
19. Zhang T, Nanney LB, Luongo C, Lamps L, Heppner KJ, DuBois RN, et al. Concurrent overexpression of cyclin D1 and cyclin-dependent kinase 4 (Cdk4) in intestinal adenomas from multiple intestinal neoplasia (Min) mice and human familial adenomatous polyposis patients. Cancer Res. 1997;57(1):169-75.
20. Sotillo R, Dubus P, Martin J, de la Cueva E, Ortega S, Malumbres M, et al. Wide spectrum of tumors in knock-in mice carrying a Cdk4 protein insensitive to INK4 inhibitors. EMBO J. 2001;20(23):6637-47.
21. Rane SG, Dubus P, Mettus RV, Galbreath EJ, Boden G, Reddy EP, et al. Loss of Cdk4 expression causes insulin-deficient diabetes and Cdk4 activation results in beta-islet cell hyperplasia. Nat Genet. 1999;22(1):44-52.
22. Tsutsui T, Hesabi B, Moons DS, Pandolfi PP, Hansel KS, Koff A, et al. Targeted disruption of CDK4 delays cell cycle entry with enhanced p27(Kip1) activity. Mol Cell Biol. 1999;19(10):7011-9.
23. Matsuura I, Denissova NG, Wang G, He D, Long J, Liu F. Cyclin-dependent kinases regulate the antiproliferative function of Smads. Nature. 2004;430(6996):226-31.
24. Novartis. LEE011 Investigator's Brochure. 2015.
25. Bardia A, Modi S, Gregor MC, Kittaneh M, Marino AJ, Matano A, Bhansali S, Hewes B, Cortes J. Phase Ib/II study of LEE011, everolimus, and exemestane in postmenopausal women with ER+/HER2- metastatic breast cancer. J Clin Oncol. 2015;32(15, Suppl):Abstr 535.
26. Kovarik JM, Kaplan B, Tedesco Silva H, Kahan BD, Dantal J, Vitko S, et al. Exposure-response relationships for everolimus in de novo kidney transplantation: defining a therapeutic range. Transplantation. 2002;73(6):920-5.
27. Kovarik JM, Hartmann S, Figueiredo J, Rordorf C, Golor G, Lison A, et al. Effect of food on everolimus absorption: quantification in healthy subjects and a confirmatory screening in patients with renal transplants. Pharmacotherapy. 2002;22(2):154-9.
28. Urva S, Bouillaud E, Delaney R, Jappe A, Cheung W. A phase I study evaluating the effect of everolimus on the pharmacokinetics of midazolam in healthy subjects. J Clin Pharmacol. 2013;53(4):444-50.
29. Novartis. Afinitor® Package Insert. 2015.

30. American Cancer Society: Cancer Facts and Figures. 2015 [Available from: http://www.cancer.org/research/cancerfactsfigures/index.html.
31. Trede M, Schwall G, Saeger HD. Survival after pancreatoduodenectomy. 118 consecutive resections without an operative mortality. Ann Surg. 1990;211(4):447-58.
32. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. Am J Surg. 1993;165(1):68-72; discussion -3.
33. Paez D, Labonte MJ, Lenz HJ. Pancreatic cancer: medical management (novel chemotherapeutics). Gastroenterol Clin North Am. 2012;41(1):189-209.
34. Poplin E, Feng Y, Berlin J, Rothenberg ML, Hochster H, Mitchell E, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2009;27(23):3778-85.
35. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB, 3rd. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol. 2002;20(15):3270-5.
36. Herrmann R, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schuller J, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol. 2007;25(16):2212-7.
37. Pelzer U, Kubica, K., Stieler, J., Schwaner, I., Heil, G., Görner, M., Mölle, M., Hilbig, A., Dörken, B., Riess, H., Oettle, H. A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO 003 study. J Clin Oncol. 2008;26(15S):4508.
38. Assaf E, Verlinde-Carvalho M, Delbaldo C, Grenier J, Sellam Z, Pouessel D, et al. 5-fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) as second-line chemotherapy in patients with metastatic pancreatic adenocarcinoma. Oncology. 2011;80(5-6):301-6.
39. Altwegg R, Ychou M, Guillaumon V, Thezenas S, Senesse P, Flori N, et al. Second-line therapy for gemcitabine-pretreated advanced or metastatic pancreatic cancer. World J Gastroenterol. 2012;18(12):1357-64.
40. Boeck S, Hoehler T, Seipelt G, Mahlberg R, Wein A, Hochhaus A, et al. Capecitabine plus oxaliplatin (CapOx) versus capecitabine plus gemcitabine (CapGem) versus gemcitabine plus oxaliplatin (mGemOx): final results of a multicenter randomized phase II trial in advanced pancreatic cancer. Ann Oncol. 2008;19(2):340-7.
41. Xiong HQ, Varadhachary GR, Blais JC, Hess KR, Abbruzzese JL, Wolff RA. Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. Cancer. 2008;113(8):2046-52.
42. Boeck S, Weigang-Kohler K, Fuchs M, Kettner E, Quietzsch D, Trojan J, et al. Second-line chemotherapy with pemetrexed after gemcitabine failure in patients with advanced pancreatic cancer: a multicenter phase II trial. Ann Oncol. 2007;18(4):745-51.
43. Demols A, Peeters M, Polus M, Marechal R, Gay F, Monsaert E, et al. Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. Br J Cancer. 2006;94(4):481-5.
44. Cereda S, Reni M, Rognone A, Fugazza C, Ghidini M, Ceraulo D, et al. Salvage therapy with mitomycin and ifosfamide in patients with gemcitabine-resistant metastatic pancreatic cancer: a phase II trial. Chemotherapy. 2011;57(2):156-61.
45. Reni M, Pasetto L, Aprile G, Cordio S, Bonetto E, Dell'Oro S, et al. Raltitrexed-eloxatin salvage chemotherapy in gemcitabine-resistant metastatic pancreatic cancer. Br J Cancer. 2006;94(6):785-91.
46. Tsavaris N, Kosmas C, Skopelitis H, Gouveris P, Kopterides P, Loukeris D, et al. Second-line treatment with oxaliplatin, leucovorin and 5-fluorouracil in gemcitabine-pretreated advanced pancreatic cancer: A phase II study. Invest New Drugs. 2005;23(4):369-75.
47. Cantore M, Rabbi C, Fiorentini G, Oliani C, Zamagni D, Iacono C, et al. Combined irinotecan and oxaliplatin in patients with advanced pre-treated pancreatic cancer. Oncology. 2004;67(2):93-7.
48. Milella M, Gelibter A, Di Cosimo S, Bria E, Ruggeri EM, Carlini P, et al. Pilot study of celecoxib and infusional 5-fluorouracil as second-line treatment for advanced pancreatic carcinoma. Cancer. 2004;101(1):133-8.
49. Ulrich-Pur H, Raderer M, Verena Kornek G, Schull B, Schmid K, Haider K, et al. Irinotecan plus raltitrexed vs raltitrexed alone in patients with gemcitabine-pretreated advanced pancreatic adenocarcinoma. Br J Cancer. 2003;88(8):1180-4.
50. Oettle H, Arnold D, Esser M, Huhn D, Riess H. Paclitaxel as weekly second-line therapy in patients with advanced pancreatic carcinoma. Anticancer Drugs. 2000;11(8):635-8.
51. Kim HJ, Yun J, Kim HJ, Kim KH, Kim SH, Lee TH, et al. Phase II study of palliative S-1 in combination with cisplatin as second-line chemotherapy for gemcitabine-refractory pancreatic cancer patients. Oncol Lett. 2012;3(6):1314-8.
52. Zaniboni A, Aitini E, Barni S, Ferrari D, Cascinu S, Catalano V, et al. FOLFIRI as second-line chemotherapy for advanced pancreatic cancer: a GISCAD multicenter phase II study. Cancer Chemother Pharmacol. 2012;69(6):1641-5.
53. Yoo C, Hwang JY, Kim JE, Kim TW, Lee JS, Park DH, et al. A randomised phase II study of modified FOLFIRI.3 vs modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. Br J Cancer. 2009;101(10):1658-63.

54. Hurwitz H, Uppal N, Wagner S. A randomized double-blind phase 2 study of ruxolitinib (RUX) or placebo (PBO) with capecitabine (CAPE) as second-line therapy in patients (pts) with metastatic pancreatic cancer (mPC). J Clin Oncol.2014.
55. Chen LT VHD, Li CP, Wang-Gillam A, Bodoky G, Dean AP, Shan YS, Jameson GS, Macarulla T, Lee KH, Cunningham D, Blanc JF, Hubner R, Chiu CF, Schwartsmann G, Siveke JT, Braiteh FS, Moyo VM, Belanger B, Bayever E. Expanded analyses of napoli-1: Phase 3 study of MM-398 (nal-IRI), with or without 5-fluorouracil and leucovorin, versus 5-fluorouracil and leucovorin, in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy. J Clin Oncol. 2015;33(Suppl 3):234.