The TEEL Study: A Phase I Trial of Tamoxifen with Ribociclib (LEE011) in Adult Patients with Advanced ER+ (HER2 Negative) Breast Cancer

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TITLE PAGE

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SYNOPSIS

Title:

The TEEL Study: A Phase I trial of Tamoxifen with Ribociclib (LEE011) in adult patients with advanced ER+ (HER2 negative) breast cancer.

Patient Population
Patients with estrogen or progesterone receptor positive, HER2-negative advanced (metastatic) breast cancer that are in one of the following populations

Premenopausal Women:

A) Premenopausal women who received adjuvant Aromatase Inhibitor and Ovarian Suppression (AI + OS) in the adjuvant setting and completed at least 12 months of hormonal therapy.
B) Premenopausal patients who have de-novo metastatic disease (metastatic disease at presentation).
C) Premenopausal women who have not received Tamoxifen in the metastatic setting, but have received up to two lines of chemotherapy.

Post-Menopausal Women or Men

D) Postmenopausal patients who have progressed on first-line or second-line therapy with an aromatase inhibitor in the metastatic setting
E) Postmenopausal patients who have recurred while on or after completion of adjuvant treatment with aromatase inhibitors (they have completed at least one year of adjuvant AI in the adjuvant setting before progression on AI).
F) Postmenopausal patients who are not considered candidates for treatment with an aromatase inhibitor by their oncologist , patients not willing not to go on to AI, or were intolerant to AI
G) Post-menopausal women or men who have been treated with up to three lines in the escalation arm and up to two lines of chemotherapy in the dose expansion arm in the metastatic setting.

Type of Study
Open labeled, non-randomized; phase I dose escalation followed by phase Ib dose expansion

Prior Therapy

- Progression on any aromatase inhibitor for metastatic disease
- Recurrence $\geq$12 months after commencement of adjuvant aromatase inhibitors
- Patients are allowed (but not required) to have up to two prior chemotherapy regimens for metastatic disease

Rationale for Study

Cell cycle progression is directly regulated by cyclin-dependent serine-threonine protein kinases. The cyclin D proteins are important in cancer, as their abundance and functions are regulated by extracellular growth factor and adhesion signaling. The cyclin D proteins act through the CDK4 and CDK6 protein kinases to promote G1 progression (1). CDK4 and CDK6, in turn, hyperphosphorylate and activate the retinoblastoma protein Rb to promote cell cycle entry and cell proliferation. Consistent with their having an important role in human cancer, focal copy number abnormalities that result in increased CDK activity are among the most commonly described genetic events observed in diverse tumor types; these events

include amplifications of the genes that encode cyclin D1 or CDK4, and deletions affecting the CDKN2A locus, which encodes the p16INK4a inhibitor of CDK activity (2-4).

Data from The Cancer Genome Atlas highlight the importance of the Cyclin/CDK/Rb pathway in breast cancer (2, 3). Abnormalities that result in CDK activation are highly enriched in the luminal A and B molecularly defined subgroups, ~85% of which were ER+/Her2- (5). Cyclin D1 amplifications were observed in 29% and 58% of the luminal A and B subtypes, respectively, and CDK4 amplifications were observed in 14% and 25% of luminal A and B subtypes, respectively. Luminal A subtype tumors also have loss of CDKN2C, which encodes p16Ink4a, a CDK inhibitor. The luminal subtypes also maintain expression of Rb, which would be essential for benefit from treatment with a CDK4/6 inhibitor (2-4). PD0332991 is an oral, potent, selective inhibitor of CDK4/6 that was shown to inhibit proliferation and induce apoptosis in multiple preclinical models of endocrine-resistant breast cancer, both in vitro and in vivo (11, 4). In the clinic, PD0332991 was studied in a randomized Phase II study in combination with the non-steroidal aromatase inhibitor letrozole. This combination significantly prolonged median progression free survival in postmenopausal women with locally recurrent or advanced ER+/HER2- breast cancer treated in the front-line setting (median PFS 26.1 vs 7.5 months, reported in Finn et al (6).

Most breast tumors that initially respond to anti-estrogen therapy acquire resistance in time. Given the above pre-clinical data, there may be benefit from a combination of Tamoxifen and Ribociclib, in women with hormone sensitive tumors as well as those whose tumors became unresponsive. Current and recently completed studies restrict CDK trials and limit the patient population to only postmenopausal patients but it is well known that younger, pre-menopausal and peri-menopausal patients often have more "aggressive" disease and more endocrine-resistant disease an d this combination may be very helpful in delaying endocrine resistance in this patient population.

Rationale for the combination of CDK4/6 inhibitors with Tamoxifen plus goserelin

Multiple adjuvant studies have described amenorrhea as a positive prognostic factor in patients with overall survival after adjuvant chemotherapy. Based upon a number of adjuvant studies, the NCCN guidelines recommend goserelin to be strongly considered in premenopausal women who are menstruating despite receiving chemotherapy (7). In a retrospective study done at one hospital, over 150 patients with stage Ia to IIIa ER + breast cancer who received goserelin or chemotherapy were reviewed. Survival analysis was assessed by the Kaplan-Meier method. Survival at 11 years was significantly better in the goserelin group ($P < 0.0012$). The lifetime lost was lower in the goserelin group (42 months vs. 66 months). The quality adjusted survival (QAS) of patients who received goserelin was longer (122.5 ± 6.3 vs. 112.2 ± 6.7 months. The quality-adjusted life-year was higher in the goserelin group. Goserelin therapy results in better survival and higher utility-weighted life-years, and is more cost-effective (8). We plan to add goserelin to all women who are not postmenopausal. We estimate that of the 40 patients on study, approximately 20 will not meet the standard criteria of a post-menopausal state (no menstrual cycles for greater than 12 months and FSH of ≥ 40). We will not stratify for menopausal status. This

study is inclusive of all women regarding of menopausal status and explores the combination of Tamoxifen with this CDK4/6 inhibitor.

We will additionally explore two cohorts in the Phase Ib expansion. Having a continuous dosing cohort has multiple advantages. There is sustained inhibition of the cell cycle and less AEs. This cohort will allow us to further explore a cohort with increased safety and better patient compliance. Patients will not have to remember whether they are on the "on week" or the "off week." Continuous dosing was done in Ph I CLEE011X2101 and both continuous and intermittent dosing revealed increased rates of grade 3 or 4 neutropenia rates at day 15 of every cycle on doses of 600 mg of Ribociclib and higher. **At lower doses, ribociclib had lower rates of neutropenia and continuous dosing should be tolerated.**

Type of Study:

Open labeled, non-randomized, Phase I escalation study with a Phase Ib dose expansion.

Phase I

The phase I portion of the study is a ***dose escalation*** to confirm the safety of the combination and to determine the MTD and the RP2D for ribociclib with Tamoxifen.

Phase I will be conducted in all patients with HR+/HER2- locally advanced or metastatic breast cancer with any prior endocrine therapy and up to three prior cytotoxic chemotherapy regimens administered in the metastatic or locally advanced setting.

Phase Ib dose expansion

Phase I trials are increasingly including dose-expansion cohorts (Ib) after the maximum-tolerated dose (MTD) has been reached to better characterize the toxicity profile and identify early signs of efficacy within this specific disease population. Our goal is to assess the anti-tumor activity Ribociclib + Tamoxifen and to further evaluate their safety in adult patients with HR+/HER2- locally advanced or metastatic breast cancer. Patients in the phase 1b expansion will have the same exclusion and inclusion criteria except that they will only be allowed to have up to two lines of cytotoxic chemotherapy in the metastatic setting.

Tamoxifen will be administered orally according to the standard regimen used in clinical practice (20 mg oral QD). Ribociclib will be administered orally, once daily for 21 consecutive days followed by a 7-day planned break (28-day cycle). In the *continuous dose cohort*, ribociclib will be administered daily (QD) without a break in each cycle. Tamoxifen will be administered in combination with ribociclib until disease progression or if unacceptable toxicity occurs that precludes any further treatment and/or if

treatment is discontinued at the discretion of the investigator or the patient, or the patient's death, whichever occurs first.

Phase I Study drugs (ribociclib dose may change depending on results of phase I)

TAMOXIFEN: 20 mg po daily

RIBOCICLIB: Phase I: starting at a dose of 400 mg po for 21 days of a 28-day treatment cycle; increased to 400 mg po daily (continuous dosing); increased to 600mg po daily for 21 days of a 28 day cycle.

Phase 1b expansion will look at two cohorts: 600 mg po for 21 days of a 28 day cycle with Tamoxifen and a continuous dosing cohort of ribociclib 400 mg daily with Tamoxifen.

Please note, that per NCCN guidelines for treatment of ER positive breast cancer, Goserelin acetate (Zoladex) (3.6 mg subcutaneous every 28 days) will be given per SOC practice to pre-menopausal and peri-menopausal women. This is standard of care for the treatment of pre- and peri- menopausal women and is not considered part of the study. The metabolism of goserelin is not CYP-mediated; rather hydrolysis of C-terminal amino acids is the major clearance mechanism. Based on the available information, goserelin is not expected to affect the metabolism of ribociclib nor be affected by co-administered drugs.

Safety Evaluation

Toxicity assessment, interim history and physical exam, CBC and chemistry profile weekly in cycle 1, then at day 1 of each cycle thereafter. Adverse Events and other symptoms will be assessed continuously and graded according to the NCI Common Toxicity Criteria, (CTCAE) v.4. Patients will be followed for evaluation of safety for at least 30 days after the last dose of study drug or until resolution of the AE. Any study drug-related serious adverse events will be followed until resolution, return to baseline grade, or deemed irreversible by the investigator.

Dose and Treatment Schedule

No of pts	Cohort Level	Ribociclib	Tamoxifen
3-6 (phase 1)	**1**	**400 mg oral days 1-21, followed by 1 week break**	**20mg oral daily**
3-6 (phase 1)	**2**	**400 mg continuous**	**20 mg oral daily**
3-6 (phase 1)	**3**	**600 mg oral day 1-21 followed by 1 week break**	**20 mg oral daily**

15 (dose expansion)	**Phase Ib dose expansion**	**600 mg oral day 1-21 followed by 1 week break**	**20 mg oral daily**
15 (dose expansion)	**Phase Ib –dose continuous dosing cohort**	**400 mg oral daily**	**20 mg oral daily**

***** Goserelin acetate (Zoladex) 3.6 mg subcutaneous every 28 days will be given per NCCN guideline to pre-menopausal and peri-menopausal patients as described above. We will define this further in the full protocol.

* If the daily dosing is too bone marrow suppressive, then this arm will switch to 400 mg oral days 1-21, followed by 1 week break of a 28 day cycle.

Prohibited Medications:

- No other chemotherapy, hormonal therapy, radiotherapy, or experimental anticancer medications for the primary disease will be permitted while the patient is on study.
- Strong inhibitors or inducers of CYP3A4/5
- Substrates of CYP3A4/5 with narrow therapeutic windows
- Medications that carry a strong risk for QT prolongation
- Herbal medications/preparations not prescribed by treating MD

Statistical Considerations

Patient Population:

Patientswith estrogen and/or progesterone receptor positive, HER2-negative advanced (metastatic) breast cancer that are in one of the following populations

Pre-menopausal Women:

A. Pre-menopausal women who received adjuvant Aromatase Inhibitor and Ovarian Suppression (AI + OS) in the adjuvant setting and completed at least 12 months of hormonal therapy.
B. Pre-menopausal women who have never been treated with endocrine therapy with de-novo metastatic disease.
C. Pre-menopausal women who have not received Tamoxifen in the metastatic setting, but have received up to two lines of chemotherapy for dose expansion and up to three lines for dose escalation.

Post-Menopausal Women or Men

D. Post-menopausal women or men who have progressed on first-line or second-line therapy with an aromatase inhibitor
E. Post-menopausal women or men who have recurred while on or after completion of adjuvant treatment with aromatase inhibitors (they have completed at least one year of adjuvant AI in the adjuvant setting before progression on AI).
F. Post-menopausal women or men who are not considered candidates for treatment with an aromatase inhibitor by their oncologist, refused AI, or intolerant to AI
G. Post-menopausal women or men who have been treated with up to two lines of chemotherapy for dose expansion and up to three lines for dose escalation in the metastatic setting.

Total number of patients: 40

Number of Centers: 1 (will be adjusted, increased if accrual goals are not met).

Sample Size Justification (will be updated by statistician):
For a total of **40 subjects**, about 9-12 will be accrued during phase 1 portion and **about 30 patients for the phase 1b expansion.**

Part 1: phase 1 portion:
We will evaluate the first 9-12 patients in the phase I portion for safety.
The Primary objective is safety.

Part II: phase Ib expansion:

For the phase one expansion we will include pre- menopausal women, post-menopausal women, and menevaluated as one group. We will further evaluate both a three weeks on and one week off cohort (i.e. once daily for 21 consecutive days followed by a 7-day planned break) and a *continuous dose cohort* of ribociclib administered daily (QD) without a break in each cycle. Tamoxifen will be administered daily per standard of care in both cohorts.

The **primary objective** in the phase I study is to confirm safety, tolerability, confirm DLT, and determine the RP2D of Ribociclib with Tamoxifen

The **secondary objective** is to evaluate 2 dose expansion cohorts after the maximum-tolerated dose (MTD) has been reached to better characterize the toxicity profile and identify early signs of efficacy. Our goal is to assess the anti-tumor activity Ribociclib + Tamoxifen and to further evaluate their safety in adult patients with HR+/HER2- locally advanced or metastatic breast cancer.

To determine whether treatment with ribociclib improves response rate (RR) compared to the historical response rate with treatment with Tamoxifen alone. We know that the expected RR for Tamoxifen after failure of first line AI is about 10 % and therefore we hypothesize an improvement of RR to 25%.

Efficacy Evaluation

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). This will be expanded in protocol.

DEFINITIONS:

DLT – Dose-Limiting Toxicity
MTD – Maximum tolerated dose
PFS – Progression-Free Survival
DDI – Drug-Drug Interaction
ER – Estrogen Receptor
PR – Progesterone Receptor
HER2 – Human Epithelial Receptor 2
PO – by mouth (per orum)
SERMS (selective estrogen receptor modulators)
SOC – standard of care
RR- Response Rate
FIH – First in human

Protocol:

The TEEL Study: A Phase I trial of Tamoxifen with Ribociclib (LEE011) in adult patients with advanced ER+ (HER2 negative) breast cancer.

1 BACKGROUND AND RATIONALE

1.1 Introduction

Breast cancer is one of the most common cancers in the Western Hemisphere and the second most common cause of cancer deaths in women. Endocrine therapy, including ovarian ablation; estrogen; and, more recently, antiestrogen administration, has been a major component of antitumor therapy in breast cancer for more than a century. Hormone sensitive metastatic breast cancer remains a therapeutic challenge despite the many recent advances in therapy. Barring a few exceptions, cure is not achieved in this disease. While hormonal interventions have clearly shown to decrease the tumor burden and to prolong life, the majority of patients eventually recurs and succumbs to their disease.

More than two thirds of all the advanced breast cancers are dependent on estrogen. Estrogen-withdrawal by physical removal of the ovaries or inhibition of their function has been one of the earliest successful interventions against breast cancer; however this intervention was limited to premenopausal women. The introduction of the SERMS (selective estrogen receptor modulators) has dramatically improved the survival of women with breast cancer, both pre and postmenopausal. The most prominent SERM is Tamoxifen, which until recently has been the gold standard for first-line therapy for women with advanced hormone-sensitive breast cancer. The introductions of several aromatase inhibitors (AIs) have added greatly to the arsenal against breast cancer and have replaced Tamoxifen as first-line therapy. The production of estrogen in postmenopausal women requires an enzyme called aromatase. This aromatase enzyme has been successfully blocked chemically. The most commonly used aromatase inhibitors include letrozole, anastrozole and exemestane.

However, the AIs are reserved for women who have naturally entered menopause or have their ovarian function suppressed. For premenopausal women or women who are unable to tolerate AIs, Tamoxifen remains the gold standard. In addition to that, there are many postmenopausal women who cannot tolerate the side effect profile of Aromatase Inhibitors. The response rate to first line hormonal therapy determined from four pivotal randomized Phase III trials ranges from 20-33% (1, 5, 6, 10). The response

rate to second line hormonal therapy is considerably less (10-20%) (6), suggesting a clear need for more effective therapy.

1.2 Tamoxifen

Tamoxifen is the most commonly used anti-estrogen or SERM; it is currently being used in the prevention of breast cancer, for ductal carcinoma in situ, in women with early stage breast cancer and for those with metastatic cancer. It is generally well tolerated and due to its extensive use, its toxicities and long-term sequelae are well characterized. Women being treated with Tamoxifen may experience flushing (similar to those women experience during the menopause), vaginal dryness and vaginal discharge. The most serious side effects are the slightly increased risk of thromboembolic events. In a trial involving 900 women treated with either Tamoxifen or letrozole, 9 out of 455 patients treated with Tamoxifen experienced a thromboembolic event (2%), compared to 3 patients out of 455 in the group treated with letrozole (<1%). Other side effects included hot flashes (25%), headaches (5%), fatigue (5%) and nausea (8%) (5). The observation of endometrial cancer (<0.5%) has been predominantly observed when used in the preventive or adjuvant setting (4). Hence, the cumulative administration of Tamoxifen is rarely hampered by toxicity but rather by the emergence of resistance suggested by clinical progression while on the drug.

1.3 CDK Inhibitors

A promising new class of drugs showing activity in cancer is CDK Inhibitors. Cell cycle progression is directly regulated by cyclin-dependent serine-threonine protein kinases. The cyclin D proteins are important in cancer, as their abundance and functions are regulated by extracellular growth factor and adhesion signaling. The cyclin D proteins act through the CDK4 and CDK6 protein kinases to promote G1 progression (1). CDK4 and CDK6, in turn, hyperphosphorylate and activate the retinoblastoma protein Rb to promote cell cycle entry and cell proliferation. Consistent with their having an important role in human cancer, focal copy number abnormalities that result in increased CDK activity are among the most commonly described genetic events observed in diverse tumor types; these events include amplifications of the genes that encode cyclin D1 or CDK4, and deletions affecting the CDKN2A locus, which encodes the p16INK4a inhibitor of CDK activity (2-4).

Data from The Cancer Genome Atlas highlight the importance of the Cyclin/CDK/Rb pathway in breast cancer (2, 3). Abnormalities that result in CDK activation are highly enriched in the luminal A and B molecularly defined subgroups, ~85% of which were ER+/Her2- (5). Cyclin D1 amplifications were observed in 29% and 58% of the luminal A and B subtypes, respectively, and CDK4 amplifications were observed in 14% and 25% of luminal A and B subtypes, respectively. Luminal A subtype tumors also have loss of CDKN2C, which encodes p16Ink4a, a CDK inhibitor. The luminal subtypes also maintain expression of Rb, which would be essential for benefit from treatment with a CDK4/6 inhibitor (2-4).

PD0332991 is an oral, potent, selective inhibitor of CDK4/6 that was shown to inhibit proliferation and induce apoptosis in multiple preclinical models of endocrine-resistant breast cancer, both in vitro and in vivo (4, 11). In the clinic, PD0332991 was studied in a randomized Phase II study in combination with the non-steroidal aromatase inhibitor letrozole. This combination significantly prolonged median progression free survival in postmenopausal women with locally recurrent or advanced ER+/HER2- breast cancer treated in the front-line setting (median PFS 26.1 vs 7.5 months, reported in Finn et al (6).

Most breast tumors that initially respond to anti-estrogen therapy acquire resistance in time. Given the above pre-clinical data, there may be benefit from a combination of Tamoxifen and Ribociclib, in women with hormone sensitive tumors as well as those whose tumors became unresponsive. Current and recently completed studies restrict CDK trials and limit the patient population to only postmenopausal patients but it is well known that younger, pre-menopausal and peri-menopausal patients often have more "aggressive" disease and more endocrine-resistant disease and this combination may be very helpful in delaying endocrine resistance in this patient population.

1.4 Role of the CDK4/6 pathway in breast cancer

Cell cycle progression is directly regulated by cyclin-dependent serine-threonine protein kinases (CDKs). Extracellular growth and adhesion signals increase the level and function of cyclin D proteins within the cell. In turn, the cyclin D proteins associate with and activate CDK4 and CDK6 (1). CDK4 and CDK6 phosphorylation leads to inactivation of the retinoblastoma protein (pRb) and thus releases E2F which in turn leads to the transcription initiation of proteins involved in cell cycle propagation and cell proliferation. The luminal A and B subtypes of breast cancer (85% of which are ER+/HER2-negative) have high rates of cyclin D/CDK activation; in the luminal A and B subtypes, cyclin D1 (CCND1) amplifications were observed in 29% and 58%, and CDK4 amplifications were observed in 14% and 25% respectively (5, 9).

Luminal A subtype tumors also have loss of CDKN2A, which encodes p16Ink4a, a CDK inhibitor (12). The luminal subtypes also maintain expression of Rb, which is essential for benefit from treatment with a CDK4/6 inhibitor (4). Dysregulation of cell cycle checkpoints is common in cancer. Modulating the cell cycle has always been an attractive therapeutic target in cancer, and previously published data have suggested that CDK4/6 inhibition may play a key role in the treatment of subsets of breast cancers. Patients with HR+ breast cancer exhibiting a gene expression signature of Rb loss had shorter recurrence-free survival following adjuvant tamoxifen (13). A tumor gene expression signature of E2F activation was associated with higher residual tumor cell proliferation following pre-surgical AI therapy. Therefore, activation of the CDK4/CDK6/E2F axis promotes endocrine resistance, and treatment with a CDK4/6 inhibitor or knockdown of CDK4 expression abrogates endocrine-resistant cell proliferation. In conclusion, loss of cell cycle control is a hallmark of cancer, and aberrations in the cyclin/CDK/Rb pathway are common in breast cancer. Consequently, inhibition of this pathway (at the level of CDK4/6)

leads to reactivation of Rb and binding of E2F, thus leading to cell cycle arrest. Therefore, targeting the inhibition of this pathway is considered an attractive therapeutic strategy. Additionally, preclinical and clinical data demonstrate that CDK4/6 inhibitors are active in advanced HR+ breast cancer. Palbociclib (PD 0332991) is a selective inhibitor of CDK4/6 that inhibits proliferation and induces apoptosis in preclinical models of endocrine-resistant breast cancer (4, 11). Preclinical data with palbociclib demonstrated synergy with tamoxifen in ER+ breast cancer cell lines; moreover, palbociclib enhanced sensitivity to tamoxifen in cell lines with conditioned resistance to ER blockade (6).

2 INTRODUCTION TO INVESTIGATIONAL TREATMENT(S) AND OTHER STUDY TREATMENT(S)

This study includes RIBOCICLIB, Tamoxifen, and Goserelin (if indicated)

2.1 Overview of RIBOCICLIB

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

Ribociclib should be administered as a flat-fixed dose (400 mg or 600 mg daily), and not by body weight or body surface area.

Patients should be instructed to return unused study drugs to the site at discontinuation or completion of treatment. The site personnel will ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed.

In order to minimize the inter-patient variability of PK assessments, ribociclib should be taken as follows:

- Patients should be instructed to take the ribociclib capsules with a large glass of water (~250 ml) at the same time each morning.
- Patients can take meals with their study treatment.

[redacted]

[redacted]

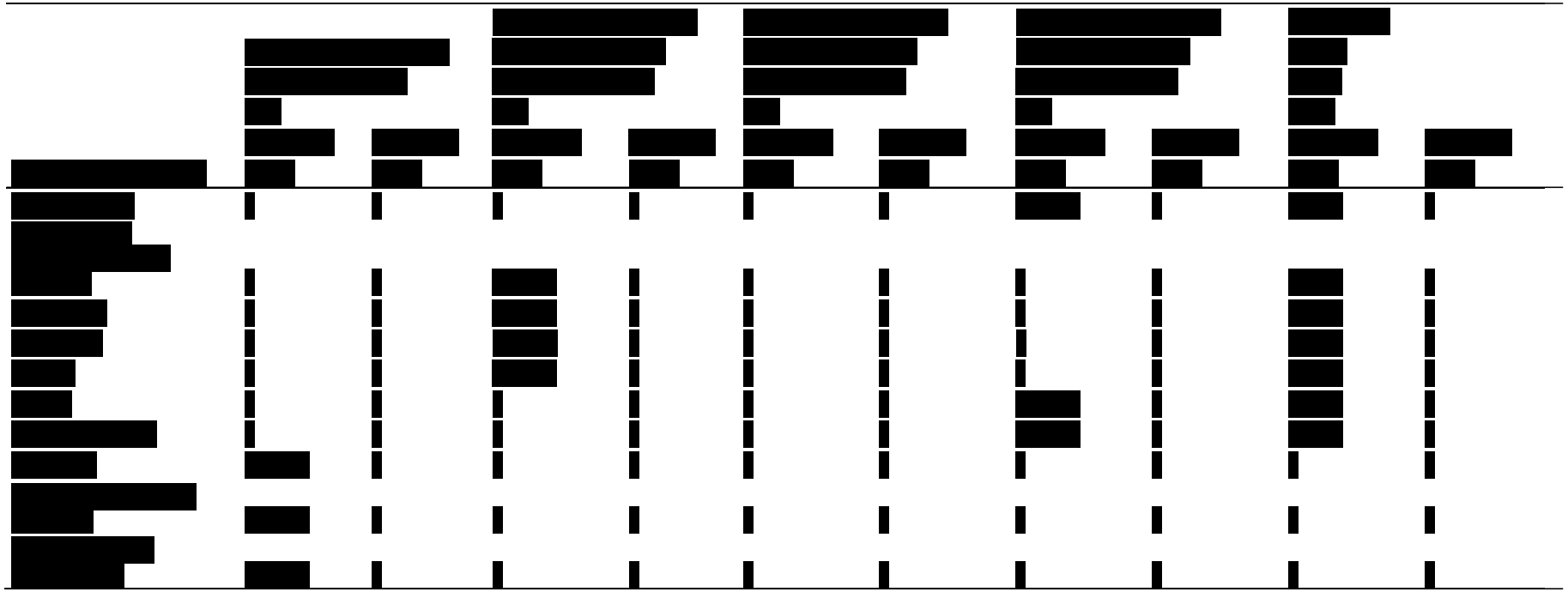
- Based on these data, ribociclib can be taken without regard to meals. Patients should be instructed to swallow the ribociclib capsules whole and not to chew, crush or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.

2.1.1 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.

[redacted]

[redacted]



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2.2 Overview of Tamoxifen

Tamoxifen has been used for over 30 years to treat both pre- and postmenopausal women with HR+ breast cancer. Its antitumor effects are thought to be due to its anti-estrogenic activity, mediated by competitive inhibition of estrogen

binding to ER (15). Adjuvant therapy with Tamoxifen for 5 years resulted in a 34% reduction in the annual breast cancer death rate, with an absolute reduction in mortality of 9.2% at 15 years (16).

The recommended dose for treatment of breast cancer is 20 mg daily (17). Tamoxifen is generally well tolerated and side effects are mainly attributable to estrogen deprivation. However, in some tissues, Tamoxifen acts as an estrogen agonist, and these estrogenic effects may be beneficial or detrimental, depending on the target organ. For example, tamoxifen has favorable effects on bone health, lipid metabolism and the cardiovascular system, but long-term tamoxifen use is also associated with serious, potentially life-threatening adverse events, including invasive endometrial cancer and thromboembolic disease (18).

Following oral administration of a single dose of Tamoxifen (20 mg), Tmax was achieved approximately 5 hours post-dose and concentrations declined with a terminal elimination T1/2 of approximately 5-7 days. Steady-state is achieved for Tamoxifen in approximately 4 weeks, while for its metabolite, N-desmethyltamoxifen, steady-state is achieved in approximately 8 weeks (17). Tamoxifen metabolism is complex and extensive after oral administration. Tamoxifen is a substrate of CYP3A4/5, CYP2D6, and CYP2C9 and an inhibitor of P-glycoprotein (P-gp) (17). Tamoxifen is predominantly metabolized by CYP3A4/5 to N-desmethyltamoxifen. A minor route of metabolism occurs via CYP2D6 to form the pharmacologically active metabolite, 4- hydroxytamoxifen. These metabolites are further metabolized to several secondary metabolites, one of which is the pharmacologically active metabolite, 4-hydroxydesmethyltamoxifen (endoxifen), formed mainly via CYP2D6 from N-desmethyltamoxifen. The two pharmacologically active metabolites, 4-hydroxytamoxifen and endoxifen, are 30- to 100-fold more potent than tamoxifen in terms of ER binding affinity and effects on breast cancer cell proliferation and gene expression (19). In breast cancer patients, endoxifen plasma concentrations are 5- to 10-fold higher than 4-hydroxytamoxifen (20, 21), suggesting that endoxifen may contribute significantly to the overall response to tamoxifen therapy. However, it is also likely that the combined pharmacologic activity of tamoxifen and its active metabolites contribute to the clinical efficacy of tamoxifen (19).

Formation of the pharmacologically active metabolites (4-hydroxytamoxifen and endoxifen) occurs predominantly through CYP2D6 (21). Reduced CYP2D6 activity, either through genetic polymorphisms of the enzyme or through concomitant administration of drugs that are CYP2D6 inhibitors, could lead to reduced exposure to endoxifen (21, 22). In addition, inhibition or induction of CYP3A4 may affect the metabolism of tamoxifen. Based on the prescribing information of tamoxifen, no dose adjustment is required for CYP2D6 poor metabolizers or for individuals taking medications that are strong inhibitors or inducers of CYP3A4. CYP2D6 poor metabolizer status has been associated with poorer invasive disease-free survival in tamoxifen treated patients in a number of studies, though not in others (23). The value of CYP2D6 genotyping in tamoxifen therapy is therefore still under investigation and is not standard of care. For information on tamoxifen and management of potential tamoxifen related adverse events refer to the Tamoxifen SmPC or Prescribing Information.

2.3 Potential for a drug-drug interaction between Ribociclib and Tamoxifen

The prescribing information for Tamoxifen suggests that Tamoxifen may affect the metabolism of co-administered drugs. A significant increase in anticoagulant effect may occur when Tamoxifen is co-administered with coumarin-type

anticoagulants. These medications should be avoided if possible, otherwise careful monitoring of prothrombin time is recommended. In addition, tamoxifen has been shown to reduce letrozole plasma concentrations following coadministration (17).

Tamoxifen could potentially affect the metabolism of co-administered drugs that are substrates for CYP3A4 since *in vitro* data indicate tamoxifen is a reversible and time-dependent inhibitor of CYP3A4 (24) as well as an inducer of CYP3A4 (25). Ribociclib is mainly metabolized by CYP3A4 with a minor contribution by FMO3 based on *in vitro* data. Clinical drug interactions studies of tamoxifen and drugs that are mainly metabolized by CYP3A4 (e.g., gefitinib, palbociclib) resulted in no significant changes in exposure in the presence of steady-state levels of Tamoxifen when compared with exposures when given alone (26, 27). Therefore, based on these in vivo data, Tamoxifen is not expected to affect ribociclib PK due to CYP-mediated interactions. Tamoxifen is also an inhibitor of P-gp (17) and could potentially affect substrates of this transporter. However, since ribociclib is a low-affinity substrate of P-gp with moderate permeability, ribociclib PK is not expected to be significantly affected by inhibition of P-gp by Tamoxifen.

Ribociclib may increase the exposure of co-administered drugs that are substrates for CYP3A4 due to time-dependent inhibition of the enzyme. *In vitro* studies indicate ribociclib is a reversible (Ki = 35 μM) and time-dependent inhibitor (KI = 5.06 μM, kinact = 0.0245 min-1) of CYP3A4. Tamoxifen is a substrate of CYP3A4/5, CYP2D6, and CYP2C9 (28). *In vitro*, troleandomycin and ketoconazole (CYP3A4 inhibitors) reduced the formation of N-desmethyltamoxifen (21); however the clinical significance is unknown. No clinical studies have been conducted to evaluate the effect of a strong inhibitor of CYP3A4/5 on the PK of Tamoxifen. However, the effect of coadministration of strong CYP3A4/5 inducers (e.g., rifampicin, aminoglutethimide) with tamoxifen has been evaluated and resulted in reduced concentrations of Tamoxifen and its metabolites (20, 29). Based on this information, a potential DDI with coadministration of ribociclib cannot be fully excluded.

2.4 Overview of goserelin

Goserelin (Zoladex®) is a synthetic decapeptide analog of gonadotropin releasing hormone (GnRH) indicated for prostatic carcinoma, endometriosis, endometrial thinning, and advanced breast cancer. Goserelin is administered subcutaneously every 28 days at a dose of 3.6 mg. Following subcutaneous administration of goserelin (3.6 mg for 2 months), Tmax was 12-15 days post-dose in males and 8-22 days post-dose in females. The metabolism of goserelin is not CYP-mediated; rather it is metabolized by hydrolysis of C-terminal amino acids. More than 90% of a radiolabeled dose was excreted in the urine, with approximately 20% of the dose in urine accounted for by unchanged goserelin. The adverse events occurring in > 20% of women included hot flushes, headache, sweating, acne, emotional lability, depression, decreased libido, vaginitis, breast atrophy, seborrhea and peripheral edema (30).

For information on goserelin and management of goserelin related adverse events refer to the Zoladex® SmPC or Prescribing Information.

2.4.1 Very Low potential for drug-drug interactions with goserelin

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 and has been combined with Tamoxifen as SOC. Based on the available information, goserelin is not expected to affect the metabolism of nor be affected by co-administered drugs (30).

2.5 Rationale for the combination of CDK4/6 inhibitors with Tamoxifen plus goserelin

Data from The Cancer Genome Atlas highlight the importance of the Cyclin/CDK/Rb pathway in breast cancer (2, 3). Abnormalities that result in CDK activation are highly enriched in the luminal A and B molecularly defined subgroups, ~85% of which were ER+/Her2- (5). Cyclin D1 amplifications were observed in 29% and 58% of the luminal A and B subtypes, respectively, and CDK4 amplifications were observed in 14% and 25% of luminal A and B subtypes, respectively. Luminal A subtype tumors also have loss of CDKN2C, which encodes p16Ink4a, a CDK inhibitor. The luminal subtypes also maintain expression of Rb, which would be essential for benefit from treatment with a CDK4/6 inhibitor (2-4). PD0332991 is an oral, potent, selective inhibitor of CDK4/6 that was shown to inhibit proliferation and induce apoptosis in multiple preclinical models of endocrine-resistant breast cancer, both in vitro and in vivo (4, 11). In the clinic, PD0332991 was studied in a randomized Phase II study in combination with the non-steroidal aromatase inhibitor letrozole. This combination significantly prolonged median progression free survival in postmenopausal women with locally recurrent or advanced ER+/HER2- breast cancer treated in the front-line setting (median PFS 26.1 vs 7.5 months, reported in Finn et al (6).

Most breast tumors that initially respond to anti-estrogen therapy acquire resistance in time. Given the above pre-clinical data, there may be benefit from a combination of Tamoxifen and RIBOCICLIB, in women with hormone sensitive tumors as well as those whose tumors became unresponsive. Current and recently completed studies restrict CDK trials and limit the patient population to only postmenopausal patients but it is well known that younger, pre-menopausal and peri-menopausal patients often have more “aggressive” disease and more endocrine-resistant disease and this combination may be very helpful in delaying endocrine resistance in this patient population. Multiple adjuvant studies have described amenorrhea as a positive prognostic factor in patients with overall survival after adjuvant chemotherapy. Based upon these studies, the NCCN guidelines recommend goserelin to be strongly considered in premenopausal women who are menstruating despite receiving chemotherapy (7).

In a retrospective study done at one hospital, over 150 patients with stage Ia to IIIa ER + breast cancer who received goserelin or chemotherapy were reviewed. Survival analysis was assessed by the Kaplan-Meier method. Survival at 11 years was significantly better in the goserelin group ($P < 0.0012$). The lifetime lost was lower in the goserelin group (42 months vs. 66 months). The quality adjusted survival (QAS) of patients who received goserelin was longer (122.5 ± 6.3 vs. 112.2 ± 6.7 months. The quality-adjusted life-year was higher in the goserelin group. Goserelin therapy results in better survival and higher utility-weighted life-years, and is more cost-effective (8). We plan to add goserelin to all women who are not postmenopausal. We estimate that of the 40 patients on study, approximately 20 patients will be post-

menopausal and 20 will not meet the standard criteria of a post-menopausal state (no menstrual cycles for greater than 12 months and FSH of $\geq$ 40).

3 OBJECTIVES

3.1 Primary Objective

***Phase I - Confirm DLT**:*

The phase I portion of the study is a dose escalation to confirm the safety of the combination and to determine the DLT and the RP2D for ribociclib with Tamoxifen.

Phase Ib Dose Expansion:

Our goal is to further evaluate their safety in adult patients with ER+/HER2- locally advanced or metastatic breast cancer. Phase I trials are increasingly including dose-expansion cohorts after the maximum-tolerated dose (MTD) has been reached to better characterize the toxicity profile or identify early signs of efficacy within a specific disease population. We will evaluate two cohorts in the phase I expansion. The first will be the standard 21 days of ribociclib dosing with 7 days rest period and the second will be the continuous dosing (daily). Tamoxifen, per SOC, will be dosed daily in both cohorts. We will attempt to assess the anti-tumor activity ribociclib + Tamoxifen.

3.2 Secondary Objectives:

- Time to progression
- Overall survival from study initiation at 6 months, 12 months, 18 months and 24 months.
- Pre-treatment and post-treatment ER receptor expression in tumor in those patients who volunteer for optional tissue evaluation.
- **Pharmacokinetics** in the dose escalation as well as the dose expansion arms.

4 INCLUSION CRITERIA

A. <u>Shared Eligibility</u>

1. Histologically and/or cytologically confirmed diagnosis of ER+ and/or PR+ breast cancer by local laboratory.
2. HER2-negative breast cancer defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing.
3. Patients are allowed (but not required) to have up to **two** lines of prior chemotherapy regimens in the metastatic setting for the dose expansion phase (). For the dose escalation cohort, up to three previous lines of chemotherapy in the metastatic setting is acceptable.

4. Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria only **for expansion cohorts.**

5. For **escalation cohorts**,bone only disease is allowed. For expansion cohorts, there must be measurable disease as stated above (#4)..
6. ECOG PS 0 or 1.
7. Written informed consent must be obtained prior to any screening procedures and according to local guidelines.
8. Patient has adequate bone marrow and organ function as defined by the following laboratory values:
   a. Absolute neutrophil count $\geq 1.5 \times 10^9$/L.
   b. Platelets $\geq 100 \times 10^9$/L.
   c. Hemoglobin ≥ 9 g/dl.
   d. Potassium, total calcium (corrected for serum albumin), magnesium, and sodium within normal limits for the institution or corrected to within normal limits with supplements before first dose of study medication
   e. INR ≤ 1.5.
   f. Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min
   g. In the absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5 x ULN. If the patient has liver metastases, ALT and AST < 5 x ULN.
   h. Total bilirubin $\leq$ ULN; or total bilirubin ≤ 3.0 x ULN or direct bilirubin in patients with well-documented Gilbert's Syndrome
9. Must be able to swallow ribociclib and Tamoxifen capsules/tablets

B. <u>Pre-menopausal Women Eligibility</u>

1. Premenopausal women who received adjuvant Aromatase Inhibitor and Ovarian Suppression (AI + OS) in the adjuvant setting and completed at least 12 months of hormonal therapy.
2. Pre-menopausal women with *de novo* metastatic disease are eligible if they have had no prior endocrine therapy.
3. Premenopausal women who have not received Tamoxifen in the metastatic setting. Patients are allowed (but not required) to have up to **two** lines of prior chemotherapy regimens in the metastatic setting for the dose expansion phase. For the dose escalation cohort, up to three previous lines of chemotherapy in the metastatic setting is acceptable.

C. <u>Post-menopausal Women and Men Eligibility</u>

1. Postmenopausal women or men who have progressed on first-line or second line therapy with an aromatase inhibitor in the metastatic setting
2. Postmenopausal women or men who have recurred while on or after completion of adjuvant treatment with aromatase inhibitors (they have completed at least one year of AI in the adjuvant setting before progression on AI).
3. Postmenopausal women or men who are not considered candidates for treatment with an aromatase inhibitory by their oncologist, patients not willing to go on AI, or patients who were intolerant to AI.
10. Postmenopausal women or men are allowed (but not required) to have up to **two** lines of prior chemotherapy regimens in the metastatic setting for the dose expansion phase . For the dose escalation cohort, up to three previous lines of chemotherapy in the metastatic setting is acceptable.

4.

5 EXCLUSION CRITERIA

1. Patients with inflammatory breast cancer.
2. Prior CDK4/6 inhibitor exposure.
3. Patient has received Tamoxifen in the metastatic setting (for more than 30 days) or has progressed while on Tamoxifen in the adjuvant setting.
4. Patient has a known hypersensitivity to ribociclib or excipients of tamoxifen..
5. Patient has a concurrent malignancy or malignancy within 3 years of starting study drug, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.
6. Patients with central nervous system (CNS) involvement unless they meet ALL of the following criteria:
   a. At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment
   b. Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme-inducing anti-epileptic medications for brain metastases
7. 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).
8. Patient has a known history of HIV infection (testing not mandatory).
9. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.).
10. Clinically significant, uncontrolled heart disease and/or a recent events including any of the following:
    a. History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 12 months prior to screening.
    b. History of documented congestive heart failure (New York Heart Association functional classification III-IV).
    c. Documented cardiomyopathy.
    d. Patient has a Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) at screening.
    e. History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, conduction abnormality in the previous 12 months of screening.
    f. Congenital long QT syndrome or family history of long QT syndrome
    g. Sustained systolic blood pressure (SBP) >160 mmHg or <90 mmHg at screening. Must be corrected or controlled prior to starting study.
    h. Bradycardia (heart rate <50 at rest) by ECG or pulse, at screening
    i. On screening inability to determine the QTcF interval on the ECG (i.e.: unreadable or not interpretable) or QTcF>_ 450 msec (using Fridericia's correction). All as determined by screening ECG (mean of triplicate ECGs).
11. Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to starting study drug (see Table 7-5) :
    a. Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges.
    b. That have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.

c. That have a known risk to prolong the QT interval or induce Torsades de Pointes.
d. Herbal preparations/medications, dietary supplements, not prescribed by an MD

12. Patient is currently receiving or has received systemic corticosteroids ≤2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.
13. The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).
14. 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.
15. Participation in a prior investigational study within 30 days prior to enrollment
16. Patient who has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug, and who has not recovered to grade 1 or better from related side effects of such therapy (exceptions include alopecia) and/or in whom ≥ 25% of the bone marrow was irradiated.
17. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects (tumor biopsy is not considered as major surgery).
18. Patient has not recovered from all toxicities related to prior anticancer therapies to NCI-CTCAE version 4.03 Grade equal or less than one ≤1 (Exception to this criterion: patients with any grade of alopecia are allowed to enter the study).
19. Patient with a Child-Pugh score B or C.
20. Patient has a history of non-compliance to medical regimen or inability to grant consent.
21. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.]
22. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception throughout the study and for 12 weeks after study drug discontinuation. Highly effective contraception methods include:
    a. Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of tubal ligation alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    c. Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
    d. No patients with HR+ disease should receive hormonal contraception, however the two following methods can be combined: Placement of an intrauterine device (IUD) or intrauterine system (IUS and barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository.

Note: The use of oral contraception is not allowed.

Women are considered **post-menopausal** and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.]

6 PATIENT REGISTRATION:

- Patients who meet the eligibility criteria may be registered and enrolled on the trial. We will complete phase I portion of the study before proceeding to phase Ib expansion. At time of phase Ib expansion, we will alternate enrollment to both cohorts of our study, until both cohorts are complete.

- A signed copy of the institution's IRB-approved informed consent document must be placed on file.

- Patients must not start protocol treatment prior to registration.

7 TREATMENT PLAN:

Investigational Study Treatment

RIBOCICLIB will be supplied by Novartis or its designee in the form of 200 mg hard gelatin capsules/tablets as individual patient supply packaged in bottles.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

Dose and treatment schedule

Study treatment	**Pharmaceutical form and route of administration**	**Dose**	**Frequency and/or Regimen**
RIBOCICLIB	Capsules/tablets for oral use	400 mg	21 days on and 7 days off Or Daily (in continuous cohort)
RIBOCICLIB	Capsules/tablets for oral use	600 mg	21 days on and 7 days off

RIBOCICLIB will be administered as a flat-fixed dose (400 mg or 600 mg daily), and not by body weight or body surface area.

Patients must be instructed to return unused study drugs to the site at discontinuation or completion of treatment. Additionally, patients must be instructed to return empty bottles and/or any unused medication during their scheduled study visits to ensure compliance. The site personnel must ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed.

In order to minimize the inter-patient variability of PK assessments, RIBOCICLIB should be taken as follows:

- Patients should be instructed to take the RIBOCICLIB capsules with a large glass of water (~250 ml) at the same time each morning.

- 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
- No major food effect on RIBOCICLIB exposure is expected. RIBOCICLIB is a high solubility (>30 mg/mL in physiological media), high permeability compound with a good dissolution profile at high doses, indicating that the exposure of RIBOCICLIB is not likely to be limited by solubility or dissolution.
- Patients should be instructed to swallow the RIBOCICLIB capsules whole and not to chew, crush or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Patients must avoid consumption of grapefruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.

On days with PK, ECG sampling, chemistry panel and/or lipid panel sampling, the following additional guidelines should be followed:

- On a day when PK blood collection is scheduled at the clinic, patients must take study treatment in the clinic under the supervision of the Investigator or designee. On all other days patients may take the study treatment at home.
- On a day of chemistry panel and/or lipid panel sampling, patients must also take study treatment in the clinic under the supervision of the Investigator or designee. On all other days patients may take the study treatment at home.
- Pre-dose samples should be drawn prior to dosing. The sampling time of the PK samples and the dosing time must be precisely recorded in the CRF. Furthermore, the dosing date and time the study medication was taken on the day before the PK assessment must be precisely recorded in the CRF.
- Post-dose PK samples should be collected after dosing of the study treatment.
- A standard 12 lead ECG will be performed after the patient has been resting for 5-10 min prior to each time point indicated in study calendar. On cycle 1 day 1 (pre-dose), 3 ECG recordings must be taken at a minimum of 2-minute intervals. The combined QTcF values from these 3 ECGs will be averaged to provide a single baseline value for each patient. If an abnormal ECG is obtained at any time, patient's electrolytes must be reviewed and repeat ECG measurements must be done after correction of electrolyte abnormalities. In the event that a QTcF value of ≥ 501 ms is observed, a blood sample for PK will be collected to determine plasma levels of LEE011 and any other identified metabolites

7.1 Dose Modifications

Dose Limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as having a reasonable possibility of relatedness to the study medication, unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment (cycle 1) with RIBOCICLIB and Tamoxifen and meets any of the criteria included in below modification tables. National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) **version 4.03** will be used for all grading.

In this study, a DLT will occur if CTCAE grade 4 neutropenia lasts more than 4 consecutive days, if CTCAE grade 3 thrombocytopenia is associated with clinically significant bleeding or if there is grade 4 thrombocytopenia. Please see the following table (7-1) for other DLT criteria.

Table 7-1 Criteria for defining dose-limiting toxicities

TOXICITY	DLT CRITERIA
Hematology	≥ CTCAE grade 4 neutropenia lasting more than 4 consecutive days
	CTCAE grade 3 thrombocytopenia with clinically significant bleeding
	CTCAE grade 4 thrombocytopenia
	Febrile neutropenia (decrease in neutrophils associated with fever, ANC <1.0 x 10^9/L, fever ‡38.5°C)
	CTCAE grade 4 lymphopenia lasting more than 7 consecutive days
Skin and subcutaneous tissue disorders	CTCAE grade 3 Rash > 7 days despite optimal management and does not resolve to Grade 0 or 1
	CTCAE grade 4 Rash that is thought to be related to study drug
	≥ CTCAE grade 3 photosensitivity
Metabolism	Grade 2 hyperglycemia (Fasting glucose 200 – 249 mg/dL) (confirmed with a repeat Fasting glucose within 24 hours) that does not resolve to Fasting glucose <200 mg/dLwithin 14 consecutive days (despite optimal oral anti-diabetic therapy, i.e. glimepiride, glibenclamide and/or metformin)
	Grade 3 hyperglycemia (Fasting glucose 250-499 mg/dL) (confirmed with a repeat Fasting glucose within 24 hours) for > 14 consecutive days despite optimal oral anti-diabetic treatment
	Grade 4 hyperglycemia (Fasting glucose >499 mg/dL)
	Hyperglycemia leading to diabetic keto-acidosis, hospitalization for IV insulin infusion, or non-ketotic coma
	CTCAE grade 3 amylase and/or lipase, not reversible to ≤ CTCAE grade 2 for > 7 consecutive days
	CTCAE grade 4 amylase and/or lipase
Gastro-intestinal	≥ CTCAE grade 3 vomiting ≥ 48 hrs despite optimal anti-emetic therapy
	≥ CTCAE grade 3 diarrhea ≥ 48 hrs despite optimal anti-diarrhea treatment
	≥ CTCAE grade 3 pancreatitis
Hepato-biliary	≥ CTCAE grade 3 total bilirubin
	≥ CTCAE grade 3 ALT lasting >4 days (isolated increases in AST without concomitant increases in ALT will not be considered dose-limiting, because of the non-specific nature of AST)
	≥ CTCAE grade 2 ALT with a ≥ Grade 2 bilirubin elevation of any duration
	≥ CTCAE grade 4 ALT of any duration
ECG QT Interval	QTc interval ≥ 501 ms on at least two separate ECGs
Renal	≥ CTCAE grade 3 serum creatinine
Events not described above	≥ CTCAE grade 3, except for the exclusions noted below
Exceptions to DLT criteria	Grade 3 alopecia
	CTCAE grade 3 fatigue < 5 days

	CTCAE Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant
	CTCAE grade 3 edema <48 hours
CTCAE version 4.03 will be used for all grading. Optimal therapy for vomiting or diarrhea will be based in institutional guidelines, with consideration of the prohibited medications listed in this protocol.	

Table 7-2 Dose modification guidelines

	Ribociclib (LEE011) Dose	
Starting dose	600 mg 3 x 200 mg capsules/tablets	400 mg 2 x 200 mg capsules/tablets
First dose reduction	400 mg 2 x 200 mg capsules/tablets	200 mg 1 x 200 mg capsules/tablets
Second dose reduction	200 mg 1 x 200 mg capsules/tablets	N/A

There are no scheduled dose reductions for Tamoxifen.

Table 7-3 Ribociclib dose adjustment and management recommendation for hematological adverse reactions

Toxicity/Grade	**Dose Adjustment and Management Recommendations**
Thrombocytopenia	
Grade 1 ($\geq$75 x 10^9/L)	No dose adjustment required.
Grade 2 ($\geq$50 x 10^9/L - <75 x 10^9/L)	Dose interruption until recovery to grade $\leq$1. Re-initiate ribociclib at the same dose.
Grade 3 ($\geq$25 x 10^9/L - <50 x 10^9/L)	Dose interruption until recovery to grade $\leq$1. Re-initiate ribociclib at the same dose level. • If toxicity recurs at grade 3: temporary dose interruption until recovery to grade $\leq$1 and reduce ribociclib to the next lower dose level.
Grade 4 (<25 x 10^9/L)	Dose interruption until recovery to grade $\leq$1. Re-initiate ribociclib at the next lower dose level. • If toxicity recurs at grade 4: discontinue ribociclib.
Absolute neutrophil count (ANC)	

Grade 1 ($\geq$1.5 x 10^9/L)	No dose adjustment required.
Grade 2 (1.0 - <1.5 x 10^9/L)	No dose adjustment required.
Grade 3 (0.5 - <1.0 x 10^9/L)	Dose interruption until recovery to >1.0 x 10^9/L. Re-initiate ribociclib at the same dose level. • If toxicity recurs at grade 3: temporary dose interruption until recovery to >1.0 x 10^9/L. If resolved in $\leq$ 7 days, then maintain dose level. If resolved in > 7 days, reduce ribociclib dose to the next lower dose level.
Grade 4 (<0.5 x 10^9/L)	Dose interruption until recovery to $\geq$1.0 x 10^9/L. Re-initiate ribociclib at the next lower dose level. • If toxicity recurs at grade 4: temporary dose interruption until recovery to $\geq$1.0 x 10^9/L and reduce ribociclib at the next lower dose level.
<u>Febrile neutropenia</u>	
Grade 3 ANC <1.0 x 10^9/L with a single temperature of >38.3°C (101°F) or a sustained temperature of $\geq$38°C (100.4°F) for more than one hour	Dose interruption until improvement of ANC $\geq$ 1.0 x 109/L and no fever. Restart at the next lower dose level. • If febrile neutropenia recurs, discontinue ribociclib.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue riblocicilb.
<u>Anemia (Hemoglobin)</u>	
Grade 1 ($\geq$10.0 – LLN g/dL)	No dose adjustment required.
Grade 2 ($\geq$8.0 – 10.0 g/dL)	No dose adjustment required.
Grade 3 (<8.0 g/dL)	Dose interruption until recovery to grade $\leq$ 2. Re-initiate RIBOCICLIB at the same dose.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.

Table 7-4 Recommendations for ribociclib dose modification in case of hepatic toxicities

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)
TOTAL BILIRUBIN without ALT/AST increase above baseline value

Grade 1 (> ULN – 1.5 x ULN) (confirmed 48-to 72hrs later)	Maintain dose level with LFTs monitored bi-weekly
Grade 2 (> 1.5 – 3.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ grade 1 in ≤ 21 days, then maintain dose level If resolved to ≤ grade 1 in > 21 days or toxicity recurs, then reduce 1 dose level If toxicity recurs after two dose reductions, discontinue ribociclib
Grade 3 (> 3.0 – 10.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ grade 1 in ≤ 21 days, lower 1 dose level of ribociclib If resolved to ≤ grade 1 in > 21 days or toxicity recurs, discontinue ribociclib
Grade 4 (> 10.0 x ULN)	Discontinue ribociclib
Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤ 1 x ULN) due to hemolysis or Gilbert Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.	

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

Additional follow-up for hepatic toxicities

Hepatic toxicity monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2 x ULN), 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.
- 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.

7.2 Ribociclib dose adjustment and management recommendation for all other adverse reactions

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

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 QTc 450-480 ms	No dose adjustment required.
2 QTc 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 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 QTc ≥ 501 ms on at least two separate ECGs	Interrupt ribociclib • 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 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
4 QT/QTc ≥ 501 **or** > 60 ms change from baseline **and** Torsades de pointes **or** polymorphic ventricular tachycardia, **or** signs/symptoms of serious arrhythmia	Discontinue ribociclib • Obtain local cardiologist consultation • Perform a repeat ECG and cardiac monitoring as indicated until the QTcF returns to <481 ms.

Guidance for QTc prolongation

Management of All Other 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 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
- Check compliance with correct dose and administration of ribociclib.

7.3 Adjustment of Starting Dose in Special Populations

Renal impairment

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

Patients with baseline renal impairment are excluded from the study. Patients who experience renal impairment of grade 2 or higher during the treatment period should discontinue treatment and should be followed for safety assessments.

Elderly

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

7.4 Follow-up for toxicities

Patients who complete treatment or whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event. All patients will be followed up for safety up to 30 days following the last dose of study treatment.

7.5 Concomitant Medications

Permitted concomitant therapy

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

The patient must be told to notify the investigational site about any new medications she takes after the start of the study treatment.

Bisphosphonates and denosumab

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

Hematopoietic growth factors

Hematopoietic growth factors may be used according to ASCO guidelines.

Palliative radiotherapy

Palliative radiation is permitted if done solely for bone pain relief. Study treatment will be held during XRT and can be resumed thereafter.

Refer to the ribociclib Investigator Brochure or tamoxifen package insert for information on possible interactions with other drugs (14).

7.6 Permitted concomitant therapy requiring caution

- Medications to be used with caution during ribociclib and tamoxifen [in this study are listed below (see Table 2). 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.
  Moderate inhibitors or inducers of CYP3A4/5.
- Strong inhibitors or inducers of P-gP.
- Sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index.
- Strong inhibitors of BSEP.
- Substrates metabolized predominantly by CYP1A2 with a narrow therapeutic index.
- Medications that carry a moderate-low risk for QT prolongation.

7.7 Prohibited concomitant therapy

The following medications are **prohibited** during study treatment in the study (see Table 7-5). 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 narrow therapeutic index.
- Medications that carry a known risk for QT prolongation.
- Herbal medications/preparations, dietary supplements.
- Other investigational and antineoplastic therapies not part of the study.

Table 7-5 List of prohibited medications during study drug treatment

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Category	Drug Name
Strong CYP3A4/5 inhibitors	Boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, voriconazole
Strong CYP3A4/5 inducers	Avasimibe[2,3], carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[3]
Strong CYP2D6 inhibitors	Bupropion, dacomitinib, ecstasy (MDMA, (3,4-methylenedioxymethamphetamine), fluoxetine, paroxetine, quinidine
CYP3A substrates with NTI[1]	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

Medications with a known risk for QT prolongation[4]	Amiodarone, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, flecainide, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, moxifloxacin, pentamidine, pimozide, probucol, procainamide, quinidine, sotalol, sparfloxacin, terfenadine, thioridazine, vavdetanib
Herbal preparations/ medications	Herbal preparations/medications are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug
Other investigational and antineoplastic therapies	Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued study drug.

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

Table 7-6 List of medications to be used with caution during study drug treatment

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, darunavir, diltiazem, dronedarone, fluconazole, fosamprenavir, grapefruit juice (citrus paradisi fruit juice), imatinib, Schisandra sphenanthera[1], tofisopam, verapamil
Moderate CYP3A4/5 inducers	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, talviraline, thioridazine
P-gp inhibitors	Captopril, carvedilol, diltiazem, dronedarone, elacridar (GF120918), erythromycin, felodipine, fexofenadine, fluvoxamine, milk thistle (silybum marianum), nifedipine, nitrendipine, paroxetine, quercetin, ranolazine, Schisandra chinensis, talinolol, telmisartan, ticagrelor, tolvaptan, valspodar (PSC 833), verapamil
P-gp inducers	Any known P-gp inducers
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine, aplaviroc, aprepitant, atorvastatin, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, sildenafil, simvastatin, ticagrelor, tolvaptan, triazolam, vardenafil, vicriviroc

Strong BSEP inhibitors	Bosentan, fusidate, glibenclamide, lovastatin, sulindac, troglitazone (TGZ-sulfate)
CYP1A2 substrates with NTI[2]	Theophylline, tizanidine
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, tamoxifen, tizanidine, vardenafil, venlafaxine, ziprasidone
MATE1 and OCT2 substrates[3]	Acyclovir, amantadine, amiloride, cephalexin, cephradine, cimetidine, famotidine, fexofenadine, memantine, metformin (also a substrate for OCT1, MATE1, and MATE2K), pindolol, procainamide, ranitidine, and varenciclineRosuvastatin and sulfasalazine
BCRP substrates 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, ziprasidoneDaunorubicin, doxorubicin,
[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] 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). [3] Source: (31, 32)	

7.8 Packaging and labeling

Study Treatment	Packaging	Labeling
Ribociclib (LEE011)	Capsules in bottles	Labeled as 'Ribociclib'
Tamoxifen	Prescription tablets	Prescription (SOC)

7.9 Drug Supply and Storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel

have access. Upon receipt, the study treatment should be stored according to the instructions specified on the medication label. Medication labels will comply with the legal requirements of each country and be printed in the local language.

Supply and storage of study treatment

Study Treatment	Supply	Storage
Ribociclib (LEE011)	Bulk supplied by Novartis	Refer to study treatment label

7.10 Study Drug Compliance and Accountability

Study drug compliance

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

On PK sampling days, compliance will be assured by administration of the study treatment under the supervision of investigator or his/her designee, and will be verified by determination of ribociclib in plasma.

Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log.

Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

8 TREATMENT PLAN

Phase I/ Phase Ib dose expansion:

TAMOXIFEN: 20 mg PO daily will be given with RIBOCICLIB:

Ribociclib (LEE011)

In phase I: Ribociclib PO starting at a dose of 400 mg po for 21 days of a 28-day treatment cycle; this will be increased to 400 mg continuously. We will then evaluate 600 mg po daily for 21 days of a 28 day cycle if tolerated.

If there are no dose limiting toxicities, in the phase I portion, Tamoxifen 20 mg will be given with the MTD dose of Ribociclib in 15 patients. This is expected to be 600mg three weeks on and one week off. These patients will *not be stratified* for menopausal status.

If the 400mg continuous dose was well tolerated in the escalation arm, we will then expand this cohort in the phase Ib expansion, we will have an additional cohort of Tamoxifen 20 mg with 400 mg ribociclib in a continuous daily dose in an additional 15 patients. These patients will *not be stratified* for menopausal status.

Goserelin acetate (Zoladex) (3.6 mg subcutaneous every 28 days) will be given per NCCN guidelines to pre-menopausal and peri-menopausal. This will be given on day 1 of every cycle. We estimate that up to 20 of 40 patients on this protocol will require goserelin.

Goserelin is given if patient is premenopausal or peri-menopausal at the time of study entry.

Premenopausal status is defined as either:

- Patient had last menstrual period within the last 12 months.
- In case of therapy induced amenorrhea, with a plasma estradiol ≥10 pg/mL and/or FSH ≤40IU/l or in the premenopausal range according to central laboratory definition.
- Patients who have undergone bilateral oophorectomy do not need goserelin.

Peri-menopausal status is defined as neither premenopausal nor postmenopausal (see exclusion criteria for definition).

8.1 Study Design:

Dose and Treatment Schedule – Table 8-1

No of pts	Cohort Level	RIBOCICLIB	Tamoxifen
3-6 (phase 1)	**1**	**400 mg oral days 1-21, followed by 1 week break**	**20mg oral daily**
3 -6 (phase 1)	**2**	**400mg continuous**	**20 mg oral daily**
3 -6 (phase 1)	**3**	**600 mg oral day 1-21 followed by 1 week break**	**20 mg oral daily**
15 (Ib dose expansion)	**Phase Ib dose expansion**	**600 mg oral day 1-21 followed by 1 week break**	**20mg oral daily**
15 (Ib dose	**Phase Ib dose expansion-**	**400 mg oral daily**	**20 mg oral daily**

expansion)	**continuous cohort**		

Ribociclib Capsules/tablets for oral use 400 mg OR 600 mg Days 1-21 of each 28 day cycle or daily.

Tamoxifen Tablets for oral use 20 mg daily (all days of every cycle without interruption).

Goserelin Subcutaneous injection 3.6 mg Day 1 of each 28 day cycle.

The study drugs will be administered as a flat-fixed dose, and not by body weight or body surface area. All study treatment drugs must be administered together at approximately the same time each day.

All oral study treatment drugs can be administered with or without food.

The investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (promote compliance). Patients will be instructed to return unused study drugs to the site at discontinuation or completion of treatment. The site personnel will ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed.

8.2 Dosing regimen

- Ribociclib will be taken orally once daily on days 1-21 of each 28 day cycle. Days 22-28 will be a "rest" period from dosing with RIBOCICLIB.
- In the continuous cohort, 400 mg ribociclib will be taken daily (QD).
- Tamoxifen will be taken orally once daily on a continuous daily schedule (e.g. days 1-28 of each 28 day cycle) Goserelin will be given as an injectable subcutaneous implant on day 1 of every 28 day cycle. This will be given in pre and peri-menopausal women.

8.3 General dosing guidelines

The study treatments should be taken as follows:

Ribociclib will first be dosed orally for the first 21 days out of a 28 day cycle, then it will be given in a continuous dose (in the dose escalation or in the phase I dose expansion), it will be dosed daily of a 28 day cycle. Tamoxifen is dosed orally daily (28 days out of the 28 day cycle).

Per SOC, Goserelin is subcutaneously injected on Day 1 of each 28 day cycle.

Patients should be instructed to take the study treatment of **Ribociclib capsules** and one tablet of **Tamoxifen** together with a large glass of water (~250 mL) at the same time each morning within 5 minutes.

All oral study treatment drugs can be administered with or without food.

Patients should be instructed to swallow the capsules and tablets whole and not to chew, crush or open them.

Goserelin should be administered as a subcutaneous injection every 28 days into the anterior abdominal wall below the navel line using an aseptic technique under the supervision of a physician or health care surrogate. Administration technique should be in accordance with the locally approved label (SmPC).

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF.

Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.

Patients must avoid consumption of grapefruit, grapefruit hybrids, pummelos, star-fruit, Seville oranges or products containing the juice of each during the entire study and preferably for an additional 7 days before the first dose of study medications and during the study, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.

8.4 Safety Evaluation

Toxicity assessment, interim history and physical exam, CBC and chemistry profile weekly in cycle 1, then at day 1 of each cycle for the first 6 months and at least every 2 cycles thereafter.

Adverse Events and other symptoms will be assessed after the subject has had her first dose, and will be graded according to the NCI Common Toxicity Criteria version 4.03. Patients will be followed for evaluation of safety for at least 30 days after the last dose of study drug. Any study drug-related serious adverse events will be followed until resolution, return to baseline grade, or deemed irreversible by the Investigator.

8.5 STUDY CALENDAR

TESTS AND VISITS: Table 1-2

Test/ Study	Baseline[c]	C1 D1	C1 D8	C1 D15	C1 D22	C2 D1	C2 D22	C3 D1	C3 D15	C3 D16	C4 D1	C4 D22	C5 D1	C6 D1	C6 D22	C7 D1	C8 D1	C8 D22	C9 D1	C10 D1	C10 D22
Medical history	X																				
Vital Signs	X	X	X	X	X	X		X			X		X	X		X	X		X	X	
Child Pugh Score	X																				
Menopause status	X	X				X		X			X		X	X		X	X		X	X	
Physical exam	X	X	X	X	X	X		X			X		X	X		X	X		X	X	
Height	X																				
Weight	X	X				X		X			X		X	X		X	X		X	X	
Toxicity Assessment [a]		X	X	X	X	X		X			X		X	X		X	X		X	X	
PK Samples [b]									X	X											
Tumor Biopsy [d]	X																				
CBC w/Diff	X	X	X	X	X	X		X			X		X	X		X	X		X	X	
CMP[j]	X	X	X	X	X	X		X			X		X	X		X	X		X	X	
Lipid Panel	X										X						X				
PT & INR	X																				
Uric acid	X																				
FSH[k]	X																				
LDH	X	X				X		X			X		X	X		X	X		X	X	
Biomarkers [e]	X	X					X	X				X	X		X	X		X			X
Urinalysis	X	X				X		X			X		X	X		X	X		X	X	
Pregnancy Test [f]	X																				
Staging Scans	X						X					X			X			X			X
2D Echo	X						X					X			X			X			X
12 Lead EKG[i]	X	X	X	X	X	X		X			X		X	X		X	X		X	X	
Disease assessment[h]	X						X					X			X			X			X
Study Drug		X				X		X			X		X	X		X	X		X	X	

Dispensing																					

Test/ Study	C11 D1	C12 D1	C12 D22	C13 D1	C14 D1	C15 D1	C15 D22	C16 D1	C17 D1	C18 D1	C18 D22	C19 D1	C20 D1	C21 D1	C21 D22	C22 D1	C23 D1	C24 D1	C24 D22	30 day F/U[g]
Medical history																				
Vital Signs	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
Menopause status	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
Physical exam	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
Height																				
Weight	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
Toxicity Assessment [a]	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
PK Samples [b]																				
Tumor Biopsy [d]																				X
CBC w/Diff	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
CMP[j]	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
Lipid Panel		X						X					X					X		
PT & INR																				
Uric acid																				
FSH[k]																				
LDH	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
Biomarkers [e]			X				X				X				X				X	X
Urinalysis	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
Pregnancy Test [f]																				
Scans			X				X				X				X				X	
2D Echo			X				X				X				X				X	
12 Lead EKG[i]	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X
Disease assessment[h]			X				X				X				X				X	
Study Drug Dispensing	X	X		X	X	X		X	X	X		X	X	X		X	X	X		

a. Toxicity assessment must be performed until all treatment-related toxicities have been resolved or decreased to grade 1. Adverse events must be recorded up to 30 days after termination on study.

b. PKs to be collected at C3D15 and C3D16 for steady state evaluation at 7 time points: Pre-dose, 0.5 hr post dose, 1 hr post dose, 2 Hrs post-dose, 4 Hrs Post dose, 8 hours post dose, 24 hours post dose.
c. Tests done within 28 days can be used for baseline eligibility.

d. Tumor Biopsy is optional. Baseline tumor biopsy for predictive markers (optional) if accessible, if not accessible based on surgical evaluation, then archival tissue from metastatic site allowed). Baseline tumor sample will be collected at screening, or following progression on prior treatment and prior to C1D1. A newly obtained post-progression tumpr sample for resistance is optional. Should patient agree, it will be collected at time of progression and before a new treatment is initiated.

e. Biomarkers to be collected include: CTC, CEA, Ca15-3, Ca 125, Ca 27-29/ (If clinically indicated) at time of restaging scans. Further biomarker testing for exploratory circulating tumor DNA will be collected predose on C1D1, predose C3D1, Predose C5D1, and C7D1. Biomarkers will also be collected at EOT, or within 15 days of the last dose.
f. for women of childbearing potential. Pregnancy test will be repeated if clinically indicated.
g. Thirty day follow up to occur after last dose of study drug. Used for either end of treatment or study completion. Includes resolution of serious adverse events and adverse events related to study treatment.
h. Disease assessment is determined at visit every 8 weeks after staging scans and tumor marker collection
i. EKG to be done in triplicate. Two minutes apart, after patient has been resting for 5-10 minutes
j. Baseline CMP to include magnesium and phosphorous level for screening criteria.
k. Female participants only

8.6 Efficacy Evaluation for Dose I Expansion Cohorts:

Imaging tumor assessments:

Tumor response will be assessed according to RECIST Version 1.1 (Eisenhauer et al 2009). Patients should have at least one documented measurable lesion (per RECIST v1.1) or in the absence of measurable disease, have at least one predominantly lytic bone lesion at study entry.

Imaging assessments will be performed at screening within 28 days prior to randomization and subsequently every 8 weeks during the first 12 months and every 12 weeks thereafter. See Table 1-2 for details of assessments.

The 8-week (or 12 week) interval should be respected regardless of whether study treatment is temporarily withheld. After baseline, all assessments should be performed within ± 7 days of the scheduled day of assessment. The same method of assessment and the same technique should be used to characterize each individual and reported lesion at baseline and during follow up.

If a patient discontinues treatment for reasons other than radiological documentation of progression of disease, an efficacy assessment should be performed at the time of End of Treatment unless a CT/MRI for tumor measurement was performed within 21 days.

All patients will undergo CT or MRI of the chest, abdomen and pelvis at baseline and subsequent scheduled visits per Table 1-2. The preferred imaging methodology is CT with intravenous (i.v.) contrast. However, if at baseline, a patient is known to have a contraindication to CT i.v. contrast media or develops a contraindication during the trial, a non-contrast CT of chest (MRI is not recommended due to respiratory artifacts) plus contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.

A whole body bone scan or FDG-PET should be acquired at baseline for all subjects. Skeletal lesions identified on the whole body bone scan at baseline, which are not visible on the chest, abdomen and pelvis CT (or MRI) scan should be imaged at baseline and followed at scheduled visits using localized CT, MRI or x-ray. Whole body bone scans need not be repeated after baseline unless clinically indicated.

Other metastatic disease sites will be followed by CT or MRI, as clinically indicated. Chest x-ray or ultrasound should not be used to assess tumor lesions. Partial Response (PR) and Complete Response (CR) must be confirmed by repeat assessments performed not less than 4 weeks and after the criteria for objective response are first met. In case tumor assessment is performed <8 weeks from the first assessment of an objective response to confirm PR/CR, subsequent tumor assessments should revert back to the protocol schedule outlined in study calendar. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (see Appendix 1). If possible, a

single radiologist should perform all tumor response evaluations for an individual patient. Any lesions in previously irradiated areas should not be considered measurable unless they have experienced progression since the radiotherapy.

8.7 Treatment Duration

Eligible patients will receive treatment as described above, in consecutive 4-week cycles, until progression of disease or unacceptable toxicity. Patients are expected to receive treatment for at least 2 cycles, at which time the first evaluation for efficacy will occur. If there is continued safety and tolerability in the absence of any documented disease progression, treatment may continue for 2 years or until progression or non-tolerance.

Patients will be followed for evaluation of safety for at least 30 days after the last dose of study drug. Any study drug-related serious adverse events will be followed until resolution, return to baseline grade, or deemed irreversible by the Investigator.

9 PHARMACOKINETICS

PK blood samples will be obtained from all patients in both the phase I dose escalation and Ib dose expansion (when feasible) for the analysis of plasma concentrations of ribociclib (and any relevant metabolites such as LEQ803) and tamoxifen (and any relevant metabolites such as N-desmethyltamoxifen, 4-hydroxytamoxifen, and endoxifen) to evaluate any potential DDI. PK blood samples will be collected at steady-state on Cycle 3 Day 15 & 16 at pre-dose, 0.5, 1, 2, 4, 8 and 24 hrs post dose to allow for evaluation of exposure-response (efficacy endpoints and/or safety endpoints) relationships.

Steady-state for RIBOCICLIB, Tamoxifen (and metabolites), is generally achieved after daily dosing for 8 days, 4-8 weeks, 14-40 days, and 7 days, respectively; therefore, an assessment on Cycle 3 Day 15 is considered appropriate to evaluate steady-state PK.

Plasma concentrations of RIBOCICLIB and Tamoxifen will be determined by the Clinical Pharmacology Laboratory of the Translational Research Core at the Moffitt Cancer Center using LC/MS/MS methods that are validated according to ICH/FDA guidelines for bio-analytical analysis.

Tamoxifen with ribociclib will be compared to historical single agent ribociclib PK data, if feasible. If a patient discontinues from the study treatment due to toxicities related to study treatment, an unscheduled PK blood sample may be obtained as soon as possible after the last dose and the date and time of last dose recorded. In addition, an unscheduled blood sample may be collected if additional ECG measurements are conducted.

The date and exact time of dosing on PK collection days, as well as the date and actual time of blood sampling must be recorded on the appropriate eCRF pages and PK requisitions. In addition, the exact time of dosing on the previous day must be precisely recorded. Any sampling problems (e.g., patient took study drug before blood sample, scheduled sampling time is missed, sample is not drawn according to the schedule) should be noted as a comment on the eCRF.

If vomiting occurs during the course of treatment, no "re-dosing" of the patient is allowed, and medication should resume on the next day. The occurrence and frequency of any vomiting must be noted in the adverse events section of the eCRF. In addition, the date and exact time of vomiting should only be recorded if it occurs within 4 hours of dosing on the days of full PK sampling. If a vomiting episode occurs within the first 4 hours post-dosing during the day of the last dose prior to trough PK sample the exact time (whenever possible) must be noted on the eCRF.

PK parameters, such as Cmax, Tmax, and AUC0-24h, will be estimated (when feasible) from individual plasma concentration-time profiles using appropriate methods and software (Phoenix WinNonlin® ver6.3).

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Considerations for Phase I Study

A standard 3+3 design will be used (33) for the primary toxicity study under Phase I. A cohort of 3 patients will be recruited for each dose level at a time at a time. The first dose level will be level 1 and gradually increased to Level 2 and 3 if toxicity AEs are observed within the predefine statistical criterion/limit below.

Level 1: Ribociclib PO starting at a dose of 400 mg po for 21 days, followed by 1 week break of a 28-day treatment cycle;
Level 2: Ribociclib PO treated with a dose of 400 mg po daily for 28 days;
Level 3: Ribociclilb PO treated with a dose of 600 mg po for 21 days, followed by 1 week break of a 28-day treatment cycle

If 1 patient out of 3 experiences a dose limiting toxicity (DLT; see below for definition) at level 1, 3 additional patients will be recruited at that dose level. If only 1 out of 6 patients in that dose level experiences a DLT, a new cohort of 3 patients will be treated with the next escalated dose level. That is, the dose escalation continues until at least two patients among a cohort of three to six patients experience dose-limiting toxicities (i.e., $\geq$ 33% of patients with a dose-limiting toxicity at that dose level). If 2 out of 3 or 2 out of 6 patients experience a DLT, no further dose escalation will occur. The recommended phase II dose (RP2D) is defined as the dose level at which $\leq$1/6 patients experience DLT. There will be no dose escalation beyond dose level 3, meaning that if $\leq$1/6 patients experience DLT at this level, dose level will become the RP2D. No intra-patient dose escalation is allowed. Our dose escalation schedule follows a modified Fibonacci sequence in which the dose increments become smaller as the dose increases (e.g., the

dose first increases by 100% of the preceding dose, and thereafter by 50%, 33%, and 25% of the preceding doses). The RP2D will be defined as the dose level just below this toxic dose level.

Patients who achieve complete response (CR) or partial response (PR) or have stable disease (SD) may continue on study treatment until disease progression, as defined by RECIST v1.1 criteria, or intolerable toxicity.

10.2 Statistical Considerations for Phase Ib Dose expansion Study

If no MTD is observed with Level 1 through 3, we plan to continue/conduct the phase Ib dose expansion study as below. This expansion study is planned to understand and obtain initial efficacy data for the secondary endpoints.

Since the identical patient inclusion/exclusion criteria will be used in phase Ib dose expansion, all patient data from phase I dose escalation and phase Ib dose expansion studies can be combined for our statistical analysis, therefore, the required sample size of patients below will be both for phase I dose escalation and phase Ib dose expansion studies.

We obtained our statistical power and required sample size as a single-arm prospective study. In particular, for our evaluation of early efficacy we designed the study particular, for our evaluation of early efficacy we designed the study for testing H0: $P \leq 0.10$ versus H1: $P \geq 0.25$at one-sided significance level 0.05 and power 0.80 as below.

				Cut-Off		Actual	Actual
P0	P1	Alpha	Beta	R + 1	N	Alpha	Beta
0.100	0.250	0.050	0.200	8	40	0.042	0.182

Where P0 is the maximum response proportion of standard care (tamoxifen alone), P1 is the minimum response proportion of our experimental treatment group, and N is the sample size.

For our statistical testing, if the number of responses $\geq$ R+1, P0 is rejected based on Fisher's Exact test (34, 35). Alpha is the probability of rejecting that $P \leq P0$ when this is true.

Beta is the probability of rejecting that $P \geq P1$ when this is true.

Thus, the study requires 6 subjects under phase I dose escalation and 30 subjects under phase Ib dose expansion who will be treated with ribociclib (total 36) in order to test whether the proportion responding, P, is less than or equal to 0.100 or greater than or equal to 0.25. If the number of responses is 8 or more, the hypothesis that $P \leq 0.100$ is rejected with a target Type I error rate, α, of 0.050 and an actual error rate of 0.045. The null hypothesis will be rejected if 8 or more responses are observed in 40 patients. This design yields a type I error rate of 0.045 and power of 0.818 when the true response rate is 0.25.

10.3 Statistical Considerations for Safety

Toxicity assessment, interim history and physical exam, CBC and chemistry profile weekly in cycle 1, then at day 1 of each cycle for the first 6 months and at least every 2 cycle thereafter. Adverse Events and other symptoms will be assessed continuously and graded according to the NCI Common Toxicity Criteria Version 4.03. Patients will be followed for evaluation of safety for at least 30 days after the last dose of study drug. Any study drug-related serious adverse events will be followed until resolution, return to baseline grade, or deemed irreversible by the Investigator.

In this protocol, the routine use of any and all anti-emetics is allowed as clinically appropriate; these include the use of dexamethasone and 5-HT3 receptor antagonists.

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11 CRITERIA FOR RESPONSE, PROGRESSION AND RELAPSE

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Committee. (15) Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

For the purposes of this study, patients should be evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained ≥4 weeks following initial documentation of objective response.

11.1 Criteria for Target Lesions

11.1.1 Measurable disease

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

11.1.2. Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

11.1.3. Target lesions

• All measurable lesions up to a **maximum of two lesions per organ** and **five lesions in total**, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.
• Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible repeated measurements.
• All measurements should be recorded in metric notation using calipers if clinically assessed. A **sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions**) for all target lesions will be calculated and reported as the baseline sum diameters, which will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

11.1.4 Non-target lesions

All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline.
Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

11.2 Evaluation of response criteria

11.2.1 Target lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

11.2.2 Evaluation of non-target lesions

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

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

11.3 Evaluation of Best Overall Response

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

Note:

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- The best overall response for an early death, i.e., a patient who dies without documentation of disease progression and before it was time to conduct the first tumor reassessment, will be considered unevaluable or not assessed adequately. Response will also be considered unevaluable for any patient receiving treatment (regardless of how much was received) who did not have any follow-up assessment completed before initiation of alternative treatment. These patients must be replaced in both the phase I portion and the phase Ib expansion.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be imaged by PET scan or be investigated by fine needle aspirate/biopsy before confirming the complete response status.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

11.4 Guidelines for Evaluation of Measurable Disease

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

11.4.1 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If measured by calipers, measurements have to be confirmed by two independent health care professionals.

11.4.2 Conventional CT and MRI

Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis.

11.5 Confirmation Measurement/Duration of Response

11.5.1 Duration of Overall Response

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

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

11.5.2 Duration of Stable Disease

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

11.6 Evaluable disease

Patients must have measurable disease for dose expansion phase. Patients with bone only disease for this protocol are eligible if at least one lesion can be measured by MRI that is measurable by RECIST 1.1. Tumor markers are not considered measurable.

12 ADVERSE EVENT REPORTING

Investigators are required by Federal Regulations to report serious adverse events. This study will utilize the Common Toxicity Criteria version 4.03 to determine the severity of the reaction for adverse event reporting.

A serious adverse event is any adverse drug experience occurring at any dose that:

1. results in death;
2. is life-threatening;
3. results in in-patient hospitalization or prolongation of existing hospitalization (admissions for elective surgeries or procedure do not qualify);
4. results in a persistent or significant disability/incapacity; or
5. results in congenital anomaly/birth defect.

Reporting requirements and procedures depend upon: (1) whether agents are suspected of causing the adverse event, (2) whether the possibility of such an adverse event was reported in the protocol, consent form, or manufacturer's literature (expected or unexpected adverse event), (3) the severity or grade of the adverse event, (4) the phase of the study and attribution (the determination of whether an adverse event is related to a medical treatment or procedure). Any serious adverse event from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment has ended but which is felt to be treatment related must be reported.

12.1 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 is utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only
- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

12.2 Investigator Reporting: Novartis instructions for rapid notification of serious adverse events

All serious adverse events must be reported to Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E) and reporting will be done via the Investigators or his/her designee.

All events must be reported, by FAX [redacted] to Novartis Pharmaceuticals DS&E Department within 24 hours of learning of its occurrence. This includes all serious, related, not related, labeled (expected) and unlabeled (unexpected) adverse experiences.

All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 24 hours.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

Pregnancies

Any pregnancy that occurs during study participation should be reported by the site. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

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

13 DATA SAFETY MONITORING

Adverse events

Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, **the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used.**

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates or if continuing at the Safety Follow-up Visit)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, hospitalized, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

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

Information about common side effects already known about the investigational drug can be found in the Investigators' Brochure (14). This information should be included in the patient informed consent and should be discussed with the patient during the study as needed.

Internal Monitoring

13.1 Data Reporting

Data will be captured in Oncore, Moffitt's Clinical Trials Database.
Regulatory documents and case report forms will be reviewed routinely by the MCC Clinical Research Monitroing Core for accuracy, completeness, and source verification of data entry, validation of appropriate informed consent process, adherence to study procedures, and reporting of SAEs and protocol deviations according to MCC Monitoring Policies.

13.2 Study Suspension/Termination

The Protocol Monitoring Committee (PMC) and/or the IRB may vote to suspend or terminate approval of a research study not being conducted in accordance with the IRB, the Cancer Center and/or regulatory requirements or that has been associated with unexpected problems or serious harm to subjects. The PMC/IRB will notify the PI in writing of such suspension or terminations. It is the responsibility of the PMC/IRB Chairperson to ensure prompt written notification of any suspensions or terminations of PMC/IRB approval to the relevant Federal Agencies, including OHRP, FDA, the study sponsor/funding source and if applicable, the Affiliate Program.

13.3 Trial Discontinuation

For reasonable cause, the Investigator and/or sponsor (Novartis/Moffitt Cancer Center) may terminate this study prematurely. Conditions that may warrant termination include, but are not limited to: the discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study or if the accrual goals are met. A written notification of termination will be issued.

14 INCLUSION OF PATIENTS AND MINORITIES:

All patients regardless of ethnicity, race or **gender** are encouraged to participate in clinical trials. This trial is a treatment for metastatic breast cancer. Based on the fact that only 1% of all breast cancers occur in men, this trial will weighted towards women. Men with breast cancer are encouraged to participate.

15 CORRELATIVES

15.1 Biomarkers in a sub-group of patients

All patients will have the option to provide a representative tumor specimen upon progression. Our goal is to attain 10 specimens (volunteers). Patients may supply a tumor specimen that may be from a previous biopsy (archival tumor specimen) or a newly obtained tumor specimen. Additionally, a pathology report if available must be submitted along with the patient's archival tumor block/slides.

Genetic aberrations that lead to a gain in CDK signaling are observed in breast cancer. Investigating aberrations of the CDK pathway of patients enrolled in this study will therefore allow for the assessment of the potential predictive value of pathway activation for benefit from ribociclib in metastatic breast cancer. Biomarkers allowing identification of markers of resistance to treatment will also be investigated.

Tumor and blood samples will be collected according to Table 15-1.

All assessments will be performed by a Novartis designated laboratory. Instructions for collection, preparation and shipment can be found in the laboratory manual. Optional sample collection information must be entered on the appropriate eCRF pages and requisition forms.

Tumor samples will be taken pre-treatment and following progression. Tumor tissue samples will be obtained only from patients whose tissue is accessible to minimally invasive biopsy (fine needle aspiration, core needle, or superficial excision biopsy).

The pre-treatment (baseline) biopsy sample may be taken anytime between discontinuation of last endocrine therapy or after cytotoxic therapy and the start of study treatment. If not accessible, an archival sample from metastatic site is allowed. A pathology report must be submitted along with the patient's archival tumor block/slides.

Biopsy collection is requested (optional) at time of tumor progression for identifying potential markers of lack of response/resistance.

Tumor samples will be tested retrospectively for Rb protein and PTEN protein by immunohistochemistry. The status of molecules (e.g., gene expression, mutations, amplifications, deletions and/or protein expression/activation etc.) that are involved in the D-cyclin-CDK4/6-INK4a-Rb and mTOR pathways, such as mutations of CCND1, PIK3CA, PTEN and CDK4; gene amplification of CCND1 and CDK4, deletion of CDKN2, as well as potential resistant/escape pathways to CDK 4/6 inhibitors and other cancer associated genes, will also be investigated in the tumor tissue from all patients (provided that acceptable assays exist), with the intention of understanding potential mechanisms of resistance to CDK 4/6 inhibitors and identify the patient population that would benefit from this combination.

The results from these exploratory analyses will be correlated with clinical outcome to determine potential predictive biomarkers of ribociclib/everolimus/exemestane response.

Table 15-1 Biomarker sample collection plan

Sample	Tissue/Volume	Visit	Sample Collection
Baseline tumor biopsy for predictive markers (optional) if accessible, if not accessible based on surgical evaluation, then archival tissue from metastatic site allowed)	N/A	Screening	Following progression on prior treatment and prior to Cycle 1 Day 1

Newly obtained post-progression tumor samples for resistance (optional)	N/A	Post- progression	At progression and before new treatment is initiated
Exploratory Circulating tumor DNA (mandatory)	Blood/Plasma 20mL	Screening or Cycle 1, day 1	Predose
	Blood Plasma 10mL	Cycle 3 Day 1 Cycle 5 Day 1 Cycle 7 Day 1	Predose
	Blood/plasma 20ML	End of treatment	Within 15 days from last dose

Biomarkers assessment for pathway inhibition and efficacy

Assessments in tumor tissue

Tumor tissue samples will be collected in this trial for identifying biomarkers that may be predictive of benefit from ribociclib + Tamoxifen. Approximately 15-20 unstained slides (minimum of 10) should be made available for biomarker studies. If a biopsy is not possible, then an archival Formalin-Fixed, Paraffin-Embedded (FFPE) tumor will be acceptable (metastatic lesion preferred).

All specimens will be sent to a Novartis designated laboratory for analysis. Further details on preparation of the tumor biopsies and biomarker analysis will be provided in the Laboratory Manual.

Exploratory circulating tumor DNA

Assessment of circulating tumor DNA (ctDNA) will allow additional testing for mutations of genes that are relevant to HR+ breast cancer (e.g. PIK3CA, AKT, ESR1) and the CDK4/6 pathway using multiplexed approach such as next generation sequencing. The use of ctDNA offers a unique opportunity for serially monitoring tumor mutations in a non-invasive manner during the course of treatment, allowing for the detection of changes in tumor burden and monitoring response to treatment (Esposito et al 2014). Evaluation of tumor mutations at time of progression may provide information regarding potential mechanisms of resistance to therapy with ribociclib + tamoxifen. Blood samples for plasma ctDNA will be collected at baseline (20 mL at screening or cycle 1 day 1) and then day 1 of cycles 3, 5, 7 and end of treatment (20mL) for multiplexed analysis of cancer genes.

Exploratory analysis of potential mechanism of resistance

The biopsy collected at progression/end of treatment will be dedicated to understanding resistance to treatment. This study provides a unique opportunity to investigate the potential mechanisms of resistance to ribociclib in patients.

The specimens will be handled and shipped as described in the Laboratory Manual. The sample collection date must be entered on the appropriate tumor biopsy collection log eCRF page(s) and laboratory requisition form(s).

Additional biomarker assessments

During the study, in addition to the biomarkers specified above, exploratory research may be conducted on any tumor and blood samples collected. These studies would extend the search for other potential biomarkers relevant to the effects of ribociclib, goserilin, and Tamoxifen and/or prediction of these effects and/or resistance to the treatment, and/or safety. This may include the development of ways to detect, monitor or treat cancer. These additional investigations would be dependent upon clinical outcome, reagent and sample availability.

While the goal of the biomarkers is to provide supportive data, this is strictly optional in this study.

[redacted]

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