Local Protocol #: AAAP9506 NCT02632045
TITLE: A randoMized phAse II trIal of fulvestraNt or exemestane wiTh or without Ribociclib After progression on AntI-estrogeN therapy plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER2 negative breast cancer (MAINTAIN Trial)

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Novartis Supplied Agent(s):	**1) Ribociclib (a.k.a. LEE011, NVP-LEE011) [the primary investigational drug.]** 2) Letrozole (a.k.a. Femara, $C_{17}H_{11}N_5$). [Standard of care.]
Other Agent(s):	1) Fulvestrant (a.k.a. Faslodex, $C_{32}H_{47}F_5O_3S$). [Standard of care.] **2) Exemestane (a.k.a. Aromasin, 6-methylenandrosta-1,4-diene-3,17-dione). [Standard of care)**

Protocol Signature Page

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I will promptly submit the protocol to the applicable IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modification made during the course of the study must first be approved by the IRB, prior to implementation except when such modification is made to remove an immediate hazard to the subject. I certify that I, and the study staff, have received the requisite training to conduct this research protocol. I agree to maintain adequate and accurate records in accordance with Columbia University and Herbert Irving Comprehensive Cancer Center policies, Federal, state and local laws and regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Instructions to Principal Investigator: Sign and Date this signature page and print your name. Return the original, completed and signed to the Clinical Protocol & Data Management Office. Retain a copy in the regulatory binder.

_____ _____
Signature of Principal Investigator Date

_____
Principal Investigator Name (Print)

_____
Name of Institution

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1. SYNOPSIS

Title: A randomized phase II trial of fulvestrant or exemestane with or without Ribociclib after progression on aromatase inhibition plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER2 negative breast cancer.

Short Title: **Study of efficacy of ribociclib plus fulvestrant or exemestane after progression on CDK4/6 inhibition in patients with HR+ HER2- metastatic breast cancer.**

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Patient Selection (Section 3 for complete inclusion and exclusion criteria details)

1. Men or women at least 18 years of age with histologically or cytologically confirmed adenocarcinoma of the breast with metastatic **or** unresectable disease.
2. Hormone receptor positive (HR+) status, defined as **either** estrogen receptor positive (ER+), progesterone receptor positive (PgR+), or both, as defined by immunohistochemistry (IHC) ≥1% as per the ASCO-CAP guidelines.
3. HER2/Erbb2 negative (HER2-) status as per ASCO-CAP
4. Postmenopausal status **or** receiving ovarian suppression, including GnRH agonists (such as goserelin).
5. Evidence of measurable **or** unmeasurable disease.
6. Stable CNS disease allowed.
7. Eastern Cooperative Group (ECOG) performance status of 0 **or** 1.
8. No evidence of clinically significant congestive heart failure or other serious cardiac disease.
9. Adequate renal, liver, and bone marrow function.

10a. Written informed consent and HIPAA authorization obtained from the subject/legal representative prior to performing any protocol-related procedures;
10b. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study

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Study Design: This is a phase II, multi-center, randomized, double-blind, placebo-controlled trial to evaluate fulvestrant (or exemestane) +/- ribociclib in patients with HR+HER2- breast cancer who have previously progressed on aromatase inhibitor (AI: letrozole, arimidex, exemestane), selective estrogen receptor downregulator (SERD): tamoxifen), or fulvestrant plus CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib). Progression free survival is the primary endpoint. The trial will determine whether there is clinical benefit to continuing CDK4/6 inhibition beyond progression.

Patients can be screened and registered at two different time points:
Registration Scenario #1: Before receiving any CDK4/6 inhibitor **or**
Scenario #2: At the time of disease progression while being treated with a CDK4/6 inhibitor (ribociclib **or** palbociclib **or** abemaciclib)+ AI, tamoxifen or fulvestrant

In scenario #1, the study will provide patients with ribociclib + letrozole, but patients will not be randomized until they demonstrate objective evidence of disease progression on treatment. If the patient has previously received letrozole, an alternative AI can be prescribed but will not be provided by the study, i.e. administered as standard of care (ribociclib and letrozole will still be provided by the study). Patients are allowed to have received 4 consecutive weeks of an aromatase inhibitor prior to protocol registration for scenario 1. In scenario #2, patients will be randomized after registration.

At randomization, patients will be assigned to one of the two arms in a 1:1 ratio: 1) Fulvestrant (or exemestane) + ribociclib **or** 2) Fulvestrant (or exemestane) + placebo. Fulvestrant will be given as a 500 mg dose intramuscularly (IM) every 2 weeks for 3 times (loading dose) and then every 4 weeks, as per standard of care. Exemestane will be given as 25 mg orally daily, as per standard of care. The investigational drug ribociclib will be given as 600 mg daily, 3 weeks on/1 week off. Placebo will be administered on the same schedule. For all patients, ribociclib/placebo will be supplied by the study. Fulvestrant or exemestane will be given, as standard of care.

If patient received prior fulvestrant, exemestane must be the hormone therapy backbone in the randomization. If patient received prior exemestane, fulvestrant must be the hormone therapy backbone in the randomization. If neither has been administered, selection of fulvestrant or exemestane in the randomization will be per investigator discretion.

Accrual Target: N= 120 randomized, evaluable patients. Patients will be accrued from 11 academic medical centers in the US, with a goal of completing accrual in two years.
We will ensure that neither registration scenario contains > 60% (N=80) of total study accrual.

Patients will receive treatment on study until disease progression, unacceptable toxicity, or death or withdrawal from study based on patient choice or treating physician's discretion. Every effort will be made to follow patients for primary and secondary outcomes regardless of treatment discontinuation for any reason. Crossover is not built into the study.

Evaluations
Safety Assessment:
History, physical exam, and routine blood work such as blood counts and comprehensive metabolic panel will be performed on day 1 of each treatment cycle, including prior to randomization in patients registered under scenario #1. (i.e. at least every 4 weeks- Section 10: Study Calendar.)

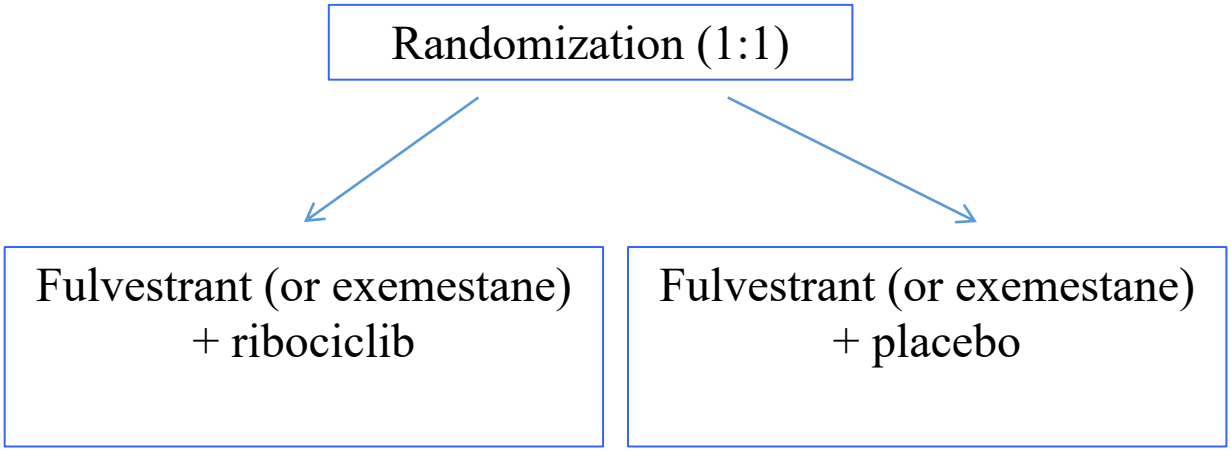
Primary and Secondary Endpoint Evaluations:
CT scans of the chest, abdomen, and pelvis and bone scan are to be performed prior to every third cycle of treatment (approximately every 12 weeks, depending on potential treatment delays), and prior to randomization in patients registered under scenario #1. PET scans can substitute for CT scans + bone scan, at the discretion of the onsite investigator. Additional off-schedule scans may be performed if concern for interval disease progression or other disease/treatment related complications. Disease progression will be determined at the local institution, per RECIST 1.1 criteria.

Skin color photography (if skin lesions are present) is recommended every 12 weeks (+/- 1 week) to assess for disease progression or response, particularly in patients with no measurable disease by radiologic criteria. (Appendix I).

Biomarker Assessment:

1) Archived tissue from primary and/or metastatic tissue is required, unless not available. If patient is amenable and has accessible tumor, repeat biopsy is optional. These biopsies should be considered in patients with accessible disease. Biopsies can be within 7 days of the cycle (+/- 7 days). Optional biopsies for tissue biomarker assessment will be performed in consenting patients prior to study treatment, at time of initial progression in patients registered under scenario#1, and when the patient goes off study.
2) Serum, plasma, and whole blood will be collected at multiple time points (Section 10: Study Calendar) and stored for future biomarker driven studies.

1.1 STUDY SCHEMA



- Scenario #2 – Patient may progress on AI or tamoxifen or fulvestrant plus prior CDK4/6 inhibitor.
- Patient may receive fulvestrant OR exemestane in the randomization, if they have not received before

1.2 OBJECTIVES

1.2.1 Primary Objectives:

1. To evaluate the progression-free survival (PFS) of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibitor in patients with hormone receptor positive (HR+), HER2- breast cancer.
    - **Endpoint: PFS.** Defined as the interval from time of randomization until objective disease progression (local assessment) or death from any cause. Kaplan-Meier estimates will be used to calculate medians and 95% confidence intervals for PFS. A one-sided log-rank test will be used to test for a difference in PFS between the two arms.

1.2.2 Secondary/Exploratory Objectives:

1. To assess the Overall Response Rate (ORR = complete + partial response rate) and Clinical Benefit Rate (CBR= ORR + stable disease rate at ≥ 24 weeks of follow up) in the study population in both arms of the trial, post-randomization.
    - **Endpoints: ORR, CBR.** Evaluation of disease will be made according to RECIST criteria (version 1.1) in patients with measurable disease. As this study will enroll patients with measureable and un-measurable disease as defined by RECIST v1.1, ORR will only be assessed in evaluable patients. CBR will also be determined. Patients with non-measurable disease only can be categorized as 'complete response', 'non-complete response', 'non-progressive disease', or 'progressive disease', but are sometimes not evaluable. (Section 11.1.4.2: Evaluation of Non-Target Lesions).
    - **Duration of overall response:** The duration of overall response is measured as the time interval from when measurement criteria are met for complete or partial response (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented

2. For patients in registration scenario #1, to assess the PFS, ORR, CBR, and safety of ribociclib with an aromatase inhibitor in patients with metastatic or unresectable HR+ HER2- breast cancer. This analysis will be based on data collected in the pre-randomization component of the trial for patients registered under scenario #1. There is no comparator arm for this component of the trial, but it will add to the available clinical safety and efficacy data with ribociclib + AI in this population.

3. To explore differences in clinical outcome (PFS, ORR, CBR) in patients receiving an aromatase inhibitor plus ribociclib vs. palbociclib vs. abemaciclib (scenario 1), both prior to randomization and then after continuation of CDK4/6 inhibition. In addition to potential differences between clinical outcomes based on the choice of CDK4/6 inhibitor for initial treatment, there might also be differential mechanisms of resistance that could impact outcomes when CDK4/6 inhibition is continued beyond progression along with fulvestrant or exemestane. Patterns of resistance, including location of resistance, and any differences in tissue-based markers will be explored.

    - **Endpoints: PFS, ORR, CBR, Site of Recurrence**. This is exploratory. Given the fact that patients with HR+ metastatic breast cancer have an improved PFS when adding CDK 4/6 inhibition to hormone therapy and given the small sample size of this study, there will not be enough patients to power this trial to evaluate the difference between CDK 4/6 inhibitors in those who register in scenario #1. Patients who received abemaciclib (LY2835219) are eligible for this trial (scenario #1).

4. To evaluate the rates of adverse events and tolerability of the combination of fulvestrant or exemestane with and without ribociclib.
    - **Endpoint: Adverse Events**. The frequency of subjects experiencing toxicities will be tabulated based upon the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0.
5. To explore potential predictive tumor and blood-based predictive biomarkers.
    - **Biomarkers**: Exploratory tumor tissue biomarkers that will be examined include overexpression or amplification of Cyclin D1 and Cyclin E, phospho-Rb expression, Rb1 loss, $p16^{INK4A}$ loss, and TK1 and TOP2A expression (as measures of E2F1 transcriptional activity). Serum and plasma will be collected and stored for potential future exploratory analyses. Differences in resistance between those who received ribociclib vs. palbociclib vs. abemaciclib will be explored.
6. To assess the impact of the combination therapy vs. fulvestrant or exemestane alone on patient reported global health assessment and quality of life.
    - Survey Instruments. Patient reported outcomes will be assessed using validated questionnaires (PROMIS Global Health and PROMIS 29; EQ 5D 3L)[87,88].

1.2.3 Summary Table of Objectives:

	Objective	**Endpoint**
Primary	To evaluate the progression free survival (PFS) of fulvestrant (or exemestane) +/- ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibitor.	**PFS**
Secondary / Exploratory	To compare the ORR and the CBR in the fulvestrant (or exemestane) /placebo vs. fulvestrant (or exemestane) /ribociclib arms.	**Complete and Partial Response Rate, and Stable Disease Rate** by RECIST criteria in patients with measurable disease. **Duration of Response** (in responders).
	For patients in registration scenario #1, to assess the efficacy and safety of ribociclib with anti-estrogen therapy	**PFS, ORR, CBR, Adverse event rates.**
	To explore the efficacy and patterns of resistance of ribociclib vs. palbociclib vs. abemaciclib in combination with anti-estrogen therapy	**PFS, Response Rates, Location of Distant Metastasis**: This is exploratory, as the study is not adequately powered to detect a difference.
	To evaluate the rates of adverse events and tolerability of fulvestrant (or exemestane) +/- ribociclib	**Adverse Events:** Events will be tabulated based upon the CTEP Active Version of the CTCAE v4.0.
	To explore potential predictive biomarkers, including exploring differences in tissue-based biomarkers in those who progressed on ribociclib vs. palbociclib vs. abemaciclib	**Tissue Biomarkers:** Overexpression or amplification of cyclin D1 and cyclin E, phospho-Rb expression, Rb1 loss, p16 loss, and TK1 and TOP2A expression. **Serum and plasma** will be collected and stored for potential future exploratory analyses.
	To assess impact on patient reported global	**Validated Survey Instruments.** PROMIS

	health assessment / Q.O.L.	(Global Health and PROMIS-29) and EQ-5D-3L will be used.

2. BACKGROUND

2.1 Overview:

Despite advances in early detection and therapeutic options, unresectable or metastatic breast cancer remains incurable and is one of the leading causes of cancer-related mortality.[1] Breast cancer is a molecularly heterogeneous disease, with three distinct molecular subtypes.[2] The first group is characterized by estrogen receptor (ER) expression positivity and/or progesterone receptor (PgR) positivity with the absence of over-expression or amplification of HER2. The second group is characterized by over-expression or amplification of HER2, with more than half of these tumors also positive for expression of ER/PgR. The third group lacks expression of ER, PgR, and HER2, and is thus referred to as triple negative breast cancer. Approximately 65% of newly diagnosed breast cancers are ER/PgR-positive and HER2-negative (sometimes referred to as luminal tumors), while an additional 20% of newly diagnosed cases are HER2-positive. Hormonally targeted drugs, specifically drugs that antagonize estrogen binding to the ER (tamoxifen), drugs that block estrogen biosynthesis (non-steroidal and steroidal aromatase inhibitors- only effective in postmenopausal patients), and drugs that antagonize and down-regulate the ER (fulvestrant), have been the mainstay of systemic treatment for patients with both localized and metastatic ER/PgR-positive breast cancers.[3] Fulvestrant is the most recent addition to the armamentarium of hormonal therapies available to treat these patients. However, acquired resistance (and occasionally primary resistance) to anti-estrogen therapy universally develops in patients with metastatic breast cancer.[4] Interestingly, even after acquired resistance develops, breast cancer cells appear to still depend on low-level ER activity in addition to signaling through newly acquired aberrant signaling pathways.[5] In addition, in patients initially diagnosed with ER/PgR positive localized breast cancer who later recur, tumors usually demonstrate some degree of resistance to anti-estrogen therapy at the time of recurrence.[6]

Traditionally, chemotherapy with minimal activity and significant toxicity has been the only option to treat patients with anti-estrogen resistance. This changed in 2012 with the approval of the molecularly targeted mTOR inhibitor everolimus to be used in combination with the steroidal aromatase inhibitor exemestane in patients with metastatic ER-positive HER2-negative breast cancer who have progressed on a non-steroidal aromatase inhibitor. Everolimus appears to at least temporarily restore sensitivity to anti-estrogen therapy and results in a progression free survival benefit.[7] More recently, inhibitors of the cyclin dependent kinases 4 and 6 (CDK4/6) have been developed and demonstrated impressive activity in patients with ER-positive HER2-negative breast cancer with marked improvements in progression free survival.[8,83] Identifying well tolerated targeted therapies that obviate the need for systemic chemotherapy, delay disease progression, and, ideally, prolong survival, as well as characterizing their optimal usage, remains a primary objective in breast cancer research.

2.2 Targeting the Cell Cycle:

The cell cycle is a tightly regulated series of events that allow the cell to replicate its genetic material and proliferate.[9] The cell cycle progresses from a G1 growth phase during which the cell grows and accumulates nutrients, to the S-phase during which replicated DNA is synthesized, to the G2 growth phase marked by further cell growth, mitochondrial division, and a final check on the fidelity of DNA replication, and finally to the M phase during which mitosis and cytokinesis occur resulting in two daughter cells.[9] Multiple checkpoints within the cell cycle ensure that only cells with appropriate growth factor stimulus, adequate nutrients, and without significant DNA damage are allowed to divide.[10] Cells that do not meet these criteria are either forced into a quiescent state, an arrest phase pending repair of DNA damage, or to undergo apoptosis/cell death. Most healthy cells spend the majority of their lifespan in the quiescent G0 phase, which is entered shortly after the completion of M-phase. Sustained proliferation in the absence of appropriate growth factor stimulus, in the absence of adequate nutrient supply, and in the presence of DNA damage is one of the hallmarks of cancer, and thus disruption of the cell cycle is an almost universal feature of malignancy.[11] Many cancers achieve this disruption through disabling one or more checkpoints in the cell

cycle, either through mutations, epigenetic silencing, or post-translational modification.[12]

The cyclin dependent kinases (CDKs), a family of evolutionarily conserved serine-threonine kinases, are critical effector proteins of the cell cycle machinery, which when activated, allow for progression from one phase of the cell cycle to the next.[9,13] Expression and activation of the CDKs are positively and negatively regulated by a diverse set of proteins. They are regulated positively by the cyclins, a family of proteins that bind to CDKs to form a functional holoenzyme. The CDKs are regulated negatively by a large number of endogenous inhibitor proteins, including p16, p19, and p21, many of which are able to sense DNA damage and then bind to the cyclin-binding domain of CDKs and thus inhibit the activation of CDKs.[13] (see figure 1).

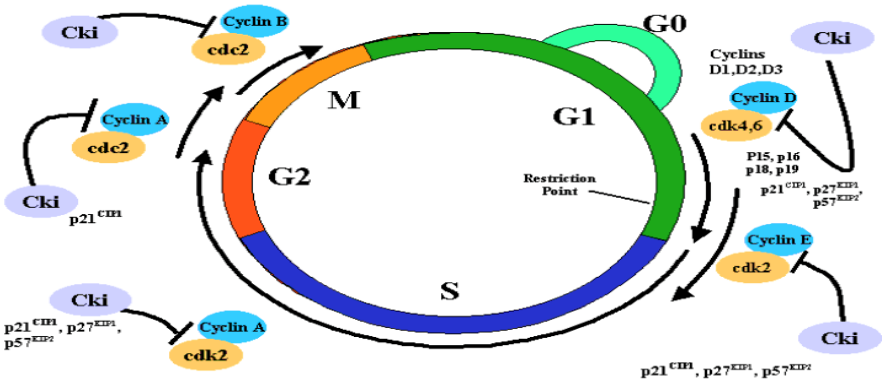


Fig 1 Simplified diagram of the cell cycle checkpoints and their regulation by CDK/cyclin complexes and their endogenous inhibitors. [14]

CDK4 and CDK6 are a pair of highly homologous proteins with largely redundant biological function that interact with D-type cyclins (either the D1, D2, or D3 subunit), and regulate the so called restriction checkpoint that occurs during G1 phase.[15] Cells at the restriction point can either progress to S phase and thus commit to another cycle of cell division or can withdraw to the quiescent G0 phase.[15] A variety of pro- and anti-growth signals from the extracellular and intracellular environment determine this fate.[15] Growth factor signaling frequently leads to increased downstream transcription and expression of cyclin D. Anti-proliferative signals are communicated through the tumor suppressor retinoblastoma protein (Rb1, also known as Rb and p110) as well as Rb-related proteins p107 and p130. Hypophosphorylated Rb represents its activated form and is able to sequester the elongation factor 2 (E2F) family of transcription factors, and thus leads to decreased expression of genes involved in cell cycle progression.[15] Alternatively, hyperphosphorylation of Rb by CDK4/6 in complex with cyclin D, and subsequently by CDK2 in complex with cyclin E in late G1 phase, results in the inactivation of Rb and allows increased synthesis of genes involved in DNA replication including thymidylate synthase and dihydrofolate reductase.[15]

Endogenous inhibition of CDKs is normally mediated through the Cip-Kip family of pan-CDK inhibitors, including p21, p27, and p57, and by the INK4 family of CDK4/6-specific inhibitors, including $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$, and p19.[16] Tumors increase cyclin D dependent activity through a number of different mechanisms including CDK4 amplification, CDK4/6 mutations resulting in decreased binding to $p16^{INK4a}$, cyclin D over-expression or amplification of its encoding gene CCND1, and $p16^{INK4a}$ inactivation by deletion or epigenetic silencing.[17] CCND1 amplification is a commonly occurring event in breast cancer, with approximately 30% of luminal A, 60% of luminal B and 40% of HER2 expressing tumors demonstrating amplification.[18,19] In addition, CDK4 over-expression or amplification is seen in approximately 25% of luminal and HER2-positive tumors. Alternatively, approximately 75% of basal-like breast cancers demonstrate loss of heterozygosity for the Rb alleles combined with markedly decreased expression of Rb, a downstream event that allows for progression through the cell cycle at the restriction point even in the absence of CDK4/6-cyclin D activity.[19] (see table 1 based on data from The Cancer Genome Atlas).

Table 1: RB Pathway Alterations by Breast Cancer Subytpe

Subtype	Luminal A	Luminal B	Basal-like
ER+/HER− (%)	87	82	10
HER2+ (%)	7	15	2
TNBC (%)	2	1	80
RB pathway	Cyclin D1 amplification (29%)	Cyclin D1 amplification (58%)	RB mutation/loss (20%
	CDK4 gain (14%)	CDK4 gain (25%)	Cyclin E amplification (9%)
	Low expression CDKN2C		High expression CDKN2C
	High expression RB1		Low expression RB1

The functional significance of CDK4 and cyclin D1 to oncogenesis has been investigated in murine models of breast cancer.[20,21] In both CDK4 and cyclin D1 knockout mice, implanted breast cancers demonstrate significant reduction in tumor growth. In particular, breast cancer models driven by HER2 signaling and by hormone receptor signaling appear to be dependent on CDK4/6-cyclin D1 activity. There is also some evidence that cyclin D1 has additional non-CDK dependent functions that may drive oncogenesis, including induction of chromosome instability by transcriptional regulation of chromosome instability related genes, induction of cellular migration and invasiveness, and pro-angiogenic effects.[22] In addition, CDK6 has recently been found to have kinase-independent function in promoting angiogenesis.[23] This latter effect is likely not inhibited by the currently available CDK4/6-inhibitors that all target the kinase domain.

Preclinical models suggest a particular role for CDK4/6 inhibition in ER-positive breast cancer cells, including both cells that remain sensitive to estrogen inhibition and cells that have developed acquired resistance to estrogen inhibition.[24] The ER regulates the transcription of cyclin D1, with estrogen mediated ER signaling resulting in increased expression of cyclin D1 on the RNA and protein level, accompanied by hyperphosphorylation of Rb and progression through the cell cycle. In ER-positive breast cancer cell lines that are sensitive, treatment with anti-estrogens results in growth arrest and marked reduction in cyclin D1 expression.[25] Cyclin D1 also appears to function in the recruitment of SRC family co-activator of ER, and thus augments ER mediated transcriptional activity, forming a feed forward loop.[26] The development of resistance to anti-estrogens in ER-positive breast cancer models is associated with persistent cyclin D1 expression and hyperphosphorylation of Rb. [27]

Targeting the cell cycle has been challenging due to the difficulty of developing specific inhibitors to the cyclins and CDKs.[28] However, in recent years, CDK4/6 specific inhibitors have been developed and demonstrated significant clinical activity in metastatic hormone-responsive breast cancer and in well-differentiated and de-differentiated liposarcoma (a disease marked by minimal responsiveness to traditional chemotherapy and in which CDK4 amplification occurs in >90% of cases).[29,30] In fact, inhibitors of CDK1, CDK2, CDK4/6, CDK7 and CDK9 as well as pan-CDK inhibitors have been developed and are entering into early and late phase clinical trials in a large number of oncologic settings.[31] The various CDK inhibitors induce cell cycle arrest at different points of the cell cycle and inhibiting certain CDKs (CDK7 and 9) also significantly impacts transcriptional activity.[31] In February 2015, the CDK4/6 inhibitor palbociclib gained accelerated US approval by the FDA for the first line treatment of patients with ER-positive HER2-negative metastatic breast cancer.

2.3 Clinical Trials Involving CDK4/6 inhibition in ER-positive Breast Cancer:

Flavopiridol was the first CDK inhibitor to be investigated in clinical trials.[32] Flavopiridol is a non-selective inhibitor that targets CDK1, 2, 4/6, and 7. In preclinical studies, flavopiridol induces G0 and G1 arrest in a variety of tumor cells as monotherapy. The effects of flavopiridol synergizes with chemotherapy, which typically induces an S-phase delay as the result of DNA damage. Flavopiridol demonstrated minimal clinical activity when used as a single agent.[33] While there was some activity seen in solid tumors including breast cancer in early phase clinical trials when combined with cytotoxic chemotherapy, there was also substantial

dose limiting toxicity seen with these combination regimens, most notably neutropenia and diarrhea.[34] Moreover, because these regimens required precise timing of flavopiridol, usually administered a few hours after chemotherapy, they were impractical for implementing in larger clinical trials. There is *in vitro* evidence that if the timing of administration is not properly synced, that CDK-inhibitors can reduce the efficacy of cytotoxic chemotherapy due to the reduction of tumor cells actively entering the cell cycle, on which the latter depends.[35] There is also a theoretical concern that because CDKs are involved in DNA repair mechanisms, that the combination of CDK-inhibition with cytotoxic chemotherapy or radiation therapy may increase the adverse effects on healthy tissue as well as increase the mutational burden in cancer cells.[35]

Three selective CDK4/6 inhibitors, palbociclib, abemaciclib and ribociclib have all entered advanced phase clinical trials in breast cancer, and are described in detail below. All three drugs competitively bind to the ATP-binding pocket of the CDK4/6 kinase domain.[36]

Palbociclib (PD0332991):
Given the biological interplay between cyclin D1 and the ER, discussed above, highly selective CDK4/6-specific inhibitors were evaluated in breast cancer. *In vitro* studies with palbociclib, a pyridopyrimidine compound, demonstrated selective growth inhibition in luminal type breast cancer cell lines, including anti-estrogen resistant cell lines, and demonstrated minimal activity in basal-like cell lines. It demonstrated marked G1-phase arrest in the MDA-MB-435 luminal breast cancer cell line.[37] Activity was also observed in most HER2-positive breast cancer cell lines, in particular those that were also ER-positive.[37] There was synergy when palbociclib was combined with tamoxifen in ER-positive cell lines including those with tamoxifen resistance and there was also synergy when palbociclib was combined with trastuzumab in HER2-positive cell lines.[37] There was minimal activity in cell lines with Rb deleted. As a single agent, palbociclib demonstrated significant tumor regression in some xenograft models.[38]

Palbociclib was first investigated in humans in an open label phase I dose-finding study open to patients with Rb-intact solid tumors or lymphomas.[39] The drug was administered orally on a 2-week on, 1-week off schedule, with the 200 mg dose of palbociclib being established as the maximum tolerated dose. Neutropenia was the only dose limiting toxicity observed. This myelosuppressive effect was consistent with the expected effects of CDK inhibition on rapidly dividing cells such as hematopoietic progenitor cells. A separate phase I trial investigated a 3-week on/1-week off schedule of palbociclib in 41 patients with Rb-intact solid tumors and lymphoma.[40] In this study, neutropenia was again the only dose limiting toxicity, and a dose of 125 mg daily on a 3 week on/1 week off schedule was established as the recommended dose for phase II studies. Common non-dose limiting toxicities included fatigue, low-grade diarrhea, nausea, and constipation.

In a phase II study of 28 heavily pretreated patients with Rb-intact metastatic breast cancer, palbociclib 125 mg daily was administered on a 3 week on / 1 week off schedule as monotherapy.[41] Only two of the 28 patients (7%) were noted to have a partial response, while an additional four patients (14%) were noted to have stable disease beyond six months. None of the patients with ER-negative breast cancer demonstrated a partial response or stable disease at six months. As several of the patients in this study had received several prior lines of chemotherapy, it was felt that there might be acquired cross-resistance between chemotherapy and palbociclib. Thus, further clinical trials with palbociclib focused mainly on minimally pre-treated patients with ER-positive breast cancer, and in combination with anti-estrogens. The only grade III/IV toxicities observed in this trial were neutropenia (50%) and thrombocytopenia (21%), with one patient developing febrile neutropenia requiring hospitalization after cycle 1. The relative infrequency of febrile episodes in neutropenic patients has led some investigators to hypothesize that CDK4/6 inhibition leads to a temporary cytostatic but not cytotoxic effect on bone marrow progenitor cells, which is different than the cytotoxic effects of traditional chemotherapy.[42] In addition, the infrequency of severe GI mucositis accompanying the neutropenia seen with these drugs likely contributes to decreased infection risk.[42]

The multicenter randomized phase I/II PALOMA-1 study evaluated the combination of palbociclib 125 mg daily on the 3 week on/1 week off schedule with the non-steroidal aromatase inhibitor letrozole 2.5 mg daily

vs. letrozole alone in patients with previously untreated metastatic ER-positive/HER2-negative breast cancer.[43] The phase I component of the study established the safety of this combination. The phase II component of the study accrued 165 patients and was divided into two parts, with the first part open to all participants in the study and a second part open only to patients selected for CCND1 amplification or p16 loss (N=99). After exploratory analysis failed to demonstrate that CCND1 amplification or p16 loss predicted response to palbociclib, the two parts were combined for a final efficacy analysis. Compared to letrozole alone, the combination of palbociclib and letrozole provided a very impressive increase in progression free survival, the predefined primary outcome, from 10.2 months to 20.2 months (Hazard Ratio (HR)=0.37; p=0.0004). A statistically significant difference in overall survival has not yet been achieved, but the majority of patients in both arms of the study were still alive at the time of the most recent analysis. The combination treatment arm tolerated treatment well for the most part, with grade III/IV neutropenia (54% vs. 1%), grade II-IV anemia (35% vs. 6%), grade II-IV thrombocytopenia (16% vs. 1%), and fatigue (40% vs. 23%) being the most commonly reported serious events. There was also a slight increase in the incidence of pulmonary embolism and grade III/IV infections in the combination arm compared to letrozole alone (5% vs. 0% for each). Based on these results, in February 2015 the FDA granted accelerated approval for the use of palbociclib and letrozole in the first line treatment of patients with metastatic ER-positive HER2-negative breast cancer. The confirmatory phase III randomized PALOMA-2 study accrued 450 patients and has been completed.[44]

The double blind phase III PALOMA-3 trial is investigating the combination of hormonal therapy and palbociclib in pre- and post-menopausal patients with metastatic ER-positive/HER2-negative breast cancer, with disease relapse or progression after at least one line of hormonal therapy and at most one line of chemotherapy.[45] (All patients were naïve to CDK4/6 inhibition.) Postmenopausal patients received the ER downregulator fulvestrant with or without palbociclib 125 mg daily 3 weeks on/1 week off, while premenopausal and peri-menopausal women also received the LHRH analog goserelin to shut down the pituitary-ovarian axis. The primary endpoint was investigator determined progression-free survival, with secondary endpoints of overall survival, response rate, patient reported outcomes and safety analysis. The interim analysis of PALOMA-3 was presented at ASCO 2015.[46,83] A total of 521 patients were randomized in a 2:1 ratio to the combination (N=347) and hormonal therapy alone (N=174) arms. The median age at enrollment was 57 years, with the majority of patients postmenopausal (79%), with visceral metastatic disease (60%), and with previously demonstrated sensitivity to anti-estrogen therapy prior to disease progression (79%). 33% of patients in this trial had previously received one line of chemotherapy, while the majority of patients had not been pretreated with chemotherapy. The PFS at time of interim analysis was 9.2 months in the combination arm vs. 3.8 months for fulvestrant alone. (HR=0.42; p<0.000001). Benefit was seen with the addition of palbociclib in both pre- and post-menopausal patients. The most commonly seen adverse events in the combination arm were neutropenia (78% vs. 4%), leukopenia (45% vs. 4%), and fatigue (38% vs. 27%). In spite of the very high occurrence of neutropenia, only 0.6% of patients developed febrile neutropenia in the combination arm and only 2% of patients required treatment discontinuation due to adverse events.

There are ongoing clinical trials investigating the role of palbociclib in combination with HER2-targeted therapies in metastatic HER2-positive breast cancers as well as studies investigated the role of palbociclib in the adjuvant or neoadjuvant setting, in particular in patients with residual disease after neoadjuvant therapy.

Abemaciclib (LY2835219):
Abemaciclib is another selective CDK4/6-specific inhibitor that is being evaluated in early phase clinical trials. In preclinical *in vitro* testing, it results in G1 phase arrest and inhibits the formation of phosphorylated Rb.[47] In the dose escalation phase of a monotherapy study (N=55), grade III fatigue was the main dose limiting toxicity, and a dose of 200 mg twice daily was established as the maximum tolerated dose[49]. The largest cohort in the phase I study were patients with heavily pretreated metastatic breast cancer (N=47), 36 of whom had ER-positive disease. As monotherapy, abemaciclib resulted in partial responses in 9 of these 47 patients (19%), all of whom had ER-positive disease, and stable disease in 24 patients (51%). Common

adverse events included diarrhea, nausea, vomiting, and fatigue, with neutropenia the only common grade III/IV toxicity, seen in 11% of patients. In other early-phase studies in metastatic breast cancer, there appears to be a significantly higher rate of diarrhea with abemaciclib compared with palbociclib and ribociclib.[51] Ongoing phase II/III studies are evaluating abemaciclib as monotherapy or in combination with anti-estrogen therapies in patients with ER-positive breast cancer in a variety of clinical settings. [50-52]

2.4 Primary Investigational Drug Ribociclib (a.k.a. LEE011, NVP-LEE011):

Ribociclib is a small molecule inhibitor of CDK4/6 that is highly specific for the CDK4-Cyclin D1 and CDK6-Cyclin D3 complexes (Section 5: additional pharmaceutical information).[53] It demonstrates superior selectivity compared to palbociclib and abemaciclib for CDK4/6 in *in vitro* studies, and thus may potentially be better tolerated at higher/more pharmacodynamically active doses. In preclinical *in vitro* and *in vivo* testing, ribociclib at concentrations in the nanomolar range results in dose dependent anti-tumor activity that correlates well with reduction of phospho-Rb.[53] In murine models, ribociclib demonstrates growth inhibition and occasional tumor regression, similar to palbociclib, and has activity against both ER-positive as well as HER2-positive breast cancer.[53] It has also demonstrated activity in BRAF-positive and NRAS-positive melanoma models, suggesting that the drug has activity in tumors driven by downstream signaling from the epidermal growth factors.[53] Preclinical pharmacockinetic studies indicate that ribociclib is metabolized and eliminated by the cytochrome p450 system, with drug levels potentially affected by drugs that inhibit or induce CYP3A[3,54] CYP3A4 inhibitors include HIV protease inhibitors and several anti-bacterials and to a lesser extent anti-emetic medications, while CYP3A4 inducers include anticonvulsants, some diabetic medications such as pioglitazone, and HIV NNRTIs.[53,54] Several chemotherapeutic medications are also substrates for CYP3A4 and the co-administration of ribociclib with these medications could potentially affect their levels.[53,54]

In the first in human phase I trial, 132 patients with multiple tumor types were treated with ribociclib monotherapy, with doses ranging from 50 mg to 1200 mg daily on a 3 weeks on / 1 week off schedule.[55] The majority of reported adverse events were grade I/II, including neutropenia, leukopenia, nausea, and fatigue. Asymptomatic QTc prolongation was observed with increasing frequency at doses above 600 mg daily; no adverse cardiac events occurred. Based on this concern, the recommended phase II dosing for ribociclib was established as 600 mg daily on a 3 weeks on / 1 week off schedule.

Ongoing phase I, II and III trials are evaluating ribociclib in ER-positive breast cancer, BRAF-mutant melanoma, as well as other solid tumors such as liposarcoma, neuroblastoma, and head and neck cancers.[56] A phase Ib/II open label trial is evaluating the combination of letrozole, the PI3K**α**–specific inhibitor BYL719 and ribociclib in patients with newly diagnosed metastatic ER-positive breast cancer.[57] The initial phase of this trial evaluated the doublet combinations of BYL719/ribociclib and letrozole/ribociclib in seven patients, with both arms demonstrating acceptable safety. Another phase Ib/II study is evaluating the combination of the steroidal aromatase inhibitor exemestane, the mTOR inhibitor everolimus and ribociclib in patients with ER-positive breast cancer.[58] These combinations were conceived as the result of preclinical testing that suggests that CDK4/6 inhibition can overcome primary or acquired resistance to inhibition of the PI3K-Akt-mTOR pathway.[53,54] Given these findings, evaluating ribociclib in combination with other targeted therapies and in the context of heavily pretreated cancers with acquired resistance to standard treatments has been a major focus of clinical trial development compared to the other CDK4/6 inhibitors. Preliminary data from 16 patients enrolled in the exemestane/everolimus/ribociclib study suggests that the combination is safe and feasible.[58] A planned phase II study will evaluate the safety and efficacy of this triplet combination compared to the doublets exemestane/everolimus and exemestane/ribociclib. In BRAF or NRAS-mutant metastatic melanomas, ribociclib is being evaluated in combination with BRAF and MEK inhibitors.

Additional studies in breast cancer are ongoing. The large randomized, placebo-controlled, double blind phase III MONALEESA-2 trial is evaluating the combination of ribociclib and letrozole vs. letrozole alone in patients with previously untreated ER-positive HER2-negative metastatic breast cancer. A smaller open label phase II trial (MONALEESA-1) is a pre-surgical pharmacodynamics study evaluating ribociclib in the

neoadjuvant setting, and has completed accrual.

2.5 Fulvestrant (a.k.a. Faslodex, $C_{32}H_{47}F_5O_3S$)):

Fulvestrant is currently a standard of care hormonal therapy option in patients with ER-positive breast cancer.[59] As described above, fulvestrant has been evaluated in combination with the CDK4/6 inhibitor palbociclib in the phase III PALOMA 3 trial (N=521), and is currently being evaluated in the large phase III MONARCH-2 trial in combination with abemaciclib. No major safety concerns have been raised in these trials, and thus the combination of fulvestrant with CDK4/6 inhibition appears to be feasible.

Fulvestrant is a selective estrogen receptor downregulator (antagonist) used in the treatment of ER-positive breast cancer that has demonstrated activity in both untreated patients as well as those previously treated with hormonal therapy. It competitively binds to the ER with an affinity 100 times greater than that of tamoxifen.[60] Fulvestrant is able to markedly inhibit ER mediated transcriptional activity in a dose-dependent manner by impairing ER dimerization, preventing ER localization to the nucleus and by increasing ER degradation.[61] Unlike tamoxifen, fulvestrant does not have ER agonist activity and unlike any of the other available anti-estrogen therapies, it also results in a consistent reduction in PgR levels in breast cancer cells.[61] In preclinical studies, fulvestrant demonstrates anti-proliferative effects and induces apoptosis in ER-positive breast cancer cell lines, including those that are resistant to tamoxifen. [61] There appears to be minimal *in vitro* cross-resistance between fulvestrant and tamoxifen or non-steroidal aromatase inhibitors such as anastrozole or letrozole.[62] Cells and murine models treated with fulvestrant eventually acquire resistance to the drug, with resistance thought to be partially conferred by an over-expression of the micro-RNAs 221 and 222.[63] Interestingly, miR-221/222 over-expression results in decreased levels of the endogenous pan-CDK inhibitors $p27^{kip1}$ and $p57^{kip1}$, thus increasing progression through the cell cycle at the G1 restriction point and at the S->G2 transition point.[64] Combining fulvestrant with a CDK 4/6 inhibitor could potentially prevent this mechanism of resistance.

Initial studies with lower dose fulvestrant 250 mg intramuscular monthly were disappointing, as they demonstrated minimal improvement over previously available anti-estrogen therapies. Two phase III non-inferiority trials compared fulvestrant 250 mg intramuscular once monthly with anastrozole 1 mg daily in a total of 851 post-menopausal patients who had previously progressed on anti-estrogen therapy, with the majority having previously received tamoxifen.[65,66] (A previous study had established anastrozole as a modestly effective second line hormonal therapy compared to megestrol acetate in patients who had progressed on tamoxifen.[67]) The time to progression on fulvestrant was 5.5 months vs. 4.1 months for anastrozole (HR=0.95; p=0.48) and the overall response rate was 19.2% vs. 16.5% (p=0.32), with a median duration of response of 16.7 mo vs. 13.7 mo. Subsequently, a phase III randomized trial compared fulvestrant 250 mg intramuscular once monthly to tamoxifen 20 mg daily as the initial anti-estrogen therapy in 587 postmenopausal patients with newly diagnosed or recurrent metastatic breast cancer.[68] In the 78% of patients who were ER-positive or PgR-positive, the two treatments were essentially equivalent in the first line setting, with an overall response rate of 31.6% vs. 33.9%.

The EFECT trial was a randomized phase III, double blind, placebo controlled trial comparing fulvestrant vs. the steroidal aromatase inhibitor exemestane 25 mg daily in 693 post-menopausal patients with ER or PgR-positive metastatic breast cancer who had disease progression on a non-steroidal aromatase inhibitor (anastrozole or letrozole)[69]. Fulvestrant was administered with a loading dose of 500 mg intramuscular on day 0, followed by 250 mg doses on days 14 and 28, followed by 250 mg doses every four weeks. The median time to progression in both arms was equivalent (3.7 mo) and the overall response rate was 7.4% on fulvestrant vs. 6.7% on exemestane. (p=0.736). There was a trend towards more durable responses in patients who were treated with fulvestrant (13.5 mo vs. 9.8 mo).

More recent clinical studies have established that higher dose fulvestrant 500 mg intramuscular monthly is more effective than 250 mg and equally well tolerated and safe. Pre-surgical biomarker studies of fulvestrant indicate that PgR expression specifically is only decreased at higher doses of fulvestrant.[70-72] In the phase II

open-label FIRST trial, 205 postmenopausal patients with hormone receptor positive metastatic breast cancer were randomized to receive either fulvestrant 500 mg intramuscular monthly (with an additional 500 mg loading dose on day 14) vs. anastrozole 1 mg daily.[73] There was no difference in the primary outcome of clinical benefit rate (overall response rate plus stable disease) at 24 weeks, but the secondary outcome of time to progression was significantly prolonged in the fulvestrant arm (23.4 mo vs. 13.1 mo; HR-0.66; p=0.01). Updated results from FIRST were presented at the 2014 San Antonio Breast Cancer Symposium.[74] There was a surprising and impressive improvement in overall survival in the fulvestrant arm (54.1 mo vs. 48.4 mo; p=0.041). Overall survival was not a predefined outcome in the study but was added as an amendment to the protocol after interim analysis. The phase III, double-blind randomized FALCON trial comparing fulvestrant 500 mg intramuscular monthly to anastrozole 1 mg daily in postmenopausal women with hormone receptor positive locally advanced or metastatic breast cancer who had not previously been treated with any hormonal therapy has completed accrual.
The phase III double-blind CONFIRM trial directly compared fulvestrant 500 mg monthly (with an additional dose on day 14) with the fulvestrant 250 mg monthly dose in 736 postmenopausal patients with metastatic recurrent breast cancer who had progressed on prior anti-estrogen therapy.[75] There was a statistically significant improvement in the primary outcome of progression free survival on the higher dose of fulvestrant (6.5 mo vs. 5.5 mo; HR=0.80; p=0.006). On long term follow up, there was also an improvement in overall survival with the higher dose (26.4 mo vs. 22.3 mo; p=0.016), although this was not a predefined outcome measure. Both doses were well tolerated, with 20% of patients in each arm complaining of mild gastrointestinal disturbances, 19% reporting joint aches and pain, and 13% in each arm reporting injection site pain or reaction. There was a slight increase in hot flashes reported in the higher dose group (8% vs. 6%) and there were very rare serious events reported only in the higher dose arm of bronchitis (2 patients) and dyspnea (3 patients), which were not felt to be treatment related.

Fulvestrant offers one additional benefit compared to other anti-estrogens. It has been estimated that approximately 20% of patients receiving oral endocrine therapy do not take their medication regularly.[76] As fulvestrant is a parenteral agent administered once monthly in the clinic, it has the potential to improve adherence.

2.6 Rationale for the proposed study:

The optimal CDK4/6 inhibitor and the optimal hormonal therapy to combine it with is yet to be determined, as there have been several ongoing clinical trials in ER-positive breast cancer that have been running in parallel over the past several years. Each of the available CDK4/6 inhibitors has different side effect profiles and slight differences in biological effects based on preclinical studies. Moreover, the optimal sequencing of CDK4/6 inhibition in the treatment of breast cancer is open to investigation. The majority of clinical trials to date have investigated the effects of CDK inhibition in patients with metastatic breast cancer with minimal pre-treatment with hormonal, targeted, or cytotoxic therapies, primarily due to the concern that there might be acquired cross-resistance between these other agents and CDK inhibitors.

However, in spite of these concerns, there is clearly a role for continuing targeted therapies in patients with breast cancer, even beyond the point of disease progression. Fulvestrant has demonstrated impressive clinical activity and possibly prolongs survival in patients previously treated with one or more lines of anti-estrogen therapy, as described in Section 2.5, establishing a role for continuing ER targeted therapy beyond the point of disease progression. Everolimus appears to restore sensitivity to anti-estrogens by inhibiting resistance mediated by the PI3K/Akt/mTOR pathway. In patients with HER2-positive breast cancer, it has become standard practice to continue HER2-targeted therapies beyond progression on HER2-targeted therapy. The BIG 03-05 and EMILIA trials demonstrated that continuing HER2 targeted therapies in patients with HER2-positive breast cancer who have had progression of disease on trastuzumab improves response rates and survival on the order of several months.[77,84]

Ribociclib has been shown to inhibit growth in several breast cancer cell lines and has anti-tumor activity in patient-derived xenograft models.[53,54] As described above, early phase clinical trials with ribociclib have demonstrated very good tolerability and safety, even when combined with other targeted therapies. In

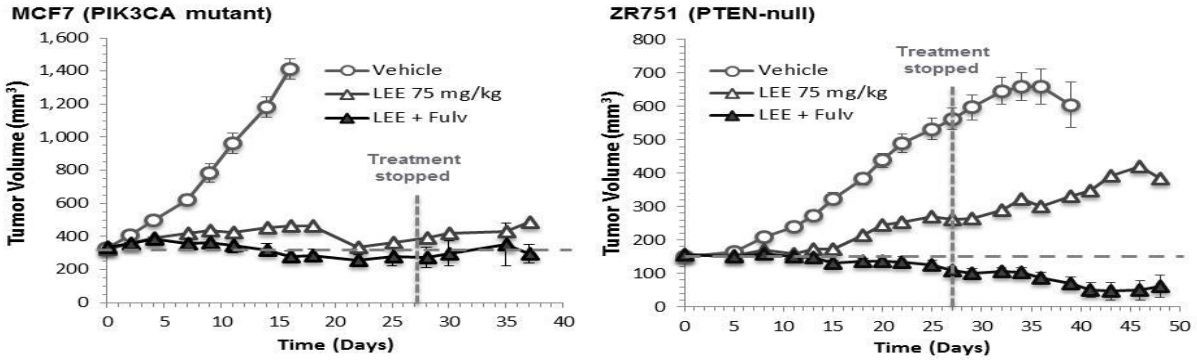
addition, all three of the available CDK4/6 inhibitors have been combined with fulvestrant in clinical trials, and the combination appears to be well tolerated and quite feasible. Given the similar preclinical profile and mechanism of action to palbociclib, it is anticipated that ongoing phase II/III studies of ribociclib will demonstrate clinical benefit when used in patients with ER-positive HER2-negative breast cancer.

Considering how well tolerated these medications are, a very important remaining question is whether there is a role for continuing CDK4/6 inhibition beyond progression, similar to what is seen with the continuation of hormonal therapy and the continuation of HER2-targeted therapies in HER2-positive breast cancers. A second important question is whether there is enough of a difference between the available CDK4/6 selective inhibitors that patients may derive benefit from switching agents after disease progression on one of them, as is seen with the multiple bcr-abl targeted tyrosine kinase inhibitors used to treat chronic myeloid leukemia. *In vitro* work suggests that acquired resistance to CDK4/6 inhibition is related to either functional loss of Rb or through the activation of alternative signaling pathways;[78] the former likely would not benefit from continuation of CDK4/6 inhibition or switching medications, but the latter might as compensatory activation of alternative pathways may be suboptimal for tumor growth. In addition, little is known about *in vivo* acquired resistance to CDK4/6 inhibition, which may potentially be related to various complex pharmacokinetic and pharmacodynamics factors that cannot be studied or predicted from *in vitro* studies. Moreover, as all of the first line trials with CDK4/6 inhibitors have combined the drug with an aromatase inhibitor, it is not always clear if disease progression occurs due to the development of resistance to CDK4/6 inhibition or due to resistance to first line anti-estrogen therapy. Thirdly, it will be important to determine if the large proportion of patients who have received cytotoxic chemotherapy or multiple lines of anti-estrogen therapy as the initial therapy for metastatic breast cancer may still benefit from the addition of CDK4/6 inhibition later in the sequence of treatment.

Preclinical data suggests that patients may indeed benefit from treatment with CDK4/6 inhibition and fulvestrant after progression on a CDK4/6 inhibitor. There is evidence that resistance to hormonal therapy, mTOR inhibition, and cytotoxic chemotherapy is at least in part mediated by upregulation of CDK4/6-cyclin D activity in breast cancer, suggesting that there might be a role for CDK4/6 inhibition in patients who have progressed on these therapies. There is also growing preclinical evidence that persistent inhibition of CDK4/6 may be beneficial even after resistance develops to CDK4/6 inhibitors.

In the MCF-7 luminal breast cancer cell line, acquired fulvestrant resistance is associated with CDK6 over-expression, as demonstrated by both qt-PCR and western blot.[79] When these cells are treated with the combination of fulvestrant and a CDK4/6 inhibitor, growth is significantly attenuated. In an MCF-7 xenograft mouse model, fulvestrant and CDK4/6 inhibition results in estrogen-independent growth reduction while decreasing phospho-Rb and p107, and downregulating E2F1 and E2F2.[5] In a separate pre-clinical study, the downstream effects of CDK4/6 inhibition were reported as being relatively rapid but transient, with phosphorylation of Rb at amino acids Ser^{780} and Ser^{795} being reduced within 4 hours of drug administration and reversal of this effect within 2 hours of removal of the drug.[38] By 16 hours after removal, the cells were proliferating again, suggesting that benefit from treatment with CDK4/6 inhibitors does not persist for long after discontinuation of the drug. This finding was recapitulated in Colo-205 (colonic carcinoma cell line) xenograft mouse models that demonstrated significant tumor regression (>90% tumor growth inhibition) after initial treatment with an oral CDK4/6 inhibitor for 14 days.[38] Tumors began to grow again approximately 50 days after drug withdrawal. At the time of regrowth, tumors were harvested and reimplanted into naïve mice. With doses and a schedule identical to the originally treated mice, the tumors regressed with equal sensitivity to drug. Similar findings were seen in a breast cancer MDA-MB-435 xenograft model.[38] (see figure below.)

Ribociclib plus fulvestrant in ER+ breast cancer xenograft models



Thus, our proposal is to randomize patients with metastatic HR-positive HER2-negative breast cancer who have progressed on anti-estrogen therapy plus a CDK4/6 inhibitor (either palbociclib or ribociclib or abemaciclib) to either fulvestrant alone or fulvestrant with ribociclib. The purpose of the trial is to determine whether there is continued benefit for patients to remain on a CDK4/6 inhibitor at the time of switching anti-estrogen therapy.. As ribociclib, abemaciclib, and palbociclib have a similar mechanism of action, we feel that it is appropriate for patients to receive any of these CDK 4/6 inhibitors with anti-estrogen therapy prior to randomization.

Patients will be potentially eligible and registered for the trial at 2 time periods: either a) no prior CDK4/6 plus an aromatase inhibitor - **or** – b) patients who have progressed on palbociclib or ribociclib or abemaciclib plus an aromatase inhibitor or tamoxifen or fulvestrant. Patients not previously treated with a CDK4/6 inhibitor will be provided with ribociclib with letrozole by the study supplier (Novartis), after registration. If and when these patients demonstrate evidence of disease progression on this combination, and if they continue to meet the other eligibility criteria, they will be randomized to receive either fulvestrant (or exemestane) with ribociclib or fulvestrant (or exemestane) with placebo. Eligible patients who register after disease progression on ribociclib or palbociclib or abemaciclib (received either as part of a clinical trial or as standard of care) will be immediately randomized to receive fulvestrant with ribociclib or placebo.

2.7 Biomarker Studies:

While most patients with ER-positive, HER2-negative metastatic breast cancer do appear to obtain a clinical benefit from CDK4/6 inhibition (either partial response or prolonged stable disease), validated biomarkers to predict which patients would benefit the most from CDK4/6 inhibition and to predict the small group of patients who may not benefit at all from CDK4/6 inhibition have not yet been identified. We propose to evaluate tissue biomarkers on archived formalin-fixed paraffin-embedded (FFPE) tissue, available from diagnostic biopsy procedures, and to perform optional biopsies prior to treatment, at time of disease progression (in the case of patients registered under scenario # 1), and at progression on fulvestrant (or exemestane) + ribociclib/placebo. We also plan to collect peripheral blood specimens (serum and plasma) for the purposes of future blood based biomarker studies. This serum and plasma will be stored and processed at the local institution and then requested to be shipped to CUMC when requested. Further details are available in the biomarkers section of this protocol **(**Section 9).

In addition to the serum and plasma above, we will analyze plasma ctDNA biomarkers (ESR-1 and PI3K) isolated from whole blood samples. As per Section 10, whole blood samples (2x10mL fresh peripheral whole blood) will be collected using the Biocept sample collection tubes provided in the Biocept Sample Kit. Samples will be inverted multiple times and shipped for analysis in the CAP-accredited CLIA-certified Biocept laboratory using the shipment materials provided. Study specific Requisitions provided by Biocept will be submitted with the samples. Plasma will be processed for ctDNA biomarker studies using the SELECTOR technology (Appendix D)

3. PATIENT SELECTION

3.1 Inclusion Criteria:

A subject **must meet all of the following criteria** to be eligible for the study:

- Men or women at least 18 years of age with histologically or cytologically confirmed adenocarcinoma of the breast with unresectable or metastatic disease.

- Most recent tumor biopsy or surgical resection specimen must be either ER positive, PgR positive, or both, as defined by immunohistochemistry (IHC) ≥1% (as per the ASCO-CAP guidelines).[85]

- HER2-negative breast cancer defined as a negative in situ hybridization test or an IHC status of 0 or 1+. If IHC is 2+ (i.e. indeterminate), a negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing. (as per the ASCO-CAP guidelines). [86]

- Postmenopausal status **or** receiving ovarian ablation with a GnRH agonist such as goserelin. Postmenopausal status is defined by any one of the following criteria:
  - Prior bilateral oophorectomy.
  - Age ≥60 years.
  - Age <60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression) and FSH, LH, and estradiol in the postmenopausal range per local normal.

  If the patient does not meet criteria for postmenopausal status but is receiving ovarian ablation therapy with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin, the patient is eligible for this study, provided that the GnRH agonist is started at least 2 weeks prior to C1D1 of anti-estrogen therapy.

- Have evidence of measurable or unmeasurable disease.

- Eastern Cooperative Group (ECOG) performance status of 0 **or** 1. (Appendix A)

- Scenario 1: No prior cdk 4/6 inhibitor (Closed to Accrual). If patient has not previously received letrozole, letrozole will be supplied by Novartis. If previously progressed on letrozole, another aromatase inhibitor that the patient has not previoulsy received is allowed, per standard of care (anastrazole or exemestane, not supplied by study). Ribociclib will be supplied by Novartis. If patient has previously received letrozole, anastrazole, and exemestane, (s)he is not eligible. For scenario 1, patients are allowed to have started the aromatase inhibitor within 4 consecutive weeks prior to protocol registration. For instance, it is acceptable for patient who will be treated with letrozole in scenario #1, to have started letrozole within 4 consecutive weeks prior to protocol registration. No prior fulvestrant allowed.

- Scenario 2: the patient must have received an aromatase inhibitor (letrozole, arimidex, exemestane) or tamoxifen or fulvestrant plus palbociclib as standard of care **or** received a CDK4/6 inhibitor (palbociclib or ribociclib or abemaciclib), **and** demonstrated evidence of disease progression. If the patient was enrolled in a randomized clinical trial involving ribociclib or abemaciclib or palbociclib (such as the MONALEESA or PALOMA series of trials), then it **must** be known after study discontinuation and unblinding that the patient received the investigational drug and not placebo. Ribociclib or abemaciclib or palbociclib can also be given as standard of care. Documentation of progression and duration of response on aromatase inhibitor or tamoxifen plus CDK 4/6 inhibitor should be provided whenever possible. If patient received prior fulvestrant, exemestane must be the hormone therapy backbone in the randomization. If patient received prior exemestane, fulvestrant

must be the hormone therapy backbone in the randomization. If neither has been administered, selection of fulvestrant or exemestane in the randomization will be per investigator discretion.

- Adequate baseline laboratory studies (hematologic and chemistry), including the following parameters:
  - Absolute neutrophil count ≥ 1500 per microliter, Platelets ≥ 75,000 per microliter, Hemoglobin level ≥ 8.0 gm/dL on screening complete blood count
  - Potassium and total calcium (corrected only in the case of hypoalbuminemia) within normal limits of the local laboratory (Screening values can be rechecked after electrolyte repletion and before the first dose of study medication, if necessary.)
  - Serum creatinine level ≤ 1.5 mg/dL **or** estimated glomerular filtration rate ≥ 50 mL/min.
  - In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be below 2.5 × the upper limit of normal (ULN). If the patient has liver metastases, ALT and AST should be < 5 × ULN.
  - Total bilirubin ≤ 1.5 x ULN. (In patients with well documented Gilbert's Syndrome, total bilirubin ≤ 3 × ULN with direct bilirubin within normal range.)
  - INR ≤ 1.5

- (a) Written informed consent and HIPAA authorization obtained from the subject/legal representative prior to performing any protocol-related procedures;

(b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study

- Must be able to swallow ribociclib and oral aromatase inhibitor, such as letrozole or exemestane.

3.2 Exclusion Criteria:

A subject **who meets any of the following criteria is ineligible** for the study:

1. Patient has a known hypersensitivity to any of the excipients of ribociclib, aromatase inhibitors (such as letrozole) or fulvestrant.

2. **Active** central nervous system (CNS) disease. History of CNS metastases or cord compression is allowable if the patient has been clinically stable for at least 4 weeks since completion of definitive treatment and is off systemic steroids. In the case of brain metastases, the patient must have stable or improved imaging at least 4 weeks after completion of definitive treatment. If there is evidence of active leptomeningeal disease, the patient is ineligible.

3. Identified as having visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis. Visceral crisis is not the mere presence of visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease.

4. Received more than 1 prior systemic chemotherapy in the unresectable or metastatic setting. If the patient received 1 prior systemic chemotherapy, the patient is eligible. Having received prior therapies for breast cancer (such as everolimus or experimental agents) does not affect eligibility for this study.

5. Completion of major surgery, chemotherapy, targeted therapy (such as everolimus or experimental agents_ or radiation within 14 days prior to starting investigational drug **or** has not recovered from major side effects. There is no required washout period from completion of prior anti-estrogen therapy (either scenario) or prior CDK 4/6 inhibitor (if scenario 2) to initiation of ribociclib/placebo and anti-estrogen on trial.

6. Residual acute toxic effects of prior anti-cancer therapy that have not resolved to CTCAE v.4 Grade ≤1. Exception to this criterion: patients with grade 1 taxane-induced neuropathy, any grade of alopecia, amenorrhea or other toxicities not considered a safety risk for the patient as per investigator's discretion, are allowed to enter the study.

7. Presence of a concurrent malignancy or malignancy diagnosed within 5 years of randomization, with the exception of basal or squamous cell carcinoma, non-melanomatous skin cancer, curatively resected cervical cancer, localized prostate cancer treated with curative intent, and stage I colorectal cancer treated with curative resection.

8. 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).

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

10. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality including any of the following:

    - History of myocardial infarction (MI), angina pectoris, symptomatic pericarditis, or coronary artery bypass graft (CABG) within 6 months prior to study entry
    - Documented cardiomyopathy
    - Patient has a known Left Ventricular Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO).
    - Long QT syndrome or family history of long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
        i. Risk factors for Torsades de Pointe (TdP) including uncorrected hypocalcemia, hypokalemia or hypomagnesaemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
        ii. Concomitant medications(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued or replaced by safe alternative medication (e.g. within 5 half-lives or 7 days prior to starting study drug)
        iii. Inability to determine the QTc interval
    - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
    - Systolic Blood Pressure (SPB) >160 or <90 mmHg

11. Corrected QT interval (QTcF) > 450 msec (QT interval using Fridericia's correction) on screening electrocardiogram. If QTc prolongation is felt to be related to electrolyte imbalance, an EKG can be repeated after correction of electrolytes. Mean resting heart rate 50-100 bpm (determined from ECG).

12. The presence of any other concurrent severe and/or uncontrolled medical condition that would, in the investigator or treating physician's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol. This includes uncontrolled infections that could potentially be exacerbated by anti-neoplastic treatment, active untreated or uncontrolled fungal bacterial or viral infections, etc.

13. Currently receiving treatment, including medications and herbal preparations, with known strong inducers or inhibitors of cytochrome p450 enzymes CYP3A4/5 medications that have a narrow therapeutic window and are predominately metabolized through CYP3A4/5 or herbal preparations/medications, dietary supplements, which cannot be discontinued prior to receiving investigational drug. Anti-retrovirals, anti-microbials, and anti-arrhythmics are the most common medications that interact with these enzyme. Please refer to Section 5: Pharmaceutical Information and Appendix B for more information and a list of drugs that should not be used concurrently with ribociclib.

14. Patients who are receiving any other investigational agents concurrently or have received investigational agents within 14 days or 5 half-lives of the compound or active metabolites, whichever is longer before the first dose of the study treatment

15. Patient is concurrently using hormone replacement therapy.

16. Subject is pregnant or nursing. Serum or urine Beta-HCG must be checked in all non-postmenopausal patients or patients of childbearing potential. (Fulvestrant is pregnancy category D and CDK4/6 inhibitors have demonstrated teratogenicity/fetotoxicity in animal studies.)

4. REGISTRATION PROCEDURES

***** Please see Appendix F for Guidelines for Affiliate Institutions for Registration and Data Reporting Requirements.**

CUMC Research Participant Registration (CUMC Subjects ONLY)
Confirm eligibility as defined in Section 3.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (i.e., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation to confirm subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case-by-case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures:
Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@cumc.columbia.edu or fax to 212-304-6330, with the subject line **"[PROTOCOL# AAAP9506 Pending Subject Registration Request (PHI)".** Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's

institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (i.e. tissue, DNA, etc.) as applicable
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (i.e., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by a Physician level Investigator)
- Copies of source documentation necessary for each item to be verified on the CUMC specific Eligibility Checklist, including but not limited to:
    - Copy of required laboratory test and procedure reports (i.e., hematology, serum chemistry, pregnancy test when applicable, and pertinent radiology reports such as CT/bone scans, PET/CT scans, MRI reports, etc.)
    - Copy of pathology and surgical reports
    - Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc)
    - Protocol deviation/waiver approvals (if applicable)
- **Please note**: subject line of email or fax should include the following: "PROTOCOL# AAAP9506 Complete Subject Registration Request (PHI)."

Upon Receipt of the above-mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. All applicable finalized registration/eligibility information will then be entered into HICCC's institutional database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team, which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subjects who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

***** Please see Appendix F for Guidelines for Affiliate Institutions for Registration and Data Reporting Requirements.**

5. PHARMACEUTICAL INFORMATION

This is a randomized study that will evaluate the efficacy of the combination of the ER downregulator fulvestrant (or exemestane) with the CDK4/6 inhibitor ribociclib vs. fulvestrant (or exemestane) with placebo, administered in patients with metastatic breast cancer who have previously had disease progression on the combination of CDK4/6 inhibition with an AI. For patients registered prior to having ever received a

CDK4/6 inhibitor with an AI (scenario # 1), the combination of ribociclib and letrozole will be provided by the study supplier (Novartis). If the patient has received letrozole previously, another aromatase inhibitor may be used that the patient has not previously received (anastrazole, exemestane) – this will be given as standard of care and not supplied by the study (ribociclib will be supplied). Following disease progression, these patients will be randomized and switched to the combination of fulvestrant (or exemestane) +/- ribociclib. (Section 6 for full treatment plan).

A list of the adverse events and potential risks associated with the investigational agent ribociclib, as well as a brief review of the adverse events associated with the two standard of care agents letrozole, exemestane, and fulvestrant can be found in Section 8.

5.1 Ribociclib (Investigational agent, supplied by Novartis):

5.1.1 Overview:

Ribociclib is an orally bioavailable and highly selective small molecule inhibitor of the CDK4/cyclin-D1 and CDK6/cyclin-D3 enzyme complexes with IC_{50}'s of 0.01 and 0.039 μM in biochemical assays, respectively. (Investigator's Brochure = IB)

5.1.2 Drug Product: (IB)

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

5.1.3 Drug Storage: (IB)

The shelf life of the drug product is established based on ongoing stability studies and may be extended during the clinical study. Capsules/tablets should not be stored at temperatures above 25 °C and should be protected from moisture and light.

5.1.4 Pharmacodynamics:

Enzymatic Studies (IB)

The potency and selectivity of ribociclib as a CDK4/6 inhibitor were testing using biochemical assays. Isolated enzyme complexes were used to determine the compound's IC_{50} against cyclin D bound CDK4 and CDK6 as well as additional kinases including other CDK family members. An enzymatic assay in TR-FRET format was established to monitor CDK4/cyclin D1 kinase activity following the phosphorylation of Ser780 and p-Rb152 (the C-terminus fragment of phospho-Rb containing avi-tag.) In the presence of CDK inhibitors, the reduction in the TR-FRET signal was monitored and IC_{50} concentrations were determined. A similar assay was developed to examine the inhibition of the CDK6/cyclin D1 complex and the CDK6/cyclin D3 complex. In order to profile the compound's selectivity for CDK4 and CDK6 complexes, four additional CDK complexes (CDK1/cyclin B, CDK2/cyclin A, CDK5/p25, and CDK9/cyclin T1) and six non-CDK serine/threonine kinase assays were developed using surrogate peptide substrates in an IMAP format. Ribociclib was profiled in these assays and the resulting IC_{50} values are summarized in the table below. The results demonstrated that ribociclib inhibited CDK4/cyclin D1 and CDK6/cyclin D3 with IC_{50}s of 0.01 μM and 0.039 μM, respectively, while demonstrating poor inhibition (high μM IC_{50}s) against other CDK family members. This demonstrated that ribociclib was a selective inhibitor of CDK4/6 kinases. The detailed assay protocols are available from Novartis upon request. Extended profiling was also carried out against the NIBR internal kinase selectivity panel, which covers 38 different serine/threonine kinases and tyrosine kinases. Ribociclib was inactive (IC_{50} > 10 μM) against the vast majority of kinases (35 of 38) in the panel, and demonstrated weak inhibition of the remaining three kinases (Aurora A, HER1, and LCK). This further demonstrated ribociclib's strong selectivity for CDK4/6 with relative inactivity against all other kinases tested.

Table 4-1 In vitro assay data for NVP-LEE011

Assay	IC_{50} (µM)	% Inhition
CDK4/cyclin D1 kinase activity - phosphorylation of pRb: TR-FRET assay	0.010 (3 µM ATP)	
CDK family kinase selectivity profiling:		
CDK1/cyclin B	113 (20 µM ATP)	
CDK2/cyclin A	75.9 (20 µM ATP)	
CDK5/p25	43.9 (4 µM ATP)	
CDK6/cyclin D3	0.039 (10 µM ATP)	
CDK9/cyclin T1	1.51 (6 µM ATP)	
Other Ser/Thr kinase selectivity profiling:		
CK1δ	>10 (12.5 µM ATP)	4% at 10 µM
p38α	>10 (2.50 µM ATP)	8% at 10 µM
ERK2	>10 (20.0 µM ATP)	12% at 10 µM
MSK1	>10 (12.5 µM ATP)	11% at 10 µM
PKA	>10 (1.50 µM ATP)	15% at 10 µM
PKCµ	7.82 (5.00 µM ATP)	

(Table courtesy of IB.)

Kinase selectivity in transduced BaF3 cell line (IB)
The cellular kinase selectivity of ribociclib was assessed using the BaF3 signaling pathway selectivity panel. This panel consists of a series of BaF3 murine pro-B-cell sublines whose proliferation and survival has been rendered IL-3-independent by stable transduction with individual constitutively activated tyrosine kinases (either by mutation or fusion with a dimerization-promoting protein domain.) Ribociclib-mediated suppression of BaF3 cell proliferation and viability was assessed after 48 hours by the AlamarBlue assay. Concentrations up to 10µM were tested; ribociclib did not reach half-maximal proliferative inhibition in 8 of the 11 transduced BaF3 panel models, nor in the parental wild type cells grown in the presence of IL-3. Ribociclib only marginally inhibited the proliferation of the other three models (Tel-IGF1R, FLT3-ITD and Tel-PDGFRβ models), displaying IC50s in the 5-10 µM range. In summary, ribociclib can be considered to be devoid of relevant inhibitory activity against the respective kinases as assessed in the BaF3 model context.

In vitro studies with ribociclib (IB)
CDK4/6-cyclin D complexes phosphorylate Rb at specific serine residues located at codons 780, 795 and 807/811.[80] Phosphorylation at these sites is a prerequisite for subsequent phosphorylation of Rb at other residues by the CDK2-cyclin E complex, which occurs late in G1 phase.

A panel of human breast cancer cell lines was treated with titrated doses of ribociclib and dose-dependent inhibition of proliferation was observed across the panel with enhanced activity against ER+ breast cancer cell lines. An IC_{50} < 1µM was observed for most ER-positive breast cancer lines. (IB / Novartis internal data). Ribociclib as a single agent has been shown to have activity in preclinical models of ER+ breast cancer.

In the Jeko-1 mantle cell lymphoma cell line that overexpress cyclin D1 as a result of the chromosomal translocation t(11;14), ribociclib inhibits the phosphorylation of Rb at CDK4/6-specific sites with an average IC_{50} of 0.060 µM. Ribociclib also inhibits the growth of many other tumor cell types *in vitro*, including liposarcoma, melanoma, malignant rhabdoid, and esophageal, breast, lung and pancreatic carcinomas.

The ability of ribociclib to inhibit cell proliferation was assessed using the BrdU uptake assay and by cell cycle analysis using flow cytometry. Ribociclib inhibited BrdU uptake with an average IC_{50} of 0.1 µM in Jeko-1 cells. Alternatively, in H2009 cells that lack functional Rb, a greater than10 µM IC_{50} was observed, confirming that Rb must be present for ribociclib sensitivity. Flow cytometry confirmed that the main cause

of ribociclib's anti-proliferative effects in Jeko-1 cells was G1-phase arrest (with a full G1-phase arrest observed at a concentration of <1 μM), whereas H2009 cells did not demonstrate this effect. Regardless of the various genetic aberrations that may be present in the cancer cells, the anti-tumor activity of ribociclib requires the presence of functional Rb. As discussed in Section 2, the vast majority of ER-positive breast cancer has Rb intact, while a high percentage of triple negative breast cancers demonstrate Rb loss.

In vivo studies with ribociclib (IB)
In early *in vivo* studies in mice and rats, ribociclib was well tolerated, with body weight loss not exceeding 12.5% at treatment doses as high as 250 mg/kg per os daily and 150 mg/kg daily, respectively. No significant changes in blood chemistry tests were observed after 28 days of consecutive dosing. However, myelosuppression was observed and tightly correlated with phospho-Rb target inhibition. Treatment with ribociclib resulted in significant tumor regression in the Jeko-1 mantle cell lymphoma xenograft model (in SCID immunodeficient mice) at doses greater than or equal to 75 mg/kg daily. *In vivo* pharmacokinetic/pharmacodynamics and efficacy studies demonstrated that plasma levels corresponding to approximately 0.5 - 4 μM over a 24 hour dose interval are required to obtain near complete target inhibition and complete regression in the Jeko-1 MCL xenograft model. Continuous dosing over at least 3 days was required to achieve optimal target inhibition in this model. Moreover, near complete (>80%) target inhibition over the entire 24 hour dosing interval appeared requisite to achieve tumor regression.

Ribociclib also showed significant anti-tumor activity in a panel of patient-derived tumor xenograft models when dosed at 250 mg/kg daily. Ribociclib efficacy was only observed in tumors that demonstrate phosphor-Rb expression at baseline, and all Rb-null tumors showed no effect, consistent with the known mechanism of action of CDK4/6 inhibition. Tumor types where anti-tumor activity corresponding to near stasis of tumor growth included breast, pancreas, and melanoma.

5.1.5 Safety/Toxicology (IB)
Ribociclib was assessed for off-target activity on 147 G-protein couple receptors, transporters, ion channels, nuclear receptors, and enzymes, using *in vitro* biochemical assays. Greater than 50% inhibition at concentrations as high as 10 μM was found only against three targets: phosphodiesterase 4d (PDE4d) at an IC_{50} of 0.39 μM, apelin receptor at an IC_{50} of 10 μM, and the orexin-2 receptor at an IC_{50} of 10 μM. There was minimal binding and essentially no activity against the remaining 144 targets at the concentrations assessed.

In vivo rat safety studies did not reveal any effects on the central nervous system or on respiratory function. Cardiac safety studies did demonstrate a signal for prolongation of the QT interval with the potential to induce rare premature ventricular contractions at higher exposure levels. (More serious ventricular arrhythmias were not observed in rats.)

The effects of ribociclib on the bone marrow (myelosuppression), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation) and testes (atrophy) in rats and dogs is considered to be on-target off-tumor effects of CDK4/6 inhibition resulting in impaired cell proliferation in these normally proliferative healthy tissues. An increased number of ovarian corpora lutea were observed in a single female dog at the highest dose tested (20 mg/kg/day) and this effect could also be related to the pharmacology of ribociclib (arrest of estrous cycle). The hepatobiliary system was also affected in dogs treated with ribociclib, with toxic effects including proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile in the extrahepatic bile ducts. These were felt to be off-target effects of unclear etiology. Inflammatory changes in the lungs of dogs' were considered secondary to aspiration of the investigational agent and are indicative of the irritant potential of the formulation if directly inhaled.

Correlating hematologic and/or biochemical changes were seen for the effects described on the bone marrow, lymphoid system and liver. In rats, the changes seen in the bone marrow demonstrated a clear tendency towards reversibility, and all other findings fully reversed shortly following drug withdrawal. In dogs, the

changes seen in the testes and lungs demonstrated a clear trend towards reversibility and all other changes were full reversed shortly after drug withdrawal.

Based upon these findings, hematologic and hepatobiliary parameters have been closely followed in early phase clinical trials with ribociclib, and gastrointestinal effects have been monitored. *In vitro*, mutagenic and phototoxic potential have not been demonstrated with ribociclib. In addition, given the *in vivo* QT prolongation, QTc will be closely monitored during the trial.

Safety assessment in clinical studies:
Section 8.1**: Synopsis of common adverse events with the study drugs.**

5.1.6 Pharmacokinetics and metabolism

The pharmacokinetic profile of ribociclib has been investigated *in vivo* in mice, rats, dogs, and cynomolgus monkeys. The plasma profiles of ribociclib following oral administration in mice, rats, and monkeys are characterized by moderate terminal half-lives (2 to 7 hours in duration), as compared to longer terminal half-lives in dogs of approximately 18 hours.

The bioavailability of ribociclib was evaluating using a radiolabeled formulation. In adult male rats, 48-84% of the dose was absorbed, consistent with moderate absorption. The final bioavailability is low to moderate in rats (10-65%) and in cynomolgus monkeys (10-23%), while it is moderate in mice (65%) and dogs (64%). Following oral administration, peak ribociclib plasma concentrations occurs within 2 to 4 hours in all species tested.

Gender dependent toxicokinetics were identified in rats, with higher exposure to ribociclib in males as compared to females (3.2 to 7 fold difference in area under the curve (AUC)) and with higher exposure to its metabolite LEQ803 (6.2 to 17.8 fold difference in AUC during the 24 hours post administration).

Distribution:
Plasma protein binding was moderate and showed no major concentration dependency across all species tested, with unbound fractions in plasma for humans of 30±2% and animals ranging from 20±1% to 32±6%. Extensive distribution of ribociclib and its metabolites to rat tissues was seen following a 10 mg/kg oral dose, but there was no uptake into the central nervous system. The highest concentrations were found in glandular tissues such as the thyroid gland (following oral or intravenous administration), the pineal body (intravenous), the pituitary gland (oral), Harderian gland (oral), preputial gland (oral) and adrenal medulla (intravenous). The highest concentrations were seen in the thyroid gland. In addition to glandular tissues, kidney (intravenous), liver (oral) and spleen (oral and intravenous) tissues demonstrated high concentrations of the investigational drug and its metabolites. Distribution was also observed in the melanin-containing structures of pigmented male rats, such as the choroids, ciliary body, and meninges. In body tissues, clearance of radioactively labeled drug and metabolites occurs with half-lives on the range of less than 10 hours across all species, with nearly complete clearance within one week (with <0.04% retention in animals harvested at that time point.)

Metabolism:
In all species, N-demethylation is the most common metabolic reaction, resulting in the production of the drug metabolite LEQ803. Traces of two potential unique human metabolites were detected in hepatocytes. In mice, rats, monkey and humans, glutathione adducts were found which were detected but could not be seen in plasma or excreta (urine, bile, feces) in the rat pharmacokinetic studies. In male rats, unchanged NVP LEE-011 (45.5%) and its N-demethylated and N-acetylated metabolite M11 (15.3%) are the major components in plasma. The pharmacologic activity of M11, a rat specific metabolite is not known. In hepatocyte incubations with ribociclib, LEQ803 is the major metabolite observed in human, rat and monkey, while it is the only metabolite in dog.

In male rats, ribociclib is eliminated mainly by hepatic metabolism. The major metabolism pathway seems to be the direct sulfation of ribociclib to M8 and excretion in the bile. Considering the recovery of ribociclib in urine, bile, and feces of bile duct-cannulated rats, the clearance of direct ribociclib excretion amounted to 18.2% of the total plasma clearance.

Excretion:
Results from pharmacokinetics studies in male rats demonstrated that 3H-components (including ribociclib and its major metabolites) were predominantly excreted with bile (61.4±8.22% of dose), with urine excretion representing a minor percentage (5.44±2.36% of dose after oral administration and 10.1±2.09% after intravenous administration.) The majority of the administered dose (87.3%) was excreted within 24 hours via bile, feces (direct enteric secretion), and urine. Recovery was good, indicating little retention in the body.

Drug-drug interactions:
Oxidative metabolism of ribociclib is predominantly by CYP3A4 with a minor contribution of approximately 20% by FMO3. Uptake of ribociclib in Caco-2 cells and hepatocytes occurs by moderate to high passive permeation modulated by some active transport. Ribociclib is a substrate of P-glycoprotein (MDR1) and likely also of an unidentified uptake transporter in hepatocytes.

Ribociclib is a time-dependent CYP3A4 inhibitor (Ki= 5 μM, kinact = 0.0245 / min) and demonstrated reversible inhibition of CYP1A2 (Ki = 16 μM). No pregnane X receptor (PXR)-mediated CYP3A4 induction was observed with the drug. Ribociclib was found to inhibit P-glycoprotein (IC_{50} of 143 μM), MXR transporter (IC_{50} of 24 μM) and human bile salt export pump (BSEP) (IC_{50} of 4.7 μM). The elimination of ribociclib may potentially be affected by co-administration of drugs that inhibit or induce CYP3A4 or drugs that are strong inhibitors of P-glycoprotein. (Appendix B). In addition, depending on the therapeutic dose, ribociclib may inhibit CYP3A4 and to a lesser extent CYP1A2, BSEP, and MXR, and thus levels of medications that are metabolized by these enzymes may be affected by co-administration.

Pharmacokinetics in Human Studies: (IB)
As of March 2014, pharmacokinetic data were available from 128 patients from the first-in- human study of ribociclib (CLEE011X2101.) Following oral dosing, ribociclib was rapidly absorbed with median Tmax ranging from 1 to 5 hours. Ribociclib plasma exposure exhibited slightly over-proportional increases in exposure across the dose range tested (50 to 1200 mg), with no clear evidence of time-dependent auto-inhibition of its clearance mediated by CYP3A4. Steady state was generally reached by day 8 and the mean effective $T_{1/2}$ based on the accumulation ratio ranged from 15.9 to 32.6 hours across the dose range tested. The accumulation ratio based on AUC obtained in a dosing interval across the studied doses ranged from 1.55 to 2.52. The maximum tolerated dose and recommended dose for expansion from this study were declared as 900 mg daily and 600 mg daily on a 3 weeks on/1 week off schedule, respectively.

A food effect study conducted in healthy subjects indicated that ribociclib administered as drug-in-capsule can be taken without regard to meals. A drug-drug interaction study with ritonavir (a strong CYP3A4 inhibitor) and rifampicin (a strong CYP3A4 inducer) conducted in healthy subjects (CLEE011A2101) indicated that concurrent use of strong CYP3A4 inhibitors or strong CYP3A4 inducers may markedly affect ribociclib exposure and should be avoided.

A different drug-drug interaction cocktail study with midazolam (a sensitive CYP3A4 substrate) and caffeine (a sensitive CYP1A2 substrate) was conducted in healthy subjects (CLEE011A2106). Preliminary PK data indicate that ribociclib (400 mg) is a moderate inhibitor of CYP3A4, but did not have a substantial effect on CYP1A2 substrates in humans. Concurrent use of sensitive CYP3A4 substrates with a narrow therapeutic index should be avoided. Concurrent use of CYP1A2 substrates is not expected to lead to clinically important DDIs. (**Appendix B**).

5.1.7 Agent Ordering

Ribociclib is an investigational agent supplied to investigators by Novartis Pharmaceuticals Corporation. Ribociclib supplied for this protocol is intended for clinical trial use only and is not commercially available. Ribociclib is shipped directly from the company to the participating institution (Appendix H for Drug Order Form). For further details on molecule characterization, see the ribociclib Investigator's Brochure.

5.2 Fulvestrant (standard of care medication after randomization, not supplied by the study)

5.2.1 Overview: (Prescribing information, PI)

Fulvestrant is a selective estrogen receptor downregulator (SERD). It is an antagonist of the ER, and competitively binds to receptors on tumors and other tissue that expresses the ER. Binding of fulvestrant to the ER produces a nuclear complex that causes a dose-related down-regulation of estrogen receptors and inhibits tumor growth. Fulvestrant was FDA approved in 2002 for the treatment of postmenopausal women with metastatic breast cancer whose disease progressed on first line anti-estrogen therapy with tamoxifen or an AI.

Fulvestrant is contraindicated during pregnancy. In animal studies, fulvestrant causes fetal loss or fetal abnormalities at or below doses in the range of those approved for prescription in humans. It is listed as pregnancy category D.

In vitro studies demonstrated that fulvestrant is a reversible inhibitor of the growth of tamoxifen-resistant as well as estrogen-sensitive human breast cancer (MCF-7) cell lines. In *in vivo* tumor studies, fulvestrant delayed the establishment of tumors from xenografts of MCF-7 cells in nude mice. Fulvestrant inhibited the growth of established MCF-7 xenografts and of tamoxifen-resistant breast tumor xenografts.

Fulvestrant showed no agonistic effect in *in vivo* uterotropic assays in immature or ovariectomized mice and rats. In immature rats and overiectomized monkeys, fulvestrant blocked the uterotrophic action of estradiol. In postmenopausal women, the absence of changes in plasma concentrations of FSH and LH in response to fulvestrant treatment suggests no peripheral steroidal effects.

5.2.2 Drug Product: (PI)

The active ingredient of fulvestrant is (7α,17β)-7-{9-[(4,4,5,5,5-pentafluoropentyl) sulfinyl]nonyl}estra-1,3,5(10)-triene-3,17-diol. Fulvestrant is prepared as a solution for intramuscular injection only, under the brand name of Faslodex. The solution contains alcohol, usp, benzyl alcohol, and benzyl benzoate, in addition to the active ingredient fulvestrant. It is available in 250 mg in 5 mL prefilled syringes.

Because fulvestrant is administered intramuscularly, caution should be exercised prior to administering to patients with bleeding diatheses, thrombocytopenia, or who are on anticoagulant therapy.

The proper method for intramuscular administration of fulvestrant is described below:

1) Remove glass syringe barrel from tray and check that it is not damaged.
2) Remove perforated patient record label from syringe.
3) Peel open the safety needle outer packaging.
4) Break the seal of the white plastic cover on the syringe luer connector to remove the cover with the attached rubber tip cap.
5) Twist to lock the needle to the luer connector.
6) Remove needle sheath.
7) Remove excess gas from the syringe. (A small gas bubble may remain.)
8) Administer intramuscularly in the buttock, slowly. (20-60 seconds.)
9) Immediately activate needle protection device upon withdrawal from patient by pushing lever arm completely forward until needle tip is covered.
10) Repeat steps 1->9 for second syringe.

5.2.3 Drug Storage: (PI)

Fulvestrant is typically packaged as two 5 mL clear neutral glass barrels, each fitted with a tamper evident closure, each containing 250 mg/5 mL of fulvestrant. The syringes are presented in a tray with polysterine plunger rod and safety needles for connection to the barrel.

The product should be stored in the refrigerator, at temperatures in the range of 2 to 8 degrees Celcius, until time of use. To protect from light, product should be stored in the original carton until time of use.

5.2.4 Pharmacokinetics: (PI)

Distribution:

The apparent volume of distribution at steady state is approximately 3 to 5 L/kg. This suggests that distribution is mainly extravascular. Fulvestrant is highly bound to plasma proteins (99%), predominantly to the VLDL, LDL, and HDL lipoproteins. The role of sex hormone-binding globulin appears to be minimal. In patients with breast cancer, there was no difference in fulvestrant PK profile related to age (range 33 to 89 years). There also is no difference in PK profile for fulvestrant between men and women.

Metabolism:

Biotransformation and disposition of fulvestrant in humans have been determined following intramuscular administration of ^{14}C-labeled fulvestrant. Metabolism of fulvestrant appears to involve combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids, including oxidation, aromatic hydroxylation, conjugation with glucoronic acid and/or sulphate at the 2, 3, and 17 positions of the steroid nucleus, and oxidation of the side chain sulphoxide. Identified metabolites are either less active or exhibit similar activity to fulvestrant in anti-estrogen models.

Studies using human liver preparation and recombinant enzymes indicate that CYP 3A4 is the only P450 isoenzyme involved in the oxidation of fulvestrant, although the overall contribution of P450 and non-P450 routes is unknown.

Excretion:

Fulvestrant is rapidly cleared by the hepatobiliary route with excretion primarily via the feces (>90%). Renal elimination is negligible (<1%). After intramuscular injection of fulvestrant 250 mg, the mean clearance was 690±226 mL/min with a half-life of approximately 40 days.

For patients with moderate hepatic impairment, the 250 mg dose of fulvestrant is recommended. The safety of fulvestrant in patients with severe hepatic impairment has not been adequately studied.

Drug-drug interactions:

There are no significant drug-drug interactions. While fulvestrant is metabolized by CYP3A4 *in vitro*, drug interaction studies with ketoconazole and rifampin in animal studies did not alter fulvestrant pharmacokinetics. Dose adjustments are not needed in patients co-prescribed CYP3A4 inhibitors or inducers.

5.2.5 Safety/Toxicology: (PI)

Adverse events occurring in >5% of patients in the CONFIRM trial (randomized phase III trial comparing the 250 mg vs. 500 mg dose of fulvestrant in post-menopausal patients with metastatic HR+ breast cancer who experienced progression on prior anti-estrogen therapy) are summarized in the table below. The vast majority of adverse events were grade II or lower.

Table 1: Summary of Most Commonly Reported Adverse Reactions in Study 1 (≥5% in either treatment group): Safety Population

Body System and Adverse Reaction	Number (%) of Patients	
	Fulvestrant 500 mg N=361	Fulvestrant 250 mg N=374
Body as a Whole		
Injection Site Pain	42 (11.6)	34 (9.1)
Headache	28 (7.8)	25 (6.7)
Back Pain	27 (7.5)	40 (10.7)
Fatigue	27 (7.5)	24 (6.4)
Pain in Extremity	25 (6.9)	26 (7.0)
Asthenia	21 (5.8)	23 (6.1)
Vascular System		
Hot Flash	24 (6.6)	22 (5.9)
Digestive System		
Nausea	35 (9.7)	51 (13.6)
Vomiting	22 (6.1)	21 (5.6)
Anorexia	22 (6.1)	14 (3.7)
Constipation	18 (5.0)	13 (3.5)
Musculoskeletal System		
Bone Pain	34 (9.4)	28 (7.5)
Arthralgia	29 (8.0)	29 (7.8)
Musculoskeletal Pain	20 (5.5)	12 (3.2)
Respiratory System		
Cough	19 (5.3)	20 (5.3)
Dyspnea	16 (4.4)	19 (5.1)

5.2.6 Agent Ordering:
Fulvestrant is an FDA approved medication, but it is not currently approved for usage with CDK4/6 inhibitors. The agent will be administered as standard of care.

5.3 Letrozole (Standard of care medication provided prior to randomization in patients registered under scenario #1, supplied by Novartis)

5.3.1 Overview: (Prescribing information)
Letrozole is a non-steroidal aromatase inhibitor with FDA approval for the systemic treatment of patients with both localized (in the adjuvant setting) and metastatic HR+ breast cancer. There is extensive clinical experience with letrozole, with the rates of severe adverse events exceedingly low.

In postmenopausal women whose ovaries are no longer synthesizing estrogens, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens such as androstenedione and testosterone to estrone (E1) and estradiol (E2). Thus, the suppression of estrogen biosynthesis in peripheral tissues and cancer tissue itself can be achieved by specifically inhibiting the aromatase enzyme.

Letrozole inhibits the aromatase enzyme by competitively binding to the heme of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues. In healthy

postmenopausal women, single doses of 0.1, 0.5, and 2.5 mg letrozole suppressed serum estrone and estradiol by 75-78% and 78% from baseline, respectively. Maximum suppression is achieved in 48-72 hours. In postmenopausal patients with metastatic breast cancer, daily doses of 0.1 mg to 5 mg of letrozole suppressed plasma concentrations of estradiol, estrone, and estrone sulphate by 75-95% from baseline in all patients treated. With doses of 0.5 mg and higher, many values of estrone and estrone sulphate were below the limit of detection. Estrogen suppression was maintained throughout treatment.

Letrozole is highly specific in inhibiting aromatase activity. Impairment of adrenal steroidogenesis has not been observed, and adrenal insufficiency is not an expected adverse event associated with treatment. In postmenopausal patients treated with a daily dose of 0.1 to 5 mg of letrozole, no clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxyprogesterone, ACTH, or plasma renin activity. Furthermore, ACTH stimulation test (a highly sensitive test for adrenal insufficiency) performed in these patients 6 and 12 weeks after treatment initiation did not indicate any attenuation of aldosterone or cortisol production. Steroid supplementation is not necessary/recommended for patients receiving letrozole.

5.3.2 Drug Product: (Prescribing Information)
The active ingredient of letrozole is: 4, 4'-[(1H-1,`2, 4-triazol-1-yl)-methylene] bis-benzonitrile (INN/USAN= letrozole). Letrozole is available as coated 2.5 mg tablets. Excipients include silica-colloidal anhydrous, cellulose-microcrystalline, lactose, magnesium stearate, starch-maize, sodium starch glycollate, hypromellose, iron oxide yellow, macrogel 8000, talc-purifed, and titanium dioxide.

5.3.3 Drug Storage: (Prescribing Information)
Store letrozole at 77 degrees F (25 degrees C). Brief storage at temperatures between 59 and 86 degrees F (15 and 30 degrees C) is permitted. Store away from heat, moisture, and light. Do not store in the bathroom.

5.3.4 Pharmacokinetics: (Prescribing Information)
Absorption:
Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean bioavailability is 99.9%). Co-administration with food slightly decreases the rate of absorption (median time for maximum absorption is 1 hour in the fasted state vs. 2 hours fed), but the extent of absorption is not affected. Therefore letrozole may be taken without regard to mealtimes.

Distribution:
Plasma protein binding of letrozole is approximately 60%, mainly to albumin (55%). The concentration of letrozole in erythrocytes is about 80% of that in plasma. After administration of ^{14}C-labelled letrozole 2.5 mg, approximately 80% of the radioactivity in plasma was unchanged compound. Systemic exposure to metabolites is therefore low. Letrozole is rapidly and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1.87± 0.47 L/kg.

Metabolism and Elimination:
Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway for letrozole. (mean clearance 2.1 L/hour). The cytochrome P450 isoenzymes CYP3A4 and CYP2A6 were found to be capable of converting letrozole to this metabolite. Formation of minor unidentified metabolites and direct renal and fecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of ^{14}C-labelled letrozole 2.5 mg to healthy postmenopausal volunteers, 88.2±7.6% of the radioactivity was recovered in urine and 3.8±0.9% in the feces. At least 75% of the radioactivity recovered in urine was attributed to the glucuronide of the carbinol metabolite, while about 6% was unchanged letrozole. The terminal elimination half-life in plasma is about 2 days. After daily administration of letrozole, steady-state levels are reached within 2 to 6 weeks. Plasma concentrations at steady state are approximately 7-fold higher than concentrations measured after a single dose of 2.5 mg. This indicates a slight non-linearity in the pharmacokinetics of letrozole. However, since steady-state levels are maintained

over time, it does not appear that additive accumulation of letrozole occurs. Thus, continuous daily dosing is appropriate.

In study populations (adults ranging in age from 35 to 80 years), no change in pharmacokinetic parameters was observed with increasing age. In a study comparing the PK of letrozole after a single oral dose in eight subjects with liver cirrhosis and severe hepatic cirrhosis (Child Pugh class C) to 8 healthy volunteers, average AUC and half-life increased by 95% and 187%, respectively. Breast cancer patients with this type of severe hepatic impairment are expected to be exposed to higher levels of letrozole than patients without severe hepatic dysfunction. If the opinion of the treating physician is that the risk is acceptable, a patient with severe hepatic impairment may be treated without dose reduction, but close monitoring of possible adverse drug reactions is recommended. In addition, in two well-controlled studies involving 359 patients with metastatic breast cancer, no effect of renal impairment was found on the letrozole concentration.

5.3.5 Safety/Toxicology: (Prescribing Information, PI)

There is extensive clinical experience with letrozole, and the vast majority of adverse events seen with this medication are grade II or lower. Adverse reactions occurring in >5% of patients in the randomized trial comparing tamoxifen vs. letrozole for the first line treatment of metastatic breast cancer are summarized in the table below.

Adverse Reaction	Letrozole 2.5 mg (N=455) %	Tamoxifen 20 mg (N=455) %
General Disorders		
Fatigue	13	13
Chest Pain	8	9
Edema Peripheral	5	6
Pain NOS	5	7
Weakness	6	4
Investigations		
Weight Decreased	7	5
Vascular Disorders		
Hot Flushes	19	16
Hypertension	8	4
Gastrointestinal Disorders		
Nausea	17	17
Constipation	10	11
Diarrhea	8	4
Vomiting	7	8
Infections/Infestations		
Influenza	6	4
Urinary Tract Infection NOS	6	3
Injury, Poisoning and Procedural Complications		
Post-Mastectomy Lymphedema	7	7
Metabolism and Nutrition Disorders		
Anorexia	4	6
Musculoskeletal and Connective Tissue Disorders		
Bone Pain	22	21
Back Pain	18	19
Arthralgia	16	15
Pain in Limb	10	8
Nervous System Disorders		
Headache NOS	8	7
Psychiatric Disorders		
Insomnia	7	4
Reproductive System and Breast Disorders		
Breast Pain	7	7
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	18	17
Cough	13	13
Chest Wall Pain	6	6

5.3.6 Agent Ordering:
Letrozole is an FDA approved medication for the systemic treatment of patients with HR+ breast cancer, manufactured by the trial's supplier, Novartis Pharmaceuticals. The agent will be supplied to investigators by Novartis Pharmaceuticals Corporation. Letrozole supplied for this protocol is intended for clinical trial use only. Letrozole is shipped directly from the company to the participating institution (**see** Appendix H for Drug Order Form).

If the patient has received letrozole previously, another aromatase inhibitor may be used that the patient has not previously received (anastrazole, exemestane) – this will be given as standard of care and not supplied by the study (ribociclib will be supplied).

5.4 Exemestane

5.4.1 Overview: (Prescribing information)
Letrozole is a steroidal aromatase inhibitor with FDA approval for the systemic treatment of patients with both localized (in the adjuvant setting) and metastatic HR+ breast cancer. There is extensive clinical experience with exemestane, with the rates of severe adverse events exceedingly low.

5.4.2 Drug Storage: (Prescribing Information)
Store at 25°C (77ºF); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].

5.4.3 Pharmacokinetics: (Prescribing Information)
Absorption:
Following oral administration, exemestane appeared to be absorbed more rapidly in women with breast cancer than in the healthy women, with a mean -tmax of 1.2 hours in the women with breast cancer and 2.9 hours in healthy women. Approximately 42% of radiolabeled exemestane was absorbed from the gastrointestinal tract. A high-fat breakfast increased AUC and Cmax of exemestane by 59% and 39%, respectively, compared to fasted state.

Distribution:
Exemestane is distributed extensively into tissues. Exemestane is 90% bound to plasma proteins and the fraction bound is independent of the total concentration. Albumin and α11-acid glycoprotein both contribute to the binding. The distribution of exemestane and its metabolites into blood cells is negligible.

Metabolism and Elimination:
Exemestane is extensively metabolized, with levels of the unchanged drug in plasma accounting for less than 10% of the total radioactivity. The initial steps in the metabolism of exemestane are oxidation of the methylene group in position 6 and reduction of the 17-keto group with subsequent formation of many secondary metabolites. Each metabolite accounts only for a limited amount of drug-related material. The metabolites are inactive or inhibit aromatase with decreased potency compared with the parent drug. One metabolite may have androgenic activity [see Clinical Pharmacology (12.2)]. Studies using human liver preparations indicate that cytochrome P 450 3A4 (CYP 3A4) is the principal isoenzyme involved in the oxidation of exemestane. Exemestane is metabolized also by aldoketoreductases.

Following administration of radiolabeled exemestane to healthy postmenopausal women, the cumulative amounts of radioactivity excreted in urine and feces were similar (42 ± 3% in urine and 42 ± 6% in feces over a 1-week collection period). The amount of drug excreted unchanged in urine was less than 1% of the dose.

5.4.4 Safety/Toxicology: (Prescribing Information, PI)
There is extensive clinical experience with exemestane and are similar to those described in 5.3.5.

5.3.5 Agent Ordering:
Exemestane is an FDA approved medication for the systemic treatment of patients with HR+ breast cancer, manufactured by the trial's supplier, and will be prescribed as standard of care.

5.5 Combining Fulvestrant with Ribociclib

Ribociclib and fulvestrant have the following toxicities in common: nausea, fatigue, vomiting, gastrointestinal upset, AST increase, headache, and back pain. These overlapping adverse events are expected to be tolerable and manageable.

In addition, there are no known drug interactions between fulvestrant and ribociclib. While fulvestrant itself is metabolized by CYP3A4, fulvestrant does not appear to have any affect in inhibiting or inducing the cytochrome P450 enzymes involved in the metabolism of ribociclib. Therefore, a drug-drug interaction involving fulvestrant and ribociclib is unlikely to occur.

The combination of ribociclib and fulvestrant is being evaluated in a phase I study where both drugs were given at full dose to postmenopausal women with ER+, HER2-negative locally recurrent or metastatic metastatic breast cancer (IB). Dosing began on May 22, 2014. As of November 12, 2014, a total of 7 patients have been treated with the combination. All have completed the first 28 day cycle and 6 of the 7 patients have completed 6 cycles of treatment. Of these 7 evaluable patients, there were no dose adjustments, interruptions, dose limiting toxicities, or serious adverse events. Grade 2/3 neutropenia was observed in 6 of the 7 patients. One patient had a hepatitis B reactivation. The patient with the hepatitis B reactivation was discontinued at Cycle 5 due to progressive disease. Preliminary results of ribociclib in combination with fulvestrant suggest that this combination is safe and tolerable. Preliminary PK analysis suggests that ribociclib exposure was not affected when ribociclib (600 mg) was administered with fulvestrant (500 mg) or when ribociclib (400 mg) was administered with fulvestrant (500 mg) and BKM120 (30 mg). Safety of combining ribociclib plus an aromatase inhibitor has been already published, as per the Monaleesa-2 trial.

6. TREATMENT PLAN

6.1 Study Design:

This is a phase II, multi-center, randomized, double-blinded, placebo-controlled trial to evaluate fulvestrant (or exemestane) +/- ribociclib (1:1 randomization) in patients with HR+HER2- breast cancer who have previously progressed on an aromatase inhibitor, fulvestrant, or tamoxifen plus CDK4/6 inhibitor (either palbociclib or ribociclib or abemaciclib). There is no crossover. If patient received prior fulvestrant, exemestane must be the hormone therapy backbone in the randomization. If patient received prior exemestane, fulvestrant must be the hormone therapy backbone in the randomization. If neither has been administered, selection of hormone therapy in the randomization will be per investigator discretion. Progression free survival is the primary endpoint. The trial will determine whether there is clinical benefit to continuing CDK4/6 inhibition beyond progression.

Registration:
Patients can be screened and registered at two different time points:
Registration Scenario #1: Before receiving any CDK4/6 inhibitor **or**
Scenario #2: At the time of disease progression while being treated with a CDK4/6 inhibitor (ribociclib or palbociclib or abemaciclib) + endocrine therapy

Registration Scenario #1: If the patient has never received a CDK 4/6 inhibitor previously, the patient is eligible for the trial. If the patient has not received letrozole previously, we are recommending that letrozole and ribociclib be administered (supplied by the study). If the patient has, for instance, progressed on adjuvant letrozole, the patient can receive anastrazole plus ribociclib prior to randomization (but anastrazole will need to be supplied per standard of care/insurance).

Patients are allowed to have received 4 consecutive weeks of an aromatase inhibitor prior to protocol

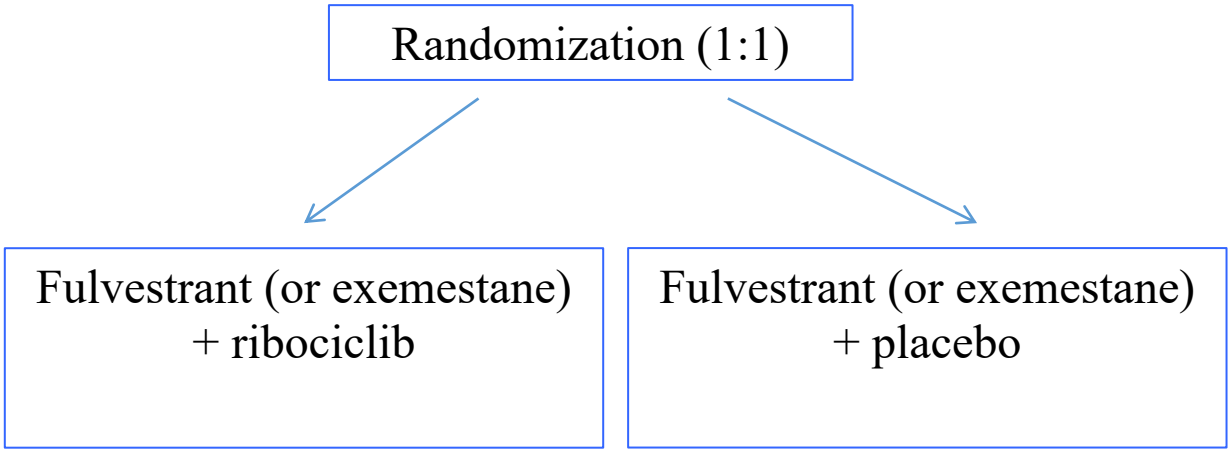
registration for scenario 1. Other studies have allowed this, including CALGB 40503 (letrozole +/- bevacizumab).

Registration Scenario #2: If a patient is on a clinical trial with ribociclib or abemaciclib or palbociclib (such as MONALEESA-2 or PALOMA-2) or abemaciclib and is clearly getting the CDK4/6 inhibitor (after un-blinding) **or** if a patient is abemaciclib or ribociclib or palbociclib as standard of care, the patient **is eligible** for this study upon progression on the combination. Any aromatase inhibitor, fulvestrant, or tamoxifen along with a CDK4/6 inhibitor is allowed. (scenario #2).

Randomization:

In scenario #1, the study will provide patients with ribociclib + an aromatase inhibitor (such as letrozole), but patients will not be randomized until there is objective evidence of disease progression on treatment. In scenario #2, patients will be randomized after registration.

At randomization, patients will be assigned to one of the two arms in a 1:1 ratio: 1) Fulvestrant (or exemestane) + ribociclib **or** 2) Fulvestrant (or exemestane) + placebo. The fulvestrant will be given as a 500 mg dose IM every 2 weeks for 3 times and then every 28 days, as per standard of care. Exemestane 25 mg by mouth daily will be per standard of care. The investigational drug ribociclib will be given as 600 mg daily, 3 weeks on/1 week off. Placebo will be administered on the same schedule.



Accrual Target: N= 120 randomized, evaluable patients.

6.2 Agent Administration

Treatment will be administered on an outpatient basis. Expected adverse events and potential risks are described in Section 8. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy while the patient is on this study.

Patients registered under scenario # 1 will receive treatment with ribociclib and letrozole (or an alternative AI) prior to randomization and until disease progression on this regimen.

Pre-Randomization Regimen Description (Only applies to registration scenario #1).

Registration Scenario	# of Pts Treated	Type of Study Drug	Compound *(specify brand or generic)*	Dose and unit	Frequency	Admin Route
Registration	27	Investigational	Ribociclib	600 mg capsule (3x	Daily, 3 weeks	Per Os (PO)

Scenario # 1	patients			200 mg capsules/tablets)	on / 1 week off	
		Co-Therapy	Letrozole (brand)	2.5 mg tablet (1x 2.5 mg tab)	Daily, continuous	Per Os (PO)

Scenario 1 is no longer accruing.

Ribociclib and letrozole should be taken as follows:

1) Patients should be instructed to take three ribociclib capsules/tablets (600 mg) with one tablet of letrozole (2.5 mg) with a large glass of water (~250 mL) at the same time each day.
2) Ribociclib and letrozole can be taken without regards to food or meals; however dietary habits around the time dosing should be as consistent as possible throughout the study
3) Patients should be instructed to swallow the ribociclib capsules/tablets and letrozole tablet whole and not to chew, crush or open them.
4) 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 case report form.
5) 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.
6) Patients should avoid consumption of grapefruit, grapefruit hybrids, pomelos/pummelos, star fruit, and 'seville oranges' or products containing the juice of either 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.

The duration of pre-randomization treatment cycles on ribociclib + AI is 28 days, with ribociclib taken orally during days 1 through 21 of each treatment cycle, and held during days 22-28 of each treatment cycle. Letrozole (or the alternative AI) is taken once daily, continuous.

Patient adherence with ribociclib plus AI will be assessed by medication diary. The patient will be requested to record each dose of medication. The medication diary will be returned to research staff at the end of each cycle.

Both patients registered under scenario # 1 and under scenario # 2 will receive the following regimen post-randomization:

Post-Randomization Regimen Description

Treatment Arm	# of Pts Planned	Type of Study Drug	Compound *(specify brand or generic)*	Dose and unit	Frequency	Admin Route
Arm A	66	Investigational	LEE-011	600 mg capsule (3x 200 mg capsules/tablets)	Daily, 3 weeks on/ 1 week off	Per Os (PO)
		Co-Therapy (Option #1)	Fulvestrant (brand)	500 mg injection	Every 2 weeks x 3, then every 4 weeks	Intramuscular (IM)
		Co-Therapy (Option #2)	Exemestane	25 mg	Daily	PO
Arm B	66	Comparator	Placebo	600 mg capsule	Daily, 3	Per Os (PO)

				(3x size '0' capsules/tablets)	weeks on/ 1 week off	
		Co-Therapy (Option 1)	Fulvestrant (brand)	500 mg	Every 2 weeks x 3, then every 4 weeks	Intramuscular (IM)
		Co-Therapy (Option #2)	Exemestane	25 mg	Daily	PO

Ribociclib should be taken as follows:

1) Patients should be instructed to take three ribociclib capsules/tablets (600 mg) with a large glass of water at the same time each day.
2) Ribociclib can be taken without regard to food or meals.
3) Patients should be instructed to swallow the ribociclib capsules/tablets whole and not to chew, crush or open them.
4) 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 case report form.
5) 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.
6) Patients should avoid consumption of grapefruit, 'seville oranges' or products containing the juice of either 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.

Post-Randomization Treatment Cycles

The duration of a treatment cycle will be 28 days. Ribociclib or placebo will be taken orally once daily, during days 1 through 21 of each treatment cycle. Ribociclib or placebo will not be taken on days 22 through 28 of each treatment cycle. (i.e. 3 weeks on, 1 week off.) An initial "loading dose" period of fulvestrant will consist of three 500 mg IM injections, starting on Cycle 1 Day 1 and concluding on Cycle 2 Day 1. Subsequently, fulvestrant will be administered in 500 mg IM injections every 4 weeks. This is the currently accepted optimal standard of care dosing regimen for fulvestrant. Fulvestrant is provided in 50 mg/mL solution for injection; 2 x 5 mL vials are injected intramuscularly with each 500 mg dose.

Injection reactions with fulvestrant are exceedingly rare, although injection site pain is common. Pre-medications are not recommended, although analgesics such as acetaminophen may provide relief from injection site pain. In the rare event of a patient who suffers an injection reaction, pre-medications are allowed at the discretion of the treating physician and should follow institutional standards. These can include acetaminophen 650mg po once, diphenhydramine 25-50 mg po/IV once 30 minutes prior to administration of drug, and/or an H2 receptor antagonist (such as famotidine 20 mg po/IV).

Patient adherence with ribociclib/placebo will be assessed by medication diary. The patient will be requested to record each dose of medication. The medication diary will be returned to research staff at the end of each cycle. Patients must be instructed to return unused study drugs to the site at discontinuation or completion of treatment.

6.2.1 Ribociclib

Ribociclib is an investigational agent for the treatment of patients with hormone receptor positive metastatic breast cancer. It does not require specific prophylactic or supportive regimens as per the Investigator Brochure (IB) and based on the precedent set in ongoing clinical trials. It is an oral therapy and can be administered with or without food according to the IB. The planned dose will be 600 mg oral daily (3 x 200 mg capsules/tablets), with dose adjustments only as specified in Section 7.

6.2.2 Fulvestrant

Fulvestrant is FDA-approved for the treatment of metastatic hormone receptor positive breast cancer. It does not require specific prophylactic or supportive regimens. It is an intramuscular therapy that should be prepared according to manufacturer's recommendations. It can be administered with or without food.

6.2.3. **Exemestane**

Exemestane is FDA-approved for the treatment of metastatic hormone receptor positive breast cancer. It does not require specific prophylactic or supportive regimens. It can be administered with or without food.

6.2.4 Treatment Duration:

Patients will receive trial treatment until disease progression, unacceptable toxicity, or death or withdrawal from study based on patient choice or treating physician's discretion. Every effort will be made to follow patients for primary and secondary outcomes regardless of treatment discontinuation for any reason. Crossover is not built into the study.

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being. Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

Premature patient withdrawal refers to the point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time, all study treatment is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival.

Patients may be withdrawn from the study treatment if any of the following occur:

- Adverse Event (Documented episode of ventricular tachycardia, or ventricular fibrillation; Complete heart block (Grade III AV block) or Second degree AV block Mobitz type II)
- Lost to follow-up
- Physician decision
- Progressive Disease
- Study terminated

Patients must be withdrawn from the study treatment if any of the following occur:

- Pregnancy
- Death
- Subject/Guardian decision

6.3 General Concomitant Medication and Supportive Care Guidelines

The patient must be told to notify the investigational site about any new medications *he/*she takes after the start of the study treatment. All medications (other than study drugs) and significant non-drug therapies (including vitamins, herbal medicines, physical therapy and blood transfusions) administered within 30 days of study

entry and during the study must be listed on the Concomitant medications/Significant non-drug therapies eCRF.

Fulvestrant, letrozole, and exemestane are FDA approved agents for the treatment of patients with metastatic breast cancer. Per manufacturer Prescribing Information, there are no concurrent supportive or prophylactic regimens recommended for either fulvestrant, exemestane, or letrozole.

Growth Factor Support:

Per manufacturer Investigator Brochure (IB), there are no concurrent supportive or prophylactic regimens recommended for ribociclib. While the rates of grade III/IV neutropenia are considerable with CDK4/6 inhibitors, the rates of febrile neutropenia (FN) are quite low, and well below the 20% threshold for which FN prophylaxis with G-CSF is recommended. Nonetheless, G-CSF is allowed at the treating physician's discretion. Hematopoietic growth factors may be used according to ASCO guidelines.

Radiation Therapy:

If a subject requires additional anti-cancer therapy, the subject must be withdrawn from study treatment, with the exception of palliative radiotherapy (i.e., to bone metastasis or for subjects who have disease progression limited to the CNS but who are otherwise benefiting from study treatment), which may be allowed during the study but must be discussed with the overall principal investigator. Study treatment should be withheld until palliative radiotherapy is terminated. This treatment break should not be considered as treatment interruption. Palliative radiation is permitted if done solely for bone pain relief. It should not be delivered to a target lesion. Cumulative courses of RT should not encompass >25% of irradiated bone marrow. If palliative radiotherapy is initiated after the start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out.

Given the transient myelosuppressive effects of ribociclib and the long-term myelosuppressive effects of Comp to the axial skeleton in adults, subjects who have received radiation to the spine, pelvis, ribs, or femur should be discussed and approved by the overall principal investigator prior to study re-entry. If anti-cancer treatment follows discontinuation of study treatment due to clinical progression determined by the investigator, the basis for this determination should be documented.

Surgery:
For subjects undergoing minor surgery, it should be scheduled during off week of LEE011/placebo, if possible. LEE011/placebo should preferably be discontinued five days prior to scheduled procedure and should remain on LEE011 hold until appropriate recovery from procedure, per treating physician's discretion.

General medication guidelines:
Medications required to treat adverse events, manage cancer symptoms, treat co-morbid conditions, and supportive care agents, such as analgesics, anti-emetics and anti-diarrhea agents are allowed. Please consult the list of prohibited medications and the list of use with caution medications for further guidance. The patient should notify the investigational site about any new medications taken after the start of the study treatment. All medications administered within 28 days of study entry and during the study period must be listed on the concomitant medications and supplements case report form.

Bisphosphanates / Denosumab:
Bone directed therapy to prevent skeletal related events (SRE's) or to treat osteoporosis with bisphosphonates or denosumab is permitted. While the use of bisphosphonates has been found to reduce the incidence of new bone metastases in patients with metastatic breast cancer, we do not anticipate this to affect

the results of this randomized control trial. Thus, treatment initiated prior to registration or after registration with these agents is permitted. The time of initiation of bone directed therapy should be clearly recorded on the case report forms.

Concomitant therapy requiring caution

Medications to be used with caution during ribociclib in this study are listed below. These medications should be excluded from patient use if possible. If they must be given based on the investigator's judgment, then use with caution and consider a ribociclib interruption if the concomitant medication is only needed for a short time.

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

Prohibited concomitant therapy

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

- Strong inhibitors or inducers of CYP3A4/5
- Substrates of CYP3A4/5 with a narrow therapeutic index
- Medications with a known risk for QT prolongation
- Other investigational and antineoplastic therapies
- Herbal preparations/medications and dietary supplements (except for vitamins) including but not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all of these listed herbal medications and dietary supplements prior to first dose of study treatment.

Drugs with QT prolongation

As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI that increases the exposure of ribociclib or the exposure of the QT prolonging drug). Please utilize a verified Clinical Drug Information system such as Lexicomp® or UpToDate® for data on drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or Torsades de Pointes (TdP).

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

Refer to the ribociclib Investigators Brochure and other drug package insert and Appendix B for information on possible interactions with other drugs.

6.4 Duration of Therapy

In the case of registration scenario #1, patients will continue on CDK4/6 inhibitor and aromatase inhibitor therapy until disease progression*. At that time, patients will be randomized to receive fulvestrant (or exemestane) +/- continuation of CDK4/6 inhibition with ribociclib. In the case of registration scenario #2, patients will be randomized immediately to receive fulvestrant (or exemestane) +/- continuation of CDK4/6 inhibition with ribociclib.

After randomization, in the absence of treatment delays due to adverse event(s), treatment may continue until

one of the following criteria applies:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator. **OR**
- Pregnancy
- Removal by Sponsor (e.g., unblinding by Sponsor-Investigator).

In the absence of one of the events listed above, there is no pre-defined limit on the number of potential cycles.

* In the case of registration scenario # 1, some patients may discontinue treatment in the pre-randomization phase due to events other than disease progression, including those listed above. (i.e. unacceptable toxicity, patient decides to withdraw from the study, etc.). Those patients will come off study prior to randomization and will not be evaluable for the primary outcome.

6.5 Duration of Follow up

The duration of follow up will vary depending on the registration scenario under which the patient is enrolled as well as the interval between treatment initiation and disease progression. Patients will have an end of treatment visit approximately 4 weeks after removal for any of the specified reasons listed above. Patients will no longer be formally followed after completion of the off-treatment visit, unless adverse event(s) occur that require subsequent follow-up (i.e. unresolved AEs). All adverse events, both serious and non-serious, and deaths that are encountered during the study and within 30 days of the last study intervention should be followed. See Section 8.2.

6.5.1 Post-treatment Follow-up Assessments (Progression-Free Survival and Overall Survival)

After end of treatment, patients will be followed for Overall Survival. Survivor information may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieved from online or other databases (eg, Social Security indexes). In addition, the start of another anticancer therapy will be recorded. For those patients who discontinue ribociclib for any reason other than radiographic disease progression, CT (with contrast) or MRI scans should be completed to further assess disease progression (per RECIST, Version 1.1), until the subject begins a new anti-cancer treatment or death. Refer to the Schedule of Events for appropriate assessments during post-treatment follow-up. Patients will no longer be followed for survival after the study is officially closed, which we anticipate will be approximately 2.5 years after the last patient has accrued.

6.6 Criteria for Removal

Patients will be removed from study when any of the criteria listed in Section 6.4 applies. The reason for study removal and the date the patient was removed must be documented in source documentation and the Case Report Form. Patients continuing study treatment following unblinding by the Sponsor-Investigator will be treated as per standard of care and therefore will no longer be required to follow the study calendar or complete any of the study assessments that are not part of standard of care. Following unblinding by the Sponsor-Investigator, study teams will no longer be required to enter data into the database aside from SAEs and patient status updates (in the Screening/Enrollment tab in Velos).

7. DOSING DELAYS/DOSE MODIFICATIONS

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue on the study. This applies both to patients in registration scenario # 1 receiving the combination of ribociclib + AI, as well as to all patients receiving fulvestrant (or exemestane) +/- ribociclib vs. placebo. These changes should be recorded on the Dosage Administration Record case

report form in a timely manner.

7.1 Letrozole and Exemestane

There is extensive clinical experience with letrozole 2.5 mg daily dosing and exemestane 25 mg daily dosing. Severe adverse events are exceedingly rare. While many patients may suffer minor adverse events including hot flushes and arthralgias/ myalgias, there is currently no established role for dose reduction to alleviate the side effects. Thus, no dose modification of letrozole or exemestane is planned in this study. Patients who do not tolerate letrozole may be switched from the generic to brand-name aromatase inhibitor with which they started (or vice versa). The toxicity profiles are similar amongst the three aromatase inhibitors (anastrazole, letrozole, and exemestane).

If the patient enrolled in scenario #1, switching to a different aromatase inhibitor (such as letrozole to anastrazole) is not allowed in combination with ribociclib. Switching from generic to brand name, or vice versa is allowed (example: letrozole and brand name femara). Patients can also switch from generic to brand name exemestane or vice versa.

7.2 Fulvestrant

There is considerable clinical experience with fulvestrant 500 mg intramuscular dosing every 4 weeks (with an initial loading dose phase), and it is generally very well tolerated, with an adverse event profile similar to AIs. As was clearly established in the CONFIRM trial, discussed in Section 2, the higher dose of fulvestrant 500 mg is more efficacious than the lower dose of 250 mg, with essentially no difference in adverse event rates. Dose reduction to 250 mg is left to the discretion of the treating physician, but it is not anticipated that dose reduction will improve adverse effects and it should generally be avoided given the inferior efficacy. In addition, dose reduction to fulvestrant 250 mg can be considered in patients with moderate hepatic impairment.

7.3 Ribociclib / Placebo

Management of severe or intolerable adverse reactions requires dose reduction, temporary interruption, and/or discontinuation of ribociclib therapy. Refer to the table below for guidance.

Dose modification guidelines: Dosing Levels

	Ribociclib/Placebo	
	Dose	**Number of capsules/tablets & strength**
Starting dose	600 mg	3 x 200 mg capsules/tablets
First dose reduction	400 mg	2 x 200 mg capsules/tablets
Second dose reduction	200 mg	1 x 200 mg capsules/tablets

Recommendations for dose reduction, interruption or discontinuation of ribociclib/placebo in the management of specific adverse reactions are summarized in the tables below. Definitions of grading of each Adverse Event are based on CTCAE 4.0. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

If ribociclib is held, the cycle continues, as the patient will be taking hormone therapy. Missed doses of ribociclib will not be made up.

Subjects enrolled on Scenario 1a who are not able to tolerate ribociclib, despite dose reduction to the lowest dose (200 mg), will come off study and not be randomized to Scenario 1b.

Dose modification for hematologic adverse reactions:

LAB ABNORMALITY /	**GRADE**	**DOSE ADJUSTMENT /**

TOXICITY		MANAGEMENT REC'S
Thrombocytopenia	Grade 1: (≥75 x 10^9/L)	No dose adjustment required.
	Grade 2: (≥50-75 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib/placebo at the same dose.
	Grade 3: (≥25-50 x 10^9/L)	Dose interruption until recovery to grade ≤1.Re-initiate ribociclib/placebo at the same dose level. If grade 3 toxicity recurs, interrupt dose until recovery to grade ≤1 and then resume at next lower dose level.
	Grade 4: (<25 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib/placebo at the next lower dose level. If toxicity recurs at grade 4: discontinue ribociclib/placebo.
Absolute Neutrophil Count*	Grade 1: (≥1.5 x 10^9/L)	No dose adjustment required.
	Grade 2: (≥1.0 - < 1.5 x 10^9/L)	No dose adjustment required.
	Grade 3: (≥0.5 - < 1.0 x 10^9/L)	Dose interruption until recovery to ≥1.0 x 10^9/L. Re-initiate ribociclib/placebo at the same dose level. If grade 3 toxicity recurs, interrupt dose until recover to ≥ 1.0 x 10^9/L. If resolved in ≤7 days, then resume at same dose level. If resolved in >7 days, then resume at next lower dose level.
	Grade 4: (< 0.5 x 10^9/L)	Dose interruption until recovery to ≥ 1.0 x 10^9/L. Re-initiate ribociclib/placebo at the next lower dose level. If toxicity recurs at grade 4: temporary dose interruption until recovery to ≥1.0 x 10^9/L and reduce ribociclib/placebo to the next lower dose level.
Febrile Neutropenia*	Grade 3: ANC <1.0 x 10^9/L with a single temperature of >38.3 C or a sustained temperature of >=38 C for more than one hour.	Dose interruption until improvement of ANC ≥ 1.0 x 10^9/L and no fever. Restart at the next lower dose level. If febrile neutropenia recurs, discontinue ribociclib/placebo.
	Grade 4: Same as grade 3, with life threatening consequences.	Discontinue ribociclib/placebo.
Anemia**	Grade 1: Hgb ≥10.0 gm/dL	No dose adjustment required.

	Grade 2: Hgb ≥8.0 - < 10.0 gm/dL	No dose adjustment required.
	Grade 3: Hgb <8 gm/dL	Dose interruption until recovery to grade ≤ 2. Re-initiate ribociclib/placebo at the same dose.
	Grade 4: Life-threatening consequences	Discontinue ribociclib/placebo.

* Growth factor is allowed, per investigator discretion.
** Transfusion allowed, per investigator discretion.

Dose modification for hepatic toxicity:
Hepatic toxicity monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2 x ULN), alkaline phosphatase, and GGT. For patients with Gilbert Syndrome: total and direct bilirubin must be monitored with intensified monitoring applying to changes in direct bilirubin only.

**** TOTAL BILIRUBIN without ALT/AST increase above baseline value. ULN=upper limit of normal.**	
Grade 1 (> ULN – 1.5 x ULN) (confirmed 48-72h later)	Maintain dose level. Recheck LFTs every two weeks until resolved.
Grade 2 (> 1.5 – 3.0 x ULN)	Dose interruption of ribociclib/placebo. Recheck LFTs weekly. If resolved to ≤ grade 1 within 21 days, then maintain dose level. If resolved to ≤ grade 1 within 21 days but toxicity recurs at grade 2, reduce 1 dose level. If resolved to ≤ grade 1 > 21 days, reduce 1 dose level. Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions, discontinue ribociclib/placebo.
Grade 3 (> 3.0 – 10.0 x ULN)	Dose interruption of ribociclib/placebo. Recheck LFTs qweek. If resolved to ≤ grade 1, lower 1 dose level of ribociclib/placebo. Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions, discontinue ribociclib/placebo.
Grade 4 (> 10.0 x ULN)	Discontinue ribociclib/placebo.
** Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤ 1 x ULN) due to hemolysis or Gilbert Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, and use of other hepatotoxic drugs. For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only.	

*****AST or ALT without bilirubin elevation**	
Grade 1: (>1 ULN - < 3.0x ULN).	Maintain dose level. Monitor LFTs per protocol if same grade as baseline or every two weeks in case of increase from baseline grade 0 to 1.
Grade 2: (> 3.0-≤ 5.0 x ULN)	Baseline at < Grade 2: Dose interruption of ribociclib/placebo. Recheck LFTs weekly. If resolved to ≤ baseline value within 21 days, then maintain dose level If resolved to ≤ baseline value within 21 days but toxicity recurs at same grade, then reduce 1 dose level. If resolved to ≤ grade 1 > 21 days, reduce 1 dose level. Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption Baseline at Grade 2: Maintain dose level
Increase from baseline grade 2 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 Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions, 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 Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs, discontinue ribociclib
Grade 4 (> 20.0 x ULN)	Discontinue ribociclib/placebo
AST or ALT and concurrent Bilirubin increase	
For patients with normal ALT or AST or total bilirubin at baseline : AST or ALT ≥ grade 2 combined with total bilirubin > 2 x ULN without evidence of cholestasis** OR For patient with elevated AST or ALT or total bilirubin at baseline : [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT 8.0 x ULN] whichever is lower **combined with** [total bilirubin 2xbaseline AND >2,0 x ULN]	Discontinue ribociclib/placebo
*** Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, ischemic liver injury, and alcohol intake.	

Additional follow-up for hepatic toxicities

Increase in transaminases combined with total bilirubin (TBIL) increase may be indicative of drug-induced liver injury (DILI), and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

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

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

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

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

Hepatic toxicity monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin, direct and indirect bilirubin , alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), creatine kinase, prothrombin time (PT)/INR 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. Recommendations include:

- 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, including history of any pre-existing liver conditions or risk factors.
- Obtaining a history of concomitant drug use (including non-prescription medications, herbal and dietary supplements), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; hepatotropic virus infections (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.
- Liver biopsy as clinically indicated to assess pathological change and degree of potential liver injury

Dose modification for QTc prolongation:

Grade	DOSE ADJUSTMENT / MANAGEMENT REC'S
For All Grades	• Check the quality of the ECG and the QT value and repeat if needed • Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If outside of the normal range, 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.
Grade 1: QTc 450-480 ms	• No dose adjustment required.
Grade 2: QTc 481-500 ms	• Interrupt ribociclib • Perform a repeat ECG one hour after the first QTc of ≥481ms • If QTcF prolongation resolves to < 481 ms, resume treatment at the next lower dose level; • • If QTcF ≥ 481 ms recurs, interrupt dose until QTcF resolves to < 481 ms; then resume KISQALI at next lower dose level. • Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patient who has therapy interrupted due to QTc≥ 481 ms
Grade 3: QTc ≥ 501 ms on at least two separate EKGs.	• Interrupt ribociclib/placebo. • Consider consulting a local cardiologist • Interrupt KISQALI treatment if QTcF greater than 500 ms • Perform a repeat ECG within one hour of the first QTcF of ≥501ms • If QTcF remains ≥ 501ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to <481ms • If QTcF prolongation resolves to < 481 ms, resume treatment at the next lower dose • level. • If QTcF remains ≥481 ms after performing steps 1-4 as directed in "For All Grades", discontinue ribociclib • After resumption, EKG should be repeated 7 days and 14 days and then at least monthly. If stable at least monthly for 3 months, then can have EKG every 3 months.

	• If QTc > 501 ms recurs, discontinue ribociclib/placebo
Grade 4: QTc ≥ 501 ms (or >60 ms increased from baseline) AND signs or symptoms of serious arrhythmias such as torsades de pointes.	Discontinue ribociclib/placebo. Obtain local cardiologist (or qualified specialist) consultation and consider repeating cardiac monitoring as indicated until the QTc returns to <481 ms.

Dose modification for ILD/pneumonitis:

Grade	Dose Adjustment and Management Recommendations
Grade 1 (asymptomatic)	No dose adjustment required..Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (symptomatic)	Interrupt ribociclib dose until recovery to Grade ≤1, then resume ribociclib at the next lower dose level*.
Grades 3 and 4 (severe)	Discontinue ribociclib

* An individualized benefit-risk assessment should be performed before resuming ribociclib

Dose modification for other adverse reactions:

Grade	DOSE ADJUSTMENT / MANAGEMENT REC'S
Grade 1	No dose adjustment recommended. Initiate appropriate medical therapy and monitor
Grade 2	Dose interruption until recovery to grade ≤1. Then resume at same dose level. If the same toxicity recurs at grade 2, interrupt ribociclib/placebo until recovery to grade ≤1. Re-initiate ribociclib/placebo at the next lower dose level.
Grade 3	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib/placebo at the next lower dose level. If the same toxicity recurs at grade 3, re-initiate ribociclib/placebo at the next lower dose level with recovery to grade ≤1, per investigator discretion
Grade 4	Discontinue ribociclib/placebo.

7.4 Renal Impairment:

Based on pharmacokinetic/excretion studies in animals, there is minimal excretion of un-metabolized ribociclib in the urine, suggesting a limited role for renal elimination of the drug. Thus, there are currently no standard recommendations for ribociclib dose reduction based on renal impairment. Renal impairment does not affect aromatase inhibitor, such as letrozole or exemestane, or fulvestrant PK in humans **(Section 5**). Patients with baseline renal impairment are excluded from the study. Patients who develop renal impairment should be managed according to the adverse event guidelines above, including dose interruption until resolution and dose reductions for mild impairment, and withdrawal from study for more severe impairment.

7.5 Interstitial Lung Disease/Pneumonitis:

Patients receiving CDK4/6 inhibitors should be monitored for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough, and dyspnea. In patients who have new or worsening

respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt treatment immediately and evaluate the patient. Treatment should be permanently discontinued in patients with recurrent symptomatic or severe ILD/pneumonitis.

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

An Adverse Event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Adverse events will be monitored from the time the subject signs informed consent. Subjects will be instructed to report all AEs during the study and subjects will be assessed for the occurrence of AEs throughout the study. All AEs (serious and non-serious) must be recorded on the source documents and case report forms regardless of the assumption of a causal relationship with the study drug.

Adverse Events that begin or worsen after informed consent should be recorded in the Adverse Events section of the case report form (CRF). Conditions that were already present at the time of informed consent should be recorded in the baseline symptoms section of the CRF. Adverse Event monitoring should be continued for at least 30 days 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 AE.

The following list of AEs (Section 8.1) and the characteristics of an observed AE (Section 8.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

8.1 Synopsis of Common Adverse Events with the study drugs

Synopsis of common adverse events with ribociclib:

Below is a synopsis of common adverse events in patients being treated with ribociclib, as provided in the investigator's brochure (IB).

Ribociclib is currently being investigated in patients as a single agent in 3 phase I studies, and in combination in 10 studies, including 8 phase Ib/II studies, a randomized phase II study, and a randomized phase III study (MONALEESA-2). Ribociclib is also being investigated in 3 clinical pharmacology studies in healthy subjects. Details on these studies can be found in the ribociclib IB, Section 5.1 and Section 5.2.

In single agent trials, a total of 196 patients have been treated. Ribociclib is also being evaluated in several combination trials with: letrozole, with letrozole and the PI3K inhibitor BYL719, with letrozole and the PI3K inhibitor buparlisib, with fulvestrant and buparlisib, with the mTOR inhibitor everolimus and exemestane, with LGX818, with MEK162, and with MEK162 and LGX818. The results of the phase I combination of letrozole and ribociclib are detailed in the IB.

In the phase I monotherapy trials, patients with metastatic solid tumors or lymphomas were treated with increasing doses of ribociclib orally, once daily for 21 days followed by a 7-day off-drug period (28-day cycles). Doses ranging from 50 mg to 1200 mg were evaluated. In addition, continuous dosing of ribociclib at 600 mg was evaluated. Treatment has been discontinued in 111 of 132 patients (84%); the primary reasons for treatment discontinuation were: progression of disease (72%), adverse events (6%); withdrawal of consent (2%); and loss to follow up (1%).

The most frequently reported AEs (≥10%), regardless of grade, causality and ribociclib dose were:

- Fatigue (53.8%)
- Nausea (50.8%)
- Neutropenia (47.7%)
- Leukopenia (46.2%)
- Anemia (37.1%)
- Vomiting (34.8%)
- Thrombocytopenia (34.1%)
- Diarrhea (32.6%)
- Lymphopenia (30.3%)
- Decreased appetite (21.2%)
- Hyperglycemia (21.2%)
- Constipation (19.7%)
- Hypoalbuminemia (18.9%)
- Dyspnea (18.2%)
- Cough (16.7%)
- Fever (15.9%)
- Rise in serum creatinine (15.9%)
- Abdominal pain (15.2%)
- aspartate aminotrans feraseincrease (15.2%)
- Edema (15.2%)
- Headache (15.2%)
- Back pain (14.4%)
- Dizziness (13.6%)
- QTc prolongation (11.4%)
- Alkaline phosphatase increase (10.6%)
- Hypocalcemia (10.6%)

For either continuous or intermittent dosing, the onset of neutropenia (most frequently Grade 2) occurs by Day 15, reaching a nadir in the third or fourth week with recovery during the week of drug holiday. Some patients require additional time for recovery (7 to 14 days). During this regime, growth factors are allowed.

QTc changes become evident in the first cycle by Day 8 and later (once steady state is reached), are associated with the maximum drug levels between 1 to 8 h post-dose, and remain stable or improve in subsequent cycles. Asymptomatic Grade 2 QTc prolongation was observed with increasing frequency at doses greater than 600 mg, and was considered the dose limiting toxicity. Two patients at 600 mg and two patients at 900 mg had asymptomatic QTc prolongation >500 ms (grade 3). One grade 1 atrioventricular block of first degree was reported as potentially related to ribociclib (at a dose of 140 mg). No other cardiac abnormalities were observed as related adverse events in any patient

There have been 4 deaths related to study drug reported as of April 2014. The following serious adverse events shown in the table below have been reported with a suspected causal relationship to ribociclib administration. For a complete list of AEs, all grades and Grade 3/4 that are suspected to be related to ribociclib refer to the Investigator Brochure.

Serious Adverse Events:

System Involved / Type of AE	**Event(s)**
Blood and lymphatic system	Anemia, febrile neutropenia, neutropenia, thrombocytopenia, Leukopenia, Lymphopenia
Gastrointestinal	Nausea, Vomiting, Diarrhea

Hepatobiliary disorders	**Hepatic function abnormal** **Hepatocellular injury** **Cholecystitis**
Investigations (incl. laboratory abnormalities)	Electrocardiogram QT prolonged Transaminases increased Blood creatinine increased

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI and other CDK4/6 inhibitors. Across clinical trials (MONALEESA-2, MONALEESA-3, MONALEESA-7), 1.1% of KISQALI-treated patients had ILD/pneumonitis of any grade, 0.3% had Grade 3 or 4, and 0.1% had a fatal outcome. Additional cases ofILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Reported frequency includes the cases reported with the following terms: pneumonitis, interstitial lung disease, pulmonary fibrosis, organizing pneumonia, acute respiratory distress syndrome (ARDS), interstitial pneumonia, pleural fibrosis. Novartis frequency includes only those events which occurred according to the broad SMQ for ILD/pneumonitis and included the following terms: ARDS, alveolitis, hypersensitivity pneumonitis, interstitial lung disease, lung infiltration, pneumonitis, pulmonary fibrosis.

Additionally, the 1 death reported in MONALEESA-3 (originally published in J Clin Oncol on August 20, 2018) was classified as acute respiratory distress syndrome in a patient who had lung metastases.

Synopsis of common adverse events with fulvestrant:
Fulvestrant is very well tolerated. Below is a table of common adverse events in patients being treated with fulvestrant 250 mg (N=374) and 500 mg (N=362), as reported in the phase III CONFIRM trial. [75] The only grade 3 toxicities that occurred in greater than 1% of patients were joint disorders/pain and GI disturbances.

	Fulvestrant 500 mg (n = 361)				Fulvestrant 250 mg (n = 374)			
	Grade 1-4		≥ Grade 3		Grade 1-4		≥ Grade 3	
Adverse Event	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Endometrial dysplasia	0	0	0	0	0	0	0	0
GI disturbances	73	20.2	8	2.2	76	20.3	1	0.3
Hot flashes	30	8.3	0	0	23	6.1	0	0
Injection site reactions	49	13.6	1	0.3	50	13.4	0	0
Ischemic cardiovascular disorders	5	1.4	0	0	7	1.9	3	0.8
Joint disorders	68	18.8	8	2.2	70	18.7	8	2.1
Osteoporosis	1	0.3	0	0	0	0	0	0
Thromboembolic events	3	0.8	2	0.6	6	1.6	4	1.1
Urinary tract infection	8	2.2	1	0.3	8	2.1	1	0.3
Vaginitis	3	0.8	0	0	1	0.3	0	0
Weight gain	1	0.3	0	0	1	0.3	0	0

Synopsis of common adverse events with letrozole and exemestane:
Common adverse events are similar amongst all 3 aromatase inhibitors (anastrazole, letrozole, and exemestane)

Below is a synopsis of common adverse events reported in patients being treated with letrozole and exemestane, based on extensive post-marketing experience, according to the Prescribing Information. While serious adverse event rates are considerable, the vast majority of serious AEs are not clearly treatment related. Moreover, as patients are frequently treated with letrozole for 5 to 10 years in the adjuvant setting, the cumulative incidence of non-treatment related adverse events can be considerable. Adverse events reported in clinical trials with shorter durations of follow up are quite comparable to those seen with other AIs and with fulvestrant.

Adverse Events Reported in >10% of patients:
Cardiovascular: Edema (7% to 18%)
Central nervous system: Headache (4% to 20%), dizziness (3% to 14%), fatigue (8% to 13%)
Endocrine & metabolic: Hypercholesterolemia (3% to 52%), hot flashes (6% to 50%)
Gastrointestinal: Nausea (9% to 17%), weight gain (2% to 13%), constipation (2% to 11%)
Neuromuscular & skeletal: Weakness (4% to 34%), arthralgia (8% to 25%), arthritis (7% to 25%), bone pain (5% to 22%), back pain (5% to 18%), bone mineral density decreased/osteoporosis (5% to 15%), bone fracture (10% to 14%)
Respiratory: Dyspnea (6% to 18%), cough (6% to 13%)
Miscellaneous: Diaphoresis (≤24%), night sweats (15%)
Adverse Events Reported in 1 to 10% of patients:
Cardiovascular: Chest pain (6% to 8%), hypertension (5% to 8%), chest wall pain (6%), peripheral edema (5%); cerebrovascular accident including hemorrhagic stroke, thrombotic stroke (2% to 3%); thromboembolic event including venous thrombosis, thrombophlebitis, portal vein thrombosis, pulmonary embolism (2% to 3%); MI (1% to 2%), angina (1% to 2%), transient ischemic attack
Central nervous system: Insomnia (6% to 7%), pain (5%), anxiety (<5%), depression (<5%), vertigo (<5%), somnolence (3%)
Dermatologic: Rash (5%), alopecia (3% to 5%), pruritus (1%)
Endocrine & metabolic: Breast pain (2% to 7%), hypercalcemia (<5%)
Gastrointestinal: Diarrhea (5% to 8%), vomiting (3% to 7%), weight loss (6% to 7%), abdominal pain (6%), anorexia (1% to 5%), dyspepsia (3%)
Genitourinary: Urinary tract infection (6%), vaginal bleeding (5%), vaginal dryness (5%), vaginal hemorrhage (5%), vaginal irritation (5%)
Neuromuscular & skeletal: Limb pain (4% to 10%), myalgia (7% to 9%)
Ocular: Cataract (2%)
Renal: Renal disorder (5%)
Respiratory: Pleural effusion (<5%)
Miscellaneous: Infection (7%), influenza (6%), viral infection (6%), secondary malignancy (2% to 4%)

Adverse Events Reported in < 1% of patients:
Anaphylactic reaction, angioedema, arterial thrombosis, cardiac failure, carpal tunnel syndrome, endometrial cancer, endometrial hyperplasia, endometrial proliferation, erythema multiforme, hepatitis, leukopenia, memory impairment, stomatitis, tachycardia, thrombocytopenia, toxic epidermal necrolysis, trigger finger

Adverse events reported in the phase III study of letrozole vs. tamoxifen in the first line setting for metastatic breast cancer in post-menopausal patients with a median follow up of 32 months is reported below.[82]

Table 4. Adverse Events Including Bone-Related Occurrences

Adverse Event	Letrozole (n = 455)		Tamoxifen (n = 455)	
	No. of Patients	%	No. of Patients	%
Irrespective of relationship, reported by ≥ 10% patients				
Bone pain	99	22	95	21
Hot flushes NOS	84	19	74	16
Back pain	82	18	86	19
Dyspnea	81	18	79	17
Nausea	78	17	77	17
Arthralgia	71	16	67	15
Cough	61	13	59	13
Fatigue	58	13	59	13
Constipation	45	10	48	11
Suspected to be related, reported by ≥ 5% patients				
Hot flushes	76	17	65	14
Nausea	30	7	29	6
Patients reporting bone fractures, any relationship	24	5	19	4
Patient-years of treatment	562.3		420.9	
Fracture rate per patient-year (95% CI)	0.0427 (0.0241 to 0.0613)		0.0451 (0.0260 to 0.0640)	

Abbreviations: NOS, not otherwise specified; CI, confidence interval.

8.2 Definitions and Reporting

8.2.1 Adverse Event (AE)

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The occurrence of AEs should be sought by non-directive questioning of the subject during the screening process after signing informed consent and at each visit during the study. As far as possible, each AE should be evaluated to determine:

• The severity grade (CTCAE Grade 1-5)
• Reasonable possibility that AE is related to the study treatment: Definite, Probable, Possible, Unlikely, Unrelated (Section 8.3.4)
• Start and end dates, unless unresolved at final exam

Action taken with respect to study drug (i.e., none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
• Outcome (e.g., not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown) the outcome ‘unknown’ should only be used when absolutely no data can be retrieved with regards to the event outcome e.g. if the subject is lost to follow-up.
• Whether it is serious, as per Serious Adverse Event (SAE) definition provided below.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements, see Section 8.2.2.

All AEs should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the AE CRF as well as the Prior/Concomitant medications CRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent; 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.

Disease progression should not be regarded or reported as an AE itself, unless it is associated with a separate AE.

Laboratory abnormalities that constitute an AE in its own right (are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the AE CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (i.e., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found.

When an abnormal laboratory or test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) event, as per CTCAE, does not automatically indicate a SAE unless it meets the definition of serious, as defined below, and/or as per the investigator's discretion.

8.2.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that either:

• Results in death.

• Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.

• Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).

• Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

• Is a congenital anomaly or birth defect; or

• Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events not considered to be serious adverse events are hospitalizations for:

• Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures.

• Elective or pre-planned treatment for a pre-existing condition that did not worsen.

• Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission.

• Respite care

8.2.3 Unanticipated Problem

An Unanticipated Problem (UP) is any incident, experience or outcome involving risk to subjects or others in any human subject research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (i.e., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

8.2.4 Suspected Adverse Reaction

A Suspected Adverse Reaction (SAR) is any AE for which there is a reasonable possibility that it was caused by the drug.

Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. Examples of reasonable possibility are:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure.
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug.
- An aggregate analysis of specific events observed in a clinical trial that indicates that those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

8.2.5 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

8.2.6 Attribution

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

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

8.2.7 Expedited Adverse Event Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

For multi-site trials where a Columbia University Medical Center investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by Columbia University Medical Center. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB per local policies and procedures. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor (i.e. Melissa Accordino, MD, MS) as described below.

In addition to the reporting requirements for SAEs, a separate case report form will be made for reporting of any grade adverse events attributable to research biopsies. These events will not require expedited reporting unless they also meet the requirements for SAE reporting, as detailed below.

Copies of all IND safety reports submitted to the FDA and/or institutional IRB by the institution under the institution's IND will be shared with the Novartis Pharmacovigilance representative, so that these reports can be evaluated and included in the Investigator Brochure and future Novartis IND safety submissions per regulations.

8.2.8 Serious Adverse Event Reporting

All serious adverse events, regardless of suspected causality, that occur after the patient began treatment, or within 30 days of the last dose of treatment must be reported to Columbia University Medical Center Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 8.2.2, as well as the following:

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to a Columbia University Medical Center Principal Investigator (Dr. Accordino) within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Name of Contact:	Melissa Accordino, MD
Address:	Columbia University Medical Center Herbert Irving Comprehensive Cancer Center 161 Fort Washington Avenue

New York, NY 10032
Email: p9506@lists.cumc.columbia.edu
Phone: 212-305-1945
Fax: 212-305-0178

Within the following 5 calendar days, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Follow-up information is sent to the same person to whom the original SAE
Report Form was sent, using a new SAE Report Form stating that this is a follow- up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the Investigator's Brochure for the study drug (new occurrence) and is thought to be related to the supplier's study drug, Novartis and Columbia University Medical Center may urgently require further information from the Investigator for reporting to Health Authorities.

The Sponsor may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.2.9. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE, unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. The procedures that will be followed based on whether a pregnancy is confirmed by a positive serum or urine test result are listed below:

- Investigator must notify the Sponsor/Principal Investigator via the p9506@lists.cumc.columbia.edu account, who in turn will notify Novartis Pharmaceuticals Corporation within 24 hours of learning of the occurrence
- Investigator must notify the Principal Investigator and Novartis Pharmaceuticals Corporation within 24 hours of learning of the occurrence
- Study drug must be discontinued immediately.
- Subject must be withdrawn from the study.
- Investigator must complete and submit the Pregnancy Initial and Follow-up report forms to the Principal Investigator and to Novartis Pharmaceuticals Corporation.
- A serum pregnancy test must be performed to confirm the urine test result. (The serum test should be performed at the investigative site to ensure the test will be performed promptly and the result available immediately for review.)

If a negative serum test does not confirm the urine test result, then:

• The Investigator will use his/her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine if it is in the subject's best interest to resume study drug and continue participation in the study.

To ensure subject safety, each pregnancy in a subject during maternal or paternal exposures to study drug must be reported within 24 hours of learning of its occurrence. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation. The pregnancy should be followed- up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to Novartis Pharmaceuticals Corporation. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome and follow-up to the first well-baby visit. Any SAE experienced during pregnancy must be reported on the SAE Report Form and to Novartis Pharmaceuticals Corporation.

8.2.10 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to one of the Columbia University Medical Center Overall Principal Investigators on the toxicity Case Report Forms.

8.2.11 Reporting to the Institutional Review Board (IRB)

Unanticipated Problems (Ups) are to be reported to the IRB. SAEs not constituting UPs are to be reported to the HICCC DSMC.

A copy of the submitted institutional SAE form should be forwarded to:

Name of Contact:	Melissa Accordino, MD
Address:	Columbia University Medical Center Herbert Irving Comprehensive Cancer Center 161 Fort Washington Avenue New York, NY 10032
Email:	p9506@lists.cumc.columbia.edu
Phone:	212-305-1945
Fax:	212-305-0178

SAEs are to be reported to the HICCC DSMC, if they are considered UPs, then they must be submitted to CUMC IRB per institutional policies.

Unanticipated Problems must be reported promptly, but not later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP.

Expected AEs must be reported at the time of continuing review of a protocol.

8.2.12 Reporting to the Food and Drug Administration (FDA)

Columbia University Medical Center's Overall Principal Investigator (Sponsor-Investigator), as holder of the IND, will be responsible for all communication with the FDA. The Sponsor-Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

The Sponsor-Investigator must report the following SARs:

- To the FDA, as soon as possible, but no later than 7 calendar days after the S-I's initial receipt of the information, any unexpected fatal or life-threatening SAR.

- To the FDA and all participating investigators, as soon as possible but no later than 15 calendar days after the S-I determines that information qualifies for reporting, in an IND safety report, any SAR that is both serious and unexpected.
- To the FDA and all participating investigators, as soon as possible but no later than 15 calendar days after the S-I determines that the information qualifies for reporting, any findings from epidemiological studies, pooled analysis of multiple studies or clinical studies, whether or not conducted under an IND or by the S-I, that suggest a significant risk in humans exposed to the drug.
- To the FDA and all participating investigators, as soon as possible, but no later than 15 calendar days after the S-I determines that the information qualifies for reporting, any findings from animal or in vitro testing, whether or not conducted by the S-I, that suggest a significant risk in humans exposed to the drug.
- To the FDA and all participating investigators, as soon as possible, but no later than 15 calendar days after the S-I determines that the information qualifies for reporting, any clinically important increase in the rate of a Serious SAR over that listed in the protocol or Investigator Brochure.
- Expected SAEs and AEs should be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800- FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

8.2.13 Reporting to Novartis Pharmaceuticals Corporation
The Sponsor-Investigator will report to investigational agent manufacturer any serious adverse events within 24 hours of becoming aware of it on the Novartis Serious Adverse Reporting and transmitted to Novartis via the telefax confirmation sheet so that these reports can be evaluated and included in the Investigator's Brochure and for IND safety submissions per regulations. Reporting will occur by sending the reporting form along with any additional documentation sent to the regulatory authorities.

The Overall Principal Investigator will send copies of any IND Safety reports submitted to the FDA to Novartis Pharmaceuticals Corporation so that these reports can be evaluated and included in the Investigator's Brochure or Novartis Pharmaceuticals Corporation IND safety submissions.

8.2.14 Reporting to Hospital Risk Management
Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

8.2.14 Monitoring of Adverse Events and Period of Observation
All adverse events, both serious and non-serious, and deaths that are encountered after the patient has provided informed consent, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record and subject binder to facilitate source data verification.

For some SAEs, the sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify Columbia University Medical Center's Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

8.3 Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The CUMC Sponsor/Principal Investigator will review all applicable IND Safety Reports and has the responsibly for forwarding the IND Safety Reports to the Affiliate Institutions. The Affiliate Institution investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents. All Affiliate site INDSR submissions, along with IRB acknowledgment (per local policies and procedures) are to be forwarded to CUMC for placement within the trial master file.

8.4 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. Second malignancies require ONLY routine reporting unless otherwise specified.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

The list of available targeted therapies to treat patients with breast cancer is growing, and as a result it is becoming increasingly important to develop biomarkers that can predict response and/or toxicity from each given therapy in order to ensure that each patient is receiving personalized therapy from which she is most likely to benefit. In addition, biomarkers that are able to capture the extent of response early within the treatment course are likely to be beneficial in guiding therapies in the future.

Several biomarkers have already been evaluated in clinical trials involving the CDK4/6 inhibitors palbociclib and ribociclib. These biomarkers mainly fall into two broad categories: 1) genetic/epigenetic events that result in alterations in activity in the p16/cyclin D1/Rb pathway and 2) downstream effects of CDK4/6 inhibition. In the PALOMA-1 study, the presence of CCND1 amplification or p16 loss did not appear to predict responses to palbociclib in the front line setting, in spite of the fact that presence of either event appears to predict response in cancer cell lines. This is likely in part because a significant majority of ER-positive HER-2-negative breast cancers do in fact have increased CDK4/6-cyclin D activity to some extent and are thus likely to benefit from CDK4/6 inhibition in the front line setting. However, the presence of genomic events such as CCND1 amplification that markedly increase CDK4/6-cyclin D activity may be more important in predicting response to continuation of CDK4/6 inhibition beyond disease progression, as these tumors are more likely to be dependent/addicted to this pathway. In addition, adequate downstream target inhibition early in the treatment course may help differentiate patients who are likely to benefit from continuation of CDK4/6 inhibition beyond disease progression.

We propose evaluating tissue biomarkers as surrogates for p16/cyclin D1/Rb activity and to assess downstream effects of CDK4/6 inhibition. In addition, we propose to collect serum and plasma specimens for future biomarker studies involving the study cohort. We will also be collecting an archival primary/metastatic FFPE tumor (required) and additional optional formalin fixed samples at the specified

biopsy time points, unless unavailable. Immunohistochemistry (IHC) data reported from the lab will include quantitative data such as percent tumor and percent positive cells or a semi quantitative measure of protein expression in cellular compartments (i.e. cytoplasm, nucleus, membrane). The pathologist determines whether the staining in a cellular compartment is absent (0+), slight (1+), moderate (2+), or strong (3+). The histoscore (i.e. H-Score) for each cellular compartment may also be calculated as a more precise measure of staining within a compartment, and ranges between 0 and 300.

Biomarker Assessment:

- Archived tissue from primary and/or metastatic tissue is required, unless not available.
- Optional biopsies for tissue biomarker assessment will be performed in consenting patients prior to starting study drugs, at time of progression on letrozole plus ribociclib (in patients registered under scenario#1), and upon progression on Fulvestrant (or exemestane) +/- ribociclib. **These optional biopsies are strongly recommended**, as they have the potential to provide invaluable information. If pre-treatment biopsy is not available or accessible, we will plan to use archived tissue from primary and/or metastatic tissue. (Appendix E).
- For registration scenario # 1, optional tissue biopsies for biomarker evaluation will be performed at 3 time points: pre-treatment, at time of progression on aromatase inhibitor plus ribociclib, and progression on Fulvestrant (or exemestane) +/- ribociclib.
- For registration scenario # 2, optional tissue biopsies for biomarker evaluation will be performed at 2 time points: prior to treatment with Fulvestrant (or exemestane) +/- ribociclib and at progression on Fulvestrant (or exemestane) +/- ribociclib.
- For patients who agree to the optional biopsies, up to 5 core biopsies are recommended. The following will be requested: 10 immunoblanks [each having 4 micron sections on charged slides], one intervening H&E stained slide, and 12 regular slides each with 10 microns sections.
- Serum and plasma will be collected at multiple time points (Section 10: Study Calendar, and Appendix C) and stored for future biomarker driven studies. In addition, whole blood samples will be collected to perform plasma ctDNA biomarkers (ESR-1 and PIK3CA mutations (Appendix D).
- For registration scenario # 1, peripheral blood will be collected for proposed and future biomarker evaluations at 5 time points: a) pre-treatment, after completing 1 cycle of treatment (Cycle2a Day1 visit), progression on aromatase inhibitor plus ribociclib, after completing 1 cycle of treatment post-randomization (Cycle2b Day1 visit), and progression on Fulvestrant (or exemestane) +/- ribociclib. One lavender (EDTA) tube and two red top (non-anticoagulant) tubes are recommended for collection.
- For registration scenario # 2, peripheral blood will be collected for proposed and future biomarker evaluations at 3 time points: pre-treatment, after one cycle of treatment (Cycle2 Day1 visit), and at progression on Fulvestrant (or exemestane) +/- ribociclib. One lavender (EDTA) tube and two red top (non-anticoagulant) tubes are recommended for collection.

Exploratory Analyses:
Potential exploratory biomarkers that will be examined when possible include:

- **Tissue overexpression or amplification of Cyclin D1 and Cyclin E** (by IHC and FISH)
- **Phospho-Rb expression** (by IHC)
- **Rb1 loss** (by IHC)
- **$p16^{INK4A}$ loss** (by IHC)
- **TK1 and TOP2A expression** (as measures of E2F1 transcriptional activity, by IHC).

Serum and plasma will be collected and stored for potential future exploratory analyses.[82]

10. STUDY CALENDAR

Baseline evaluationsare to be conducted within 28 days prior to start of registration. Scans, including CT scans and bone scan (or PET CT) must be done ≤ 28 days prior to registration. Each cycle is of 28-day duration.

10.1 Table 1: Registered Prior to Receiving AI + CDK 4/6 Inhibitor (Scenario #1)

Cycle[C]	Screen	C1a	C1D 15	C2a	C2D1 5	C3a	C4a+	Progression[A]	C1 D1 b	C1D 15b	C2b	C3b	C4b+	End of-Treatment[N]
Day	-28 to -1[B]	All pertinent assessment time points relate to Day 1 of the respective cycle +/- 4 days with the exception of scans and biopsies. [B]												
Informed consent	X													
H/P (incl PS)[C]	X	X		X		X	X	X	X	X	X	X	X	X
AE assessment[C]		X		X		X	X	X	X	X	X	X	X	X
Aromatase Inhibitor (AI)[D]		X	X	X	X	X	X							
Ribociclib [D]		X	X	X	X	X	X							
Fulvestrant (or exemestane)									X	X	X	X	X	
Ribociclib/ Placebo[D]									X	X	X	X	X	
β-HCG (premenop)[E]	X													
INR	X													
CBC/Chem7/ LFT [C, F]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG [G]	X		X	X			X	X					X	
CT C/A/P + Bone Scan (Or PET) [B, H, I, J]	X [B]						X	X					X	X
Pill diary Review				X		X	X	X		X	X	X	X	X
Blood Biomarker[K]	X			X				X			X			X[G]
Tissue Biopsy[L]	X							X						X
Questionnaire[M]	X						X	X					X	X

[A] At progression, patients are taken off of AI + CDK 4/6 inhibitor. Randomized to Fulvestrant (or exemestane) +/- ribociclib. If the window between ending progression and starting the Fulvestrant (or exemestane) +/- ribociclib is greater than 28 days, the labs should be repeated. There is no required timeline between completion of AI+CDK 3/6 inhibitor and initiation of Fulvestrant (or exemestane) +/- ribociclib.

[B] Exceptions to the +/- 4 days are CT C/A/P + bone scan (OR PET) which should be performed within 28 days of trial registration and after each third cycle of treatment (within 14 days of day 1 of each third cycle – ideally within 7 days of day 1) and tissue biopsy (+/- 7 days). The +/- 4 day window includes C1D15.

[C] Every 4 weeks, except during the first 2 cycels. Day 1 visits for each cycle should occur at 28±4 days from day 1 of the previous cycle. Blood draws on that day should also fall within this +/- 4 day window. Exceptions to the +/- 4 days are CT C/A/P + bone scan (OR PET) as described above.

[D] Ribociclib (and/or placebo) will be supplied per study. If letrozole, will be supplied by study. On D1 of every cycle prior to drug dispensation and dose administration, subject's disease status/non-progression will be confirmed by the treating investigator, including clinical and radiographic assessment. RECIST restaging will be confirmed for the most recent scans received, including documentation of investigator sign off on calculation of percentage change from baseline and nadir and overall response, prior to treatment. If the new scan information becomes available mid cycle, the study team will inform the subject if treatment discontinuation is required per protocol in real time, and document date of treatment discontinuation.

[E] Serum Pregnancy test (women of childbearing potential)

[F] Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

[G] EKG will be performed at baseline, C1D15, C2a, C4a, Progression, and C4b. If grade 3 or 4 QTC prolongation occurs, see Section 7.3 for monitoring/dose modification. If no EKG abnormalities, additional EKGs are not required for cycles after C4a or C4b, except Progression.

[H] Scans should be performed within 28 days of study registration, prior to every third cycle of treatment (i,e, preferably within 7 days

			of Cycle 4a day 1, Cycle 7a day 1, Cycle 10a day 1, and so on, but allowance for up to within 14 days of the next treatment cycle). Corresponding RECIST restaging will be conducted in real time following scans and signed (electronically or wet ink) by the investigator, including confirmation of overall disease status per RECIST v.1.1.
			[I] If patients have known brain metastases and are eligible for this trial, head CT or brain MRI must be performed along with systemic imaging. If a patient does not have known brain metastases and is asymptomatic, no baseline brain imaging is required.
			[J] Baseline bone scan required in all patients (whose baseline imaging is CTs of C/A/P) NOTE: If bone scan done ≤ 6 weeks prior to registration showed no evidence suggesting bone metastases and no clinical indication of skeletal pain or other evidence suggesting bone metastases, a repeat baseline bone scan is not required. If there is evidence of disease on the bone scan, bone scans should be continued every 3 cycles (~12 weeks of treatment +/- 4 days), as clinically indicated.
			[K] Serum (2 red top tubes) and plasma (1 lavendar tube) will be collected at each time point and stored for future potential studies. (Appendix C on collection details.) In addition, whole blood samples (2 Biocept provided tubes) will be collected and sent same day to Biocept (Appendix D).
			[L] Archived tissue from primary and/or metastatic tissue is required, unless unavailable. If patient is amenable and has accessible tumor, repeat biopsy is optional. These biopsies should be considered in patients with accessible disease. Biopsies can be within 7 days of the cycle (+/- 7 days).
			[M] PROMIS Global Health and PROMIS-29 and EQ-5D-3L will be performed at baseline, C4, Progression, C4b, and Off-Study. Questionnaires are not required for cycles after C4a or C4b, except Progression and Off-Study.
			[N] Within 4 weeks of completing study treatment. Post-treatment follow-up every 12 weeks (+/- 1 week) for survival follow-up until study closure, which we anticipate will be up to 2.5 years after last patient enrolled (Section 6.6).
			[O] Adverse event assessments every 4 weeks should include a review of concomitant medications with the patient.

10.2 Table 2: Registered After Progression on AI or tamoxifen or fulvestrant + CDK 4/6 Inhibitor (Scenario #2)

Cycle	Screen	C1D1	C1D15	C2	C2D15	C3	C4+	End of Treatment[L]
Day	-28 to - 1 [A]		All pertinent assessment time points relate to Day 1 of the respective cycle +/- 4 days with the exception of scans and biopsies.[A]					
Informed consent	X							
History and Examination (incl PS) [B]	X	X	X	X		X	X	X
Adverse event assessment [B,N]		X	X	X		X	X	X
Fulvestrant(or exemestane)		X	X	X		X	X	
Ribociclib (or Placebo)[C]		X	X	X	X	X	X	
β-HCG (if premenopausal) [D]	X							
INR	X							
CBC, Chem7, LFTs[E]	X	X	X	X	X	X	X	X
EKG [F]	X		X	X			X	
CT C/A/P + Bone Scan (Or PET) [B,G,H,I]	X						X	X
Pill Diary Review			X	X		X	X	X
Blood Biomarker[J]	X			X				X
Tissue Biopsy[K]	X							X
Questionnaire[M]	X						X	X

[A] Exceptions to the +/- 4 days are CT C/A/P + bone scan (OR PET) which should be performed within 28 days of trial registration and after every third cycle of treatment (within 14 days of day 1 of each third cycle – ideally within 7 days of day 1) and tissue biopsy (+/- 7 days).

[B] Every 4 weeks. Day 1 visits for each cycle should occur at 28±4 days from day 1 of the previous cycle. Blood draws on that day should also fall within this +/- 4 day window. Exceptions to the +/- 4 days are CT C/A/P + bone scan (OR PET) as described above. The +/- 4 day window includes C1D15.

[C] Ribociclib (or placebo) will be supplied per study. On D1 of every cycle prior to drug dispensation and dose administration, subject's disease status/non-progression will be confirmed by the treating investigator, including clinical and radiographic assessment. RECIST restaging will be confirmed for the most recent scans received, including documentation of investigator sign off on calculation of percentage change from baseline and nadir and overall response, prior to treatment. If the new scan information becomes available mid cycle, the study team will inform the subject if treatment discontinuation is required per protocol in real time, and document date of treatment discontinuation.

[D] Serum Pregnancy test (women of childbearing potential)

[E] Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

[F] EKG will be performed at baseline, C1D15, C2, and Cycle 4. If grade 3 or 4 QTC prolongation occurs, see section 7.3 for monitoring/dose modification. If no EKG abnormalities, additional EKGs are not required for cycles after C4a or C4b, except

		Progression.
		[G] Scans should be performed within 28 days of study registration, prior to every third cycle of treatment (i,e, preferably within 7 days of Cycle 4a day 1, Cycle 7a day 1, Cycle 10a day 1, and so on, but allowance for up to within 14 days of the next treatment cycle). Corresponding RECIST restaging will be conducted in real time following scans and signed (electronically or wet ink) by the investigator, including confirmation of overall disease status per RECIST v.1.1.
		[H] If patients have known brain metastases and are eligible for this trial, head CT or brain MRI must be performed along with systemic imaging. If a patient does not have known brain metastases and is asymptomatic, no baseline brain imaging is required.
		[I] Baseline bone scan required in all patients (whose baseline imaging is CTs of C/A/P) NOTE: If bone scan done ≤ 6 weeks prior to registration showed no evidence suggesting bone metastases and no clinical indication of skeletal pain or other evidence suggesting bone metastases, a repeat baseline bone scan is not required. If there is evidence of disease on the bone scan, bone scans should be continued every 3 cycles (~12 weeks of treatment +/- 4 days), as clinically indicated.
		[J] Serum (2 red top tubes) and plasma (1 lavendar tube) will be collected at each time point and stored for future potential studies. (Appendix C on collection details.). In addition, whole blood samples (2 Biocept provided tubes) will be collected and sent same day to Biocept (Appendix D).
		[K] Archived tissue from primary and/or metastatic tissue is required, unless unavailable. If patient is amenable and has accessible tumor, repeat biopsy is optional. These biopsies should be considered in patients with accessible disease. Biopsies can be within 7 days of the cycle (+/- 7 days).
		[L] Within 4 weeks of completing study treatment. Post-treatment follow-up every 12 weeks (+/- 1 week) for survival follow-up until study closure, which we anticipate will be up to 2.5 years after last patient enrolled (Section 6.6).
		[M] PROMIS Global Health and PROMIS-29 and EQ-5D-3L will be performed at baseline, C4, and Off-Study. Questionnaires are not required for cycles after C4, except Off-Study.
		[N] Adverse event assessments every 4 weeks should include a review of concomitant medications with the patient.

10.3 Table 3: Treatment Post Unblinding for Patients who were Active/On Treatment when Unblinded (Scenario #2)

The table below applies to Scenario 2 patients who were Actively receiving treatment when unblinded by the Sponsor-Investigator at the end of August 2023, due to the expiration and discontinuation of the Novartis manufactured placebo for this study. Guidance was provided to all study sites noting that all patients that are Active/On Treatment on scenario 2 will undergo an unblinding process following which patients will continue to receive the assigned treatment: patient who received Ribociclib will continue to do so and patients who received Placebo will continue to receive the endocrine treatment alone, as part of the study. Please note, the study does not allow for crossover between the study groups.

	Patient Visit[1] (ongoing)
SAE[2]	X
Disease Progression[3]	X
Patient Status on Study[4]	X

1. Visit frequency should be determined as per standard of care.
2. All SAEs experienced by patients receiving study treatment should be reported as per section 8.2.7 and entered in the Velos database.
3. Disease Progression should be documented in the patient statuses in velos, as reason for removal from study treatment, if applicable.
4. Any update to the patients' stuay status should be entered in Velos.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this phase II study, patients should be re-evaluated for response every 3 cycles (~12 weeks of treatment +/- 7 days). This includes the pre-randomization phase of the study in patients registered under scenario #1 (i.e. patients who have never received CDK4/6 inhibition with an aromatase inhibitor at time of registration).

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment on study. (Either ribociclib with letrozole (or anastrozole) in patients registered under scenario #1 or fulvestrant (or exemestane) +/- ribociclib in patients registered under scenario #2.)

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy on study, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area may be considered measurable, as long as they meet the criteria above.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be

representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. 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. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Skin color photography (if skin lesions at screening) will be performed every 12 weeks (+/- 1 week) to assess for disease progression or response, particularly in patients with no measurable disease by radiologic criteria. (Appendix I).

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scan is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site believes that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. FDG avidity is not part of the RECIST criteria, but may provide adjunct information for evaluation (see section "FDG-PET" below).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Tumor markers have a limited role in the evaluation of metastatic breast cancer, and measurements are not required under this protocol.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported

by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression, even if the sum of the diameters of the other target lesions has not increased by 20%).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: 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. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the Principal Investigator and/or review panel.

11.1.4.3 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (*i.e.*, Target Disease) +/- Non-Target Disease

Target Lesions	**Non-Target Lesions**	**New Lesions***	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	**CR**	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	**PR**	≥4 wks. Confirmation**
CR	Not evaluated	No	**PR**	
PR	Non-CR/Non-PD/not evaluated	No	**PR**	
SD	Non-CR/Non-PD/not evaluated	No	**SD**	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	**PD**	no prior SD, PR or CR
Any	PD***	Yes or No	**PD**	
Any	Any	Yes	**PD**	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint. (Not applicable in this trial).
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease Only (*i.e.*, Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease. As SD is increasingly used as an endpoint for assessment of efficacy in some trials, to assign this category when no lesions can be measured is not advised.

11.1.5 Duration of Response

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

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

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

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Percent progression-free at 24 weeks is defined as the proportion of patients who remain progression-free at 24 weeks from study entry day #1 (binary proportion). For the primary outcome measure in this study, because patients will be registered under two different scenarios, PFS will be measured using the date of randomization as day #1.

11.1.7 Response Review

All responses are reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

11.2 Safety Assessment

11.2.1 Safety

While on study patients will undergo a) standard of care history and physical exam and b) standard of care blood work including complete blood count with differential, liver function tests, and serum chemistry -- at baseline, at the beginning of each treatment cycle, at time of disease progression in patients registered under scenario#1, and at a final visit when patient is off-study. (4 weeks after final treatment). A standard comprehensive adverse event assessment will be performed at the beginning of each treatment cycle. In addition, radiological studies performed for response assessment will occasionally detect asymptomatic adverse events or provide adjunct information in the case of symptomatic adverse events.

Adverse events will be graded based on the Common Terminology Criteria for Averse Events (CTCAE) version 4.0.

11.2.2 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment on study.

11.2.3 Disease Parameters

Patients with both measurable and un-measurable disease will be enrolled in the study. Treatment will continue until disease progression as defined above or unacceptable toxicity develops as determined by the treating physician.

12. DATA REPORTING / REGULATORY REQUIREMENTS

***** Please see Appendix F for Guidelines for Affiliate Institutions for Registration and Data Reporting Requirements.**

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 12.3.

12.1 Data Collection

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system that will be used for data collection. CRFs for the study will be built into Velos for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to view study information if they are indicated as study personnel in our electronic IRB system, or an affiliate IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity

of patients via an interface with the electronic medical patient index. Staff with the appropriate IRB defined roles can run reports within the system for reporting purposes.

12.2 Data Reporting

Responsibility for Data Submission

Case Report Forms will be completed for each subject enrolled into the clinical study through Velos eResearch. It is the investigator's responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

- Please refer to the tables provided in separate documentation regarding the case report form completion and source document submission requirements.

12.3 Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is led by Dr. J. Gregory Mears and consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects (*****DSMC forms will be provided separately** ***).

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

The Coordinating Site will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the DSMC's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study the DSMC's conclusion with respect to progress or need for modification of the protocol.

12.4 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time, per institutional policies and procedures.

The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

Internal On-site Monitoring:

1. Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

    a. The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

2. The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

3. The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

12.5 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

1. What protected health information (PHI) will be collected from subjects in this study
2. Who will have access to that information and why
3. Who will use or disclose that information
4. The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects who have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

12.6 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

12.7 Reporting to Novartis Pharmaceuticals Corporation

The primary site (CUMC) Principal Investigator will send complete Data transfers every six months during the course of the study to Novartis Pharmaceuticals Corporation. Novartis Pharmaceuticals Corporation may

request additional data transfers over the course of the study. The data will be provided in a readable format for all study participants. The data will not include any protected health information as defined under HIPAA.

Additionally, Novartis Pharmaceuticals Corporation will be provided monthly study status updates including a summary of:

- Recruitment (screened, enrolled, discontinued and on-going with dates and study drug dosing regimens)
- SAEs and safety reports to regulatory authorities
- Regulatory correspondence including IRB approval letters, IRB approved protocol, informed consent documents, and documents related to Novartis Pharmaceuticals Corporation.
- Investigational product Inventory
- Payment milestones.

12.8 Records Retention

Records relating to a specific research activity, including research records collected by investigators must be maintained for at least seven years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This was selected, as New York State (location of Sponsor) requires at least seven years for information. This retention period applies whether or not any subjects were enrolled in the study.

If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies).

Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUMC and NYP policy, which is based on state law.

Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The CUMC Principal Investigator will review all applicable IND Safety Reports and has the responsible for forwarding the IND Safety Reports to the Affiliate Institutions. The Affiliate Institution investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents. All Affiliate site INDSR submissions, along with IRB acknowledgment (per local policies and procedures) are to be forwarded to CUMC for placement within the trial master file.

*** **Please see Appendix F for Guidelines for Affiliate Institutions for Registration and Data Reporting Requirements.**

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Primary Endpoint (Sample Size: N=120 randomized evaluable patients)

This is a multi-center phase II, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of fulvestrant (or exemestane) with or without ribociclib in patients who have previously progressed on an aromatase inhibitor (preferably letrozole) plus CDK4/6 inhibitor (ribociclib or palbociclib or abemaciclib).

Primary Endpoint

The primary endpoint is progression free survival, defined as the time from randomization to the development of progressive disease or death.

Disease status will be assessed with comprehensive radiographic studies every three treatment cycles (approximately every 12 weeks (+/- 1 week), but the development of new signs or symptoms of disease in between scheduled evaluations may prompt off-schedule radiographic or non-radiographic evaluations. Disease status will be assessed based on RECIST 1.1 criteria for measurable (target) and non-measurable (non-target) disease, as outlined in detail in Section 11.

Secondary Endpoints:
All secondary endpoints, including overall response rate (complete response + partial response rates), clinical benefit rate (overall response rate + stable disease rate), overall survival, duration of response, adverse event rate, and biomarker assessment are exploratory in nature. In addition, patients registered under scenario #1 will be assessed for progression free survival, overall response rate, clinical benefit rate, and safety while receiving ribociclib with an aromatase inhibitor (pre-randomization). As there is no comparator arm for this pre-randomization part of the study, further statistical analyses on these will not be possible.
Response rates will be estimated as the proportion of enrolled patients who achieve response, as defined in Section 11. Patients who are lost to follow-up without a valid response assessment will be classified as non-responders.

Statistical analysis:
Progression-free survival will be estimated by Kaplan-Meier method and group differences between groups will be assessed using log-rank tests. Sensitivity analyses for PFS will be performed taking into consideration, but not limited to imputation of incomplete lesion measurements and study discontinuation due to progression/relapse, drug toxicity or death. Missing data patterns will be examined by summarizing the number of subjects randomized but not treated, the number of subjects who discontinued prematurely and the corresponding factors for early discontinuation. Given the potential the interval between two consecutive assessments may be longer in one arm, leading to an erroneous conclusion about differences between groups, we will perform an additional analysis (i.e. generalized log-rank) with interval censoring, especially if there is a difference in assessment schedules and considerable missing data.

Summary statistics will be calculated to describe the sample characteristics in each group. The distribution of patient responses (as defined by RECIST criteria) will be described using percentages % (n). Continuous outcomes will be summarized using mean ± SD (standard deviation) or median (interquartile range) for non-normal data. Group comparisons will be evaluated using chi-squared or Fisher's Exact tests for categorical data and two-sided t-tests or ANOVA for continuous outcomes.

Analyses for of primary and secondary outcomes will be based on intention to treat principle, with the exception of safety endpoints, which will only be assessed in patients who receive at least one dose of treatment on study.

Subject to sample size limitations, subgroup analyses for subjects randomized to fulvestrant versus exemestane will also be considered.

All statistical analyses will be performed using SAS (version 9.4, SAS Institute Inc., Cary, North Carolina) with a type I error set at 0.05.

Sample Size Justification:
Assuming a median PFS of 3.8 months with fulvestrant alone upon progression[83], we predict that the addition of ribociclib to fulvestrant will lead to a median PFS of at least 6.5 months. Based upon the Evaluation of Faslodex versus Exemestane Clinical Trial (EFFECT), a randomized, double-blind, placebo-controlled, phase III trial of fulvestrant versus exemestane in patients who progressed on prior non-steroidal aromatase inhibition, the median time to progression was 3.7 months in each arm (HR=0.96, 95% CI 0.82

to 1.13, p=0.65). Thus, this new protocol amendment allows subject to be randomized to either fulvestrant or exemestane +/- ribociclib[69]., without an impact on the study design and power. A one-sided log-rank test with an overall sample size of N=120 randomized and evaluable subjects and with the significance level alpha set at 2.5%, achieves 80% power to detect an effect size (difference in PFS) of 3 months. We will accrue approximately 150 patients to allow for a 20% drop-out rate, non-evaluable and non-randomized subjects.

13.2 Accrual Rate

Number of Patients & Centers

The goal is to accrue approximately 150 patients across 11 different academic centers in the United States, with the expectation that each center will accrue approximately 7 patients per year over 2 years. We previously participated in a study with a similar patient population (Fulvestrant +/- Bortezemib: SABCS oral discussion 2014), with an accrual rate as above.

13.3 Evaluation of Toxicity

The frequency of subjects experiencing toxicities will be tabulated.
The case report form will be utilized for AE reporting, based upon the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

The descriptions and grading scales in CTEP Version 4.0 of the CTCAE can be located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All patients will be evaluable for toxicity from the time of their first treatment with the investigational drug.

13.4 Correlative Studies

Correlative studies for this phase II study are exploratory and will be used for hypothesis generation only.

13.5 Reporting and Exclusions

All patients included in the study must be assessed for toxicity and disease status.

13.6 Unblinding Procedures

The Investigator, the study site personnel, and the subject will remain blinded to each subject's treatment with Ribociclib/Placebo throughout the course of the study.

Access to blinded subject treatment information during the study will be made available to the investigator/limited site personnel, only if identification of the study drug is required for a medical emergency. Medical emergency includes a situation in which the knowledge of the specific blinded treatment will affect the immediate management of the subject/subject's conditions, or when knowledge of previous treatments is required for enrollment in another trial, or as part of managing a serious adverse event.

Investigators should note that emergency unblinding is reserved only for emergency situations where lack of knowledge about the actual study drug treatment interferes with appropriate emergency management. **The occurrence of an SAE or progressive disease should not routinely precipitate the immediate unblinding of the label.**

In the event of a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see Section 8.2.8) related to the blinded treatment, the subject's treatment code will usually be

broken before reporting to health authorities and central ethics committees in an unblinded fashion. In compliance with 21 CFR 312 on the collection and verification of presentation of AE/reaction reports arising from clinical trials on medicinal products for human use, investigators and persons responsible for the ongoing conduct of the study will not usually receive unblinded copies of SUSAR reports, unless unblinded information is judged necessary for safety reasons.

At the end of August 2023, the Placebo drug manufactured and provided by Novartis, expired and an unblinding of the Scenario 2 patients who were on treatment at the time was required. Guidance was provided to all study sites noting that all patients that are Active/On Treatment on scenario 2 will undergo an unblinding process following which patients will continue to receive the assigned treatment: patient who received Ribociclib will continue to do so and patients who received Placebo will continue to receive the endocrine treatment alone, as part of the study. Please note, the study does not allow for crossover between the study groups.

13.6.1 Unblinding requests

If emergency unblinding is necessary for the treatment of a subject, the unblinding should be first approved by the Sponsor-Investigator at least 24 business hours in advance. The request must provide the study ID, date the request is needed, an explanation of the medical need and must be made by the PI/designee.

These requests must be submitted to the study email p9506@lists.cumc.columbia.edu between the hours of 9:00 am EST – 5:00 pm EST.

Once the unblinding is processed, the appropriate designee will separately communicate the treatment allocation via email to limited personnel from the site requesting the unblinding. The study team should maintain documentation of the treatment allocation.

Investigators may only unblind subjects under emergency unblinding rules. If a subject is unblinded by the Investigator, they must first discontinue study drugs.

14. PROTECTION OF HUMAN SUBJECTS

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures. An IND annual report will be submitted to the FDA in accordance with 21.CFR 312.33.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

15. CONSENT: LEGAL AUTHORIZED REPRESENTATIVE IF PATIENT WITHOUT CAPACITY

We may enroll individuals with limited decision making capacity on to the protocol. This is not an exclusion criterion in the protocol and there is the prospect of benefit to participants in this study since participation may improve their condition. The principal investigator and co-investigator will be responsible for making an initial assessment as to whether a subject is competent to provide consent. If this is the case, the investigator will obtain an independent assessment of the individual's capacity to provide informed consent by a licensed physician, not otherwise involved in the research study.

The research team will be present to answer all the LAR's questions adequately before they decide to participate and will be given detailed information about the study purpose, procedures, requirements, risks, benefits, and possible alternatives. The research team will be present to answer all the LAR's questions adequately before they decide whether or not to participate. They will sign the consent form on the designated signature line and sign the HIPAA authorization form (unless already embedded into the informed consent document).

Although not expected given the potential subjects to be enrolled who have limited decision making capacity in this study, in the event that a subject regains their capacity to consent; their ability to provide consent will be assessed first by the principal investigator or co-investigator and then by an independent licensed physician and they will then be re-consented.

16. STUDY FINANCES

16.1 Conflict of Interest:

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Columbia University Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All CUMC investigators will follow the University conflict of interest policy.

17. PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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APPENDIX A: ECOG PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to	100	Normal, no complaints, no

	carry on all pre-disease performance without restriction.		evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: STRONG CYP3A4 AND CYP3A5 INDUCERS AND INHIBITORS

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as Facts and Comparisons or Lexicomp; medical reference texts such as the Physicians' Desk Reference may also provide this information. The Principal Investigator should be alerted if the subject is taking any agent on these lists. The list below should not be considered a complete list.

List of prohibited medications during study drug treatment

Category	Drug Name
Strong CYP3A4/5 inhibitors	Atazanavir/ritonavir, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavirnelfinavir,ombitasvir/paritaprevir/dasabuvir/ritonavir (VIEKIRA PAK), posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Strong CYP3A4/5 inducers	Apalutamide, carbamazepine3, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin3, rifabutin, rifampin (rifampicin)3, St. John's wort (hypericum perforatum)2,3

Category	Drug Name
CYP3A4/5 substrates with NTI1	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, lomitapide5, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, simvastatin, sirolimus, tacrolimus
Medications with a known risk for QT prolongation4	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil chloroquine, cocaine chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, levomethadyl, mesoridazine methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, sulpiride, sultopride, terlipressin, terodiline, terfenadine, thioridazine, vandetanib
Herbal preparations/ medications or dietary supplements	Herbal preparations/medications or dietary supplements known as strong inducers or inhibitors of CYP3A4/5 or those with a known risk of QT prolongation are prohibited throughout the study. These include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh, and ginseng. Patients should stop using these herbal medications or dietary supplements 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, hormonal therapy, including but not limited to all SERMS [including raloxifene], biologic or radiation therapy [except for palliative radiotherapy as outlined in the protocol], and surgery) other than the study treatments must not be given while the patient is on the study medication. If such agents are required, then the patient must discontinue the study drug.

Category	Drug Name
1 NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes) or drugs which have <2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood. 2 Herbal product 3 P-gp inducer 4 The list provided is as of December 2019. Check https www.crediblemeds.org/healthcare-providers/drug-list for the most updated list. 5 Drug has warning for risk of hepatotoxicity. As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI that increases the exposure of ribociclib or the exposure of the QT prolonging drug). A definitive list of drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or Torsades de Pointes (TdP) is available online at qtdrugs.org. Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University "Clinically Relevant" Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.	

List of medications to be used with caution during study drug treatment Category	**Drug Name**
Moderate CYP3A4/5 inhibitors	Aprepitant, amprenavir, asafoetida resin (Ferula asafoetida), cimetidine, crizotinib, diltiazem, faldaprevir, imatinib, isavuconazole, netupitant, nilotinib, tofisopam, Schisandra sphenanthera (nan wu wei zi), verapamil
Moderate CYP3A4/5 inducers	Bosentan, dabrafenib, efavirenz, etravirine, genistein, lopinavir5, modafinil, nafcillin, telotristat
Sensitive CYP3A4/5 substrates1	Alpha-dihydroergocryptine, apixaban, aprepitant, atorvastatin, avanafil, bosutinib, brotizolam, budesonide, buspirone, cannabinoids6, cannabidiol6, cobimetinib, darifenacin, dasatininb, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutnib, isavuconazole, ivabradine, ivacaftor, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, perospirone, quetiapine, ridaforolimus, rivaroxaban, sildenafil, simeprevir, , ticagrelor, tilidine, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin
BSEP inhibitors	Alectinib, atorvastatin, bromocriptine, candesartan, clobetasol, clofaziminie, dabigatran, dipyridamole, glyburide, grazoprevir, ledipasvir, mifepristone,pioglitazone, reserpine, rifamycin, simeprevir, telmisartan, timcodar, troglitazone, , velpatasvir

Medications that carry a possible risk for QT prolongation2	Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine , asenapine, atazanavir, atomoxetine, bedaquiline, bendamustine, bortezomib, bosutinib, buprenorphine, cabozantinib, capecitabine, ceritinib, clomipramine, crizotinib, clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, efavirenz, eliglustat, epirubicin, eribulin mesylate, ezogabine (retigabine), famotidine, felbamate, fingolimod, flupentixol, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, ketanserin, lapatinib, lenvatinib, leuprolide, loperamide, lithium, melperone, midostaurin, mifepristone, mirabegron, mirtazapine, moexipril/HCTZ, necitumumab, , nilotinib, norfloxacin, nortriptyline, nusinersen, ofloxacin, olanzapine, osimertinib, oxytocin, paliperidone, palonosetron, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, perphenazine, pilsicainide, pimavanserin, pipamperone, promethazine, prothipendyl, quetiapine, ranolazine rilpivirine, risperidone, romidepsin, sertindole, sorafenib, sunitinib, tamoxifen, telavancin,tetrabenazine, tipiracil/trifluridine, tizanidine, tolterodine, toremifene, trimipramine, tropisetron, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone
MATE1/2 substrates3	Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topotecan, varenicline
OCT1/2 substrates4	Amantadine, , carboplatin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, , oxaliplatin, oxybutynin, phenformin, picoplatin, pilsicainide, pindolol, , ranitidine, sorafenib, tropisetron, trospium, umeclidinium, and zidovudine
BCRP substrates	Daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, sulfasalazine, sofosbuvir, tenofovir, topotecan, venetoclax

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

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

3 MATE1 and MATE2 share considerable substrate specificity.

4 OCT1 and OCT2 share considerable substrate specificity.

5 Lopinavir and atazanavir is prohibited when combined with ritonavir (see Table 14-1)

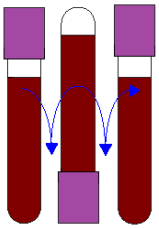
6 Based data that, exposure of cannabidiol (CBD), tetrahydrocannabinol (THC), 11-hydroxy THC, increased by ~2-3 folds when co-administered with ketoconazole (CYP3A4 inhibitor); Stott et al, Springerplus. 2013; 2: 236

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

APPENDIX C: SERUM AND PLASMA BIOSPECIMEN COLLECTION

Samples should be obtained at protocol specified time points, using supplies available onsite. All specimens will be stored onsite. Samples are collected according to the calendar in Section 10.

1. Plasma

Collect	Blood Processing	Store
		
At least 3 ml whole blood in EDTA tube (lavender top)	Gently invert 8 to 10 times to mix the blood. Centrifuge at 2400 rpm for 10 min at 4°C. Carefully aliquot 0.5 ml of plasma to each vial for a total of 3 vials. Total plasma for all 3 vials should amount to 1.5 ml.	Store at -70 Celsius. Ship to Columbia University Medical Center when requested.

1. **Serum (Two)**

Collect	Blood Processing	Store
		
At least 3 ml serum in non-anticoagulant and/or speckled tube (red top)	Gently invert 8 to 10 times to mix the blood. Centrifuge at 2400 rpm for 10 min at 4°C. Carefully aliquot 0.5 ml of serum to each vial for a total of 6 vials. Total serum for all 6 vials should amount to 3 ml.	Store at -70 Celsius. Ship to Columbia University Medical Center when requested.

Refer to Study Calendar (Section 10) for collection time points of serum and plasma.

- For registration scenario # 1, peripheral blood will be collected for proposed and future biomarker evaluations at 5 time points: a) pre-treatment, after completing 1 cycle of treatment (Cycle2a Day1 visit), progression on aromatase inhibitor plus ribociclib, after completing 1 cycle of treatment post-

randomization (Cycle2b Day1 visit), and progression on fulvestrant (or exemestane) +/- ribociclib. One lavender (EDTA) tube and two red top (non-anticoagulant) tubes are recommended for collection.

- For registration scenario # 2, peripheral blood will be collected for proposed and future biomarker evaluations at 3 time points: pre-treatment, after one cycle of treatment (Cycle2 Day1 visit), and at progression on fulvestrant (or exemestane) +/- ribociclib. One lavender (EDTA) tube and two red top (non-anticoagulant) tubes are recommended for collection.

  - Be sure to label tubes with provided labels and note date and time of collection.
  - When requested, ship batched samples along with a copy of this document, as follows:
  - Serum samples should be shipped to:

    Biovica Inc
    6195 Cornerstone Court E, St 101
    San Diego, CA 92121
    ATTN: Laboratory (or Hector Tamburini)
    PHONE: 858-230-6164
    EMAIL: hector.tamburini@biovica.com, Cc: amy.williams@biovica.com

Samples should be shipped frozen with gel packs or dry ice.
Please use overnight shipping and ship packages on a Mon, Tues, or Wed.
E-mail an inventory list with study ID and sample/tube ID's to: hector.tamburini@biovica.com and Cc: amy.williams@biovica.com

  - Please ship all residual samples to:

    Sunil Badve, MD, FRCPath
    Professor and Vice Chair, Pathology Cancer Program
    Department of Pathology and Laboratory Medicine
    Emory University School of Medicine
    1364 Clifton Road NE, Room H184,
    Atlanta, GA 30322
    sbadve@emory.edu
    Phone +1 (404) 712 8579
    Fax +1 (404) 727 3133

Please include with each shipment a sample tracker (see next page). **Prior to shipping the samples**, please reach out to the Biovica email and to Dr. Badve via email to ensure the lab team will be available to receive the shipment when anticipated to arrive. Please refrain from shipping samples towards the weekend, holidays, or days with inclement weather.

SCENARIO #1
Site Number:

Subject ID	Pre-Treatment	C2aD1	Progression on AI or tamoxifen or fulvestrant + ribobiclib	C2bD1	Progression on fulvestrant (or exemestane) <u>+</u> ribociclib	Total # of cryovials	Date Shipped/Coordinator Initials
	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum		
	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum		
	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum		
	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum		

SCENARIO #2
Site Number:

Subject ID	Pre-Treatment	C2D1	Progression on fulvestrant (or exemestane) <u>+</u> ribociclib	Total # of cryovials	Date Shipped/Coordinator Initials
	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum		
	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum		
	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum		
	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum	☐ Plasma ☐ Serum		

APPENDIX D: WHOLE BLOOD FOR CTDNA BIOMARKERS

2. **Whole Blood (Two)**

Collect	Blood Processing	Shipment
		
At least 2 x 8 ml vials of whole blood using the Biocept sample collection tube.	No processing required. Gently invert the tube 5 times.	Ship on same day to Biocept at ambient temperature.

Biocept ctDNA Target-SelectorTm Technology

Biocept has developed a proprietary minimally-invasive blood-based method for the detection of biomarkers (e.g., mutations) from patients with cancer. This ctDNA technology has uniquely high sensitivity and specificity. Recent data show >96% sensitivity and >98% specificity with 93% correlation to tissue (AMP 2015).

When detecting rare mutations associated with cancer, particularly when using circulating tumor DNA (ctDNA) from blood sample, a significant challenge is to be able to detect mutations associated with ctDNA in a vast excess of normal wild-type DNA. To make this possible the Target-SelectorTm technology was developed. This technology is designed to suppress amplification of wild-type targets, while not suppressing amplification of mutation sequences that differ from wild-type by even a single nucleotide variant (SNV). The Target-SelectorTm has been demonstrated to distinguish targets with SNVs by >20oC, which is unprecedented. This large temperature discrimination makes it possible to use amplification temperatures where the wild-type is completely blocked without effecting amplification of mutants. This is accomplished using a very sensitive switch that is embedded in the Selector construct. When the switch is “open”, due to a mismatch, amplification can take place. When the switch is “closed”, due to a perfect complement, amplification is blocked. In addition to highly selective blocking, the Selector also contains fluorescent labels and quenchers that allow the Selector construct to provide a fluorescent read-out in real-time PCR assays. When using real-time PCR, Selector assays are completely quantitative, and give high discrimination of (mutant:wild-type). The Selector can also be used to preferentially amplify sequences of interest prior to sequencing. It has been demonstrated that when Selector is combined with sequencing the detection of rare mutations is increased >20,000 fold.

Sample Collection

Draw sufficient blood and transfer into the required tubes provided in the shipping kit.
USE ONLY THE TUBES PROVIDED. Gently invert the tube 5 times after blood is added.

DO NOT refrigerate or freeze the specimen. Keep at room temperature.

Note: Expiration date is identified on the outside of the kit and on the Biocept's blood collection tube. If the kit is expired, please contact Customer Service. Label the tubes with the date of draw. Include three unique patient identifiers (study number, subject number, site number).

Packaging

Insert tubes into the absorbent sleeve, place sleeve inside the provided biohazard bag and seal. Wrap gel blanket around the bagged tubes, place inside the Styrofoam cooler, and close with lid. Please place your Biocept Study Requisition form on top and close the kit.

Shipping the Sample

Place the kit inside FedEx LabPak and seal. Contact FedEx (800-G0-FEDEX) to schedule a pickup. Please notify Biocept Customer Service with the FedEx tracking number either at CustomerService@biocept.com or 888-332-7729.

APPENDIX E: ARCHIVED TISSUE AND BIOPSY COLLECTION AND SHIPMENT

All formalin-fixed paraffin embedded (FFPE) from archived tumor and study-related biopsies will be stored onsite until requested by the coordinating center. Ideally, all slides will be cut at the same time, within 6 weeks of time of request, and sent to the coordinating center to distribute for analysis at the Columbia University Molecular Pathology Core and Columbia University Genome Center.

Ship to:
Sunil Badve, MD, FRCPath
Professor and Vice Chair, Pathology Cancer Program
Department of Pathology and Laboratory Medicine
Emory University School of Medicine
1364 Clifton Road NE, Room H184,
Atlanta, GA 30322
sbadve@emory.edu
Phone +1 (404) 712 8579
Fax +1 (404) 727 3133

Complete these forms separately for each subject; enclose with shipment along with accompanying pathology report.
The tissue samples will be shipped from each participating site to Dr. Badve's lab at Emory. **Prior to shipping the samples**, please reach out to Dr. Badve via email to ensure the lab team will be available to receive the shipment when anticipated to arrive. Please refrain from shipping samples towards the weekend, holidays or days with inclement weather.

I. Archived Diagnostic Tissue

Subject ID: _____

Archival tissue, diagnostic biopsy ☐ Not available		
Number of slides	Slide preparation	Slide IDs
	☐ 10 immunoblanks [each having 4 micron sections on charged slides] ☐ 1 intervening H&E stained ☐ 12 regular slides each with 10 microns sections	

Enclose redacted accompanying pathology report.

Archival tissue, biopsy at recurrence ☐ Not available/applicable		
Number of slides	Slide preparation	Slide IDs
	☐ 10 immunoblanks [each having 4 micron sections on charged slides] ☐ 1 intervening H&E stained ☐ 12 regular slides each with 10 microns sections	

Enclose redacted accompanying pathology report.

Date	Name of person responsible for this shipment

II. Study-related biopsies

Archived tissue from primary and/or metastatic tissue is required, unless not available.

Optional biopsies for tissue biomarker assessment will be performed in consenting patients prior to starting study drugs, at time of progression on letrozole plus ribociclib (in patients registered under scenario#1), and upon progression on fulvestrant (or exemestane) +/- ribociclib.

- For registration scenario # 1, optional tissue biopsies for biomarker evaluation will be performed at 3 time points: pre-treatment, at time of progression on aromatase inhibitor plus ribociclib, and progression on fulvestrant (or exemestane) +/- ribociclib.
- For registration scenario # 2, optional tissue biopsies for biomarker evaluation will be performed at 2 time points: prior to treatment with fulvestrant (or exemestane) +/- ribociclib and at progression on fulvestrant +/- ribociclib.

Please indicate the time point on the form below.
For patients with accessible tumor, up to 5 core biopsies are recommended.

The following will be requested, if available.

A) 10 immunoblanks [each having 4 micron sections on charged slides], one intervening H&E stained slide, and 12 regular slides each with 10 microns sections: Paraffin-embedded tissue will be requested. Sites will not cut and send to CUMC until requested (see IIA).
B) Fresh Core biopsies to be sent to Dr. Laura Kaufman at Columbia University for organoid system assessment (NY sites, if possible for pickup) OR Dr. Carlos Artega at UT-Southwestern.
C) Fresh Core biopsies to be sent to Champions Oncology for patient-derived xenograft testing and implantation

The tissue samples will be shipped from each participating site to Dr. Badve's lab at Emory, using the address below. Please include with the shipment a sample tracker (see next page) as well as the corresponding de-identified pathology report. **Prior to shipping the samples**, please reach out to Dr. Badve via email to ensure the lab team will be available to receive the shipment when anticipated to arrive. Please refrain from shipping samples towards the weekend, holidays or days with inclement weather. Following review and processing by Dr. Badve, some of the samples will be shipped to an external lab – BostonGene, for further analysis.

Sunil Badve, MD, FRCPath

Professor and Vice Chair, Pathology Cancer Program
Department of Pathology and Laboratory Medicine
Emory University School of Medicine
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Atlanta, GA 30322
sbadve@emory.edu
Phone +1 (404) 712 8579
Fax +1 (404) 727 3133

IIA. Paraffin Embedded Tissue

Paraffin-embedded tissue will be requested. Sites will not cut and send to CUMC until requested
Subject ID: _____

FFPE tissue, Pre-treatment biopsy ☐ Core biopsies			
Number of slides	Slide preparation	Date Collected	Slide IDs
	☐ 10 immunoblanks [each having 4 micron sections on charged slides] ☐ 1 intervening H&E stained ☐ 12 regular slides each with 10 microns sections		

Enclose redacted accompanying pathology report (if available).

FFPE tissue, Biopsy after progression ☐ POD on ribociclib/AI or tamoxifen or fulvestrant ☐ POD on fulvestrant (or exemestane) +/- ribociclib ☐ Core biopsies			
Number of slides	Slide preparation	Date Collected	Slide IDs
	☐ 10 immunoblanks [each having 4 micron sections on charged slides] ☐ 1 intervening H&E stained ☐ 12 regular slides each with 10 microns sections		

Enclose redacted accompanying pathology report (if available).

Date	Name of person responsible for this shipment

IIB. Fresh Core Biopsies for Organoid Assessment

A. NY Sites, if possible for pickup (Kaufman Lab)

Fresh core biopsies should be obtained and placed immediately into cryogenic tubes containing freezing media. Samples can be frozen at -80 and shipped to Dr. Kaufman in batches **overnight – or picked up by her lab members.**

1. Prepare cryogenic tubes with 1 mL BAMBANKER freezing media
2. Tubes should be labeled per study protocol
3. Obtain fresh core biopsies (2 cores)
4. Place 1 core each into 1 cryogenic tube containing 1 mL of BAMBANKER freezing media
5. Store tubes at -80 until they are ready to be shipped.
6. Samples should be shipped OVERNIGHT on dry ice to:

Dr. Laura Kafuman
Columbia University
Department of Chemistry
6th Floor, Havemeyer Hall
New York, NY 10027

B. Other sites (Arteaga Lab)

1 Collect fresh core biopsies (2 cores)

2. Tubes should be labeled per study protocol
3. Ship sample in small Ship sample in small container or 50ml tube completely filled with DMEM + 20% FBS on ice pack (at 4 degree and Avoid freezing)
4. Samples should be shipped SAME DAY or OVERNIGHT on ice pack (not dry ice) to:

Saurabh Mendiratta/Kyung-min Lee
6001 Harry Hines Blvd. NB5.112
(Simmons Comprehensive Cancer Center)
UT Southwestern Medical Center Dallas, TX- 75390-8807
Phone : 214-648-6167

FFPE tissue, Pre-treatment biopsy

☐ Core biopsies (preferred 2)

Number tubes	Date Collected	Slide IDs (if applicable)

Enclose redacted accompanying pathology report (if available).

Number tubes	Date Collected	Slide IDs (if applicable)

Enclose redacted accompanying pathology report (if available).

Date	Name of person responsible for this shipment

IIB. Fresh Core Biopsies for Patient-Derived Xenograft Evaluation

TUMORGRAFT (PDX) PROCESS

Fresh tissue is collected from patients through surgical resection or biopsy; in order to maximize the success of tumor engraftment, the preferred tissue requirements are 0.5 cm^3 or three to four 18 gauge needle cores, respectively. However, models can be generated from smaller volumes of tissue.

Specimens will be placed into 1 50-ml vial containing transport medium that will be provided by Champions and labeled with a unique trial number identifier. Tubes containing the tissue specimen will be packaged in an insulated container with a coolant block. Transportation of the specimen to the designated implantation site will be arranged in advance with Champions Clinical Operations team. Ideally, the time from tumor extraction to placement in media should be as soon as possible but less than 30 minutes. Exact times will be recorded. The site will be trained by Champions on the exact steps for tissue collection.

Upon receipt of the tumor specimen at the designated implantation site, tumor tissue is macroscopically dissected and implanted, under anesthesia, into immune-deficient mice within the flanks and/or mammary fat pad following Champions standard operating procedures (SOPs). Champions operates under approved IACUC protocols. Fresh tumor tissue is implanted into up to 5 mice (dependent upon amount of tissue received) and monitored for growth for up to 6 months. If no growth is observed models are discontinued. If a tumor grows and is palpable they are monitored until tumors reach approximately 1000 -1500 mm3 (a process known as “engraftment”), they are harvested, fragmented and re-implanted into additional mice (a process known as “expansion”). Histology is confirmed for all models developed.

The ability to establish a viable PDX model and the time it takes is dependent on a number of factors including amount and viability of tissue, tumor type, and time to implantation. The average time to establish a model also varies depending on amount of tissue and tumor type.

Once the PDX model is established the tissue can be “banked” as a live model for future use or used immediately for drug sensitivity testing. For this purpose, randomized cohorts of mice undergo treatment with drugs or drug combinations selected depending on the research hypothesis. Drug activity in the model is reported as tumor growth inhibition (% TGI) relative to the control (untreated) group of mice and in terms of a modified RECIST criteria response. Every PDX model is cyro-preserved as a living sample and can be retested at any time in the future for translational research purposes.

ASSESSMENT OF RESPONSE IN THE TUMORGRAFT

Agent Efficacy: All test agents will be formulated according to manufacturer’s specifications for testing in a mouse model. Cohorts of 3-4 mice will be randomized into treatment groups. Drug sensitivity testing will last for a total of 28 days. Beginning Day 0, tumor dimensions will measured twice weekly by digital caliper and data, including individual and mean estimated tumor volumes (Mean TV ± SEM), are recorded for each group. Tumor volume was calculated using the formula: $TV= width^2 \times length \times \pi/2$.

Tumor Growth Inhibition: At study completion, percent tumor growth inhibition (%TGI) values will be calculated and reported for each treatment group (T) versus control (C) using initial (i) and final (f) tumor measurements by the formula: $\%TGI=[1-(T_f-T_i)/(C_f-C_i)] \times 100$.

RECIST: Individual mice reporting a tumor volume >120% of the Day 0 measurement are considered to have progressive disease (PD). Individual mice with neither sufficient shrinkage nor sufficient tumor volume increases are considered to have stable disease (SD). Individual mice reporting a tumor volume ≤70% of the Day 0 measurement for two consecutive measurements over a seven day period are considered partial responders (PR). If the PR persisted until study completion, percent tumor regression (%TR) is determined using the formula: $\%TR = (1-T_f/T_i) \times 100$; a mean value is calculated for the entire treatment group. Individual mice lacking palpable tumors for two consecutive measurements over a seven day period are classified as complete responders (CR). All data collected in this study will be managed electronically and stored on a redundant server system.

FFPE tissue, Pre-treatment biopsy

☐ Core biopsies (preferred 2)

Number tubes	Date Collected	Slide IDs (if applicable)

Enclose redacted accompanying pathology report (if available).

Number tubes	Date Collected	Slide IDs (if applicable)

Enclose redacted accompanying pathology report (if available).

Date	Name of person responsible for this shipment

APPENDIX F: GUIDELEINES FOR AFFILIATE INSTITUTIONS IN MULTICENTER STUDIES

1. Multi-site Communication:

The CPDM office at CUMC provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CPDM office will coordinate regularly scheduled conference calls with affiliate sites.
The following issues will be discussed as appropriate:

- Enrollment information
- Cohort updates (i.e. DLTs)
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

2. New Protocol Distribution, IRB Submission, Modifications and Annual Renewals

- Protocol specific documents are distributed to affiliate sites once CUMC IRB approval has been obtained.
- The affiliate site must submit a draft of site specific revisions to protocol and/or consent form documents for review and approval by the sponsor-investigator prior to submission to the local IRB. Draft documents should be sent to the study specific email address. The site will be provided confirmation that they are approved to submit to their local IRB.
- Protocol amendments must be approved by the affiliate site's local IRB within 90 days of distribution to the site by the sponsor-investigator.

3. Regulatory Documents:

3.1 Prior to Site Initiation:
Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected prior to the initiation of an affiliate site.

- CV of PI, Sub-I's and other research staff listed on FDA 1572 (signed and dated copy within 2 years)
- Medical Licenses of PI and Sub-I's (current copy)
- Human subjects training certificates for PI and Sub-I's
- CLIA/Laboratory Certifications for Local Laboratories listed on FDA 1572
- Local Laboratory Director's CV and License
- Local Laboratory Reference Ranges
- IRB roster or statement of compliance
- FDA Form 1572, if applicable (wet ink originals required)
- Financial Disclosure forms for all members listed on FDA 1572 (wet ink originals required)

3.2 Ongoing Regulatory Documentation: Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected throughout the course of the study.

- IRB approval letters for all protocol modifications and all renewals
- IRB-approved consent forms
- Current IRB roster, if statement of compliance is not provided as part of site initiation
- FDA Form 1572, if applicable as updates are required
- Updated investigator and site information where relevant (e.g., CV, medical licensure and Financial Disclosure for new sub-investigator, local laboratory information)

Regulatory documents may be sent to p9506@lists.cumc.columbia.edu or to the following address if wet ink originals are required:

Clinical Protocol & Data Management Office
161 Fort Washington Ave.
Herbert Irving Pavilion
Mezzanine Level, M-203
New York, NY 10032

1. **Central Registration Procedures- **Affiliate Institution Research Participant Registration Process**:**

All Affiliate Institutions must register subjects with the coordinating center (CUMC) prior to any administration of study drug/intervention/local institution registration. Please see instructions below:

1.1 Within 48 hours of obtaining consent (excluding holidays and weekends), the Affiliate Institution CRN and/or CRC is required to submit the following documents to the coordinating center's designee (CUMC's study specific Clinical Research Coordinator or Clinical Research Nurse). The coordinating center's designee will review the documents for accurateness, and subsequently submit the documents to the CPDM Central Registration Office via email at p9506@lists.cumc.columbia.edu, with a request to register the patient "pending eligibility." The title of the email should read, "AAAP9506 Pending Subject Registration Request (PHI)". The following documents should be submitted with the pending registration request:

- Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (i.e. tissue, DNA, etc.) as applicable
- Redacted Signed HIPAA (or institutional equivalent)
- MCT CPDM Demographics Note to File form

1.2 The Affiliate Institution's investigator/research nurse/data manager/coordinator must contact the coordinating center's designee (CUMC's study specific Clinical Research Coordinator or Clinical Research Nurse) via telephone or email to communicate the following:

- Notify of pending registration request
- Confirm method of registration request submission (email or fax)
- Communicate expected time-line of registration request submission (i.e., same day, next day, within the hour, etc.)

1.3 To complete registration, the Affiliate Institution's investigator/research nurse/data manager/coordinator should then submit the following documents to the CUMC study specific designee:

- A signed Affiliate Site Eligibility Checklist (signed by the investigator)
- Copies of redacted source documentation necessary for each item to be verified on the CUMC specific Eligibility Checklist, including but not limited to:
    - Copy of required laboratory test and procedure reports (i.e., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
    - Copy of pathology and surgical reports
    - Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms. (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

Please note: subject line of email or fax should include the following: "AAAP9506 Complete Subject Registration Request (PHI)".

1.4 Upon receipt of the above mentioned documents, the designated study specific Clinical Research Coordinator will review all documents and verify patient eligibility. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable affiliate site study team personnel for clarification prior to enrollment. Upon verification, the CUMC study specific designee will then forward all documents to the CPDM Central Registration Office for central registration (as described above). The CPDM Central Registration Registrar will review all applicable documents and communicate to the CUMC study specific designee in order to clarify any items. The CUMC study specific designee will communicate with the applicable site study team personnel for additional clarifications necessary prior to enrollment.

1.5 Upon receipt of the subject registration notification email, the CUMC study specific designee will forward the notification email (which will include the study specific patient ID) to the affiliate site's Principal Investigator, Consenting Professional, and applicable research personnel. This notification should be filed in the patient research binder accordingly. Protocol therapy **may not** be initiated prior to receipt of this notification from the coordinating center.

1.6 All screenfail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

2. Protocol Deviation/Subject Waiver request for Affiliate Sites:

The Affiliate site MUST submit a prospective deviation request to the CUMC lead PI for review and submission to the HICCC DSMC and CUMC IRB. Approvals must be obtained from all entities prior to implementation at the Affiliate site. If a prospective protocol deviation request is submitted for review (from an Affiliate site), the PI/site memo(s), HICCC DSMC approval(s) and correspondence and CUMC IRB deviation approval letter(s)/correspondence should be forwarded to the Affiliate site for documentation. The Affiliate site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation. All documents and determinations must be clearly documented in the study subject's medical record, research chart and regulatory binder, as described. Please note that the HICCC DSMC will no longer be approving deviations to eligibility criteria.

3. Guidelines for Affiliate Site Monitoring

3.1 On-Site MCT Monitoring:

1. Initial, recurrent, and close-out on-site monitoring visits will also be conducted at Affiliate sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
    - The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

2. The Compliance Coordinator will communicate with the Affiliate site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

3. The Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled at the Affiliate site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable

SOPs. The Compliance Coordinator is responsible to notify the participating site PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to Coordinating Center, local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

4. An SIV (or) teleconference will be scheduled and conducted prior to study drug being made available (if applicable) and before any subjects are enrolled on a study at the Affiliate site.

3.2 MCT Remote Monitoring:

1. When necessary (due to logistical constraints), Affiliate sites will be monitored remotely by a designated Compliance Coordinator. Sites will be informed of this remote monitoring process on a site by site basis.

2. Affiliate sites will be monitored by the Compliance Coordinator on both a regulatory level, as well as a clinical data/source documentation review level.

3. Redacted source documents (applicable to supporting the protocol specific CRF data requirements) will be sent to the designated Compliance Coordinator via fax or secure email for all subjects enrolled at Affiliate sites. Timelines for submission procedures will be defined on a case-by-case basis.

4. The Compliance Coordinator will review all submitted redacted source documents against the data entered on the protocol specific CRFs. The Compliance Coordinator will issue queries when/if necessary.

5. The Affiliate site research staff will respond to queries within 30 days. If queries remain outstanding, the Compliance Coordinator will send a delinquent query reminder for the outstanding items.

6. The remote monitoring procedures will include review of applicable redacted source documentation and supporting applicable documents to determine compliance regarding:
    - Informed consent procedures
    - Eligibility criteria
    - Protocol specific treatment compliance
    - Protocol specific toxicity/outcome documentation/compliance
    - Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up)
    - Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, INDSR submissions, etc).
    - Required specimen submissions (e.g., tissue specimens, research blood specimens, etc.)
    - Pharmacy accountability records
    - Adherence to the CRF submission timeframes to CUMC (within the protocol specified timeframes)

7. Affiliate site remote monitoring reports will be sent to the lead PI, HICCC DSMC, and Affiliate sites

after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query resolution status, regulatory status, and overall Affiliate site performance. These reports will be generated by the Compliance Coordinator and reviewed with the Compliance Core Manager prior to dissemination.

4. Confidentiality

Each affiliate site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g. 04-10). All sites will be required to enter their data in the Velos eResearch, the Clinical Trial Management System used for all Cancer-related clinical research at CUMC. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials.

Subject confidentiality must be maintained according to HIPAA regulations and GCP recommendations.

Except when required by law, study information shared with persons and organizations outside of Columbia University Medical Center must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier.
If the results of this research project are published or presented at a scientific or medical meeting, the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

Data Reporting Plan
Columbia University Medical Center (CUMC) is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, CUMC encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

CUMC's policies that pertain to patient data sharing conform to CUMC IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, Statistician, Data Safety and Monitoring Board (DSMC), and, in other instances, the CUMC IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the CUMC's guidelines for Protecting the Rights and Privacy of Human Subjects.

Data Acquisition and Submission
Informed consent, including HIPPA authorization, must be obtained on all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. Velos eResearch will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into Velos eResearch via customized case report forms for the study. The research staff will generate reports from Velos eResearch to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.

APPENDIX G: DRUG ORDER FORM

Novartis Pharmaceuticals – Medical Affairs Oncology

Ribociclib (LEE011)
DRUG REQUEST FORM

Please Email Request to: **john.sabo@novartis.com**

Date: _____

Study Title: **A randomized phase II trial of fulvestrant with or without Ribociclib after progression on aromatase inhibition plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER2 negative breast cancer**

Investigator's Name: _____

Novartis Protocol Number: **CLEE011XUS18T**

Requestor's Name: _____

Requestor's Phone#: _____

Institution: _____

Shipping Address: _____

_____

_____

Shipping Phone#: _____

Is this Initial Shipment:
Yes ☐ **No** ☒

Date by when this shipment is required: _____

Drug	Label Strength	Number of Bottles Needed
PLACEBO LEE011/Ribociclib (blinded)	0mg (28 capsules per bottle)	
LEE011/Ribociclib (blinded)	200mg (28 capsules per bottle)	
LEE011/Ribociclib (open label)	200mg (28 capsules per bottle)	
Femara (Letrozole)	2.5mg (30 tablets per bottle)	

If you require assistance please contact John Sabo at 862-778-2982
Note: Please allow 10 days for processing of this request and delivery of the shipment.

APPENDIX H: SKIN COLOR PHOTOGRAPHY

In the case of patients with discrete skin lesions, one to three target lesions > 10 mm in size should be followed. Every 12 weeks (+/- 1 week), target lesion size should be documented using high quality color photography, placing a ruler next to the target lesion to accurately document size. If there are multiple target lesions, separate photographs for each lesion should be performed. Documentation should be submitted in the case report form.

In patients with diffuse or patchy skin involvement (i.e. dermal involvement), the extent of involvement should be clearly demonstrated in photographs. Photographs should be taken from a consistent distance and angle from the patient.

1. Chia S, Gradishar W, Mauriac L, et al: Double-Blind, Randomized Placebo Controlled Trial of Fulvestrant Compared With Exemestane After Prior Nonsteroidal Aromatase Inhibitor Therapy in Postmenopausal Women With Hormone Receptor–Positive, Advanced Breast Cancer: Results From EFECT. Journal of Clinical Oncology 26:1664-1670, 2008