Femara (Letrozole) Plus Ribociclib (LEE011) or Placebo as Neo-adjuvant Endocrine Therapy for Women with ER-positive, HER2-negative Early Breast Cancer

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THE UNIVERSITY OF KANSAS

CANCER CENTER

Protocol: CLEE011XUS10T

Investigator-Initiated Trial

Femara (Letrozole) Plus Ribociclib (LEE011) or Placebo as Neo-adjuvant Endocrine Therapy for Women with ER-positive, HER2-negative Early Breast Cancer

The Feline Trial

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Study Drug: Ribociclib (LEE011)

IND Number: 127673

IND Holder Name: Qamar Khan, MD

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: CLEE011XUS10T

Protocol Title: Femara (Letrozole) Plus Ribociclib (LEE011) or Placebo as Neo-adjuvant Endocrine Therapy for Women with ER-positive, HER2-negative Early Breast Cancer

Protocol Version and Date: Protocol Version 5.0 dated 08/24/2018

Investigator Signature _____ Date _____

Print Name and Title _____

Site Number: 001
Site Name: The University of Kansas Cancer Center / University of Kansas Medical Center

Investigator Signature _____ Date _____

Print Name and Title _____

Site Number: _____

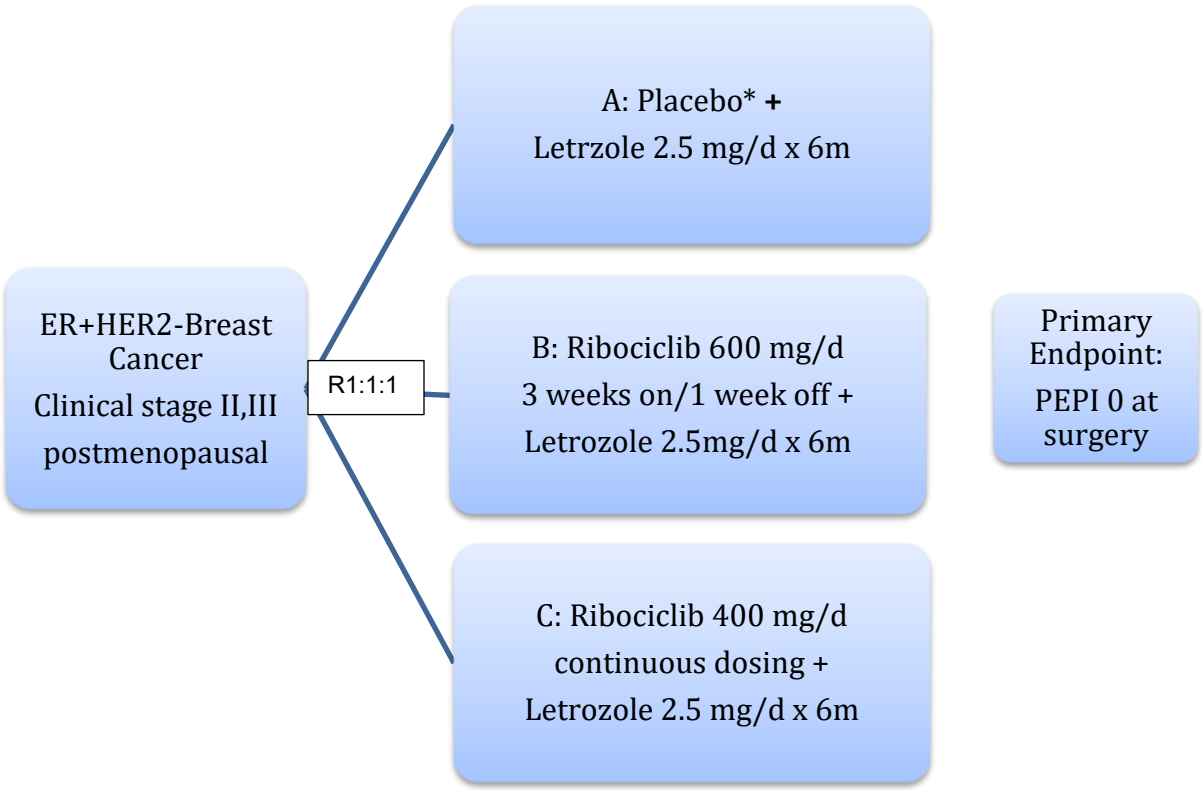
Site Name: _____

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
AI	Aromatase Inhibitor
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
cCR	Clinical Complete Response
CMP	Comprehensive Metabolic Panel
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease Free Survival
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
ER	Estrogen Receptor
hCG	Human Chorionic Gonadotropin
HER-2	ERBB2
IULN	Institutional Upper Limit of Normal
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
pCR	Pathologic Complete Response
PD	Progressive Disease
PEPI	Pre-operative Endocrine Prognostic Index
PFS	Progression Free Survival
PO	per os/by mouth/orally
PR	Partial Response
RFS	Relapse Free Survival
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable Disease
US	Ultrasound
WBC	White Blood Cells

Study Schema



- *Randomized to 3 capsules/d 3 weeks on/1week off or 2 capsules/d continuous dosing (see Section 4.1 for details)
- Research biopsies will be performed at baseline, at day 14 (+7d) and at surgery.
- A Ki67 value of >10% at day 14 biopsy will result in discontinuation of the protocol therapy since this is an early indicator of endocrine resistance.
- For the primary analysis, arms B and C will be combined vs arm A.

Study Summary

Title	Femara (Letrozole) Plus Ribociclib (LEE011) or Placebo as Neo-adjuvant Endocrine Therapy for Women With ER+, HER2-negative Early Breast Cancer
Short Title	FELINE trial
Phase	II
Methodology	Placebo controlled randomized trial
Study Duration	26 months (Date of accrual of first subject to surgery date of last subject)
Study Center(s)	Multi-center
Objectives	To determine if ribociclib in combination with letrozole for 24 weeks as neoadjuvant endocrine therapy increases the proportion of women with PEPI score of 0 at surgery compared to patients treated with letrozole alone therefore allowing more patients excellent outcomes without chemotherapy.
Number of Subjects	120 (40 in each arm) - 6 subjects a month
Diagnosis and Main Inclusion Criteria	Stage II or III women with ER+, HER2-negative breast cancer
Study Product(s), Dose, Route, Regimen	Letrozole 2.5 mg PO daily; Ribociclib 600 mg PO daily 21 days on/7 days off; Ribociclib 400 mg continuous daily dosing.
Duration of Administration	22 weeks
Reference Therapy	Letrozole 2.5 mg (control arm)
Statistical Methodology	In the ACOSOG Z1031 study, 16% of the patients in the letrozole alone arm had a PEPI score of 0. The sample size of this trial was determined with the assumption that 16% of the patients taking letrozole will have a PEPI score of 0. Assuming that addition of ribociclib will increase the rate of PEPI 0 by 20%, 80 women in the two treatment arms (B+C) and 40 women in the control arm (A) are needed to show significance.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background:

Breast cancer accounts for an estimated 232,670 of all cancer cases in 2014 with an estimated 40,000 deaths in 2014 (Howlader 2011). The majority of breast cancer occurs in postmenopausal women, and 80% of cases are ER+ (Anderson 2002). Because the majority of patients are diagnosed with early stage disease and are ER+, this group accounts for a large percentage of breast cancer recurrences and deaths.

Adjuvant therapy following surgery has significantly improved breast cancer outcome. In ER+ breast cancer, systemic chemotherapy followed by endocrine treatment with tamoxifen has been shown to decrease breast cancer mortality rate by one half (Early Breast Cancer Trialists' Collaborative 2011). Adjuvant aromatase inhibitors (AIs) in early stage breast cancer has further reduced the recurrence rate, however a significant number of patients experience recurrence of disease despite the current standard treatment. Using a median follow-up of 120 months, patients enrolled in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, experienced recurrence in 20% and 24% of patients treated with 5 years of adjuvant anastrozole and tamoxifen, respectively, with a persistent risk of relapse over time observed in both treatment arms [Cuzick 2010]. Thus, there is a need to improve the current standard therapy.

1.2 Rationale for neo-adjuvant endocrine therapy for early breast cancer:

Despite the success of adjuvant therapy, evaluation of new agents in this setting has traditionally required large number of patients and years of follow up to demonstrate the effectiveness in reducing cancer relapse and/or mortality. Use of surrogate endpoints for disease free survival (DFS) and overall survival (OS) in the neo-adjuvant setting would allow drug screening and expedite the drug development process. Furthermore, response to neo-adjuvant endocrine therapy may help clinicians to identify endocrine sensitive tumors that would not require adjuvant chemotherapy. In addition, the neoadjuvant setting has become an important research tool in studying mechanisms of endocrine resistance [Ellis 2004].

1.3 Rationale for including stage II and stage III patients for neo-adjuvant endocrine therapy:

Neoadjuvant endocrine trials of aromatase inhibitors have shown objective response rates of between 37% and 60% and conversion from mastectomy to BCS in up to 50% of patients [POL trial, IMPACT trial, P24 trial (below)]. In these studies, all of whom included women with clinical stage II and III, ER positive breast cancer, progression of disease on therapy occurred in <10% of patients. Thus, progression on an AI is an uncommon event.

Many randomized trials of neo-adjuvant endocrine therapy using an AI have been completed and many such trials are ongoing. A summary of these is outlined below. All of these trials have included stage II and stage III patients and were approved by the respective regulatory authorities:

POL trial (Olson 2009) was a single arm phase II trial of women with clinical stage II and stage III ER positive breast cancer in which 106 patients with good performance status were enrolled. Clinically node positive patients were included. Early (4 week) Ki67 of ≤10% was predictive of freedom from relapse. Only 1/41 patients who had a Ki67 of ≤10% at 4 weeks had a relapse with no adjuvant chemotherapy. Thus, on therapy Ki67 response to neo-adjuvant endocrine therapy predicts endocrine sensitive disease and therefore predicts relapse. Conversely, women with Ki67 of >10% had a RFS of 23% (5/21), indicating endocrine resistance.

In the IMPACT trial (Smith 2005, Dowsett 2007), patients with operable or locally advanced breast cancer including clinically node positive patients were included. Although clinical response was not predictive of RFS, 2 week Ki67 was. Patients who had Ki67 ≤10% at 2 weeks had a RFS of 11% (13/118), without adjuvant chemotherapy. Similar to the POL trial, RFS was 26% if 2 week Ki67 was >10%.

The P024 trial randomized patients with clinical stage II or III ER+ breast cancer to letrozole or tamoxifen in the neoadjuvant setting (Eiermann 2011). The primary endpoint was clinical response which was higher in the letrozole arm (55% vs 36%). No relapses were observed in patients with PEPI score of 0 (see section on PEPI below). In a combined analysis of POL and P24 trials, no relapse was observed in patients with a PEPI score of 0, after a FU of 62.5 months.

It is therefore clear that on-therapy assessment of short term Ki67 and of PEPI score at surgery is able to identify a group of women with clinical stage II or III breast cancer who have such a low relapse rate that they can consider foregoing adjuvant chemotherapy. Moreover, these data establish that the benefits of neoadjuvant endocrine therapy are very similar to neoadjuvant chemotherapy, i.e., not only improving surgical outcomes (POL trial) and response rates (P024 trial), but determining “on treatment” prognosis based on the response of the primary tumor to neoadjuvant therapy. Furthermore, the rather uncommon rate of clinical progression (<10%) in addition to the on therapy assessment of Ki67 and PEPI makes it a safe intervention for this group of women.

The ongoing Alliance trial A011106 is a randomized trial of stage II and stage III ER positive breast cancer. Sample size of this trial is 2820 patients. It includes stage II and stage III postmenopausal women (including T4 and clinical N3 disease), randomized to Anastrozole or Anastrozole + Fulvestrant. Short term Ki67 and PEPI scores are the main endpoints. This large trial designed by a co-operative group and approved by the regulatory authorities is a testament that neo-adjuvant endocrine therapy is considered a standard of care for this population.

The NCCN guidelines Version 3.2015 states that preoperative endocrine therapy alone may be considered for receptor positive disease in postmenopausal women who have stage II and III breast cancer, including T4 and N3 disease.

1.4 Rationale for using letrozole as the standard arm:

Neoadjuvant endocrine therapy with an AI such a letrozole has become a standard of care in postmenopausal women with ER+ breast cancer because of improvement in the rate of breast conserving surgery observed in previous neoadjuvant tamoxifen and aromatase inhibitor trials [Chia 2010]. In the letrozole P024 trial, 337 previously untreated ER+ and/or PR+ post-menopausal breast cancer patients were randomized between 2.5mg of letrozole or 20mg of tamoxifen daily for 4 months followed by surgery (Eiermann 2011). The clinical response rate was superior in the letrozole group (55% vs 36%, p<0.001). The secondary endpoint, qualification for breast conserving surgery, was improved in the letrozole group (45% letrozole vs 25% tamoxifen, p=0.02). Furthermore, the reduction in proliferation marker Ki67 was greater with letrozole over tamoxifen (87% vs 75%, p=0.0009).

1.5 Study Agent (s) Background and Associated Known Toxicities:

Ribociclib is an orally bioavailable highly selective small molecule inhibitor of CDK4/6. CDK4/6 induces G1 arrest in a variety of pRb positive cancer cells, in vitro. In the mammalian cell cycle, entry into S phase is achieved by cyclin-dependent kinases 4 and 6 (CDK4/6) that activates a family of E2F transcription factors by phosphorylating and deactivating the retinoblastoma

protein (pRb). Several lines of evidence suggest that increased CDK4/6 activity contributes to tumorgenesis. Agents that inhibit the activity of CDK4/6 may be able to slow or stop the proliferation of these cancers and thereby function as effective anti-cancer drugs.

Elimination of ribociclib is dominated by oxidative metabolism mainly via CYP3A4 with a minor contribution by flavin-containing monooxygenase 3 (FMO3). The elimination of ribociclib may be affected by co-administered drugs that inhibit or induce CYP3A4.

Based on its mechanism of action, the results of the preclinical toxicology studies and available clinical safety data as of September 10, 2014, the following are identified as the main adverse reactions for ribociclib: bone marrow suppression including leukopenia, neutropenia, anemia, and thrombocytopenia, renal toxicity, fatigue, nausea, vomiting, abdominal pain, diarrhea, pneumonia and prolongation of the QT interval. The risk of these toxicities may be amplified by concomitant administration of strong inhibitors of CYP3A4 or other combination treatments.

1.6 Rationale for combining CDK4/6 inhibitor ribociclib and letrozole:

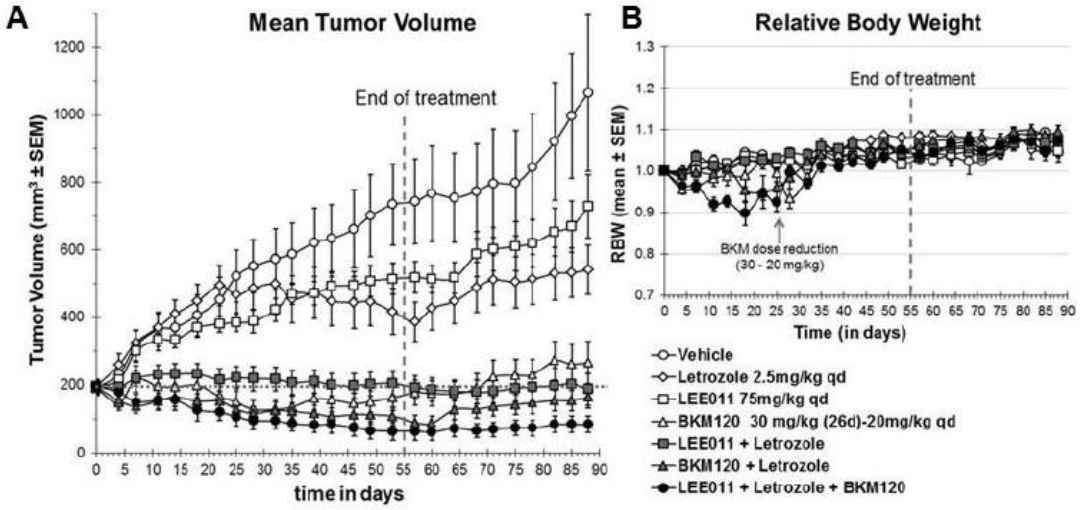
Ribociclib has shown activity in ER+ breast cancer and has been evaluated in combination with letrozole in phase I studies. Tumor growth delay was seen in the letrozole plus ribociclib arm.

Palbociclib is a CDK4/6 inhibitor, similar to ribociclib, being developed by Pfizer. In the phase II study, continuous daily letrozole was administered at 2.5 mg with or without palbociclib at 125 mg daily for 3 weeks followed by 1 week of rest until progression. Patients with postmenopausal ER+, HER2-negative advanced breast cancer were randomized in a 1:1 ratio in two parts, Part 1 contained 66 patients and Part 2 had 99 patients. Data from the combination of both groups (n = 165) were present at the AACR meeting in 2014. The median PFS was 20 months with letrozole plus palbociclib compared with 10 months for letrozole alone (hazard ratio [HR] =0.5, $p < .0004$). The combination resulted in a response rate of 45% compared with 31% for the monotherapy. The overall clinical benefit rate was 70% versus 44%, for the combination and single-agent, respectively (Finn 2014)).

Ribociclib has demonstrated *in vivo* anti-tumor activity in subsets of tumor xenograft models. Consistent with the compounds mechanism of action, efficacy was only observed in tumors expressing pRb. Tumor types where ribociclib has demonstrated robust anti-tumor activities include but are not limited to breast, melanoma, neuroblastoma, malignant rhabdoid, lung, pancreas and hematological malignancies (Ribociclib IB Edition 7, 9/10/2014).

The combination of ribociclib with the nonsteroidal aromatase inhibitor letrozole was evaluated using a primary model of ER+ breast cancer derived from a patient tumor with a known sensitivity to letrozole (see Figure below). Tumor growth delay was seen in the letrozole plus ribociclib arm, confirming the potential for full stabilization with the double combination. These data provide strong rationale for the combination of CDK4/6 inhibitors with modulators of the estrogen receptor pathway such as letrozole (Ribociclib IB Edition 7, 9/10/2014).

Figure 4-10 **LEE011, buparlisib (BKM120) and letrozole in ER+, PIK3CA wild type, breast cancer patient-derived xenograft model**



In a phase Ib/II, multicenter, study, the combination of ribociclib with letrozole in adult patients with advanced ER+ breast cancer is being studied. Three arms (ribociclib + letrozole, BYL719 + letrozole, ribociclib + BYL719 + letrozole) are included in this study. The primary endpoints of the study are to estimate the MTD(s) and/or RP2D(s) for the 3 combinations. The phase Ib part is followed by a phase II part to compare the clinical efficacy of ribociclib + BYL719 + letrozole compared with ribociclib + letrozole or BYL719 + letrozole. The study is currently in the dose escalation phase Ib part. As of 28-Mar-2014, 17 patients have been enrolled: 10 have been treated with at least one ribociclib dose 600 mg PO daily (3-weeks-on/1-week-off) + 2.5 mg letrozole PO once-daily.

The median age of 10 patients treated with ribociclib was 59 (range: 45–67) years, all the patients were female, and the distribution of ECOG performance status of 0/1 at baseline was 5/5 patients, respectively. Among 10 patients treated with ribociclib, 2 patients were discontinued from the study due to progressive disease and 8 patients were still ongoing. Among 10 patients treated with ribociclib, the only grade 3 or 4 toxicity was neutropenia, which occurred in 50% of the patients.

In addition to the intermittent dosing regimen, continuous dosing of ribociclib at 600 mg, 400 mg, and 300 mg has been evaluated in 18 patients. The median age of patients in continuous dosing schedule was 57 years. Male/female ratio was 5/13. Treatment has been discontinued in 12 patients, only one discontinuation has been due to toxicity and remaining due to disease progression. A total of 5 events meeting the DLT criteria were observed in 5 patients and included grade 3 febrile neutropenia (n=1), grade 3 neutropenia (n=2), grade 4 neutropenia (n=1), grade 3 ALT increase (n=1). In the 5 patients receiving 400 mg continuous dosing, only one patient had grade 3 or 4 neutropenia. (Ribociclib IB Edition 8, 9/7/2015).

Given that the safety and efficacy of letrozole is well-established, the 1:1:1 randomization (letrozole plus placebo vs. letrozole plus continuous dosing of ribociclib vs. letrozole plus intermittent dosing (3-weeks-on/1-week-off) of ribociclib) increases a patient's opportunity of

receiving a potentially active combination. It also allows for the collection of more data from the two experimental arms to better evaluate the biological activity of treatment with ribociclib plus letrozole for future design of clinical trials.

Ribociclib has mostly been studied with 3-weeks-on/1-week-off dosing (above). However, ribociclib is a cytostatic agent and there is potential for tumor escape during the off week. Continuous dosing will potentially prevent the potential for tumor escape. A lower dose of ribociclib, 400 mg will be used given the safety of this dose in the continuous fashion. This dose of 400 mg is less than 50% of the single agent MTD of ribociclib (900 mg 3 weeks on/1 week off).

1.7 Preoperative Endocrine Prognostic Index (PEPI) Score as a surrogate marker at surgery to identify women with excellent outcomes without adjuvant chemotherapy:

Whereas pathologic complete response is an excellent surrogate biomarker of outcomes in women receiving neoadjuvant chemotherapy, the incidence of pCR is extremely low after neoadjuvant endocrine therapy and is not a useful marker (Calleoni 2004). Clinical response, which is measured by calipers or measuring tapes was the primary endpoint in the four major randomized neoadjuvant aromatase inhibitor (AI) studies conducted in postmenopausal women with stage II-III ER+ breast cancer, including the P024 trial (Letrozole vs Tamoxifen) [Eiermann 2001], the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial [Smith 2005], and the Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) trial [Catallioti 2006], which compared an AI to tamoxifen, and the recently reported ACOSOG Z1031 (letrozole vs anastrozole vs exemestane) that compared the three AIs [Ellis 2011]. Secondary endpoints of these studies have included radiologic response and breast conservation rate. These endpoints are unsatisfactory since 1) measurement of clinical responses vary between individual examiners; 2) radiological response may not truly reflect tumor response; and 3) surgical outcome are impacted by bias and practice differences among surgeons. More importantly, clinical response rates did not correlate well with outcomes in the large IMPACT trial.

The P024 trial randomized patients with clinical stage II or III ER+ breast cancer to letrozole or tamoxifen in the neoadjuvant setting. The primary endpoint was clinical response which was higher in the letrozole arm (55% vs 36%). In a multivariable analysis conducted on this trial, 4 post-neoadjuvant endocrine therapy tumor factors were determined to have independent prognostic value for relapse and death after relapse and are included in the PEPI score [Ellis 2008]. These included pathological tumor size (T1/2 versus T3/4), pathological node status (positive or negative), the natural logarithm of the Ki67 value and the ER status of the tumor. A prognostic score, the preoperative endocrine prognostic index (PEPI), was developed, which weighs each of these factors according to their associated hazard ratios. PEPI was then validated in an independent data set from the IMPACT trial [Ellis 2008]. No relapses were recorded in either trial in patients with T1, N0 tumors with a PEPI score of 0 (residual tumor with Ki67 index of 2.7% - natural logarithm of 1- or less with maintained ER expression) or in the rare patient with a pCR. PEPI has also recently been validated in the POL Trial (PreOperative Letrozole trial: A multicenter phase II trial of letrozole in postmenopausal women with clinical stage II or III hormone receptor positive breast cancer) [Olson 2009]. In the combined analysis of P024 trial/POL trial, no relapse was observed with a median follow up of 61.3 months in the 24 patients (16 pT1N0, 8 pT2N0) in the PEPI 0 category.

Thus, with the above data, our primary objective is to determine if ribociclib in combination with letrozole as a 24 week neoadjuvant endocrine therapy increases the proportion of endocrine sensitive tumors with a PEPI score 0, compared to patients treated with letrozole alone. An

increase in the proportion of women with a PEPI score of 0 will increase the number of women with endocrine sensitive disease that would have excellent outcomes without receiving cytotoxic chemotherapy.

1.8 Rationale for day 14 biopsy for Ki67 assessment:

One of the shortcomings of PEPI score is that although it is a robust predictor of outcome without adjuvant chemotherapy, PEPI information is only available at surgery, after neo-adjuvant therapy is complete. Thus, there is a need for on therapy assessment of a marker that is able to identify endocrine sensitivity and resistance early on during neo-adjuvant endocrine therapy. Data from previous neoadjuvant endocrine trials indicate that 2-4 week tumor Ki67 expression on endocrine therapy is predictive of individual patient outcome long term [Dowsett 2007]. In the IMPACT trial, 2-week Ki67 was a significant independent predictor of RFS (HR = 1.95; 95% CI = 1.23–3.07; P = .004) [Dowsett 2007]. The 5-year RFS rates were 85%, 75%, and 60% for the lowest, middle, and highest values of 2-week Ki67 expression, respectively. In addition, patients who had Ki67 of ≤10% at 2 weeks had a risk of recurrence of 11% (13/118), without adjuvant chemotherapy. Conversely the risk of recurrence was 26% if 2 week Ki67 was more than 10%. Similar to the IMPACT trial, early (4 week) Ki67 of ≤10% was predictive of relapse in the POL trial (Olson). Only 1/41 patients who had Ki67 of ≤10% had a relapse with no adjuvant chemotherapy. Thus, on therapy response to neo-adjuvant endocrine therapy predicts endocrine sensitive disease and therefore predicts relapse. Conversely, women with Ki67 of >10% had a RFS of 23% (5/21), indicating endocrine resistance. Day 14 determination of Ki67 will allow us to detect breast tumors with endocrine resistance (Ki67 of >10%) early on toward the beginning of therapy. These patients will be offered immediate surgery or neo-adjuvant chemotherapy at the discretion of the treating oncologist.

1.9 Standard treatment options for the study population:

Besides participation in this clinical trial, other options for women with stage II and III, ER+ breast cancer include standard neoadjuvant endocrine therapy with an aromatase inhibitor for 4-6 months followed by surgery, primary surgery followed by adjuvant therapy, or neo-adjuvant chemotherapy followed by surgery.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective:

- To determine if ribociclib in combination with letrozole as a 24 week neoadjuvant endocrine therapy increases the proportion of women with PEPI score of 0 at surgery compared to patients treated with placebo and letrozole therefore allowing more patients to have excellent outcomes without chemotherapy.

2.2 Secondary Objectives:

- To determine if ribociclib in combination with letrozole as a 24 week neoadjuvant endocrine therapy increases the proportion of tumors with complete cell cycle arrest (defined below) compared to placebo and letrozole therefore increasing the number of women who would have excellent outcomes with endocrine therapy alone.

- To determine if ribociclib in combination with letrozole for 24 weeks results in improved 5 year RFS compared to letrozole alone.

- To examine the differences in clinical, pathologic and radiologic response rates between the two ribociclib containing arms (combined) vs letrozole. An increase in response rate

with the addition of ribociclib will be an indication of synergistic activity of ribociclib when combined with letrozole and will help design future adjuvant trials.

- To examine the difference in clinical, pathologic and radiologic response as well as PEPI scores between the three treatment arms.

- To examine if short term Ki67 expression at 2 weeks and degree of Ki67 suppression compared to baseline differs between the two ribociclib containing arms (combined) vs letrozole.

2.3 Exploratory Objectives:

- To evaluate tumor tissue, serum, and plasma specimens collected at baseline, on-therapy, and at surgery for biomarker discovery (through methods such as gene expression profiling, DNA and RNA sequencing and proteomics) in studies that aim to understand signaling pathways associated with endocrine therapy sensitivity and pathways of resistance.

2.4 Primary Endpoint:

- Rate of PEPI score 0 at surgery between ribociclib containing arms (combined) vs letrozole alone arm. PEPI score 0 is defined as**:**
    - pT stage 0, 1 or 2 at surgery, after 24 weeks of neoadjuvant therapy
    - Negative axillary lymph nodes present at surgery
    - Ki67 of ≤ 2.7% at surgery
    - Tumor is ER+ at surgery.

2.5 Secondary Endpoints:

- Rate of complete cell cycle arrest at 2 weeks between ribociclib containing arms (combined) vs letrozole alone arm: Complete cell cycle arrest is defined as Ki67 at day 14 of ≤ 2.7%.

- Pathologic complete response rate (pCR rate): pCR rate is defined as the proportion of patients with no histologic evidence of invasive tumor cells in the surgical breast specimen and the axillary lymph nodes.

- Clinical complete response rate (cCR rate): cCR rate is defined as the proportion of patients with no residual tumor by clinical exam.

- 5 year RFS

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria:

Subjects must meet all of the inclusion criteria to participate in this study.

3.1.1 Ability to understand and the willingness to sign a written informed consent

3.1.2 Pathologically confirmed invasive breast cancer by core needle biopsy

3.1.3 Female subjects, age ≥ 18 years.

3.1.4 Only postmenopausal women will be eligible. Subjects will be classified as being postmenopausal if they have had:

- Bilateral surgical oophorectomy, or
- No spontaneous menses > 1 year or
- No menses for < 1 year with FSH and estradiol levels in postmenopausal range, according to institutional standards

3.1.5 Performance Status ECOG 0-2

3.1.6 Invasive breast cancer must be ER+ in ≥66 % of the cells or ER Allred score 6-8. If ER is positive in < 66%, the staining intensity (weak, intermediate, strong) is needed to calculate the Allred Score to determine eligibility. In institutions where ER expression is classified only by <1%, 1-10%, and >10% cut-offs, >10% expression is required for inclusion.

3.1.7 Invasive breast cancer must be HER2 negative. HER2 negative is defined as a single test or both tests used to determine HER2 status (ISH and IHC) show:

- IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within > 10% of the invasive tumor cells;
- IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of the invasive tumor cells
- ISH single-probe average HER2 copy number < 4.0 signals/cell
- ISH dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell

3.1.8 Documentation of mammogram, ultrasound and MRI of the ipsilateral breast all performed within 42 days prior to registration.

3.1.9 Clinical T2-T4c, (by clinical measurement and/or breast imaging), any N, M0 invasive breast cancer, by AJCC 7th edition clinical staging, with the goal being surgery to complete excision of the tumor in the breast and the lymph node. For clinically node positive disease, any T is allowed. Palpable breast primary is not required.

Note:

- Patients with contralateral invasive breast cancer are not eligible.
- Patients with ipsilateral multifocal/multi-centric invasive breast cancer are eligible. The largest lesion will be evaluated for response assessment and calculation of PEPI score.
- Patients with ductal carcinoma in situ in either breast are eligible.

3.1.10 Tissue acquisition: Subject must agree to provide the required research biopsies at baseline, at day 14 (+7 d) and at surgery for biomarker and correlative studies.

3.1.11 Subject has adequate bone marrow and organ function as defined by the following laboratory values at screening:

- Absolute neutrophil count ≥ 1500 /uL
- Platelets ≥ 100,000 /uL
- Hemoglobin ≥ 9.0 g/dL
- Potassium, total calcium (corrected for serum albumin), magnesium, sodium and phosphorus within institutional upper limit of normal (IULN) or corrected to within normal limits with supplements before first dose of study medication.

(Supplements used for this purpose to be approved by PI). However, if the investigator believes the lab abnormalities are minor and clinically insignificant, the patient may be enrolled in the study.

- INR ≤ 1.5
- Serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 50mL/min
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5 x ULN.
- Total bilirubin ≤ IULN; or total bilirubin ≤ 3.0 x IULN or direct bilirubin ≤ 1.5 ULN in patients with well documented Gilbert's Syndrome.

3.1.12 Subject has fasting cholesterol panel and triglyceride done before first treatment

3.1.13 Must be able to swallow ribociclib / placebo capsules

3.2 Exclusion Criteria:

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

3.2.1 Current use of other investigational agents.

3.2.2 Inflammatory breast cancer defined as clinically significant erythema of the breast and/or documented dermal lymphatic invasion (not direct skin invasion by tumor or peau d'orange without erythema).

3.2.3 An excisional biopsy of this breast cancer

3.2.4 Surgical axillary staging procedure prior to study entry.

Note: FNA or core needle biopsy of axillary node is permitted.

3.2.5 Hormone replacement therapy of any type, megestrol acetate, or raloxifene within four weeks prior to first study treatment.

3.2.6 Clinical or radiographic evidence of metastatic disease. Metastatic workup is not required.

Note: isolated ipsilateral supraclavicular node involvement is permitted

3.2.7 Treatment for this cancer including surgery, radiation therapy, chemotherapy, biotherapy, hormonal therapy or investigational agent prior to study entry.

3.2.8 History of invasive breast cancer prior to the current diagnosis.

3.2.9 Patient has a known hypersensitivity to any of the excipients of ribociclib or Letrozole.

3.2.10 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.

3.2.11 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).

3.2.12 Patient has a known history of HIV infection (testing is not mandatory).

3.2.13 Patient has any other concurrent severe and/or uncontrolled medical conditions 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.). Hepatitis testing at screening is not mandatory, but may be done per investigator discretion.

3.2.14 Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects (tumor biopsy is not considered a major surgery).

3.2.15 Patient with Child-Pugh score B or C

3.2.16 Patient has a history of non-compliance to medical regimen or inability to grant consent.

3.2.17 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.

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

3.2.19 Clinically significant, uncontrolled heart disease and/or recent events 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 12 months prior to screening.
- History of documented congestive heart failure (New York Heart Association functional classification III-IV)
- Documented cardiomyopathy
- Patient has a Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) at screening
- History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality within 12 months of screening
- Congenital long QT syndrome or family history of long QT syndrome
- Bradycardia (heart rate <50 at rest), by ECG or pulse, at screening
- Systolic blood pressure (SBP) >160 mmHg or <90 mmHg at screening.

3.2.20 On screening, inability to determine the QTcF interval on the ECG (i.e.: unreadable or not interpretable) or QTcF> 450 msec (using Fridericia's correction). All as determined by screening ECG.

3.2.21 Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to starting study drug (**APPENDIX B**):

- Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pomelos, star fruit, and Seville oranges
- Those having a narrow therapeutic window and are predominantly metabolized through CYP3A4/5
- Those having a known risk to prolong the QT interval or induce Torsades de Pointes
- Herbal preparations/medications as listed in Appendix B

3.3 Staging Criteria:

Subjects will be staged prior to registration according to the clinical staging criteria adapted from the American Joint Committee on Cancer (AJCC) Cancer Staging Data Forms of the AJCC

Cancer Staging Manual, 7th Edition, 2009.

4.0 TREATMENT

4.1 Treatment Dosage and Administration:

Arm A (Control):

Agent	Dose and Route	Day	Schedule
Letrozole	2.5 mg daily by mouth	Days 1-28	Every 4 weeks x 6 cycles
Ribociclib matching placebo (random assignment of placebo)	3 capsules daily by mouth **or** 2 capsules daily by mouth	Days 1-21 (21 days on, 7 days off) **or** Days 1-28	

Arm B (Experimental):

Agent	Dose and Route	Day	Schedule
Letrozole	2.5 mg daily by mouth	Days 1-28	Every 4 weeks x 6 cycles
Ribociclib	600 mg daily by mouth (3 capsules of 200 mg)	Days 1-21 (21 days on, 7 days off)	

Arm C (Experimental):

Agent	Dose and Route	Day	Schedule
Letrozole	2.5 mg daily by mouth	Days 1-28	Every 4 weeks x 6 cycles
Ribociclib	400 mg daily by mouth (2 capsules of 200 mg)	Days 1-28	

- Protocol treatment to begin within 14 days of randomization
- Each cycle is 28 days (+/-3 days) or 4 weeks, except cycle 6 (see below).
- Surgery must be performed between days 8-22 of cycle 6.

4.1.1 Ribociclib or Placebo must be taken as follows:

- Subjects should be instructed to take the ribociclib/placebo capsules with a large glass of water (~250mL) at the same time each day.

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

4.1.2 Letrozole should be taken at the same time each day with water.

4.2 Treatment assignment and randomization:

Each subject is identified in the study by a Subject Number (Subject No.) that is assigned when the subject is first enrolled and is retained as the primary identifier for the subject throughout her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database.

Subjects will be randomized 1:1:1 to one of **three** treatment arms (Section 4.1). Within the placebo arms, subjects will be randomized to either receive ribociclib placebo on days 1-21 or days 1-28 of each cycle.

A randomization scheme (block of randomization numbers) will be sent to each affiliate site from the University of Kansas Biostatistics Department. This will be maintained in a location accessible only to designated unblinded personnel OR unblinded pharmacist. Subjects will be assigned to the next sequential number corresponding to the treatment assignment. Only the affiliate site unblinded pharmacists will have access to the treatment assignment to maintain the blind. The unblinded pharmacist will prepare and label the study medication in a blinded fashion for dispensing.

4.3 Schedule of evaluations:

4.3.1 Tumor (breast and axilla) will be clinically assessed by measuring tape, ruler or caliper prior to the start of study treatment, every four weeks (+/- 3 days) during, and at the discontinuation of neo-adjuvant endocrine therapy. Bi-dimensional measurements should be obtained using the same technique (measuring tape, ruler or caliper) and if possible, by the same person at each evaluation.

4.3.2 Mammogram, MRI and ultrasound of the diseased breast will be performed at baseline and a mammogram and ultrasound will be performed at completion of neoadjuvant therapy. A MRI of the breast at completion of treatment may be performed at the discretion of treating physician (surgeon).

4.3.3 A core biopsy of the breast cancer will be performed on Day 14 (+7d) of cycle 1 and Ki67 will be measured. If the Ki67 is expressed in >10% of the cells, subject will be taken off the study treatment and treatment will be provided at the discretion of the treating physician. See section 9 for details regarding details of specimen handling and turnaround time for this Ki67 measurement. Any chemotherapy administered prior to

surgery will be recorded. Tumor biopsies for research and Ki67 calculation at surgery will be performed per Section 6.5.3.

4.3.4 MRI of the breast will be performed after completion of 2 cycles of treatment (Day 1 of cycle 3 (+/- 7 days) for response assessment. If there is evidence of progression on MRI, subject will be taken off the study and treatment will be provided at the discretion of the treating physician.

4.3.5 If there is physical evidence for clinical progression with bi-dimensional measuring tape, ruler or caliper tumor measurements of the primary tumor an MRI should be done to confirm/rule out progressive disease. If there is physical evidence for clinical progression with clinical assessment of the lymph node mass, an ultrasound of the axilla should be done to confirm/rule out progressive disease.

4.3.6 If progression is confirmed by MRI of the breast or ultrasound of axilla, subject will be taken off the study and treatment will be provided at the discretion of the treating physician, such as surgery as soon as possible or to begin other anti-neoplastic approaches such as chemotherapy.

NOTE: Other anti-neoplastic approaches such as chemotherapy or radiation must not be administered while the patient is taking study drug.

4.3.7 Study drug should be continued until the day before surgery. If immediate surgery is the decision, due to disease progression, collect the core biopsies (two frozen and two formalin fixed) and the correlative blood samples at the time of surgery. See section 9.

4.3.8 If the subject is to discontinue her assigned neo-adjuvant therapy and go on to receive non-protocol treatment, correlative blood specimens and core biopsies (two frozen and two formalin fixed) should be obtained before discontinuing assigned neoadjuvant treatment.

4.3.9 If disease progression is not confirmed by MRI of breast or US of axilla, study drug may be continued at the investigator's discretion.

4.3.10 Clinical progression outside the primary site (i.e., the development of a new breast mass or the development of clinical suspicion for advanced disease) should lead to further imaging evaluation and if confirmed, study drug will be discontinued after correlative samples of the primary tumor have been obtained. Subsequent management is at the investigator's discretion.

4.4 Dose modifications and management of toxicity for Letrozole:

There will be no letrozole dose reductions. If unanticipated grade 3 or 4 toxicity is encountered, which is considered at least possibly related to letrozole, the patient will be discontinued from letrozole therapy. Missed doses of letrozole are not made up.

4.5 Dose modifications and management of toxicity for Ribociclib/Placebo:

For severe adverse reactions the following dose reduction guidelines will be used:

ARM B (Intermittent dosing arm)	**Ribociclib/Placebo**	
	Dose	**Number of capsules**
Starting dose	600 mg	3 x 200 mg capsules
First dose reduction	400 mg	2 x 200 mg capsules
Second dose reduction	200 mg	1 x 200 mg capsule
Discontinue	NA	NA

ARM C (Continuous dosing arm)	Ribociclib/Placebo	
	Dose	**Number of capsules**
Starting dose	400 mg	2 x 200 mg capsules
First dose reduction	200 mg	1 x 200 mg capsule
Discontinue	NA	NA

If a patient discontinues ribociclib/placebo, she will continue on study taking letrozole alone.

If a patient requires a temporary hold of study drug on Day 1 of a cycle, Day 1 will be delayed until patient restarts study drug. There is no need to repeat all procedures listed for Day 1 in Section 5.0.

4.5.1 Ribociclib/Placebo dose adjustment and management recommendation for related hematological adverse reactions:

Toxicity/Grade	**Dose Adjustment and Management Recommendations**
Thrombocytopenia	
Grade 1 (≥ 75,000 /uL)	No dose adjustment required.
Grade 2 (50,000/uL - < 75,000/uL)	Dose interruption until recovery to ≥ 75,000/uL. Re-initiate ribociclib/placebo at the same dose.
Grade 3 (25,000/uL - < 50,000/uL)	Dose interruption until recovery to grade ≥ 75,000/uL. Re-initiate ribociclib/placebo at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to ≥ 75,000/uL and reduce ribociclib/placebo to the next lower dose level.
Grade 4 (< 25,000/uL)	Dose interruption until recovery to ≥ 75,000/uL. Re-initiate ribociclib/placebo at the next lower dose level. If toxicity recurs at grade 4: discontinue ribociclib.
Absolute neutrophil count (ANC)	
Grade 1 (≥ 1,500/uL)	No dose adjustment required.
Grade 2 (1,000 - < 1,500/uL)	No dose adjustment required.
Grade 3 (500 - < 1,000/uL)	Dose interruption until recovery to > 1,000/uL. Re-initiate ribociclib/placebo at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to > 1,000/uL and reduce ribociclib/placebo dose to the next lower dose level.
Grade 4 (< 500/uL)	Dose interruption until recovery to > 1,000/uL. Re-initiate ribociclib/placebo at the next lower dose level. If toxicity recurs at grade 4: temporary dose interruption until recovery to > 1,000/uL and reduce ribociclib/placebo at the

	next lower dose level.
Febrile neutropenia	
Grade 3 ANC < 1,000/uL with a single temperature > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than one hour	Dose interruption until ANC ≥ 1,000/uL and no fever. Restart at the next lower dose level. If febrile neutropenia recurs: discontinue ribociclib/placebo.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib/placebo.
Anemia (Hemoglobin)	
Grade 1 (≥ 10 g/dL)	No dose adjustment required.
Grade 2 (8 – 10 g/dL)	No dose adjustment required.
Grade 3 (< 8 g/dL)	Dose interruption until recovery to ≥ 8 g/dL. Re-initiate ribociclib/placebo at the same dose.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib/placebo.

4.5.2 Recommendations for Ribociclib/Placebo dose modification in case of related hepatic toxicities

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 1 > IULN – 1.5 x IULN (confirmed 48 to 72hrs later)	Maintain dose level with LFTs monitored bi-weekly
Grade 2 > 1.5 – 3.0 x IULN	Dose interruption of ribociclib/placebo If resolved to ≤ grade 1 in ≤ 21 days, maintain dose level If resolved to ≤ grade 1 in > 21 days or toxicity recurs, reduce 1 dose level If toxicity recurs after two dose reductions, discontinue ribociclib/placebo
Grade 3 > 3.0 – 10.0 x IULN	Dose interruption of ribociclib/placebo If resolved to ≤ grade 1 in ≤ 21 days, reduce 1 dose level If resolved to ≤ grade 1 in > 21 days or toxicity recurs, discontinue ribociclib/placebo
Grade 4 > 10.0 x IULN	Discontinue ribociclib/placebo

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 IULN) due to hemolysis or Gilbert Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. Hepatitis testing is not mandatory; to be done per investigator discretion.

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

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
AST or ALT	
AST or ALT without bilirubin elevation > 2 x IULN	
Same grade as baseline or increase from baseline grade 0 to grade 1 (confirmed 48 to 72 hrs later)	No dose adjustment required with LFTs monitored per protocol if same grade as baseline or bi-weekly, in case of increase from baseline grade 0 to 1.
Increase from baseline grade 0 or 1 to grade 2 > 3.0– 5.0 x IULN or from baseline grade 2 to grade 3 > 5.0 – 20.0 x IULN	Dose interruption of ribociclib/placebo. If resolved to ≤ baseline value in ≤ 21 days, then maintain dose level If resolved to ≤ baseline value in > 21 days or toxicity recurs, then reduce 1 dose level If toxicity recurs after two dose reductions or recovery to ≤ baseline value is > 28 days, discontinue ribociclib/placebo
Increase from baseline grade 0 or 1 to grade 3 > 5.0 – 20.0 x IULN	Dose interruption of ribociclib/placebo until resolved to ≤ baseline value, then lower 1 dose level of ribociclib/placebo If recovery to ≤ baseline value is > 28 days, discontinue ribociclib/placebo If toxicity recurs, discontinue ribociclib/placebo
Grade 4 > 20.0 x IULN	Discontinue ribociclib/placebo
AST or ALT and concurrent Bilirubin	
AST or ALT ≥ grade 2 > 3 x IULN in patients with normal values at baseline and total bilirubin > 2 x IULN Or AST or ALT ≥ grade 3 > 5 x IULN in patients with grade 1 or 2 at baseline, and total bilirubin > 2 x IULN	Discontinue ribociclib/placebo
Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new liver metastasis, and alcohol intake.	

4.5.3 Additional follow-up for related hepatic toxicities

Hepatic toxicity monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2 x IULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT. For patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only.

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

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or return to normal values.
- Obtaining a more detailed history of current symptoms.
- Obtaining a more detailed history of prior and/or concurrent diseases.
- Obtaining a history of concomitant drug use (including non-prescription medications, herbal and dietary supplements), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; hepatotropic virus infections (CMV, EBV or HSV); autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease. Hepatitis testing is not mandatory; to be done per investigator discretion.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.
- Assessing cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure as possible etiologies for liver dysfunction.

4.5.4 Ribociclib/placebo dose adjustment and management recommendation for related non-hematological adverse reactions

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

4.5.5 Dose modification guidance in case of QT prolongation

Grade	Dose Modification
For all grades	• Check the quality of the ECG • Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If below the lower limit of normal, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal • Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval • Check compliance with correct dose and administration of ribociclib
1	No dose adjustment required.

QTcF 450-480 ms	
2 QTcF 481-500 ms	Interrupt ribociclib Perform a repeat ECG one hour after the first QTcF of ≥481ms If QTcF <481 ms, restart ribociclib at the same dose. No dose adjustment required for the first occurrence • If QTcF remains ≥481 ms, repeat ECG as clinically indicated until the QTcF returns to <481 ms. Restart ribociclib at the same dose level. No dose adjustments required for first occurrence. • If QTcF ≥481 ms recurs, ribociclib should be reduced by 1 dose level (please refer to the dosing schedule table) Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patient who has therapy interrupted due to QTcF ≥481 ms
3 QTcF ≥ 501 ms on at least two separate ECGs	Interrupt ribociclib/placebo • Consider consulting a local cardiologist • Perform a repeat ECG one hour after the first QTcF of ≥501 ms. • If QTcF remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 481 ms. • If QTcF returns to < 481 ms, ribociclib/placebo should be reduced by 1 dose level (please refer to the dosing schedule table). Repeat ECGs 7 days and 14 days after dose resumption for any patient who has therapy interrupted due to QTcF ≥ 501 ms • If QTcF of ≥ 501 ms recurs, discontinue ribociclib/placebo
4 QT/QTcF ≥ 501 **or** > 60 ms change from baseline **and** Torsades de pointes **or** polymorphic ventricular tachycardia, **or** signs/symptoms of serious arrhythmia	Discontinue ribociclib/placebo • Obtain local cardiologist consultation • Perform a repeat ECG one hour after the first QTcF of ≥501 ms If QTcF remains ≥501 ms, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to <501 ms.

4.5.6 Management of All Other Related Adverse Reactions:

Consider performing an analysis of serum potassium, calcium, phosphorus, and magnesium, for all adverse reactions that are potentially associated with electrolyte imbalance (e.g. diarrhea, nausea/vomiting). If the electrolyte values are below the lower limit of normal, interrupt ribociclib administration, correct electrolytes with supplements as soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes.

4.6 Surgery:

4.6.1 Schedule: Surgery should be scheduled during days 8-22 of the 6th cycle of neoadjuvant endocrine therapy. Protocol therapy will be continued until the day before surgery.

Note: A surgical delay beyond the time frame described above, requires a discussion with the principal investigator or co-investigator. Given the subject population (older with co-morbid illnesses) it may be appropriate for a subject to remain on the endocrine agent to allow a delay in surgery to allow a recovery from inter-current illness for example. These issues will be dealt with on a case-by-case basis.

4.6.2 Breast surgery: The type of breast surgery (either mastectomy or lumpectomy) is determined by the treating surgeon according to institutional standard, with the goal to

completely excise the tumor. A negative margin is required unless further excision is not possible.

4.6.3 Lymph node surgery: The type of lymph node surgery (sentinel lymph node with or without axillary lymph node dissection) will be determined by the treating surgeon according to institutional standard.

4.6.4 Surgical pathology report: Size of the breast tumor; number of lymph nodes examined and the number of positive by H&E staining; final tumor margins; and extent of surgery should be reported with submission of surgical and pathology reports.

4.6.5 Required tissue sampling at surgery: Two core biopsies frozen in separate blocks and two formalin-fixed core biopsies should be obtained (preferred). Tumor samples may also be removed by dissection of the surgical specimen (not preferred) as long as the samples are frozen or fixed within 30 minutes of removal from the subject. In addition, slides for PEPI score will be collected from fixed surgical pathology tumor tissue blocks.

4.7 Postoperative chemotherapy:

PEPI 0 Group: Adjuvant chemotherapy is not recommended. However, decision regarding use of adjuvant chemotherapy will be left to the discretion of treating physician.
PEPI >0 Group: Adjuvant chemotherapy is recommended at the discretion of treating physician and will be documented by online data submission. Subject may participate in other adjuvant clinical trials.

4.7.1 Postoperative endocrine therapy

In subjects who received adjuvant chemotherapy, adjuvant endocrine therapy is to be administered within 2-8 weeks of the completion of adjuvant chemotherapy based on evaluation of chemotherapy related toxicities.

In subjects for whom adjuvant chemotherapy is not planned, adjuvant endocrine therapy is to be administered within 2-8 weeks postoperatively.

5.0 Study Calendar: (Cycle length is 28 days)

	Screening[A]	Prior to start of study treatment	Day 14 of Cycle 1 (+7 days)	Day 1 of Cycles 2-6 (+/-3 days)	Day 1 of Cycle 3 (+/- 7 days)	EOT Days 8-22 of Cycle 6	EOT (any reason other than treatment completion)	SURGERY
Informed Consent	X							
Medical History/Demographics	X							
Review Eligibility Criteria	X							
Physical Exam (including vitals, height & weight)	X			X			X	
Prior & Concomitant Medications[J]	X			X			X	
Performance Status	X			X			X	
Adverse Event Assessment	X			X			X	Days 8-22 of Cycle 6
CBC, CMP, PT/INR	X			X		X[I]	X	
Magnesium, Phosphorus	X							See section 5.1 for post-op follow-up
Fasting Lipid Profile	X			X[E]				
Urinalysis	X			X			X	
Measurement of breast lesions[B]	X			X			X	Research biopsies will be obtained at surgery (G)
Randomization		X						
Drug dispensing		X		X				
Drug compliance assessment (Participant Pill Diary Review)				X			X	
Mammogram, US of breast/axillary masses	X[C]					X	X	
MRI breast	X				X	X[H]	X	
ECG	X			X				
Echocardiogram	X[F]							
Tumor Biopsies	X[D]		X[D]			X[G]	X[G]	
Research blood samples	X[D]					X	X	

See footnotes below

A. No more than 21 days prior to registration
B. Using a standard cm calibrated caliper, measuring tape or ruler, the longest axis and the perpendicular axis of the tumor are to be measured and recorded in metric notation. Baseline evaluation should be done no more than 21 days prior to initiation of study therapy.
C. Baseline mammogram, MRI and ultrasound of the diseased breast must be completed within 42 days of registration. MRI must include bi-dimensional breast tumor measurements. Mammogram of the contralateral breast is required to be within 12 months unless a mastectomy was performed. If a subject cannot have an MRI for any reason they will still be able to enroll. US and mammogram alone will then be used for tumor assessments.
D. Pre-treatment core biopsies and research blood sample for correlative studies are required prior to the initiation of protocol therapy. Samples obtained at the time of diagnosis before registration may be submitted if they were collected according to the tissue acquisition instructions outlined in protocol (Section 9). It is advised that the baseline samples are harvested during ultrasound guided clip placement (section 9). A core biopsy will also be performed on day 14 and Ki67 will be calculated. If more than 10% of the cells express Ki67, subject will be removed from the study.
E. Fasting Lipid Profile at Screen and Cycle 4 only.
F. ECHO at screening and as clinically indicated throughout dose administration
G. Required research tumor tissue biopsies will be obtained at the time of surgery. Sample submission for Ki67 and correlative studies is required (Section 9). Calculation of PEPI score is described in Section 2.4)
H. May be obtained at the discretion of the surgeon.
I. CBC only
J. Concomitant medications will be reviewed at each study visit, only prohibited concomitant medications will be entered into the CRFs

5.1 Post-Operative Study Calendar

	Post-Op 1-4 weeks	Post-Op 2-8 weeks	Every 6 mo Years 1-5[F]	Once per year Years 1-5
Medical History/Demographics	X			
Clinical Breast Exam	X		X	
Physical Exam (including vitals, height & weight)	X			
Prior & Concomitant Medications[G]	X			
Performance Status	X			
Adverse Event Assessment	X			
Adjuvant Therapy		X[A, C]		
Endocrine Therapy		X[B]		
Adjuvant Radiation		X[D]		
Mammogram				X[E]

A. Adjuvant therapy should begin 2-8 weeks following the last surgery date.
B. Standard adjuvant endocrine therapy of treating physician's choice is administered for 4.5 years. Participation in other adjuvant trials is permitted.
C. The choice and regimen of adjuvant chemotherapy is at the discretion of the treating physician. Participation in other adjuvant trials is permitted
D. Administration of whole breast radiation, rather than partial breast or brachytherapy, is recommended for patients in whom adjuvant radiation is indicated.
E. Patients with breast tissue remaining will undergo annual mammograms of both breasts.
F. The timing of the office visit and imaging is also documented if recurrence is suspected.

G. Concomitant medications will be reviewed at each study visit, only prohibited concomitant medications will be entered into the CRFs

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures:

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

All screening procedures must be performed within 21 days prior to registration unless otherwise stated. The screening procedures include:

6.1.1 Informed Consent

6.1.2 Medical history

Complete medical, surgical and oncology history is obtained at screening. Any changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

6.1.3 Demographics

Demographic profile will include date of birth, gender, race, and zip code.

6.1.4 Review subject eligibility criteria

Review of eligibility criteria as described in Section 3 to ensure subject qualification for study entry.

6.1.5 Review previous and concomitant medications

All prior medication taken by the subject within 4 weeks before starting the study is to be recorded. Concomitant medications taken by the subject during the study are to be recorded up until 30-days after last study dose. If a reportable adverse event (see Section 7) occurs within 30-days after last study dose, recording of concomitant medications should continue until resolution of the adverse event.

6.1.6 Physical exam including vital signs, height and weight

Vital signs (temperature, pulse, blood pressure), height, weight

6.1.7 Performance status (APPENDIX A): Performance status evaluated prior to study entry

6.1.8 Adverse event assessment

Baseline assessment of subject status for determining adverse events. See Section 7 for Adverse Event monitoring and reporting.

6.1.9 Hematology

Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential.

6.1.10 Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, total bilirubin, magnesium, and phosphorus. PT/INR.

6.1.11 Serum fasting lipid panel

6.1.12 Urinalysis

6.1.13 Tumor Biopsies for research: See Section 9.0 for details

6.1.14 Blood draw for correlative studies: See Section 9.0 for details.

6.1.15 Tumor assessment

- Using a standard cm calibrated caliper, measuring tape or ruler, the longest axis and the perpendicular axis of the tumor are to be measured and recorded in metric notation. Baseline evaluation should be done no more than 21 days prior to initiation of study therapy.
- Baseline mammogram, MRI and ultrasound of the diseased breast must be completed within 42 days of registration. MRI must include bi-dimensional breast tumor measurements. Mammogram of the contralateral breast is required to be within 12 months unless a mastectomy was performed.

6.1.16 Other: ECG, Echocardiogram.

6.2 Day 14 (+7 days) of Cycle 1 (28 day cycle): Tumor Biopsies for research and calculation of Ki67.

6.3 Day 1 (+/-7 days) of Cycle 3 (28 day cycle): MRI of the breast for response assessment.

6.4 Days 1 (+/-3 days) of Cycle 2-6 (28 day cycle):

6.4.1 Physical exam including vital signs, height and weight

6.4.2 Performance status (APPENDIX A): Performance status evaluated at every cycle.

6.4.3 Adverse event assessment: See Section 7 for AE monitoring and reporting.

6.4.4 Hematology

Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential.

6.4.5 Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. PT/INR

6.4.6 Urinalysis

6.4.7 Serum fasting lipid profile (Cycle 4 only)

6.4.8 Tumor assessment

Using a standard cm calibrated caliper, measuring tape or ruler, the longest axis and the perpendicular axis of the tumor are to be measured and recorded in metric notation.

6.4.9 Drug compliance assessment (Participant Pill Diary Review): Letrozole and ribociclib/placebo medication diary is to be used.

6.4.10 Echocardiogram, when clinically indicated

6.4.11 Special consideration at the beginning of cycle 6: In order for the blood counts to be adequate for surgery and for the importance of continuing therapy until the last day prior to surgery (for accurate Ki67 assessment), ANC should be ≥1500/uL and platelet count should be ≥100,000/uL on day 1 of cycle 6. If ANC is <1500 and platelet count is < 100,000 on day 1 of cycle 6, resumption of cycle 6 will be delayed until the recovery of the counts. Growth factor support with filgrastim may be used at the discretion of the

treating physician for ANC <1500 to help with the recovery of the counts at surgery.

6.5 At completion of study treatment – (Days 8-22 of Cycle 6):

6.5.1 Hematology

Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential.

6.5.2 Tumor assessment

Mammogram and ultrasound of the diseased breast. MRI may be obtained at the discretion of the surgeon and must include bi-dimensional breast tumor measurements.

6.5.3 Tumor Biopsies at surgery for research and calculation of Ki67 and PEPI score

See Section 9.0 for details. Required research tumor tissue biopsies can be obtained at the time of surgery. Sample submission for Ki67 and correlative studies is required. Calculation of PEPI score is described in Section 9.

6.5.4 Blood draw for correlative studies: See Section 9.0 for details.

6.6 Discontinuation of therapy for reasons other than treatment completion

See Section 6.8

6.6.1 Physical exam including vital signs, height and weight

6.6.2 Performance Status

6.6.3 Adverse event assessment: See Section 7 for AE monitoring and reporting.

6.6.4 Hematology

Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential.

6.6.5 Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. PT/INR.

6.6.6 Urinalysis

6.6.7 Tumor assessment

Using a standard cm calibrated caliper, measuring tape or ruler, the longest axis and the perpendicular axis of the tumor are to be measured and recorded in metric notation.

Mammogram, ultrasound, and MRI of the diseased breast. MRI must include bi-dimensional breast tumor measurements

6.6.8 Drug compliance assessment (Subject Pill Diary Review): letrozole and ribociclib/placebo. Medication diary is to be used. See APPENDIX F.

6.6.9 Tumor Biopsies at surgery for research and calculation of Ki67 and PEPI score

See Section 9.0 for details. Required research tumor tissue biopsies can be obtained at the time of surgery. Sample submission for Ki67 and correlative studies is required. Calculation of PEPI score is described in Section 9.

6.6.11 Blood draw for correlative studies: See Section 9.0 for details.

6.7 Follow-Up:

Subjects who have been registered to the study and signed a consent form, but have withdrawn consent prior to receiving any study therapy will be considered a cancellation. No further follow-up is required.

Subjects who discontinue their assigned neoadjuvant therapy due to progression, treatment refusal, intolerable toxicity, desire for alternative non-protocol therapy or other trials, or are unable/unwilling to undergo surgery will enter the follow-up phase of the study.

After the completion of neoadjuvant endocrine therapy and surgery, subjects will enter the follow-up phase of the study, where they will undergo disease evaluations every 6 months of years 1-5.

6.8 Removal of Subjects from Study Treatment and Study:

Subjects can be taken off the study treatment and/or study at any time by their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

6.8.1 Subject voluntarily withdraws from treatment (subject agrees to follow-up)

6.8.2 Subject withdraws consent (termination of treatment and follow-up)

6.8.3 Subject is unable to comply with protocol requirements

6.8.4 Subject demonstrates disease progression

6.8.5 Subject experiences toxicity that makes continuation in the protocol unsafe

6.8.6 Treating physician judges continuation on the study would not be in the subject's best interest

6.8.7 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

6.8.8 Lost to follow-up.

If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented.

7.0 ADVERSE EVENTS

7.1 Definitions:

7.1.1 Adverse Event [21 CFR 312.32(a)]

An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

This study will use the descriptions and grading scales from Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) for hematologic and non-hematologic toxicities. Detailed information may be found on the Cancer Therapy Evaluation Program (CTEP) website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Information for adverse events, whether reported by the subject, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported in the CRF as described in the following sections.

Adverse events experienced by subjects will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of protocol therapy. Subjects who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the principal investigator. Study subjects should also be instructed to report any new serious post-study event(s) that might reasonably be related to participation in this study.

Medical conditions/diseases, or cancer related symptoms present before starting study treatment are considered adverse events only if they worsen after initiation of study drug. Adverse clinical events occurring before starting study drug but after signing the informed consent form are to be recorded on the CRF where Medical History/Current Medical Conditions are recorded. All cancer-related symptoms that have occurred in the last 30 days prior to start of study drug must also be recorded on the CRF.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or require therapy. In this case they will be recorded on the Adverse Events CRF, along with the associated signs, symptoms or diagnosis. As far as possible, each adverse event will also be described by:

- its duration (start and end dates)
- grading of severity
- its relationship to the study drug
- the action(s) taken
- outcome

7.1.2 Suspected Adverse Reaction [21 CFR 312.32(a)]

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event. Inherent in this definition, and in the requirement to report suspected adverse reactions, is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event.

Factors to be considered in assessing the relationship of the adverse event to study drug include:

- The temporal sequence from study drug administration: The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subject's response after study drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual subject's pharmacodynamics should be considered.

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

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

7.1.3 Unexpected [21 CFR 312.32(a)]

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

This definition relies entirely on a listing of the adverse events or suspected adverse reactions in the investigator brochure as the basis for determining whether newly acquired information generated from clinical trials or reported from other sources is unexpected. This means that events not listed for the particular drug under investigation in the investigator brochure are considered "unexpected" and those listed are considered "expected." When new adverse event information is received, it is the sponsor's responsibility to determine whether the event is "unexpected" for safety reporting purposes.

7.1.4 Serious [21 CFR 312.32(a)]

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important

medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.5 Life-threatening

An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.2 Reporting Requirements for Adverse Events:

7.2.1 Submitting Serious Adverse Events Reports to IRB

For serious adverse events, the clinical research site will follow local IRB policies and procedures.

7.2.2 Study Investigator Notification of Adverse Events

All **expected** and **unexpected** serious adverse events occurring after the subject has signed the informed consent and has started protocol treatment must be reported to the study principal investigator within 24 hours of becoming aware of the event:

PI Name: Qamar Khan
Office Phone: 913-710-6387
Fax: 913-588-4085
Email: qkhan@kumc.edu

7.2.3 DSMC Notification of SAEs

All **expected** and **unexpected** serious adverse events occurring after the subject has signed the informed consent and has started protocol treatment must be reported by phone or email to the KUCC DSMC within 24 hours of becoming aware of the event to:

KUCC DSMC
Email: kucc-dsmc@kumc.edu

A follow-up written report in the form of MEDWATCH Form FDA 3500A is required within 5 days.

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

MEDWATCH Form FDA 3500A must be faxed to:
Novartis Drug Safety and Epidemiology Safety Desk
877-778-9739

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

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

7.2.5 Pregnancies

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

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

7.2.6 Recording Adverse Events and Documentation in eVELOS

All **expected** and **unexpected** adverse events and serious adverse events occurring after the subject has signed the informed consent and has started protocol treatment must be fully recorded in the subject's case record form.

All AEs and SAEs regardless of causality must be entered in the KU implementation of eVELOS, (also often called the Comprehensive Research Information System [CRIS]). All SAEs regardless of causality must be entered into eVELOS within 24 hours. Unexpected and expected adverse events must be entered within 15 days and include: new unexpected adverse events; worsening baseline conditions; clinically significant laboratory findings; disease-related signs and symptoms that were not present at baseline, and any event or findings that the Investigator feels is clinically significant.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

7.2.7 Reporting of Unexpected, Related SAEs for Concomitant Medications

For concomitant medications, all unexpected, related serious adverse experiences will be forwarded to the product manufacturer by the investigator using the Voluntary MEDWATCH Form FDA 3500A.

7.2.8 Summary of Expedited Serious Adverse Event Reporting

	Relationship to Study Drug	KUCC DSMC	IRB	Novartis	PI	Velos
Unexpected SAE	Related	24 hrs	Follow local IRB reporting requirements	24 hrs	24 hrs	24 hrs
Unexpected SAE	Not-related	24 hrs		24 hrs	24 hrs	24 hrs
Expected SAE	Related	24 hrs		24 hrs	24 hrs	24 hrs
Expected SAE	Not-related	24 hrs		24 hrs	24 hrs	24 hrs

8.0 DRUG INFORMATION

8.1 Letrozole (Please refer to package insert for more comprehensive information):

- Other names for the drug(s): Femara
- Classification - type of agent: Non-steroidal aromatase inhibitor
- Mode of action: In postmenopausal women, the principal source of circulating estrogen (primarily estradiol) is conversion of adrenally-generated androstenedione to estrone by aromatase in peripheral tissues, such as adipose tissue, with further conversion of estrone to estradiol. Many breast cancers also contain aromatase; the importance of tumor-generated estrogens is uncertain.
- Letrozole is a potent and selective non-steroidal aromatase inhibitor. It significantly lowers serum estradiol concentrations and has no detectable effect on formation of adrenal corticosteroids or aldosterone.
- Storage and stability: Controlled room temperature
- How supplied: 2.5 mg tablet
- Route of administration for this study: Oral (non-liquid only). Take with or without food.
- Potential drug interactions: Letrozole is generally safe to administer with other medicines. However, concomitant use of agents and herbal products that alter ER function are specifically not allowed.
- Availability: Provided by Novartis
- Side effects: Hot flashes, asthenia, arthritis, pain, pharyngitis, HTN, depression, nausea, vomiting, rash, osteoporosis, fractures, headache, bone pain.

8.2 Ribociclib:

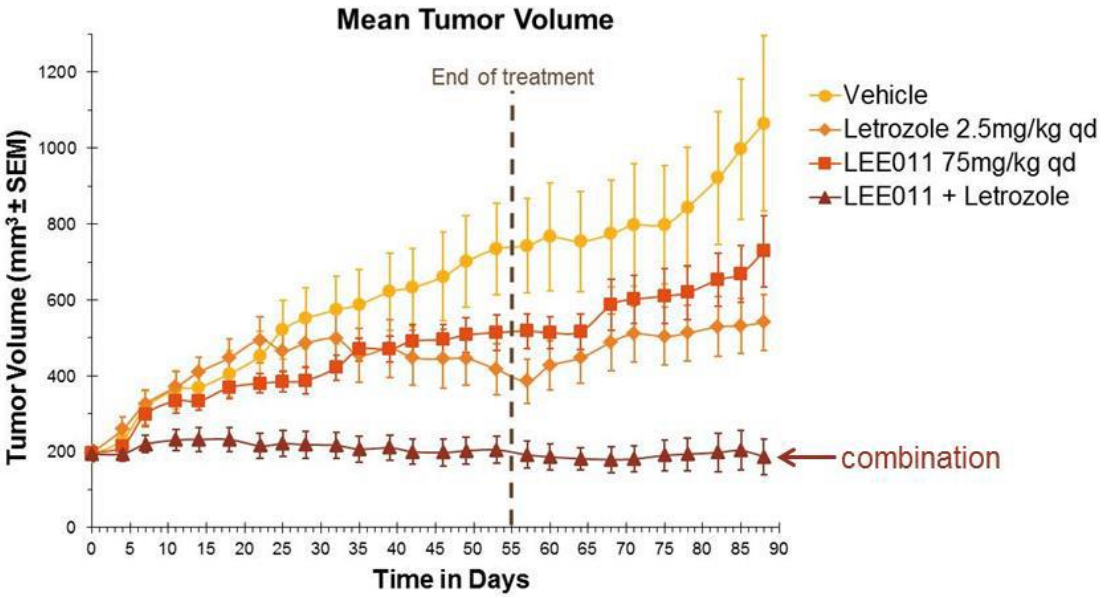
Ribociclib is an orally bioavailable, highly selective small molecule inhibitor of CDK4/6 that potently induces G1 arrest with sub-micromolar IC50's in a variety of pRb-positive cancer cells.

- Other names for the drug(s): LEE011
- Classification: CDK4/6 inhibitor
- Non-clinical pharmacology:
- In Jeko-1 MCL cells that overexpress cyclin D1 as a result of the t (11; 14) chromosomal translocation, ribociclib inhibits the phosphorylation of pRb at CDK4/6-specific sites with an average IC50 of 60 nM. In nude rats bearing Jeko-1 subcutaneous xenografts, ribociclib demonstrates dose-dependent target inhibition in the tumors. Ribociclib doses that induce >75% inhibition of pRb phosphorylation in this model are associated with complete tumor regression. Ribociclib also inhibits the growth of many other tumor cell types *in vitro* and in vivo, including liposarcoma, melanoma, rhabdoid cancer, and

carcinomas of the esophagus, breast, lung and pancreas. Regardless of the various genetic aberrations that may be present in the cancer cells, the anti-tumor activity of ribociclib requires the presence of functional pRb. Refer to Ribociclib (LEE011) Investigators Brochure for more details.

- Preclinical data with ribociclib in a primary model of ER+ breast cancer demonstrated synergy when given in combination with letrozole, showing complete and sustained inhibition of tumor growth (Figure below).

Figure: Ribociclib in combination with letrozole in an ER+ primary breast cancer model



Mean tumor volumes in mice treated at clinically relevant doses for 56 days with ribociclib (75 mg/kg qd) alone; letrozole (2.5 mg/kg qd) alone; ribociclib (75 mg/kg qd) plus letrozole (2.5 mg/kg qd); or vehicle. The combination arm shows complete inhibition of tumor growth that was sustained for more than 30 days of post-treatment observation.

Nonclinical pharmacokinetics and metabolism:
The pharmacokinetics (PK) of ribociclib was investigated in mouse, rat, dog and monkey. The absorption of ribociclib after oral administration was moderate for rats (48-84%). Oral bioavailability (BA) ranged between 10% and 65% across animal species. Time to maximum plasma drug concentration (Tmax) was between 2 and 4 hours. Terminal half-life (T1/2) of ribociclib was moderate in rodents and monkeys (~2-5 hours), and was longer in dogs (18 hours). Ribociclib is moderately bound to plasma proteins in all animal species with unbound fractions in plasma (fu) ranging from 20-34% (human fu = 30%). [3H]Ribociclib and metabolites were extensively distributed to tissues in male rats, but there was no uptake into the brain. *In vitro* metabolism studies showed that oxidative metabolism of ribociclib is dominated by CYP3A4 with a minor contribution of about 20% by flavin-containing monooxygenase 3 (FMO3). In rat ADME studies, ribociclib was predominantly excreted in the bile as metabolites, with limited excretion of unchanged drug in urine. The bulk of the administered dose (87%) was excreted within 24 hours. LEQ803 (N-demethylation) is a prominent metabolite in rat, monkey, and human hepatocytes, and the only metabolite in dog hepatocytes. LEQ803 is weakly pharmacologically active; however, it interacts with hERG channels *in vitro*.

Ribociclib is a time-dependent CYP3A4 inhibitor (KI = 5.1 μM, kinact = 0.0245 min-1) and a reversible inhibitor of CYP1A2 at higher concentrations (Ki = 16 μM). Ribociclib is a low affinity substrate of P-glycoprotein (P-gp/MDR1). Ribociclib inhibits MDR1 (IC50 = 143 μM), mitoxantrone-resistant protein (MXR/BCRP) (IC50 = 24 μM) and human bile salt export pump (BSEP) (IC50 = 4.7 μM), but not rat or dog BSEP. Additionally, ribociclib has been found to inhibit OCT1 (Ki = 17.3 μM), OATP1B1 (Ki = 42.9 μM), OCT2 (Ki = 1.9 μM), MATE1 (Ki = 1.7 μM) and MATE2K (Ki = 31 μM). Overall, the elimination of ribociclib may potentially be affected by co-administered drugs that inhibit or induce CYP3A4. Ribociclib may inhibit substrates of CYP3A4, CYP1A2, BSEP, OCT2, and MATE1 if sufficiently high concentrations are achieved *in vivo*. At the recommended dose for future development (600 mg), steady-state plasma Cmax ranges from 859-5860 ng/mL (geometric mean = 1940 ng/mL or 4.46 μM) [Ribociclib Investigator's Brochure].

In GLP toxicology studies, ribociclib and LEQ803 exposure (Cmax and AUC0-24h) generally increased in a dose proportional manner in rats and dogs. Gender-differences in PK were observed in rats, with higher exposure (Cmax and AUC) to ribociclib and LEQ803 in males as compared to females, however no gender differences were identified in dogs.

Clinical experience with Ribociclib:

Ribociclib is being evaluated as a single agent in an ongoing phase I study in adult patients with solid tumors and lymphoma [CLEE011X2101], in pediatric patients [CLEE011X2102], and in adult Japanese patients with solid tumors [CLEE011X1101]. In addition, several combination studies (with investigational and/or approved drugs) [CLEE011X2105, CMEK162X2114] are ongoing or in study start-up phase. More specifically, several studies are ongoing or planned for investigating the safety and efficacy of ribociclib in combination with various hormonal agents such as letrozole [CLEE011X2107, CLEE011A2201, CLEE011A2301], fulvestrant [CLEE011X2108], and exemestane [CLEE011X2106] in patients with ER+ HER2-negative breast cancer.

Clinical safety of LEE011 plus Letrozole:

Study CLEE011X2107 is a phase Ib/II, multicenter study of the combination of LEE011 and BYL719 with letrozole in adult patients with advanced ER+ breast cancer. Three arms (LEE011 + letrozole, BYL719 + letrozole, LEE011 + BYL719 + letrozole) are included in this study. The primary endpoints of the study are to estimate the MTD(s) and/or RP2D(s) for the 3 combinations. The phase Ib part is followed by a phase II part to compare the clinical efficacy of LEE011 + BYL719 + letrozole compared with LEE011 + letrozole or BYL719 + letrozole. The study is currently in the dose escalation part in phase Ib.

As of 28-Mar-2014, 17 patients have been enrolled: 10 have been treated with at least one LEE011 dose (600 mg LEE011 (3-weeks-on/1-week-off) + 2.5 mg letrozole once-daily). The median age of 10 patients treated with LEE011 was 59 (range: 45–67) years, all the patients were female, and the distribution of ECOG performance status of 0/1 at baseline was 5/5 patients, respectively. Among 10 patients treated with LEE011, 2 patients were discontinued from the study (2 due to progressive disease) and 8 patients were still ongoing. Among 10 patients treated with LEE011, all patients experienced at least one AE. The most frequent AEs (≥10%), regardless of grade, causality and LEE011 dose, were neutropenia (90.0%); nausea (40.0%); fatigue (30.0%); leukopenia (20.0%); diarrhea, decreased appetite, weight decreased, anemia, constipation, headache, lymphopenia, rash, dyspnea, fever, flushing, increased creatinine, pleural effusion, urinary tract infection and visual impairment (10.0% each).

- How supplied: Ribociclib 200mg and matching placebo will be supplied by Novartis as hard gelatin capsules in bottles of 28 capsules per bottle.

- Route of administration for this study: Oral (Non-liquid only). Can be taken without regard to food.
- Storage and stability: The shelf life of the drug product is established based on ongoing stability studies and may be extended during the clinical study. The capsules are stored in HDPE bottles. According to drug label, storage for the capsules is listed as follows: "Do not store above 25 °C, protect from moisture". However, the drug manufacturer, Novartis, has provided additional stability information, which approves the drug storage methods at ambient temperatures, which are to be used at the University of Kansas (KU) Hospital, Investigational Drug Services (IDS). Documentation of Novartis approval will be kept on file by the University of Kansas (KU) Hospital, Investigational Drug Services (IDS)."
- Potential drug interactions between ribociclib, letrozole and goserelin:
- Letrozole is not expected to affect the metabolism ribociclib, which is mainly metabolized by CYP3A4 with a minor contribution by FMO3 based on *in vitro* data. Letrozole inhibits CYP2A6 (Ki = 4.6 μM) and CYP2C19 (Ki = 42 μM) *in vitro.* Letrozole is not an inhibitor of CYP3A4 or FMO3 and is therefore not expected to affect ribociclib metabolism. The metabolism of goserelin is not CYP-mediated; rather hydrolysis of C-terminal amino acids is the major clearance mechanism. No formal clinical DDI studies have been conducted or reported with goserelin. Based on the available information, goserelin is not expected to affect the metabolism of nor be affected by co-administered drugs (Zoladex® Prescribing Information).
- Side effects: Based on its mechanism of action, the results of the preclinical toxicology studies and available clinical safety data as of September 10, 2014, the following are identified as the main adverse reactions for ribociclib: bone marrow suppression including leukopenia, neutropenia, anemia, and thrombocytopenia, renal toxicity, fatigue, nausea, vomiting, abdominal pain, diarrhea, pneumonia and prolongation of the QT interval. The risk of these toxicities may be amplified by concomitant administration of strong inhibitors of CYP3A4 or other combination treatments.
- Permitted concomitant therapy – See **Appendix D**
- Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed.
- The patient must be told to notify the investigational site about any new medications she takes after the start of the study treatment. All medications (other than study drugs) and significant non-drug therapies (including vitamins, herbal medications, physical therapy and blood transfusions) administered within 30 days of study entry and during the study must be listed on the Concomitant medications/Significant non-drug therapies section of the patient record.
- Bisphosphonates and denosumab
- Bisphosphonates and denosumab are permitted for the treatment of osteoporosis and prevention of skeletal related events for patients with bone metastases. Hematopoietic growth factors
- Hematopoietic growth factors may be used according to ASCO guidelines.
- Palliative radiotherapy
- Palliative radiation for bone pain relief is not permitted because metastasis in not permitted in this study. Refer to the ribociclib (LEE011) Investigator's Brochure [If applicable: and other drug package insert], Table 1, and Table 2 for information on possible interactions with other drugs.

8.3 Permitted concomitant therapy requiring caution:

- Medications to be used with caution during ribociclib and letrozole treatment in this study are listed in Appendix C. 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 ribociclib interruption if the concomitant medication is only needed for a short time (APPENDIX C):
- 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

8.4 Prohibited concomitant therapy:

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

- Strong inhibitors or inducers of CYP3A4/5
- Substrates of CYP3A4/5 with a narrow therapeutic index
- Medications that carry a known risk for QT prolongation
- Herbal medications/preparations, dietary supplements (unless approved for participant use by PI).
- Other investigational and antineoplastic therapies not part of the study

8.5 Study Drug Packaging and Labeling:

Study Treatment	Packaging	Labeling
Ribociclib /Placebo	Capsules in bottles	Labeled as 'LEE011/placebo'

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

NOTE – per agreement with representatives of the manufacturer, Novartis and their provision of additional stability information, drug storage methods at ambient temperatures is approved. These methods are to be used at the University of Kansas (KU) Hospital, Investigational Drug Services (IDS). Documentation of Novartis approval will be kept on file by the University of Kansas (KU) Hospital, Investigational Drug Services (IDS). Affiliate sites will follow the same guidelines for study drug storage as the University of Kansas (KU) Hospital, Investigational Drug Services (IDS), and documentation of the agreement with the drug manufacturer, Novartis regarding drug storage methods will be provided to the affiliate sites upon request.

8.6 Return and Retention of Study Drug:

Remaining drug is to be destroyed, according to University of Kansas Investigational Drug Services or affiliate site's destruction policy.

8.7 Drug Accountability/Subject Compliance:

Records of study medications used, dosages administered, and intervals between visits will be kept during the study. Subjects will be asked to fill out a pill diary and bring with them for review after each cycle of study treatment.
Drug accountability will be noted at the completion of the trial. Subjects must return all unused medication at each visit and end of study.

9.0 Sample collection and storage for future correlative studies

Tissue samples will be collected and stored as below, at baseline, Day 14 (+7) of Cycle 1, and at the time of surgery for biomarker analysis including ER and Ki67 and for future correlative studies. In addition, blood will be collected for serum, plasma, and germ-line and cell free DNA and stored at baseline for future correlative studies. The correlative studies will be performed in collaboration with Dr. Cynthia Ma at the Siteman Cancer Center and Dr. Yuan Yuan and Dr. Shiuan Chen at the City of Hope Comprehensive Cancer Center.

Sample Collection/Shipment Kit

The kit is a two-chamber kit in which it is possible to ship both frozen and ambient specimens. The kit is stocked with necessary items needed for blood and tumor sample collection. It also contains the necessary materials used to process and prepare specimens for shipment in accordance to IATA regulations.

Washington University Tissue Procurement Core Facility (WUTPC)
425 S. Euclid Ave, Room 5120
St. Louis, MO 63110-1005
Phone: 314-454-7615
Email: tbank@wudosis.wustl.edu

Sample collection/shipment kits are available for institutions by sending the request to Email: tbank@wudosis.wustl.edu with the subject “FELINE Trial Biopsy Kit Request”.

9.1 Required pre-treatment core biopsy for biomarker and correlative studies:

Samples collection is mandatory for all patients prior to initiating study therapy.

Core biopsy should be performed with image guidance using a 14 gauge needle.
The required biopsies include two core biopsies placed in 10% buffered formalin (a single pre-filled formalin container to hold both cores) and two core biopsies frozen **immediately at bedside** in separate OCT blocks. The cryo kits, formalin containing cup and blood collection tubes will be provided in the sample collection/shipment kits to the sites and are funded by this study.

Tissue may be obtained concurrent with another procedure (clip placement, axillary node biopsy, port placement) or as a separate procedure.

9.2 Required Day 14 (+7) core biopsy for biomarker and correlative studies:

Core biopsy should be performed with image guidance using a 14 gauge needle.
The required biopsies include two core biopsies placed in 10% buffered formalin (a single pre-filled formalin container to hold both cores) and two core biopsies frozen immediately at bedside in separate OCT blocks. The cryo kits, formalin containing cup and blood collection tubes will be provided in the sample collection/shipment kits to the sites and are funded by this study.

9.3 Required post-treatment core biopsy at time of surgery for all patients after the completion of neoadjuvant therapy for correlative studies

Following completion of neoadjuvant therapy, an intra-operative core biopsy of residual tumor prior to its resection is required.

The required biopsies include: Two core biopsies placed in 10% buffered formalin (a single pre-filled formalin container to hold both cores) and two core biopsies **frozen immediately at bedside** in separate OCT blocks to preserve the proteome and transcriptome of the tumor. Biopsy kits will be provided to the sites and are funded by this study.

If an intra-operative core biopsy is not practical, the site pathologist can remove the tumor samples during the dissection of the surgical specimen (using a 5-mm skin punch biopsy device) and samples frozen or fixed within 30 minutes of removal from the patient.

In addition to the above, after the pathological tumor analysis is complete, 10 unstained Superfrost Plus slides cut at 4 microns thickness from the most representative and tumor cell enriched block, and the corresponding pathology report should be submitted for central Ki67 calculation to be used for PEPI assessment. Each research site will be responsible for calculating the PEPI scores for its own specimens.

9.4 Pre and post treatment blood specimen collection and storage:

Blood samples will be collected pre-treatment, at discovery of disease progression or at end of treatment, whichever occurs first. Please see study calendar.

One 10mL lavender top EDTA vacutainer tube (for plasma and buffy coat cell pellet), 1 8.5mL red/black marble top tube (for serum) and 2 10mL Streck BCT tubes (for cell free plasma DNA) will be collected. Sample processing for serum, plasma, and viable buffy coat sections are performed at the participating site and stored at -80ºC before shipment. Streck BCT tube blood is not processed but shipped ambient overnight via the specimen collection/shipment kits with all other samples to the Washington University Tissue Procurement Core Facility (WUTPC) for further processing to cell free plasma.

All samples will be appropriately labeled (study number, subject number and date of collection) before being stored. These samples are going to be used in future studies to assess biomarkers such as tumor markers, cell free tumor DNA, SNPs, genetic changes, etc.

If a subject withdraws from the main study participation and future use of specimens is withdrawn by the subject (submitted in writing to the investigator), best efforts will be made to stop any ongoing studies and to destroy the specimens.

All specimens are to be processed and stored in the WUTPC for a period of 20 years or until used up for future research.

Upon the approval of the study PI, de-identified blood specimens may be shared with potential research collaborators outside of the University of Kansas for biomarker work related only to the hypothesis of this study. Collaborators will be required to complete an agreement (Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of the University of Kansas for publication and any licensing agreement will be strictly enforced.

The following information may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data (which does not include any protected health information)

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by the University of Kansas, the investigator or a collaborating researcher or entity.

9.5 Shipping instructions for all research samples (tissue and blood):

The Washington University Tissue Procurement Core Facility (WUTPC) will store the research samples. The formalin fixed cores in the formalin cup received from the shipment will be further processed for tumor Ki67 at the CLIA certified Anatomic and Molecular Pathology Core Labs (AMP) at Barnes Jewish Hospital at St. Louis (CLIA number 26D2013203). Slides and blocks from AMP will be returned to WU TPC for storage after completion of analysis and reporting.

Specimens collected and preserved from outside sites will be shipped overnight (may use the two-chamber kit to ship both frozen specimens (OCT embedded frozen tumor biopsy cores, serum, plasma and cell pellet) on dry ice and ambient specimens (formalin cup with biopsy cores). A completed shipping manifest will be completed, emailed to the Wash U TPC (Email: tbank@wudosis.wustl.edu), and included in the specimen shipment.

Arrange for Federal Express pick-up through your usual institutional procedure. Ship specimens to the address below:

Washington University Tissue Procurement Core
425 S. Euclid Ave, Room 5120
St. Louis, MO 63110-1005
Phone: (314) 454-7615
E-mail: tbank@wudosis.wustl.edu

On the day that specimens are sent to the specimen bank, please contact the bank by phone, fax, or e-mail to notify what is being sent and when the shipment is expected to arrive.

9.6 Tissue Processing and Ki67:

9.6.1 Baseline and Day 14 (+7d)

Upon receipt of the specimen, the 2 fixed biopsy specimens at baseline and 2-week will be further processed for tumor Ki67 analysis at the CLIA certified Anatomic and Molecular Pathology Core Labs at Barnes Jewish Hospital at St. Louis (CLIA number 26D2013203). After embedding in paraffin, one section from the tumor block will be stained with H&E to assess biopsy adequacy. Another section from the block will be incubated with antibody against Ki67 (clone 30-9) and then assayed using the Ventana Benchmark platform. The block and any remaining sections will be returned to the Tissue Procurement Core Facility at the completion of testing. Both cores will be reviewed and will be taken into account for the scoring.

Ki67 scoring is reported as a quantitative/continuously distributed value. The Ki67 data for Day 14 biopsy is available real time to the treating physician and the patients. Patients will be continued on protocol therapy while awaiting analysis results. Results of tumor Ki67 will be reported within 10 working days upon receipt of the samples. Wash U Coordinator will email and fax the results to both the CRA listed on Specimen Submission CRF that is sent with the tissue samples and Wash U CRA. Contact Wash U coordinator for questions related to the Ki67 result.

Note: If the biopsy yielded no tumor cells, the patient may continue on study drug therapy or proceed with a second biopsy for Ki67 determination.

9.6.2 Surgery

Ki67 on surgical specimen will be performed on one of the 10 unstained slides cut at 4 microns thickness from tumor rich block obtained after breast surgery.

The 2 fixed biopsy cores obtained at surgery time point will be further processed to FFPE core at the CLIA certified Anatomic and Molecular Pathology Core Labs at Barnes Jewish Hospital at St. Louis (CLIA number 26D2013203). After embedding in paraffin, the block will be stored at the Wash U TPC unless Ki67 could not be obtained on the surgical slides, in which case, further sectioning and staining for Ki67 will be performed.

9.7 Correlative studies: See Appendix E.

10.0 Measurement of Effect

10.1 Response Criteria:

10.1.1 Clinical responses will be based on the WHO criteria

Prior to each cycle of neoadjuvant treatment and at the completion of neoadjuvant treatment, the longest axis and the perpendicular axis of the measurable lesion should be measured and recorded in metric notation by bi-dimensional tape, ruler or caliper technique.

Complete Response (CR) is defined as the disappearance of all known disease based on a comparison between the pre-treatment measurements and the measurements taken at the completion of neoadjuvant therapy (that is, at the end of cycle 6 neoadjuvant endocrine therapy). In addition, there is no appearance of new lesions.

Partial Response (PR) is defined as a 50% or greater decrease in the product of the bi-dimensional measurements of the lesion (total tumor size) between the clinical pre-treatment measurements and the clinical measurements taken at the completion of neoadjuvant therapy. In addition, there can be no appearance of new lesions or progression of any lesion.

No Change (NC) occurs when a 50% decrease in total tumor size cannot be established, nor has a 25% increase in the size of the lesion been demonstrated.

10.2 Definition of pathologic response and events during follow up:

- A pathologic complete response is defined as no histology evidence of invasive tumor cells in the surgical breast specimen and sentinel or axillary lymph nodes.
- Following surgery, diagnosis of breast cancer recurrence and other cancer events:

- Local recurrence - Local recurrence is defined as histologic evidence of ductal carcinoma in situ or invasive breast cancer in the ipsilateral breast or chest wall.
- Regional recurrence - Regional recurrence is defined as the cytologic or histologic evidence of disease in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes or soft tissue of the ipsilateral axilla.
- Distant recurrence - Distant recurrence is defined as the cytologic, histologic, and/or radiographic evidence of disease in the skin, subcutaneous tissue, lymph nodes (other than local or regional metastasis), lung, bone narrow, central nervous system or histologic and/or radiographic evidence of skeletal or liver metastasis.
- Second primary breast cancer - Second primary breast cancer is defined as histologic evidence of ductal carcinoma in situ or invasive breast cancer in the contralateral breast or chest wall.
- Second primary cancer (non-breast) - Any non-breast second primary cancer other than squamous or basal cell carcinoma of the skin, melanoma in situ, or carcinoma in situ of the cervix is to be reported and should be confirmed histologically whenever possible.
- Death - Underlying cause of death is to be reported.

10.3 Safety/Tolerability

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

10.4 Central MRI Assessment

Radiographic disease response will be assessed by centralized, blinded group of Breast Radiology experts at KUCC. MRI images performed at baseline and Cycle 3 will be submitted to KUCC. The blinded radiology team will perform an independent review of the MRI images.

11.0 DATA AND SAFETY MONITORING

11.1 Oversight and Monitoring Plan:

The DSMC of the KUCC is responsible for monitoring subject safety for this trial. The DSMC is responsible for:

- Review of all clinical trials conducted by the KUCC for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Submission of recommendations for corrective action to the PI and the Deputy Director of the KUCC or designee.
- Notification of external sites participating in multiple-institutional clinical trials coordinated by the KUCC of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications.

11.2 Review and Oversight Requirements:

a) Serious Adverse Event

Serious adverse events that require expedited reporting will be reviewed by the DSMC Chair or designee who will determine if immediate action is required. Refer to Section 7.2. If determined

to be necessary by the DSMC, all participating sites will be notified of the event and any resulting action within one working day of this determination.

b) Review of Serious Adverse Event Rates
Once per month, serious adverse event rates will be monitored by the DSMC Coordinator. If any study has had 2 or more of the same SAE reported within one month, or more than 6 of the same SAE in 6 months, the DSMC will review summaries of SAEs, and discuss events in detail with the PI. The DSMC chair or designee determines whether further action is required. The DSMC Coordinator ensures that collaborating investigators and IRBs for all Participating sites are notified of any resulting action.

c) Study Safety and Progress
The multidisciplinary KUCC Data and Safety Monitoring Committee (DSMC) is charged with overseeing the monitoring of participant safety, conduct and scientific progress of research protocols, and the validity and integrity of the data for clinical trials. The KUCC DSMC has the authority to require amendments, suspend, or terminate any research activities that fall within its jurisdiction, and can institute other appropriate actions as needed to protect participant safety.

The study will be monitored at appropriate intervals, no less than those assigned by the KUCC Protocol Review and Monitoring Committee, to assure compliance to GCP and to assess the data quality and study integrity. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected.

The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The study monitor will have direct access to source data for data verification. Data verification will be conducted by comparing the data entered into the CRFs with source data

12.0 REGULATORY CONSIDERATIONS

12.1 Protocol Review and Amendments:

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

12.2 Informed Consent:

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated

consent document. The original signed copy of the consent document must be retained in the medical record or research file.

12.3 Ethics and Good Clinical Practice (GCP):

This study is to be conducted according to the following considerations, which represent good and sound research practice:

1. ICH Consolidated Good Clinical Practice: Guidelines (E6)
   www.fda.gov/cder/guidance/iche6.htm
2. US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
   - Title 21 Part 11 – Electronic Records; Electronic Signatures
     www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
   - Title 21 Part 50 – Protection of Human Patients
     www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
   - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
     www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
   - Title 21 Part 56 – Institutional Review Boards
     www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
   - Title 21 Part 312 – Investigational New Drug Application
     www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
3. State laws
4. Institutional research policies and procedures
   http://www2.kumc.edu/researchcompliance/hscpolicies.htm

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.0 REGISTRATION PROCEDURES

13.1 General Guidelines for KUCC and Other Participating Organizations:

Institutions will register eligible subjects through the KUCC Clinical Research Office central registration process. Registration must occur prior to the initiation of therapy. Any subject not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

The completed source documentation provided for eligibility verification and registration must be kept in the subject binder for monitoring purposes and documentation of subject eligibility.

Issues that would cause treatment delays should be discussed with the Principal Investigator. If a subject does not receive protocol therapy following registration, notify the KU Cancer Center Project Director or designee and change the subject's status in the eVELOS system.

13.2 Registration Process for KUCC and Other Participating Centers:

The Coordinating Center (KUCC), specifically the Project Director or designee is accessible for registration Monday through Friday from 8:00 AM to 5:00 PM Central Time.

The registration procedures are as follows:

1. Obtain written informed consent from the subject prior to the performance of any study related procedures or assessments.

2. Complete the appropriate baseline demographic information in eVELOS and the required registration form and inclusion/exclusion criteria checklist using the eligibility assessment documented in the subject's medical/research record. To be eligible for registration to the study, the subject must meet each inclusion and none of the exclusion criteria listed in Section 3.0 of this protocol. The KU department of biostatistics will grant access to eVelos for this study for access to study documents, patient enrollment and data entry into eCRFs.

3. Submit the registration form and inclusion/exclusion criteria checklist to KUMC via email. The KU Project Director or designee will send an email confirmation stating whether or not the subject may enroll.

4. The unblinded pharmacist or designee will assign the subject to a treatment group using sequential assignment of predetermined block randomized 1:1:1 treatment assignments provided by the study statistician prior to activation.

13.3 Unblinding:

Due to the objectives of the study, treatment assignments will not be known to investigators, research staff, or participants. The study blind will be broken on completion of the clinical study and after the study database has been locked.

During the study, the blind may be broken **only** in medical emergencies when knowledge of the participant's treatment group is necessary for further patient management. When possible, the investigator should discuss the emergency with the Sponsor-Investigator prior to unblinding.

If the decision is made to unblind a participant's treatment in a medical emergency, the following steps should be taken:

1. Contact the investigational pharmacy to request unblinding of the participant, providing the pharmacist with the rationale for unblinding.
2. Document the date, time, and reason for the unblinding. This documentation should be archived in the Investigator Site File, the participant's medical records, and in the eCRF.
3. Notify the Sponsor-Investigator and DSMC of the unblinding event.

If a serious adverse reaction is judged *reportable on an expedited basis*, it is recommended that the blind be broken only for that specific participant by the Sponsor-Investigator even if the investigator has not broken the blind. In the case of a SUSAR, the DSMC may be involved to ensure that the study team remains blinded.

If the blind must be broken for a participant, the case should be unblinded only to a limited number of people and access to the case should be limited so that the blind can be maintained as much as possible. It is also recommended that, when possible and appropriate, the blind be maintained for those persons responsible for the analysis and interpretation of results at the study's conclusion.

Reporting of the event will be followed according to FDA and local IRB guidelines depending upon the details of the specific event.

14.0 STUDY MANAGEMENT

14.1 Investigator Files and Retention of Documents:

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified. Original source documents supporting entries in the case report forms include but are not limited to hospital records and clinic charts, laboratory and pharmacy records, ECG, signed ICFs, subject diaries and pathology reports. All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

14.2 Case Report Forms:

Case report forms (CRFs) will be completed for each subject enrolled. All CRFs will be complete and accurate. The medical chart and any other clinical worksheets, procedural reports, etc. are the source of verification of the data captured into the study database.

14.3 Study Monitoring:

The study will be monitored at appropriate intervals to assure compliance to GCP and to assess the data quality and study integrity. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected.

The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit. The study monitor will have direct access to source data for data verification. Data verification will be conducted by comparing the data entered into the CRFs with source data.

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Design/Study Endpoints:

This is a prospective randomized phase II, multi-center study. Refer to protocol Section 2 for study endpoints.

16.0 SAMPLE SIZE JUSTIFICATION AND INTERIM ANALYSIS FOR FUTILITY

In the ACOSOG Z1031 study, 16% of the patients in the letrozole alone arm had a PEPI score of 0. The sample size of this trial was determined with the assumption that 16% of the patients letrozole will have a PEPI 0 score. Assuming that addition of LEE011, either 600 mg for 21/7 scheme (Arm B) or 400mg for 28/28 scheme (Arm C), will increase the rate of PEPI 0 by 20%, and setting Type I error rate of 10% and Type II error rates at 20% (Rubinstein et al., 2005) in the final analysis with an interim analysis at 0.5 information time for futility, a sample size of 80 women in the treatment arms (40 in each arm) and 40 women in the control arm are needed to achieve 80% power in a 1-sided unpooled z-test with continuity correction for Ha: 36% vs.H0: 16%. This calculation was performed on nQuery + nTerim 3.0 using the O'Brian-Fleming spending function, and finds the drift parameter value of 2.224 and the futility lower bound of 0.0876.

Because the total sample size is estimated to be 80 + 40 = 120 patients, the planned 0.5 information time for futility requires 120x0.5 = 60 patients. If the z-statistic is below the aforementioned lower bound 0.0876, the study will be stopped early for futility.

16.1 Accrual rate and study duration:

It is anticipated that 6 subjects per month will be enrolled. Accrual will be completed in 19 months. Pathology data will be available on the last subject 6 months after the accrual is complete. The trial should be completed for the primary endpoint analysis in 26 months after accrual is initiated.

16.2 Data Analysis Plans:

Although the trial is designed with 3 arms, the hypotheses concern about the comparisons of the two treatment arms combined vs. the control, hence 2-sample methods are planned.

The primary endpoint

The frequency and proportion of patients with PEPI score 0 at surgery will be reported for each arm. The 1-sided 90% confidence intervals (CI) will also be computed for the difference of proportions. The proportions will be compared between treatment (Letrozole with 2 ribociclib arms combined) and control by 1-sided unpooled z-test with continuity correction for both the interim futility and the final analyses at 0.02 and 0.094 significance level, respectively, to retain a cumulative 0.10 significance level. The trial will be stopped early if the z-value in the futility analysis is below the boundary of 0.0876.

The secondary endpoints

The secondary objectives concern about four endpoints. Among them, the three binary endpoints (Complete cell cycle arrest, pCR, cCR) will be analyzed in the same way as the primary endpoint described above but they will not be analyzed for futility.

The Ki-67 level is often skewed in its distribution and will be summarized by median and corresponding 95% CI (use e.g. the CIPCTLDF option in PROC UNIVARIATE, SAS) for each arm. The Ki-67 may take zero values and will be square-root transformed, and compared between arms by 1-sied 2-sample t-test, or by Wilcoxon rank-sum test if transformations fail to make distributions approximately normal.

The 5-year relapse-free survival and corresponding confidence interval will be estimated by Kaplan-Mayer estimator for each arm, and compared between treatment arms combined vs. control by 1-sided log-rank test.

Significance for the secondary endpoints will be assessed at 0.05 significance level.

In addition, we will explore differences between the two treatment doses by 2-sided Fisher's exact test, 2-sided t- or Wilcoxon test, and 2-sided log-rank test at 0.05 significance level.

Interim analysis

Since the patient accrual was almost complete by the time first 60 patients had complete information regarding PEPI scores, interim analysis will not be performed.

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18.0 APPENDICES

Appendix A: Performance Status

Zubrod (ECOG) Performance Scale

POINT	DESCRIPTION
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 self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of 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 B: List of prohibited medications during study drug treatment[5]

Category	Drug Name
Strong CYP3A inhibitors	Boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, voriconazole
Strong CYP3A inducers	Avasimibe[3], carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[3]
Medications with a known risk for QT prolongation[4]	Amiodarone, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, flecainide, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, moxifloxacin, pentamidine, pimozide, probucol, procainamide, quinidine, sotalol, sparfloxacin, terfenadine, thioridazine, vavdetanib
CYP3A substrates with NTI[1]	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine
Other investigational and antineoplastic therapies	Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the study drug.
Herbal preparations/ medications	Herbal preparations/medications are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, black cohosh, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

[2] Herbal product

[3] P-gp inducer

[4] Source: www.crediblemeds.org

[5] Topical preparations are allowed

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

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, darunavir, diltiazem, dronedarone, fluconazole, fosamprenavir, grapefruit juice (citrus paradisi fruit juice), imatinib, Schisandra sphenanthera1, tofisopam, verapamil
Moderate CYP3A4/5 inducers	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, talviraline, thioridazine
Sensitive CYP3A4/5 substrates1	Alpha-dihydroergocryptine, aplaviroc, aprepitant, atorvastatin, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, , darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, , lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, , sildenafil, simvastatin, , ticagrelor, , tolvaptan, triazolam, vardenafil, vicriviroc
Strong BSEP inhibitors	Bosentan, fusidate, glibenclamide, lovastatin, , sulindac, troglitazone (TGZ- sulfate)
Mate1 and OCT2 substrates[3]	Acyclovir, amantadine, amiloride, cephalexin, cephradine, cimetidine, famotidine, fexofenadine, memantine, metformin (also a substrate for OCT1, MATE1, and MATE2K), pindolol, procainamide, ranitidine, and varencicline
BCRP substrates	Daunorubicin doxorubicin, rosuvastatin, sulfasalazine, topotecan
Medications that carry a possible risk for QT prolongation	Alfuzosin, amantadine, atazanavir, chloral hydrate, clozapine, dolasetron, dronedarone, eribulin, escitalopram, famotidine, felbamate, fingolimod, foscarnet, fosphenytoin, gatifloxacin, gemifloxacin, granisertron, iloperidone, indapamide, isradipine, lapatinib, levofloxacin, lithium, moexipril, nicardipine, nilotinib, octreotide, ofloxacin, ondansetron, oxytocin, paliperidone, pasireotide, quetiapine, ranolazine, risperidone, roxithromycin, sertindole, sunitinib, tacrolimus, tamoxifen, telithromycin, tizanidine, vardenafil, venlafaxine, voriconazole, ziprasidone

[1] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.
[2] Source: www.crediblemeds.org
[3] Source: FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and implications for Dosing and Labeling (February 2012) and Yonezawa and Inui (2011) Importance of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics. Br J Pharmacology 164:1817-25

Appendix D: Concomitant Medications

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

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

Appendix E: Correlative Studies for the Feline Trial (Chen/Yuan/Ma)

While CDK4/6 inhibitors such as palbociclib have been approved by FDA for the use in combination with letrozole for the treatment of patients with ER+ breast cancer, at the present time, no response/predictive markers have been identified. Therefore, correlative studies will be performed to identify potential markers associated with the combination treatment of letrozole and LEE011. Four sets of correlative studies will be conducted. The objectives of these studies are:

a) To determine whether treatment with letrozole and LEE011 will be affected by gene mutation in the cancer by Exome Sequencing of tumors.
b) To perform RNA Sequencing and reverse phase protein array (RPPA) analyses to search for potential markers associated to the treatment outcome.
c) To define potential markers, identified through our preclinical studies, related to the activity of letrozole and LEE011 by IHC.
d) To determine whether miRNA and lncRNA in peripheral blood can be used as markers of the activity of letrozole and LEE011.

1. Exome sequencing

We will perform Exome Sequencing analysis on 40 tumor specimens (20 patients who have complete or very good partial response and 20 patients who had stable disease and or partial response) collected prior to treatment (diagnostic tumor biopsy specimens) to determine whether any somatic mutations in the tumors that affect the treatment outcome. Mutation status, allelic imbalance, and/or copy number variations of cancer-related genes (including, but not limited to: *RB1*, *CCND1*, *CDKN2A*, *CDK4*, *CDK6*, etc.) will be analyzed. Note that a gene will be considered as amplified if six (6) or greater copies of a given gene are present in the sample. Loss will be defined if zero (0) copies of a given gene are present in the sample. For this purpose, the results of this analysis will be correlated with clinical efficacy data. As these data are extensive and complex, only those markers that show at least 5% alteration frequency will be shown, as well as genes associated with the key pathway of interest.

2. RNA Sequencing and RPPA

As non-biased approaches, RNA Sequencing and RPPA will be performed on fresh frozen specimens collected before and six months after treatment of letrozole + LEE011 (36 pairs). These analyses will provide gene and protein expression signatures in the collected tissue. Expression changes before and after treatment will be correlated to the response of the combination treatment. In tumor tissue samples, an evaluation of the expression of genes/proteins related to the mechanism of action of CDK4/6, Rb pathway, cell cycle pathways or downstream effects, and cancer pathobiology may be evaluated (for example, loss of *CDKN2A* and/or *RB1*, amplification of *CCND1*, FOXM1; Cyclin B etc.) to assess any potential correlation with response to LEE011.

3. Immunohistochemical analysis

Pretreatment formalin-fixed paraffin-embedded tumor tissue should be in a whole block or unstained slides. Tissue will also be obtained following completion of study drugs (breast-conserving surgery or mastectomy) or at the time of progression (core biopsy). Tumor specimens submitted as a FFPE tissue block will be returned to the sites by end of study or upon request. Tumor samples will be analyzed by IHC of proteins associated with response or resistance to LEE011 therapy. IHC markers, e.g. pRB and PTEN, will be listed by marker and

treatment group and summarized using summary statistics (mean, standard deviation, median, minimum, maximum).

4. Peripheral blood

Blood will be collected prior to treatment, at discovery of disease progression or at end of treatment, whichever occurs first. In addition, paraffin blocks of formalin-fixed diagnostic tumor biopsy specimens before treatment will be requested from each patient.

Gene expression profile analysis will be performed to determine how LEE011 + letrozole treatment affects gene expression, including aromatase. The processing of the tumor for gene expression profiling of the samples will be carried out at the Wash U TPC or City of Hope Functional Genomics core facility. These facilities have experienced laboratories for expression profiling that are highly automated and that have extensive quality control procedures. Processing the samples will ensure consistent sample handling and high quality gene expression data. Collection of tumor samples for expression profiling is an important part of this study and whenever possible should be collected at the time points indicated below.

Exome Sequencing and Gene Expression Profiling of Tumor Samples

Molecular studies of clinical samples obtained from patients with cancer can provide rich clinical and biological information. For example, gene expression profiling of diagnostic breast cancer samples has been used to identify expression profiles associated with risk of metastasis (van de Veer et al., 2002; van de Vijver et al., 2002). In this protocol, pretreatment and on-treatment samples of tumor (in patients with accessible tumor) will be collected for correlative molecular studies. These samples will be used to search for (1) somatic gene mutations that affect the response to letrozole + LEE011, (2) gene expression profiles that predict response to letrozole + LEE011 and (3) expression changes that occur after exposure to letrozole + LEE011. In addition, off-treatment samples will be requested. These samples will be used to search for gene expression changes that occur after acquired resistance to letrozole + LEE011. The samples will also be used for confirmatory studies based on the gene expression results. Results from these gene expression studies may provide important information regarding the mechanisms of response and the mechanisms of resistance to letrozole + LEE011. Ultimately, these results could guide the selection of patients for treatment with letrozole + LEE011 and guide strategies for preventing or overcoming resistance to these drugs. In addition, paraffin blocks of formalin-fixed diagnostic tumor biopsy specimens will be requested from each patient. If more recent paraffin blocks of tumor biopsy specimens from the same patient are available, these will also be requested. These blocks will be used to identify molecular markers that are associated with response to letrozole + LEE011.

Appendix F: Drug Compliance Assessment Tool (Sample Participant Pill Diary)

Investigator Initiated Trial Protocol: CLEE011XUS10T
The Feline Trial - PRINCIPAL INVESTIGATOR - Qamar Khan, MD

THE UNIVERSITY OF KANSAS CANCER CENTER

PARTICIPANT PILL DIARY for CONTINUOUS DOSING
Ribociclib/Placebo + Letrozole

Participant Study Number

_____

Cycle Number

_____

AT THE SAME TIME EACH DAY
For each dose take with a large glass of water (8 ounces) or regular (not Seville) orange juice (**No** grapefruit):

400 mg of Ribociclib/Placebo
2.5 mg of Letrozole

Please write the date, amount taken and any comments.

	Date	Amount Taken		Comments
		Ribociclib/Placebo	Letrozole	
EXAMPLE:	6/1/2009	2	1	Hot flashes an hour later
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				

Continued on Next Page

Pill Diary 400mg_Version 10-Jun-2016

Investigator Initiated Trial Protocol: CLEE011XUS10T
The Feline Trial - PRINCIPAL INVESTIGATOR - Qamar Khan, MD

THE UNIVERSITY OF KANSAS CANCER CENTER

Participant Study Number_____

Cycle Number_____

	Date	Amount Taken		Comments
		Ribociclib/Placebo	Letrozole	
EXAMPLE:	6/1/2009	2	1	Hot flashes an hour later
Day 12				
Day 13				
Day 14				
Day 15				
Day 16				
Day 17				
Day 18				
Day 19				
Day 20				
Day 21				
Day 22				
Day 23				
Day 24				
Day 25				
Day 26				
Day 27				
Day 28				

Pill Diary 400mg_Version 10-Jun-2016

Investigator Initiated Trial Protocol: CLEE011XUS10T
The Feline Trial - PRINCIPAL INVESTIGATOR - Qamar Khan, MD

THE UNIVERSITY OF KANSAS CANCER CENTER

PARTICIPANT PILL DIARY for INTERMITTENT DOSING
Ribociclib/Placebo + Letrozole

Participant Study Number

_____

Cycle Number

_____

AT THE SAME TIME EACH DAY
For each dose take with a large glass of water (8 ounces) or regular (not Seville) orange juice (**No** grapefruit):

600 mg of Ribociclib/Placebo
2.5 mg of Letrozole

Please write the date, amount taken and any comments.

	Date	Amount Taken		Comments
		Ribociclib/Placebo	Letrozole	
EXAMPLE:	6/1/2009	3	1	Hot flashes an hour later
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				

Continued on Next Page

Pill Diary 600mg_Version 10-Jun-2016

Investigator Initiated Trial Protocol: CLEE011XUS10T
The Feline Trial - PRINCIPAL INVESTIGATOR - Qamar Khan, MD

THE UNIVERSITY OF KANSAS CANCER CENTER

Participant Study Number_____

Cycle Number_____

	Date	Amount Taken		Comments
		Ribociclib/Placebo	Letrozole	
EXAMPLE:	6/1/2009	3	1	Hot flashes an hour later
Day 12				
Day 13				
Day 14				
Day 15				
Day 16				
Day 17				
Day 18				
Day 19				
Day 20				
Day 21				
Day 22		DO NOT TAKE Ribociclib/Placebo		
Day 23		DO NOT TAKE Ribociclib/Placebo		
Day 24		DO NOT TAKE Ribociclib/Placebo		
Day 25		DO NOT TAKE Ribociclib/Placebo		
Day 26		DO NOT TAKE Ribociclib/Placebo		
Day 27		DO NOT TAKE Ribociclib/Placebo		
Day 28		DO NOT TAKE Ribociclib/Placebo		

Pill Diary 600mg_Version 10-Jun-2016