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COMPREHENSIVE CANCER CENTER

# evaLuation of variations pharmacokinEtics and phArmacogeNOmics of Ribociclib in rAce-based Cohorts: The LEANORA study

Georgetown Protocol #: STUDY00003100
Clinicaltrials.gov #: NCT04657679

**Protocol Version Date :** Version 3.6, 9/28/2023


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| **Funding Sources:** | Breast Cancer Research Foundation (BCRF) |
| **Study Drug:** | Ribociclib |
| **Clinical Phase:** | Phase IV |
| **Number of Patients:** | 36 |

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements including but not limited to Institutional Review Board/Ethics Committee (IRB/EC) approval.

INVESTIGATOR SIGNATURE PAGE

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

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Sandra Swain, MD Date
Georgetown University Medical Center

DOCUMENT HISTORY

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| Original Protocol (Version 1.0) | October 13, 2020 | Not applicable (N/A) |
| Original Protocol (Version 2.0) | December 7, 2020 | Clarified inclusion criteria about brain metastases, permitted not required for participation in the study. Clarified details about the study schedule. Added an adverse event monitoring form. Clarified inclusion criteria about required labs at screening. Corrected minor grammatical errors. |
| Original Protocol (Version 3.0) | January 4, 2021 | Updated investigator list – added Nanette Bishopric, removed Ian Chang<br>Added NCT # |
| Protocol Version 3.1 | June 3, 2021 | • Updated protocol to include Medstar Franklin Square Medical Center as an additional site.<br>• Added previously IRB approved clarification to inclusion criteria noting communication through an interpreter is acceptable.<br>• Added clarification to inclusion criteria for CYP3A5 metabolizers “at least 3 participants” and “No more than 15”<br>• Modified inclusion criteria minimum value for hemoglobin to allow for 8g/dl given that the FDA does not require a dose adjustment for this level. Dose adjustments are still in place for GRADE 3 events (hemoglobin < 8 g/dL) or higher, which occurred in ≤4% of patients in all trials referenced in the FDA label.<br>• Added clarification to exclusion criteria about concurrently using other anti-cancer therapy “besides those in the study protocol”; testing for hepatitis B, hepatitis C, and HIV is not required for enrollment but if results are available then the exclusion criteria may be assessed.<br>• Added clarification to the definition of uncontrolled HIV<br>• Added clarification on SAE reporting.<br>• Table 14.4 and 14.5 added note “*List applies to formulations of medications that are absorbed systemically” |

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| Protocol Version 3.2 | October 11, 2021 | • Modified language to allow gonadotropin releasing hormone agonist as a class. Previously a specific agent, goserelin, was listed. NCCN guidelines list goserelin and leuprolide as the only available agents in the US for ovarian suppression.<br>• Added clarification on enrollment procedures in the event the Georgetown Project manager is not available to confirm eligibility.<br>• Added additional site Tufts Medical Center<br>• Modified the PI for MWHC and the Georgetown Network |
| Protocol Version 3.3 | November 10, 2021 | • Clarified inclusion criteria to indicate lab values for Sodium, Potassium, Calcium, or Magnesium must have values within normal limits **or are not clinically significant per the Investigator**.<br>• Clarified exclusion criteria by merging 2 related exclusion criteria into one criteria to state: Patient is concurrently using other anti-cancer therapy besides those in the study protocol (e.g., letrozole, fulvestrant, goserelin, leuprolide). Any other prior neo-/adjuvant anti-cancer therapy must be stopped at least 5 half-lives or 7 days, whichever is longer, before the date of ribociclib initiation.<br>• Clarified exclusion criteria for concurrent malignancy to state: Patients may still enroll with a concurrent malignancy after receiving approval from the study PI.<br>• Removed “with a systolic blood pressure >160” from Uncontrolled hypertension definition in the exclusion criteria |
| Protocol Version 3.4 | January 6, 2022 | • Updated Co-Principal Investigator for Georgetown to Nadia Ashai, MD<br>• Removed Dr. Rao and Added Dr. Liu to Medstar Franklin Square Hospital<br>• Section 4.3.7 clarification added “If sample size requirements (sections 3.3 and 9.1; at least 3 participants in AA or Black cohort who are CYP3A5 poor metabolizers; at least 3 participants in the NHW cohort who are CYP3A5 intermediate or normal metabolizers) are met, then CYP3A5 |

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| | | phenotype screening may be bypassed per Principal Investigator discretion."<br>• Table 14 footnote clarification added "CYP3A5 Screening may be bypassed per Principal Investigator discretion if the necessary number of participants with each phenotype are enrolled (cohort of AA or Black participants - at least 3 poor metabolizers; cohort of NHW participants - at least 3 intermediate or normal metabolizers). If CYP3A5 is already performed it does not need to be repeated within the window of < 28 days."<br>• Clarified Inclusion criteria that consent must be obtain prior to any screening procedures that are not standard of care.<br>• Removed upper limit of mean resting heart rate (90 bpm) from Inclusion criteria. The eligibility criterion of a heart rate between 50-90 bpm was derived from the early MONALEESA studies as that is what they used. The recent COMPLEEMENT-1 trial has removed the upper limit on the heart rate in their eligibility criteria and only screen for bradycardia (< 50 bpm). Tachycardia is not listed in the FDA label as an adverse reaction, a warning, or a precaution.<br>• Clarified the grammar in section 5.6.2. |
| Protocol Version 3.5 | January 30, 2023 | • Clarified that leukopenia is not a secondary endpoint and that the last few endpoints (i.e., 2.4.4 through 2.47) are exploratory endpoint. Not secondary endpoints. See sections 2.4 and 2.5. |
| Protocol Version 3.6 | September 28, 2023 | • Clarifying title of Table 12 by adding "that are deemed related and clinically significant by the treating physician" to the title |

# Table of Contents

# Glossary of Abbreviations and Terms

Table 1. Abbreviations and Terms

| | |
|---|---|
| AA | African American |
| AE | Adverse event |
| AI | Aromatase inhibitors |
| ALT | Alanine transaminase |
| ANC | Absolute neutrophil count |
| AST | Aspartate transaminase |
| AUC | Area under the curve |
| CABG | Coronary artery bypass graft |
| CBC | Complete blood count |
| CDK | Cyclin-dependent kinases |
| CMP | Comprehensive metabolic panel |
| CRF | Case report form |
| CYP450 | Cytochrome P450 |
| DLT | Dose-limiting toxicity |
| ECOG | European Cooperative Oncology Group |
| eGFR | Estimated glomerular filtration rate |
| EKG | Electrocardiogram |
| ER | Estrogen receptor |
| ET | Endocrine therapy |
| FDA | Food and Drug Administration |
| GCSF | Granulocyte Colony-Stimulating Factor |
| GI | Gastrointestinal |
| HER2 | Human epidermal growth factor receptor 2 |
| HR | Hormone receptor |
| ICF | Informed consent form |
| LVEF | Left Ventricular Ejection Fraction |
| MI | Myocardial infarction |
| NHW | Non-Hispanic White |
| NIH | National Institutes of Health |
| ORR | Overall response rate |
| OS | Overall survival |
| PFS | Progression-free survival |
| PGx | Pharmacogenomics |
| PK | Pharmacokinetics |
| PR | Partial response |

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|---|---|
| AA | African American |
| PR | Progesterone receptor |
| PS | Performance status |
| Rb | Retinoblastoma |
| SBP | Systolic blood pressure |
| SD | Stable disease |
| SERD | Selective estrogen receptor |
| TdP | Torsades de Pointe |
| ULN | Upper limit of normal |

# Study Synopsis

Table 2. Study Synopsis

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| Title | evaLuation of variations pharmacokinEtics and phArmacogeNOmics of Ribociclib in rAce-based Cohorts: The LEANORA study |
| Short Title | Effect Racial Disparities in the Metabolism of Ribociclib |
| Protocol Number | STUDY00003100 |
| Clinicaltrials.gov number: | NCT04657679 |
| Phase | Phase IV |
| Agents | Ribociclib<br>Fulvestrant<br>Letrozole<br>Goserelin or Leuprolide |
| Indication | Advanced HR+/HER2- breast cancer |
| Study Overview | Ribociclib is an inhibitor of the cyclin-dependent kinases 4 and 6 (CKD4/6) and is approved in combination with endocrine therapy for patients with advanced hormone receptor (HR) positive metastatic breast cancer (mBC). CYP3A inhibitors increase ribociclib area-under-the-curve (AUC) by 3.2-fold; this is of clinical concern given possible associations between exposure and toxicity (e.g., QTc prolongation and neutropenia). Although there is an FDA recommendation to modify therapy for patients prescribed CYP3A inhibitors, it is unknown if modifications are needed in patients who intrinsically lack enzyme activity (e.g., genetic CYP3A5 poor metabolizers).<br><br>CYP3A function is largely derived from CYP3A4 and CYP3A5 isozymes in adults. It is difficult to differentiate relative contributions of CYP3A4 and CYP3A5 on CYP3A function due to sequence homology (~ 84%) and overlapping substrate specificity. Genetic variations in *CYP3A5* can translate into poor, intermediate, or normal CYP3A5 metabolism of different substrates. The association between *CYP3A5* genotype and drug concentrations has previously informed therapy for other drugs. Dosing recommendations based on *CYP3A5* genotype tacrolimus are published by the Clinical Pharmacogenetics Implementation Consortium (CPIC). It is unknown if a similar relationship could be present for *CYP3A5* and ribociclib. We hypothesize that patients prescribed ribociclib with CYP3A5 poor metabolism experience increased exposure to ribociclib and likely more toxicities.<br><br>Race is likely to be a significant factor when exploring ribociclib pharmacokinetics and the role of CYP3A. There are known race-based differences in CYP3A4 and CYP3A5, with CYP3A4 dominant in Non-Hispanic Whites and CYP3A5 dominant in African American/Blacks. Ribociclib pharmacokinetics have not been adequately studied in African |

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| | Americans/Blacks as only 3% of participants in the pivotal trials ribociclib were African American/Blacks. We aim to determine the pharmacological and biochemical association between ribociclib exposure and *CYP3A* variants in African American/Blacks and Non-Hispanic White patients. Our findings should allow clinicians to tailor treatments to maintain therapeutic doses while limiting toxicities. |
| Study Duration | 24-36 months |
| Study Center(s) | MedStar Georgetown University Hospital, Lombardi Comprehensive Cancer Center, Washington, DC<br>MedStar Washington Hospital Center, Washington, DC<br>MedStar, Franklin Square Medical Center, Baltimore, MD<br>Tufts Medical Center, Boston, MA |
| Objectives | **Primary**<br>To compare the pharmacokinetics of ribociclib at steady-state between CYP3A5 poor metabolizers and CYP3A5 intermediate or normal metabolizers in each independent race-based cohort of women with advance breast cancer.<br><br>**Secondary**<br>1. Evaluate toxicity profiles (e.g., QTc prolongation, leukopenia) between each race-based cohort<br>2. Characterize ribociclib pharmacokinetics in African American/Black and the Non-Hispanic White patient cohorts.<br>3. Conduct an exploratory candidate gene analysis of other genes with a biologically plausible role in ribociclib pharmacokinetics or therapeutic response |
| Number of Patients | 36 patients |
| Diagnosis and Main Inclusion and Exclusion Criteria | **Key Inclusion Criteria**<br>1) Histologically or cytologically proven diagnosis of HR+/HER2- breast cancer with evidence of metastatic or locally advanced disease, not amenable to curative treatment by surgery or radiotherapy<br>2) Women age ≥ 18 years<br>3) Self identify as Black, African American, or non-Hispanic White<br>4) Signed informed consent form<br>5) Adequate hepatic, hematologic, and renal function as defined below in the body of the protocol<br>6) Normal baseline QTc (<450 ms)<br>7) Asymptomatic and treated brain metastases are permitted<br><br>**Key Exclusion Criteria**<br>1) Patient on active treatment with CDK4/6 inhibitors<br>2) Any other prior neo-/adjuvant anti-cancer therapy must be stopped at least 5 half-lives or 7 days, whichever is longer, before the date of ribociclib initiation.<br>3) Patient is concurrently using other anti-cancer therapy (including systemic therapy or radiation) |

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| | 4) Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drug<br>5) Patient has clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality, as defined below in the body of the protocol<br>6) Patient is currently receiving any of the following substances and cannot be discontinued 7 days prior to Cycle 1 Day 1: strong inducers or inhibitors of CYP3A4/5 -including herbal medications-, chronic dosing of corticosteroids and medications that prolong the QTc interval<br>7) Patient with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's judgment.<br>8) Patient has received extended-field radiotherapy ≤ 4 weeks or limited field radiotherapy ≤ 2 weeks prior to ribociclib initiation and has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).<br>9) Patients with central nervous system (CNS) involvement unless they meet specific stability criteria<br>10) Liver or allogeneic bone marrow transplant |
| Study Design | This prospective, multicenter, cohort study will assess ribociclib (600 mg PO daily) pharmacokinetics and pharmacogenomics in female patients with HR+/HER2- metastatic breast cancer. This design will be used for two independent, race-based cohorts: 18 African American/Black patients and 18 Non-Hispanic White patients. Women are eligible if they are older than 18, have HR+/HER2- mBC and are candidates for treatment with a CDK 4/6 inhibitor and endocrine therapy. Patients are ineligible if currently prescribed a medication that inhibits or induces the CYP3A isoenzymes, have baseline electrocardiogram abnormalities, or are otherwise considered to be ineligible for ribociclib. Participants will provide serial blood samples during the first cycle. Plasma samples will be analyzed via mass spectrometry to characterize the pharmacokinetics (e.g., $AUC_{0\text{-}24}$, $C_{max}$). Pharmacogenetic testing will be performed using the PharmacoScan™ microarray, which tests 4,627 markers in 1,191 genes, including variants in *CYP3A4* and *CYP3A5*.<br>The primary outcome is powered to detect a minimum clinically meaningful change, a 2-fold change in AUC, which is less than the 3.2-fold change seen in the mentioned CYP3A drug interaction pharmacokinetic study. Based on *CYP3A5* allelic frequencies, a sample size of 36 will provide 80% power to independently test the primary outcome in the two race-based cohorts. |
| Multi-Institutional Trial Management | **Personnel**<br>At each site, personnel dedicated to this protocol will be:<br>- A study PI<br>- A research coordinator<br>- A data manager |

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| | **Patient Enrollment**<br>If a patient is being screened for enrollment, the local research coordinator must send an email within 24 hours containing the patient's name to the local Principal Investigator (PI), and to the multicenter project managers. If a patient is successfully screened, the local research coordinator must send all supporting documentation to the Principal Investigator and multicenter project managers. Patients should not start therapy until the Principal Investigator, or the local PI and the multicenter project managers have reviewed the patient's records and confirmed that the patient is indeed eligible for enrollment.<br><br>**Data Collection and Management**<br>Patient data will be entered into the on-line accessible database. This database is housed at Lombardi-Georgetown but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an on-line training session so that they may learn how to enroll data into the database. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within 10 business days of each patient visit.<br><br>**Conference Calls**<br>The Chairs of the study along with investigators when available and research staff will review the accrual, toxicities, and other protocol issues at weekly protocol meetings and on monthly network disease group teleconferences. |
| Duration of therapy | Study will evaluate patients during the first cycle of ribociclib and endocrine therapy and on day 28 prior to the second cycle of treatment to evaluate toxicities. The protocol portion of the study will be done at this point and drug treatment will be continued as determined by the treating physician per standard of care. |
| Statistical Design, Feasibility, and Trial Duration | This study will be performed at MWHC and LCCC as a part of our combined Breast Cancer Research Group. This group has a joint IRB and extensive experience collaborating in clinical trials. Each institution sees 300-400 new patients diagnosed with breast cancer each year. MWHC serves a large number of minority and underserved patient groups, including 62% African American/Black patients. A previous study in patients with breast cancer (INSPIRE) conducted at MedStar Washington Hospital Center (MWHC) enrolled 75% of all patients approached (1). Thus, 48 patients would need to be screened to enroll 36 patients. Over the past 12 months, 47 patients were treated with CDK4/6 inhibitors in these institutions.<br><br>The funding for this work has already been obtained. Dr. Swain's award from the Breast Cancer Research Foundation will be used for this study. The National Cancer Institute) has agreed to provide for pharmacogenetic testing, pharmacokinetic analyses, perform the PharmacoScan™ microarray and provide some statistical support . |

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| | Lastly, commercially available ribociclib in combination with endocrine therapy is standard of care and will be prescribed by participants' primary oncologist. |

# 1. Background and Justification

## 1.1 Background

Breast cancer is the most common type of cancer and the second leading cause of cancer-related death in women in the United States (2). Five breast cancer subtypes have been identified by receptor and genetic expression; these have a significant impact on prognosis and treatment (3). The hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER2) negative or luminal A subtype accounts for 60-70% of all breast cancer cases (3, 4). These cancers have a generally good prognosis and respond well to endocrine therapy (ET). However, one-third of the patients have disease recurrence, often years after the initial presentation (5).

ET remains the backbone of treatment of HR+/HER2- breast cancer; the estrogen receptor modulator tamoxifen is often utilized in premenopausal women – in combination with ovarian suppression with gonadotropin-releasing hormone analogs, such as goserelin or leuprolide in the metastatic setting. Aromatase inhibitors (AI), such as anastrozole, letrozole, and exemestane, are used for postmenopausal women (6, 7). Fulvestrant is a selective estrogen receptor degrader (SERD) approved for HR+/HER2- breast cancer in postmenopausal women (8). These antiestrogen therapies function on susceptible cell populations on the G1 phase of the cell cycle; while the G1/S transition is under the control of cyclin-dependent kinases (CDK) activated by specific complex formation with regulatory cyclins (9).

The CDK 4/6-p16-retinoblastoma (Rb) pathway plays a key role in cell division and proliferation in breast cancer; CDK 4/6 inhibition is a novel therapeutic target that may delay the development of endocrine resistance (10-12). The CDK 4/6 inhibitors ribociclib, palbociclib, and abemaciclib have been approved for HR+/HER2- metastatic breast cancer. CDK4/6 inhibitors have shown improvement in progression-free survival (PFS) and recently ribociclib was also associated to improvement in overall survival (OS) (11).

## 1.2 Ribociclib

Ribociclib is a highly selective orally bioavailable small molecule inhibitor of CDK 4 and 6. Ribociclib has been explored for different tumor types, including breast cancer, melanoma, and neuroblastoma. Ribociclib is metabolized by CYP3A (12). The compound inhibits cell proliferation by preventing progression of the cell cycle from G1 into the S phase (9). Ribociclib (Kisqali®) was approved in 2017 by the United States Food and Drug Administration (FDA) as a treatment of HR+/HER2- locally advanced and metastatic breast cancer in combination with ET (12).

### 1.2.1 Preclinical data

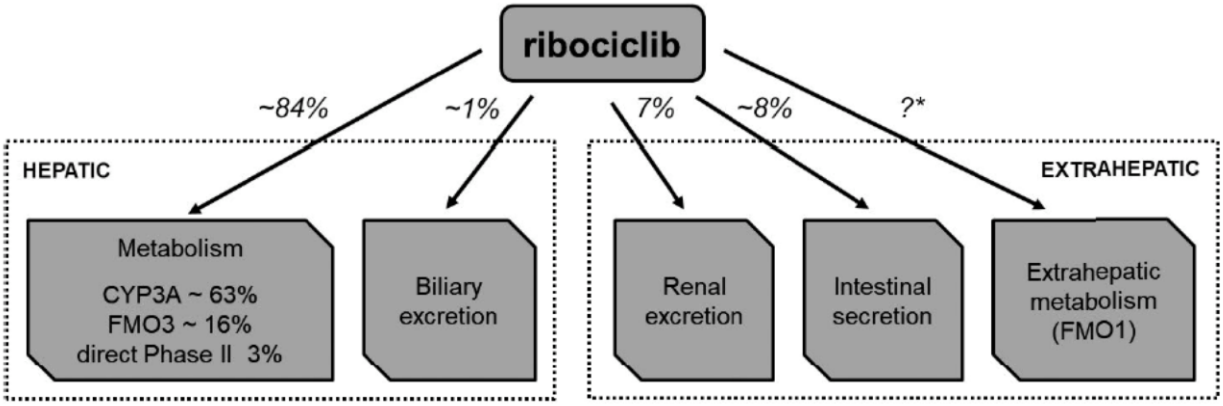
Breast tumors often harbor abnormalities of the cyclin D–CDK4/6–p16–Rb pathway (12). In a preclinical study of 50 breast cancer cell lines, ribociclib demonstrated activity predominantly against HR+ cell lines (12). *In vivo*, in xenograft models the combination of ribociclib and letrozole or fulvestrant lead to significant inhibition of tumor growth (12, 13). Ribociclib preclinical data indicate that it may be expected to have a direct effect on growth arrest as well as potential secondary cytotoxic activity.

### 1.2.2 Pharmacokinetics

According to the FDA label for ribociclib, repeated 600 mg once daily administration, steady-state was achieved after 8 days; the time to reach maximum concentration is between one and four hours after administration of ribociclib; the half-life of ribociclib is 32 hours (14).

The FDA label indicates clinical activity is primarily due to the parent drug and ribociclib is metabolized to other compounds that have a negligible contribution on clinical activity. The primary metabolic pathways of ribociclib include oxidation, N-acetylation, sulfation, cysteine conjugation, glycosylation, and glucuronidation (14). Ribociclib is the major circulating drug in plasma, accounting for 44%, however there is a possible contribution to ribociclib effect from circulating metabolites: M13 represents 22% of ribociclib exposure, M4 accounts for 20% and, M1 for 15% (14). Ribociclib is eliminated mainly via feces with a small contribution from the renal route (14).

Ribociclib undergoes hepatic metabolism mainly via CYP3A (14). Ritonavir is a strong CYP3A inhibitor, when ritonavir was given in combination with ribociclib there was an increase of the maximum concentration ($C_{max}$) and the area-under-the-curve (AUC) of ribociclib increased by 1.7 and 3.2-fold, respectively (14, 15). Ribociclib in combination with erythromycin, a moderate CYP3A inhibitor, the $C_{max}$ and AUC of the CDK 4/6 inhibitor increased by 1.3 and 1.9-fold, respectively (14). The opposite effect in ribociclib concentrations was noted with CYP3A inducers, such as rifampicin (14).




* The magnitude of extrahepatic FMO1 contribution is unknown

James, A.D., *et al. Pharmacol Res Perspect.* (2020).

### 1.2.3 Clinical Activity

Several phase 1b trials have been conducted utilizing ribociclib in patients with breast cancer (12). The NCT01857193 trial was a dose-escalation study that combined ribociclib (600 mg daily for 21 days out of 28-day cycles) with exemestane (25 mg daily, continuous) and everolimus (continuous) in six patients with metastatic breast cancer, two had partial response (PR) and six stable disease; hematologic adverse events (AEs) were reported in that study (16). Then the NCT01872260 study ribociclib (600 mg daily for 21 days out of 28-day cycles) and letrozole (2.5 mg daily, continuous) were given; of the six patients with evaluable response, one had PR, 2 stable disease, one no measurable disease and two progression of disease (16). A second arm of the study included ribociclib, letrozole, and a PI3K inhibitor, there was one dose-limiting toxicity (neutropenia), the most commonly reported AEs from both arms were neutropenia, nausea, hyperglycemia, anorexia, diarrhea, nausea (17). The NCT02088684 phase 1b/2 trial assessed safety and efficacy of ribociclib and fulvestrant (arm A: ribociclib 600 mg daily for 21 days; arm B: 400 mg daily; all received fulvestrant) 24 women (arm A= 13, arm B=11) were treated with the combination, four women had PR and 15 stable disease (18).

Based on the data demonstrating efficacy and safety of ribociclib in combination endocrine therapy, the phase 3, randomized, placebo-controlled MONALEESA-2 study was conducted (19). In this study, 668 postmenopausal women with recurrent or metastatic HR+/HER2 breast cancer were randomized to receive ribociclib (600 mg daily for 21 days of 28-day cycles) plus letrozole (2.5 mg daily) vs placebo plus letrozole. The PFS was longer in the ribociclib group than in the placebo group (95% CI 0.43-0.72, HR 0.56); the 18-month PFS was 63% vs 42% respectively (19). The objective response rate (ORR) was 52% in the ribociclib group vs 37% in the placebo group ($p < 0.001$) (19). The improvement in outcomes in the ribociclib arm was maintained in a second planned interim analysis after 26 months that revealed a median PFS of 26 months in the ribociclib group vs 16 in the placebo group (20).

Slamon and colleagues conducted the MONALEESA-3 trial in which 484 postmenopausal women with locally advanced or metastatic HR+/HER2 breast cancer that were treatment naïve or had receive one line of endocrine therapy, were randomized to receive ribociclib (600 mg daily for 21 days of 28-day cycles) plus fulvestrant (500 mg on day 1 of each cycle with an additional dose on day 15 of cycle 1) vs placebo plus fulvestrant (21). The median PFS was 20 months in the ribociclib group vs 12 in the placebo group (HR 0.5, $p < 0.001$) (21). Treatment benefits were seen in patients that were treatment naïve and in the ones who had one prior line of endocrine therapy (21). The ORR was 40% vs 28% respectively. The overall survival at 42 months was 57% in the ribociclib group and 45% in the placebo arm (22). There was a 28% difference in the relative risk of death and the benefit was consistent across most subgroups (HR 0.72, 95% CI 27.1 to 41.3) (22).

In the MONALEESA-7 phase 3 trial, Tripathy *et. al.* studied ribociclib (600 mg daily for 21 days of 28-day cycles) in combination with AI and ovarian suppression (goserelin 3.6 mg on day one of each 28-day cycle) in premenopausal women with HR+/HER2 advanced breast cancer that received up to one line of therapy (no previous treatment with CDK 4/6 inhibitors) (23). Randomization of 672 patients assigned them to receive ribociclib plus AI (letrozole or anastrozole) and ovarian suppression or placebo plus AI and ovarian suppression (23). The median PFS was 23 months in the ribociclib group vs 13 months in the placebo group (HR 0.55, $p < 0.0001$), the median OS was not reached (23).

Several ongoing trials are exploring the use of ribociclib in combination with ET and other targeted agents, such as PI3K and mTOR inhibitors in patients with advanced breast cancer; additionally, multiple studies are assessing the use of CDK 4/6 inhibitors in the neoadjuvant and adjuvant settings (24).

### 1.2.4 Toxicity

CDK 4/6 inhibitors are overall well tolerated, either as monotherapy or in combination with ET; however hematologic toxicities –particularly neutropenia- often leads to delays in treatment and dose reductions (21, 23). The prevalence of toxicities and subsequent dose adjustments (38% to 77%) vary based on the concomitant therapy and are discussed below and in Table 3.

Table 3: Adverse effects and associated changes in ribociclib therapy

| | MONALEESA-2 (14) | MONALEESA-3 (14) | MONALEESA-7 (14) |
|---|---|---|---|
| Most Common AEs (> 20%) | Neutropenia, Nausea, Fatigue, Diarrhea, Leukopenia, Alopecia, Vomiting, Constipation, Headache, Back pain | Neutropenia, Infections, Constipation, Diarrhea, Leukopenia, Nausea, Rash, Cough, Vomiting | Neutropenia, Infections, Arthralgia, Nausea, Leukopenia, Alopecia |

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|---|---|---|---|
| Most Common Grade 3 or 4 AE (>5%) | Neutropenia, Leukopenia, Abnormal liver function tests, Lymphopenia | Neutropenia, Leukopenia, ALT Increased | Neutropenia, Leukopenia, ALT Increased |
| Dose reductions due to AE | 45% [a] | 32% | 33% |
| Discontinued ribociclib due to AE | 7% [b] | 9% [c] | 3% [d] |

[a] Neutropenia was the most common AE leading to a dose reduction
[b] Increases in liver enzymes and vomiting were the most common AEs leading to treatment discontinuation (20).
[c] AEs leading to permanent discontinuation of ribociclib included ALT increased (5%), AST increased (3%), and vomiting (1%).
[d] AEs leading to permanent discontinuation of ribociclib included ALT increased (2%), AST increased (2%), and drug-induced liver injury (1%).

In the phase 1b/2 trial NCT02088684 patients received fulvestrant and ribociclib 600 mg on day 1-21 of 28-day cycles or a continuous (n= 13) dose of 400 mg (n=11); Tolaney ***et. al.*** described neutropenia as a common and dose-dependent AE, grade 3/4 neutropenia occurred in 62% of the patients that received 600 mg of ribociclib daily and in 36% of the patients treated with 400 mg of ribociclib (18). QTc prolongation was also reported in this study in 4 patients in the 600 mg arm and in 1 on the 400 mg group; again suggesting a dose-dependent effect (18, 21, 23).

In the MONALEESA-2 study, neutropenia was reported in 74% of patients in the experimental arm, of these 49% had grade 3/4 neutropenia; in the placebo arm only 5% of patients reported neutropenia; anemia was reported in 18% of the ribociclib arm and 4.5% of the placebo arm; most cases were grade 1/2, leukopenia was also reported in the ribociclib arm. Nausea was reported in 51% of patients in the experimental arm and 28% of the placebo arm. Alopecia in 32% and 15% respectively. Transaminitis was also reported in 15% of the patients in the experimental arm and only 3-4% in the placebo arm (mostly grade 1/2). An increase of more than 60 milliseconds from baseline in the QTc interval occurred in 2.7% in the ribociclib group and in no patients in the placebo group (19). Serious AEs occurred in 71 patients (21.3%) in the ribociclib group and in 39 (11.8%) in the placebo group (19). Dose adjustments secondary to an adverse effect were required for 182 (54.5%) of patients treated with ribociclib plus letrozole, which was higher than placebo plus letrozole (14, 4.2%). Median time to first dose reduction was 2.9 (range 0 to 29.4) months. Dose interruptions secondary to an adverse effect were required for 239 (71.6%) of patients treated with ribociclib plus letrozole, which was higher than placebo plus letrozole (54, 16.4%). Neutropenia was the most common reason for dose adjustments and dose interruptions.

In the MONALEESA-3 trial, neutropenia was again the most common reported AE, in the

ribociclib group 69% of the patients developed neutropenia, 53% grade 3/4 while 2% of patients in the placebo arm developed neutropenia. Other common grade 3/4 AE were nausea (45%), fatigue (31%), leukopenia (28%), vomiting (26%), pruritus (19%), alopecia (18%), anemia (17%). ALT and AST elevation occurred in 4-6% of the ribociclib arm and 1% of the placebo arm. QTc prolongation occurred in 6% of patients in the ribociclib arm; three cases discontinued treatment due to QTc prolongation, there were no cases reported of Torsades de Pointes (21). Serious AE occurred in 138 (28.6%) and 40 patients (16.6%) in the ribociclib plus fulvestrant and placebo plus fulvestrant arms, respectively; of these, 54 (11.2%) and six (2.5%) were attributed to the study medication. The most common all-grade all-causality serious AEs reported in ≥ 1% of patients (ribociclib plus fulvestrant v placebo plus fulvestrant) were pneumonia (1.9% v 0%) and dyspnea (1.2% v 2.1%) (21). Ribociclib or placebo dose reductions were reported in 183 (37.9%) and 10 patients (4.1%) in the ribociclib plus fulvestrant and placebo plus fulvestrant arms, respectively; 148 (30.6%) and nine (3.7%) had a single dose reduction. AEs were the most common reason for dose reduction (160 of 183 patients with a dose reduction) (21).

Similarly, in the MONALEESA-7 study, 76% of patients in the ribociclib arm developed neutropenia (61% grade 3/4) while 8% of patients in the placebo arm developed neutropenia. Other common AEs were leukopenia (31%), anemia (21%), alopecia (19%), transaminitis (12%). QTc prolongation was reported in 11% of the ribociclib group vs 4% of the placebo arm (23). Dose interruptions or reductions owing to an AE of QTc interval prolongation occurred in 13 (4%) of 335 patients in the ribociclib group and three (1%) of 337 patients in the placebo group. None of the patients with a QTc prolongation event had clinical symptoms or arrhythmias. Overall, dose adjustments occurred in 255 (77%) of patients who received ribociclib compared to 126 (38%) of those who received placebo. Serious AEs occurred in 60 (18%) of 335 patients in the ribociclib group and 39 (12%) of 337 in the placebo group (23).

Hematologic toxicities are seen with CDK 4/6 inhibitors in general, even though neutropenia is common, the incidence of neutropenic fever is low with these treatments (19, 21, 23, 25). There are limited data on the hematologic safety profile of CDK 4/6 inhibitors in African Americans/Blacks. The PALINA study assessed the safety of palbociclib in African American/Black women with and without benign ethnic neutropenia (BEN). A polymorphism in the Duffy antigen has been implicated in the pathophysiology of BEN. A total of 35 African American/Black patients (58% with Duffy null phenotype) with a baseline absolute neutrophil count >1000/uL were enrolled in this phase 2 study. Women with duffy null phenotype required more dose reductions due to neutropenia; however, this did not result in treatment discontinuation or febrile neutropenia. This study showed that palbociclib is safe in African American/Black women, including those with Duffy null phenotype and baseline absolute neutrophil count 1000-1499/uL (26).

Transaminitis and QTc prolongation are AEs reported with ribociclib (19, 21, 23, 25). Lung toxicity is a rare but often fatal AE of CDK 4/6 inhibitors, it was reported in one patient in MONALEESA 3, and in several case reports (21).

Based on a dedicated hepatic impairment Study A2109 in healthy subjects with normal hepatic function (N=11) and volunteers with hepatic impairment (N=17), mild (Child-

Pugh class A; N=6) hepatic impairment did not affect the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate, in 6 patients with Child Pugh class B AUC increased to 1.32 and 5 patients with; Child Pugh class C AUC increased to 1.34. Based on a population pharmacokinetic analysis that included 160 patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment did not affect the exposure of ribociclib, further supporting the findings from the dedicated hepatic impairment study there are no dose reduction recommendations for patients with hepatic impairment (27).

## 1.3 Minority Enrollment in Clinical Trials

The National Institute of Health (NIH) guidelines on the inclusion of women and minorities in clinical trials published in 1994 and updated in 2017 called for the initiation of programs and support for outreach efforts to recruit underrepresented groups into clinical trials (28). Despite multiple efforts, racial and ethnic minorities are still underrepresented in clinical trials. This diversity gap can lead to sub-optimal development of new medicines, compromise the generalization of clinical trial results, and further exacerbate minority health disparities. According to a 2011 report from the conference "Dialogues on Diversifying Clinical Trials," sponsored by the FDA, African Americans/Blacks represent 12% of the U.S. population but only 5% of clinical trial participants and Hispanics make up 16% of the population but only 1% of clinical trial participants. Recent work by Al Hadidi *et. al.* found that just 1507 of 22,075 (6.8%) of participants were African Americans/Blacks among those included in clinical trials new drugs approved by the FDA to treat breast cancer between 2014 to 2018. This under representation remained apparent after accounting for the number of African Americans/Blacks with breast cancer as seen be a participation to prevalence ratio of 0.29 (0.8 to 1.2 equates to similar representation) (29).

Race is likely to be significant factor when exploring ribociclib pharmacokinetics and the role of CYP3A.In the mentioned MONALEESA trials only 23 (1.9%) out of the 1153 women treated with ribociclib were African Americans/Blacks (19, 21, 23). The FDA's review of ribociclib concluded that "it is difficult to draw meaningful conclusions regarding the effect of race on the safety of ribociclib," which is unsurprising given that the African Americans/Blacks population was underrepresented in the initial studies (27).

## 1.4 CYP3A

The cytochrome P450 (CYP) are a superfamily of enzymes that play a critical role in the metabolism of endogenous and exogenous substances (30). More than 50 individual CYP have been identified in humans and some of the reactions carried out by CYP are *N*-dealkylation, *O*-dealkylation, aromatic hydroxylation, *N*-oxidation, *S*-oxidation, deamination, and dehalogenation (30). There are large differences in levels of expression of each CYP between individuals; interindividual variability in CYP expression is due to the presence of genetic polymorphisms and differences in gene regulation (30).

A limited number of (~15) CYP enzymes are responsible for the metabolism of the majority of drugs, most fall into the CYP families 1, 2 and, 3 (30). The most active CYP for drug metabolism are those in the CYP2C, CYP2D, and CYP3A subfamilies (30). CYP3A4, the most abundantly expressed in liver, is involved in the metabolism of over 50% of clinically used drugs (30). The human CYP3A subfamily consists of CYP3A4, CYP3A5, CYP3A7, and CYP3A43 (31). CYP3A7 expression is down-regulated after birth and CYP3A43 expression in the liver is small while CYP3A4 and CYP3A5 are responsible for activity in adults (31).

The enzymes CYP3A4 and CYP3A5 are encoded by genes of the same name. *CYP3A4* and *CYP3A5*, respectively. It can be difficult to differentiate relative contributions between CYP3A4 and CYP3A5 due to significant sequence homology (approximately 84%) between *CYP3A4* and *CYP3A5* and overlapping substrate specificity (31). It is common for substrates to be metabolized by both CYP3A4 and CYP3A5, although one enzyme may preferentially metabolize a substrate. CYP3A-dependent drug clearance is variable due to multiple factors, including genetic mutations in *CYP3A5* and *CYP3A4* (31). *CYP3A5* genotype can be translated to phenotypes that reflect enzyme function: poor metabolism, intermediate metabolism, or normal metabolism. Genetic testing interpretation is based on allelic expression of *CYP3A5*: normal metabolizers carry two functional alleles (haplotype: *1/*1, more common in African American/Blacks), while intermediate metabolizers carry one functional and one nonfunctional allele (*1/*3, *1/*6, *1/*7), finally poor metabolizers carry two non-functional alleles (*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7, more common in non-Hispanic Whites) (32). Importantly, these terms reflect enzyme function and are unrelated to prevalence (e.g., normal metabolism reflects normal enzyme function, but this could be a common or uncommon phenotype).

There are known race-based differences in *CYP3A4* and *CYP3A5*, with *CYP3A4* dominant in Whites and *CYP3A5* dominant in African Americans/Blacks (31). Counterintuitively, it is common (~85%) for White patients to have CYP3A5 poor metabolism and uncommon (~15%) for White patients to have CYP3A5 normal or intermediate metabolism. The scenario is reversed for African American/Black patients as it is common (~85%) to have CYP3A5 normal or intermediate metabolism and uncommon (~15%) to have CYP3A5 poor metabolism. This differential enzyme expression may have an enhanced importance as many drugs (e.g., ribociclib) have dosing regimens established in predominantly White populations, which do not express an enzyme that metabolizes the drug.

The clinical significance of *CYP3A5* has been described in the pharmacogenetic studies of a calcineurin inhibitor, tacrolimus, which is an active drug metabolized by CYP3A and has a narrow therapeutic index (32). This drug is often utilized after bone marrow and solid organ transplantation to prevent rejection (33). Individuals who are normal or intermediate CYP3A5 metabolizers exhibit lower dose-adjusted trough concentrations of tacrolimus when compared with poor metabolizers. This is of significant concern as low trough concentrations increase the risk of transplant rejection and higher concentrations increase risk for adverse events, such as nephrotoxicity (32). Initial tacrolimus dosing was based predominantly (92%) on White populations, which are more likely to have CYP3A5 poor metabolism; as stated above, ~85% of Whites have poor CYP3A5 metabolism and only ~15% of African American/Blacks, since most of the data on the

dosing of tacrolimus were based on White population there is a concern that if African American/Blacks are metabolizing the drug faster, they may have lower drug concentrations and therefore risk for transplant rejection (31). Recent studies have demonstrated different rates of toxicity and graft rejection between African American/Blacks and Non-Hispanic Whites. These differences have been attributed to CYP3A5 polymorphisms (33). This work and other studies have led to the publication of dosing guidelines for tacrolimus based on specific pharmacogenetic variants (32). This application of pharmacogenomics-guided dosing could be translated to other drugs metabolized by CYP3A, like ribociclib.

## 1.5 Study Rationale and Purpose

There is an unmet need to evaluate the genomic characteristics and their effect on drug metabolism and toxicities, especially in racial and ethnic minorities. This prospective cohort study aims to determine the impact of CYP3A in ribociclib metabolism.

Ribociclib is metabolized by CYP3A and the FDA recommends avoidance of CYP3A inhibitors or dose adjustments to compensate for altered ribociclib metabolism (section 1.2.2). Based on drug interaction data (section 1.2.2), a reduction in CYP3A activity can lead to clinically relevant changes in ribociclib exposure. Higher ribociclib exposure is known to be associated with toxicities (e.g., neutropenia, prolonged QTc interval) and decreased exposure can potentially lead to loss of efficacy (14).

Genetic variation in CYP3A, and specifically in *CYP3A5*, may be associated with altered ribociclib exposure but this has not been studied. Separate studies in African Americans/Black and Non-Hispanic White patients are justified given allelic frequencies and the potential for factors (e.g., CYP3A4) that may confound the association between CYP3A5 and ribociclib exposure.

Due to underrepresentation in clinical trials and race-based differences in CYP3A5 expression, African Americans/Blacks may be at particular risk of atypical ribociclib exposure. However, the dearth of pharmacokinetic evidence for ribociclib use in African Americans/Blacks patients make clinical predictions difficult. It is reasonable to suggest that African Americans/Blacks may be *either* 1) more dependent on metabolic activity from CYP3A5 and thus CYP3A5 poor metabolism may lead to increase ribociclib exposure and possibly toxicity or 2) normal CYP3A5 metabolizers have increased metabolic activity compared to the “average” White patient, which results in lower ribociclib exposure and a lack of efficacy. In order to predict which scenario is more plausible, it is critical to first understand if differences in ribociclib pharmacokinetics are associated with CYP3A5 metabolizer status. **We hypothesize that patients treated with ribociclib who are CYP3A5 poor metabolizers may be exposed to higher levels of ribociclib than CYP3A5 intermediate or normal metabolizers**. These differences can then inform the plausible clinical risk.

This work is focused on ribociclib but has potential implications for other medications metabolized by CYP3A. Many drugs have dosing regimens determined in predominantly White populations and thus may dosing regimens confounded by differential *CYP3A5*

expression. If our hypothesis is correct, it would serve as a strong similar to perform similar work in other medications metabolized by CYP3A (note, CYP3A metabolizes more drugs than any other cytochrome), particularly if no previous pharmacogenetic studies have been performed.

Two cohorts of women -one of 18 women self-identified as African American/Black and one of 18 women self-identified as Non-Hispanic White women- with HR+/HER2- metastatic breast cancer will be followed prospectively to assess the pharmacokinetics (AUC, $C_{max}$, $C_{min}$) and *CYP3A5* pharmacogenomics in each population. We aim to identify the effect of *CYP3A5* variants in the metabolism of ribociclib.

There are known race-based differences in *CYP3A4* and *CYP3A5; CYP3A4* is dominant in Non-Hispanic White patients and while *CYP3A5* plays a larger role in African American/Black patients (32, 33). By assessing pharmacogenomics and pharmacokinetics in two separate cohorts we aim to understand the effect of *CYP3A* variants in the metabolism of ribociclib and to determine if there is a clinically significant correlation based on toxicity and drug concentration (assessed by AUC). We hypothesize that there will be a difference in the AUC and toxicity profile by race as the *CYP3A* variants in different racial groups have been well established. Also note, pharmacokinetic studies of similar size had direct clinical implications by resulting in recommended dose adjustments in the FDA label.

Women will be eligible if they are premenopausal receiving ovarian suppression (with goserelin or leuprolide) or post-menopausal. The endocrine therapy selected for this study includes fulvestrant or letrozole. As seen in Table 4, this decision was made after an assessment of the FDA label for each endocrine therapy option, *in vitro* data, *in vivo* data, a well-known resource (Flockhart Table (34)), and previous major clinical trials (MONALEESA trials). This topic is not thoroughly studied but our decisions are justified by the totality of evidence. Guidelines from the National Comprehensive Cancer Network (NCCN) recommend the use of ovarian suppression (i.e., goserelin or leuprolide) in this population if patients are premenopausal.(35) The use of ovarian suppression in combination with ribociclib and a non-steroidal aromatase inhibitor in premenopausal women was shown to be safe and effective in the MONALEESA 7 clinical trial and ovarian suppression has no known effect on CYP3A (23). Letrozole and fulvestrant appear to have minimal to no effect on CYP3A (as inhibitors, inducers, or substrates) and therefore they are unlikely to have an effect in the pharmacokinetic studies. Additionally, the combinations have shown to be safe in the MONALEESA 2 and 3 trials (21, 25). Tamoxifen, anastrozole and exemestane are substrates of CYP3A and therefore their use may have an effect on the pharmacokinetic studies through competitive inhibition. Thus tamoxifen, anastrozole, and exemestane will not be used in this study. Also note, during a presentation to the GLCCC Breast Cancer Program on July 29, 2020, we had significant discussion regarding the evidence for the potential effect of letrozole and anastrozole on CYP3A. This discussion and additional data added to the investigators' confidence in permitting the use of letrozole and excluding anastrozole.

Table 4: Effect of Endocrine Therapy in CYP3A

| Drug | FDA Label[1] | *In vitro* CYP3A | *In vivo* CYP3A | Flockhart Table[2] | MONALEESA Trials |
|---|---|---|---|---|---|
| Fulvestrant | Negative | Substrate | Negative | Not listed | Allowed (#3) |
| Letrozole | Substrate | No inhibition (PMID 19198839) | Unclear | Not listed | Allowed (#2, #7) |
| Anastrozole | Inhibitor per *in vitro* data | Substrate (PMID: 21175441)<br>Inhibitor but not expected i*n vivo* (PMID 9152599) | Unclear | Not listed | Allowed (#7) |
| Goserelin | N/A | N/A | N/A | N/A | Allowed (#7) |
| Leuprolide | N/A | N/A | N/A | N/A | N/A |
| Exemestane | Substrate<br>Avoid inducers | No further justification required beyond FDA label | | Not listed | N/A |
| Tamoxifen | Substrate<br>Avoid inducers | Inhibitor (PMID: 12419016)<br>Inducer (PMID: 11950795) | Negative (PMID: 16041611) | Substrate | Allowed (#7) |
| Toremifene | Substrate<br>Avoid inhibitors | No further justification required beyond FDA label | | Not listed | N/A |

Negative: study or studies did not identify an association between CYP3A and the drug
[1]https://www.accessdata.fda.gov/scripts/cder/daf/ Accessed 07/29/20.
[2]https://drug-interactions.medicine.iu.edu/MainTable.aspxAccessed 07/29/20

# 2. Study Objectives and Endpoints

## 2.1 Primary Objective

To compare the pharmacokinetics of ribociclib at steady-state between CYP3A5 poor metabolizers and CYP3A5 intermediate or normal metabolizers in each independent race-based cohort of women with advance breast cancer.

## 2.2 Primary Endpoint

Ribociclib AUC (visit between days 8-16 of cycle 1) CYP3A5 poor metabolizers and CYP3A5 intermediate or normal metabolizers.

## 2.3 Secondary Objectives

1. To evaluate toxicity profiles (e.g., QTc prolongation, leukopenia) between each race-based cohort.
2. To characterize ribociclib pharmacokinetics in African American/Black and the Non-Hispanic White patient cohorts.
3. Conduct an exploratory candidate gene analysis of other genes with a biologically plausible role in ribociclib pharmacokinetics or therapeutic response (e.g., *CYP3A4*).

## 2.4 Secondary Endpoints

1. Ribociclib pharmacokinetic properties: maximum concentration ($C_{max}$), the time to reach $C_{max}$ ($T_{max}$), AUC, clearance, volume of distribution($v_d$), elimination half-life, and mean residence time (MRT) at steady state (visit between days 8-16 of cycle 1).
2. Change in QTc interval between:
   1) baseline and between days 8-16 of cycle 1,
   2) baseline and scheduled visit prior to initiation of cycle 2
3. Laboratory abnormalities: neutropenia, ALT, and AST, between
   1) baseline and between days 8-16 of cycle 1,
   2) baseline and scheduled visit prior to initiation of cycle 2

## 2.5 Exploratory Endpoints

4. Correlations between toxicities based on the Common Terminology Criteria for Adverse Events-Patient Reported Outcomes (CTCAE-PRO) questionnaire and ribociclib pharmacokinetic properties (e.g., AUC, $C_{max}$, $C_{min}$).
5. Correlation between candidate pharmacokinetic genes (e.g., *CYP3A4, overall CYP3A phenotype*) and pharmacokinetic properties (e.g., AUC, $C_{max}$, $C_{min}$).
6. Correlation between candidate pharmacodynamic variants or genes (e.g., Duffy antigen receptor) and toxicity (e.g., change in white blood cells [WBC]).

# 3 Patient selection

## 3.1 Indication

Women with HR-positive, HER2 negative advanced breast cancer. This phase IV trial will enroll a pre-defined number of patients (n=36) with HR+/HER2- advanced/metastatic breast cancer.

## 3.2 Patient Population, Number of Patients, and Feasibility

### 3.2.1 Patient Population

This trial will enroll 36 patients with advanced HR-positive and HER2 negative breast cancer that are eligible for treatment with a CDK4/6 inhibitor as well as adequate cardiac and hepatic function.

### 3.2.2 Number of Patients

Thirty-six patients will be enrolled in total. More specifically, 18 patients will be enrolled into each cohort based on self-identified race.

### 3.2.3 Feasibility

This study will be performed at MedStar Washington Hospital Center (MWHC), MedStar Franklin Square, and Lombardi Comprehensive Cancer Center (LCCC) as a part of our combined Breast Cancer Research Group. Each institution sees 300-400 new patients diagnosed with breast cancer each year, which is. MWHC serves a large number of minority and underserved patient groups, including 62% African Americans/Blacks patients. The study will be additionally open at Tufts Medical Center.

Approximately 30 patients were treated with CDK4/6 inhibitor (i.e., ribociclib, palbociclib, abemaciclib) at MWHC or Lombardi LCCC in the past 6 months.

At the multiple centers participating in this study, we anticipate being able to enroll ~20 patients per year. The expected accrual duration will be approximately 24-36 months.

## 3.3 Inclusion Criteria

Patients must meet all the following inclusion criteria to be eligible for enrollment in the study:

- Signed informed consent must be obtained prior to any screening procedures that are not standard of care.
- Female ≥18 years old at the time of informed consent.
- Those who self-identify as African American or Black are eligible for that respective cohort
- Those who self-identify as non-Hispanic White are eligible for that respective cohort
- Postmenopausal or premenopausal. Patient has a known menopausal status at the time of the informed consent form signature. The patient is considered postmenopausal if: i) she has had prior bilateral oophorectomy; ii) is age ≥ 60 years; iii) is age <60 years and has had amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range per local normal ranges. All other patients who do not meet the criteria for postmenopausal status are considered premenopausal and will receive a luteinizing hormone-releasing hormone (LHRH) agonist (i.e., goserelin, leuprolide) for ovarian suppression
- Each race-based cohort has a predetermined number of patients with each CYP3A5 phenotype per the sample size calculation (section 9.1). Patients will be screen for CYP3A5 according to section 3.6.1.

- African American or Black
  - At least 3 participants who are CYP3A5 poor metabolizers
  - No more than 15 participants who are CYP3A5 intermediate or normal metabolizers
- Non-Hispanic White
  - At least 3 participants who are CYP3A5 intermediate or normal metabolizers
  - No more than 15 participants who are CYP3A5 poor metabolizers

- Patient has advanced (loco-regionally recurrent or metastatic) breast cancer not amenable to curative therapy
- Treated, stable and asymptomatic brain metastases are permitted
- ECOG performance status 0-3
- Documentation of estrogen receptor (ER) positive and/or progesterone receptor (PR) positive tumor (≥1% positive stained cells) based on most recent tumor biopsy (discuss with the Principal Investigator if results in different biopsies are discordant in terms of hormone receptor positivity) utilizing an assay consistent with local standards.
- Documented HER2-negative tumor based on local testing on most recent tumor biopsy: HER2-negative tumor is determined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH) defined by current ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines. Patients with equivocal HER2 in situ hybridization results according to current ASCO/CAP guidelines are eligible, as long as they have not received and are not scheduled to receive anti-HER2 treatment.
- Must be capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by the IRB, prior to the initiation of any screening or study-specific procedures.
- Patient must be able to swallow ribociclib tablets.
- Patient must be able to communicate with the investigator and comply with the requirements of the study procedures. (Note: Communication through an interpreter is acceptable)
- Patient has adequate bone marrow and organ function as defined by the following laboratory values:
  - Absolute neutrophil count (ANC) ≥ 1,200/mm; Patients must be able to meet the criteria without receipt of colony stimulating factors within 2 weeks before obtaining sample
  - Platelets ≥ 100,000/mm3; Patients must be able to meet the criteria without receipt of transfusion within 2 weeks before obtaining sample
  - Hemoglobin ≥ 8 g/dL; Patients must be able to meet the criteria without receipt of transfusion within 2 weeks before obtaining sample
  - Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73m2 according to the CKD EPI equation (**Note:** if the eGFR is not calculated from the serum creatinine using CKD EPI equation, please enter the most recent data into this calculator: https://www.kidney.org/professionals/kdoqi/gfr_calculator)
  - Total bilirubin < ULN except for patients with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN.
  - Aspartate transaminase (AST) < 2.5 × ULN, except for patients with liver metastases, who are only included if the AST is <5 × ULN.

- Alanine transaminase (ALT) < 2.5 × ULN, except for patients with liver metastases, who are only included if the ALT is < 5 × ULN.
- Alkaline phosphatase ≤2.5 x ULN (≤5.0 x ULN if bone metastases present)

- Patient must have the following laboratory values within normal limits or corrected to within normal limits with supplements, or are not clinically significant per the Investigator:
  - Sodium
  - Potassium
  - Calcium
- The following tests are not necessary. However, if results are available, values should be as follows:
  - INR ≤ 1.5 (unless the patient is receiving anticoagulants and the INR is within the therapeutic range of intended use for that anticoagulant within 7 days prior to the first dose of study drug).
  - Magnesium within normal limits or corrected to within normal limits with supplements, or is not clinically significant per the Investigator.

- Standard 12-lead electrocardiogram values defined as (obtained from baseline electrocardiogram):
  - QTc interval at screening < 450 ms (using Fridericia's correction)
  - Mean resting heart rate ≥ 50 bpm (determined from the electrocardiogram)

## 3.4 Exclusion Criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study:

- Patient with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's judgment.
- Patient currently/actively taking a CDK4/6 inhibitor (e.g., ribociclib, abemaciclib, or palbociclib).
- Patients with central nervous system (CNS) symptomatic or untreated metastases
- History of liver transplant or allogeneic bone marrow transplantation
- Patient with a known hypersensitivity to any of the excipients of ribociclib (e.g. ribociclib tablets coating contains soya lecithin, and therefore should not be taken by patients who are allergic to peanuts or soya) or of fulvestrant.
- Patient is concurrently using other anti-cancer therapy besides those in the study protocol (e.g., letrozole, fulvestrant, goserelin, leuprolide). Any other prior neo-/adjuvant anti-cancer therapy must be stopped at least 5 half-lives or 7 days, whichever is longer, before the date of ribociclib initiation.
- Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major toxicities.
- Patient has not recovered from acute clinical and laboratory toxicities related to prior anticancer therapies to NCI CTCAE v5.0 grade ≤ 1 (except for alopecia, neuropathy, and amenorrhea or other toxicities not considered a safety risk for the patient at investigator's discretion).
- Patient has received extended-field radiotherapy ≤ 4 weeks or limited field radiotherapy ≤ 2 weeks prior to ribociclib initiation and has not recovered to grade 1 or better from

related side effects of such therapy (with the exception of alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).

- Patient has a concurrent malignancy, with the exception of adequately treated basal or squamous cell skin carcinoma, stage 1 melanoma, or curatively resected cervical carcinoma in situ. Patients may still enroll with a concurrent malignancy after receiving approval from the study PI.
- Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drug (e.g., uncontrolled ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
- Patient has any other concurrent severe and/or uncontrolled medical condition that would in the investigator's judgment, cause unacceptable safety risks to the patient, contraindicate patient participation in the clinical study, or compromise compliance with the protocol.
- Patient has clinically significant, uncontrolled heart disease or who are at significant risk of developing QT prolongation, including any of the following:
    - Documented myocardial infarction (MI), angina pectoris, coronary artery intervention, or pericarditis within 6 months prior to study entry
    - Documented cardiomyopathy, congestive heart failure, valvular heart disease, congenital heart disease, or prior cardiac surgery
    - Left Ventricular Ejection Fraction (LVEF) < 50% (testing is not mandatory)
    - Personal diagnosis of long QT syndrome, cardiac channelopathies, family history of idiopathic sudden death, congenital long QT syndrome or channelopathies
    - Personal risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia, hypomagnesemia, or need for concomitant medications with a known risk to prolong the QT interval and/or known to cause TdP that cannot be discontinued or replaced by safe alternative medication (e.g. within 5 half-lives or 7 days prior to starting study drug, whichever is longer)
    - Clinically significant cardiac arrhythmias or conduction abnormalities, including, but not limited to ventricular tachycardia, atrial tachyarrhythmia, left bundle branch block, right bundle branch block, QRS prolongation (greater than 120 ms), intraventricular conduction delay, high-grade AV block (e.g. bifascicular block, Mobitz type II and third-degree AV block)
    - Uncontrolled hypertension
    - Inability to determine the QTc interval
- Patient is currently receiving any of the following substances and cannot be discontinued 7 days prior to Cycle 1 Day 1:
    - Concomitant medications, herbal supplements, and/or fruits that are strong inducers or inhibitors of CYP3A4/5 (section 5.6).
    - Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5 (section 5.6).
    - Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to lead to induction of CYP3A enzymes, thereby potentially reducing ribociclib drug exposure to sub-therapeutic levels. Systemic corticosteroid treatment should not be given during the study treatment with ribociclib, except for:

    - Topical applications (e.g. for rash), inhaled sprays (e.g. for obstructive airways diseases), eye drops or local injections (e.g. intra-articular)
    - A short duration (< 5 days) of systemic corticosteroids ≤ to the anti-inflammatory potency of 4 mg dexamethasone (e.g. for chronic obstructive pulmonary disease or as an antiemetic).
    - Medications that prolong the QTc interval (section 5.6).
- Inability to comply with study requirements.
- Psychiatric illness or social situation that would limit compliance with study requirements.
- Patients with clinically significant liver disease, including active viral or other known hepatitis, current alcohol abuse, or cirrhosis.
- Known active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg]) or known active hepatitis C (defined as a positive test for hepatitis C viral load by polymerase chain reaction [PCR]).
    - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.
    - Patients with positive hepatitis C antibody AND negative quantitative hepatitis C by PCR AND no clinical/laboratory evidence of cirrhosis are eligible. Patients who have completed curative therapy for HCV are eligible if they meet all other parameters for enrollment.
    - Patients are not required to undergo testing for HBV or HCV for enrollment.
- Known uncontrolled HIV infection defined as <u>any</u> of the following criteria:
    - CD4 counts ≤ 350 cells/μL; or
    - HIV viral load ≥ 400 copies/mL; or,
    - Have been taking an antiretroviral regimen for < 4 weeks prior to treatment with study drugs, if anti-retroviral therapy is deemed necessary or appropriate by the investigator.
    - Patients are not required to undergo testing for HIV for enrollment.

## 3.5 Additional Study Restrictions

Granulocyte Colony-Stimulating Factor (GCSF): GCSF administration should not be given within 2 weeks of study drug initiation or during the study treatment.

Other Anticancer Therapy: For purposes of this protocol, anti-tumor treatment may be defined as, but is not limited to, anti-cancer agents (anti-estrogen endocrine therapy, cytotoxic chemotherapy, immunotherapy, or biologic therapy), radiotherapy, and investigational agents. No other anticancer therapy is permitted during the course of the study treatment for any patient. If the patient discontinues study treatment, this restriction no longer applies; however, the patient will remain enrolled in the study for the purpose of collecting subsequent outcomes.

## 3.6 Removal or Replacement of Patients

### 3.6.1 Screening Failures

All patients must continue to meet the inclusion and exclusion criteria up to and including the first day of treatment. Reasons for patients who have enrolled, but become ineligible could include (but are not limited to):

- The patient's performance status has declined

Patients who become ineligible prior to initiation of therapy per protocol will be considered screen failures. Screen failures must be replaced until 36 patients with advanced HR+/HER2- breast cancer are enrolled.

Each race-based cohort has a predetermined number of patients with each CYP3A5 phenotype per the sample size calculation (section 9.1). In order for the study to be powered at least: 1) 3 participants who are CYP3A5 poor metabolizers and identify as African American or Black and 2) 3 participants who are CYP3A5 intermediate or normal metabolizers and identify as non-Hispanic White. While allelic frequencies (section 9.1) suggest the study will enroll the appropriate number of patients, there is a chance the study may encounter a different allelic frequency than anticipated. Thus, *CYP3A5* genetic testing will be provided after participants provide informed consent. Details for the *CYP3A5* screening test are described in section 4.3.7. Participants will be considered a screen failure if:

- The participant is a CYP3A5 poor metabolizer AND identifies as non-Hispanic White AND the study has already enrolled 15 participants who meet these criteria.
  OR
- 2) The participant is a CYP3A5 intermediate or normal metabolizer AND identifies as African American AND the study has already enrolled 15 participants who meet these criteria.

### 3.6.2 Safety and Tolerability

Any patient who received ribociclib and undergoes complete pharmacokinetic and pharmacogenomic studies will be valuable for safety and tolerability as measured by NCI CTCAE v5.0.

## 3.7 Multicenter Trial Management

### 3.7.1 Study Personnel

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

a. A study PI
b. A research coordinator
c. A data manager

In addition, Georgetown University's Multicenter Project Management Office will oversee the conduct of the trial at Lombardi-Georgetown and additional sites. Georgetown

University's Multicenter Project Management Office will be the main point of contact for the PIs for any study-related concerns, including data management and regulatory.

### 3.7.2 Patient Enrollment

Enrollment at the sites will be competitive. If a patient is being screened for enrollment, the local research coordinator must send an email containing the patient's initials to the local PI, and to the Georgetown University's Multicenter Project Management Office. If a patient is successfully screened, the local research coordinator must send all supporting documentation to Georgetown University's Project Management Office by secure email to confirm eligibility. Patients should not start therapy until a principal investigator and/or Georgetown University's Project Management Office have reviewed the patient's records and confirmed that the patient is indeed eligible for enrollment. In the event the multicenter project manager is not available, then another Georgetown CRMO staff member (CRC, CRN, or Clinical Manager) may review the records and confirm eligibility.

### 3.7.3 Data Collection and Management

Patient data will be entered into an online accessible database. This database is housed at Georgetown Lombardi, but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an online training session so that they may learn how to enter data into the database. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within 10 business days of each patient visit.

### 3.7.4 Conference Calls

The Principal Investigator and with other investigators (when available) and research staff will review the accrual, toxicities, and other protocol issues at weekly protocol meetings and on monthly network disease group teleconferences.

### 3.7.5 Trial Auditing

Georgetown University's Multicenter Project Management Office will arrange all primary source documents for the patients to be audited. This will include collecting copies of the primary source data for any patients treated at other sites. Full details can be found in **SOP GU-ORQA-P01.01**, version date 07/01/2019.

# 4 Study Design

## 4.1 Study Design

Two separate cohorts, based on self-identified race, will be followed prospectively during this study. Eighteen African Americans/Blacks and 18 Non-Hispanic White women with metastatic HR+/HER2- advanced breast cancer will be enrolled. Patients will receive ribociclib 600 mg oral (PO) daily for 21 consecutive days of 28-day cycles and endocrine

therapy with either letrozole or fulvestrant. Fulvestrant 500 mg intramuscular (IM) will be administered on days 1, 15, 29 of cycle one, and then monthly. Letrozole 2.5 mg oral daily continuously. If premenopausal women have not undergone bilateral salpingo-oophorectomy, they will receive a luteinizing hormone-releasing hormone (LHRH) agonist (e.g., goserelin leuprolide) for ovarian suppression in combination with fulvestrant or letrozole and ribociclib.

The Clinical Research Unit (CRU) is located in Georgetown University (7 East, Main Hospital, 3800 Reservoir Road, NW, Washington DC) and it provides specialized institutional resources in which clinical investigators can observe and study human physiology and treat diseases with innovative approaches. Subjects may have the visit between day 8 and day 16 of cycle 1 at the CRU or locally at the site.

Between days 8 and day 16 (i.e., steady state) of cycle 1 of ribociclib and fulvestrant, participants will provide serial blood samples at the Georgetown University Clinical Research Unit or locally at the enrolling site, immediately prior to the ribociclib dose, and 0.5hr ± 5min, 1hr ± 5min, 2hr ± 15min, 4hr ± 15min, 6hr ± 15min after the daily dose of ribociclib. Plasma samples will be analyzed at the National Cancer Institute via mass spectrometry to facilitate the measurement of pharmacokinetic properties. A blood sample will be utilized for pharmacogenetic testing on the PharmacoScan™ (ThermoFisher) microarray, which includes 51 variants in *CYP3A4* and 22 in *CYP3A5.*

Per FDA labeling, periodic electrocardiogram will be obtained prior to the first cycle, between C1D8-C1D16, at the start of the second cycle, and as clinically indicated. Additionally, a complete blood count (CBC) with differential and comprehensive metabolic panel (CMP) will be obtained at baseline (medical visit prior to C1D1), between C1D8-C1D16, at the start of the second cycle

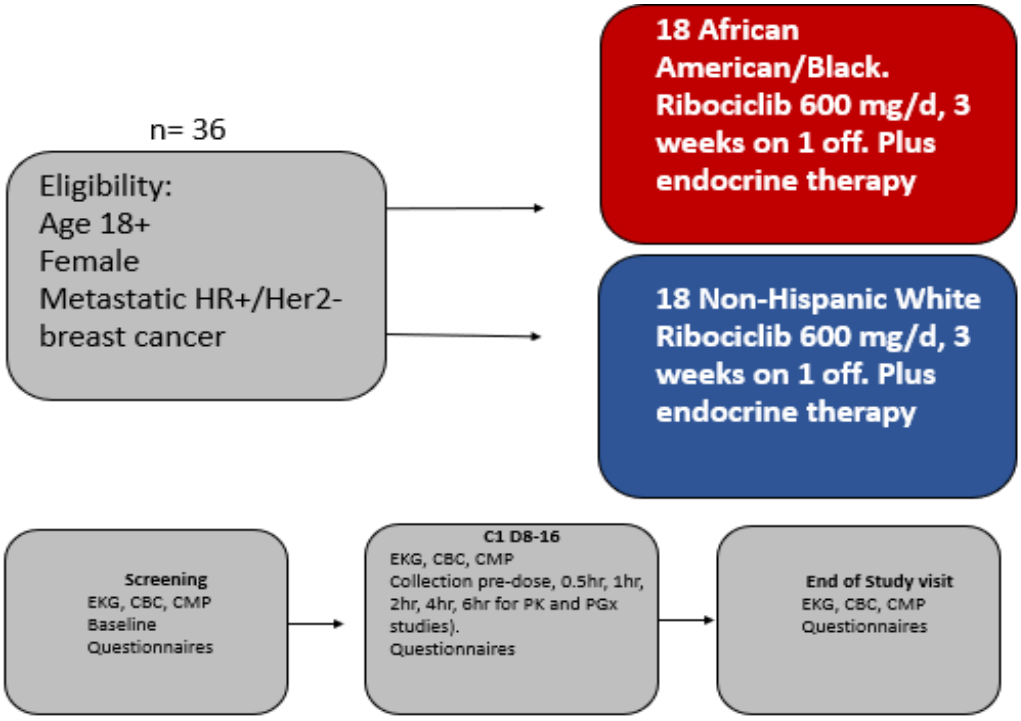


**Figure 1: Study Design**

Subjects will be asked to answer a questionnaire regarding adverse effects (Patient reported outcomes version of the common terminology criteria for AEs (PRO-CTCAE)) and medication adherence (PROMIS on medication adherence (Appendices 14.1 and 14.2) when they present for the serial blood samples for the pharmacokinetics and pharmacogenomic studies. Additionally, food collection and drug accountability (Appendix 14.3) will be done for the first cycle, prior to pharmacokinetic studies).

## 4.2 Study Regimen

This prospective, multicenter, cohort study will assess ribociclib pharmacokinetics and pharmacogenomics in female patients with HR+/HER2- metastatic breast cancer. Potential trial patients will be pre-identified at participating centers.

Patients who have adequate hematologic, hepatic, and renal function will be screened for enrollment. Patients who ultimately meet the inclusion and exclusion criteria as detailed in Section 3, and desire participation, will be enrolled.

## 4.3 Patient Screening, Enrollment, Monitoring

The screening and monitoring procedures include the following listed below. Details are provided in Table 14.

### 4.3.1 Informed Consent

Signed informed consent will be obtained from the patient before any study-specific procedures are undertaken. Additionally, patient will receive COVID-19 related documentation per IRB and Georgetown university policy.

### 4.3.2 Medical History

The following information should be collected during the screening period:

1. Complete medical history, including documentation of any clinically significant medical conditions
2. Performance status (ECOG)
3. Medication information, including over the counter medications and herbal supplements
4. Smoking history will be documented
5. Presence and severity of any symptoms/conditions associated with their advanced solid tumor malignancy
6. Detailed oncology history, including:
    a) Primary tumor: date of diagnosis, histology/cytology, and location
    b) Metastasis information: date of diagnosis, histology/cytology, and location
    c) Surgical history
    d) Anti-cancer and radiation treatments administered (including dates and type of modality, and if therapy was in the neoadjuvant, adjuvant, or metastatic setting)

### 4.3.3 Demographics

Age, sex, and self-reported race/ethnicity will be recorded.

### 4.3.4 Patient Eligibility Criteria

Inclusion and exclusion criteria (per section 3.2 and 3.2, respectively)

### 4.3.5 Review Concomitant Medications

Permitted, not recommended and prohibited concomitant medications, per section appendices 14.4 and 14.5.

### 4.3.6 Physical Exam and Assessment of Performance Status

At screening, a physical examination, height, weight, blood pressure, and pulse rate is required. Symptom-directed physical examinations, blood pressure, weight, and pulse rate will be performed. All physical examinations and vital signs assessments should be

performed by a physician or registered nurse or other qualified health care provider according to local regulations.

### 4.3.7 CYP3A5 Phenotype Screening

After informed consent is complete, participants will undergo CYP3A5 screening to ensure the necessary number of participants with each phenotype are enrolled. If sample size requirements (sections 3.3 and 9.1; at least 3 participants in AA or Black cohort who are CYP3A5 poor metabolizers; at least 3 participants in the NHW cohort who are CYP3A5 intermediate or normal metabolizers) are met, then CYP3A5 phenotype screening may be bypassed per Principal Investigator discretion.

A buccal sample will be collected from participants upon completion of informed consent. Upon collection, the sample and kit will be mailed to Kailos Genetics to perform targeted next-generation sequencing on *CYP3A5*. Samples will be processed in accordance with Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory procedures. Similar to other pharmacogenetic results (PharmacoScan™ test discussed in section 4.3.8), these results will not be returned to the participant. The test results will be provided to the study team through a secure electronic method (e.g., encrypted email, Box.com).

Patients will be considered a screen failure if:

- The participant is a CYP3A5 poor metabolizer AND identifies as non-Hispanic White AND the study has already enrolled 15 participants who meet these criteria.
  OR
- 2) The participant is a CYP3A5 intermediate or normal metabolizer AND identifies as African American AND the study has already enrolled 15 participants who meet these criteria.

The standard turnaround time for CYP3A5 screening will be one week or less. The timing can be as quick as 48 hours if the participant's situation requires a faster turnaround time.

### 4.3.8 Laboratory Samples

Laboratory samples for this study will be assessed using the certified laboratory at the Investigators' institutions or at a clinical laboratory such as Quest or LabCorp and these data will be used for all data analysis. The Principal Investigator or sub-Investigator will review, initial, and date all laboratory results and electrocardiograms. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as AEs if they meet the criteria as specified in Section 8.1.

Hematology samples (complete blood count [CBC]) will be collected and assessed using a certified laboratory. The Investigator will review, initial, and date all laboratory results. Any laboratory value outside the reference range stated in the inclusion criteria will

preclude the patient from study participation. Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. Any laboratory value outside the reference range stated in the inclusion criteria will preclude the patient from study participation. The CBC and CMP are performed per standard clinical practice and are not drawn specifically for research purposes.

Serial blood samples for pharmacokinetic and pharmacogenomic studies will be obtained during cycle one, between days 8 and 16 in the Georgetown University Clinical Research Unit, or locally at the enrolling site. Blood samples will be collected immediately prior to the ribociclib dose, and 0.5hr ± 5min, 1hr ± 5min, 2hr ± 15min, 4hr ± 15min, 6hr ± 15min after the daily dose of ribociclib. Samples will be collected in the Georgetown University Clinical Research Unit, or at the local site and shipped to the National Institute of Health to process and analyze the data.

Frozen whole blood will be used is isolate DNA via the Wizard® Genomic DNA Purification Kit (Promega). This assay is able to yield 250-500µg from 10mL of whole blood. The Tissue Culture and Biobanking Shared Resource (TCBSR) will perform DNA isolation in batches. Isolated DNA can then be used for pharmacogenomic testing.

Pharmacogenomic testing will be performed by the National Cancer Institute on the PharmacoScan™ microarray (Thermo Fischer). PharmacoScan™ analyzes 4,627 markers in 1,191 genes. These assay allows for the genotyping of multiple genes that have known pharmacogenetic value, including phase I and phase II enzymes, regulatory/modifier genes, drug target genes, and phase III/transporter genes. It includes 51 variants in *CYP3A4* and 22 in *CYP3A5*. In brief, the assay involves several steps, including amplifying DNA via multiplex polymerase chain reaction (PCR). The amplified DNA is then fragmented, precipitated, centrifuged and dried, and then resuspended and prepared for hybridization. Fragments then hybridize to the microarray and are processed by the GeneTitan™ Multi-Channel Instrument of PharmacoScan™.

Blood samples (3-4 mL for each timepoint) will also be used for serial pharmacokinetic studies. A liquid chromatography with tandem mass spectrometry (LC–MS/MS) method will be used to assess ribociclib concentrations in human plasma. An assay has been developed specifically for ribociclib (36). In brief, liquid chromatography separates compounds within, then an electrospray ionization and mass spectrometry are optimized to detect transitions between ribociclib and the internal standard [$^{13}C_6$] ribociclib. LC-MS/MS consists of serial sampling (times mentioned above) that will allow for calculation of maximum concentration ($C_{max}$), the time to reach $C_{max}$ ($T_{max}$), AUC, clearance, volume of distribution($v_d$), elimination half-life, and mean residence time (MRT). The lower limit of quantitation is 0.5 nM of ribociclib in plasma. A backup blood sample will be obtained for each timepoint in the serial collection and for the pharmacogenetic test. A summary of the amount of blood collected from each patient is listed below:

- 10 mL – 1 sample (10 mL) for pharmacogenomics assay
- 10 mL – 1 backup sample (10 mL) for pharmacogenomics assay
- 18 mL – 6 samples (3 mL each) for serial PK

- 18 mL – 6 backup samples (3 mL each) for serial PK
- Total: 56 mL

### 4.3.9 Electrocardiogram

Electrocardiograms will be obtained prior to the first cycle, middle of the first cycle (between C1D8-C1D16), at prior to the initiation of the second cycle. During the study, electrocardiogram will be assessed by the treating physician. If there are grade 2-4 cardiac toxicities the patient will be referred to cardio-oncology. At the end of the study cardio-oncology will review and tabulate results of QTc interval in all electrocardiograms (three per patient: one at baseline, cycle 1 day 8-16 and prior to initiation of cycle 2).

### 4.3.10 Adverse Event Assessment

Baseline symptoms at cycle 1 day 1 (prior to initiating therapy) should be detailed and graded. Once treatment has started, AEs will be assessed every 2 weeks during the first cycle. The individual Investigator should record any AE in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the AE to study drug, and any action(s) taken. AE grade (Based on the CTCAE 5.0) and start date will be documented in the adverse event monitoring form (Appendix 14.6). Patients will be followed for one cycle.

See section 8 for adverse event monitoring and reporting. The Principal Investigator or sub-Investigators will assess AEs, laboratory data, and vital signs throughout the study. AEs will be assessed by NCI CTCAE Version 5.0. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the patient will be recorded. All AEs will be followed to a satisfactory conclusion.

### 4.3.11 Removal of Patients from Study

Each patient has the right to withdraw from study treatment at any time. In addition, the Investigator may discontinue a patient from the study treatment at any time for any reason if the Investigator considers it necessary, including the occurrence of an AE or noncompliance with the protocol.

Each patient will be withdrawn from study treatment if any of the following occur:

- The patient requires radiotherapy or alternate antineoplastic agents during the study period
- The investigator believes it is in the best interest of the patient
- Clinically significant deterioration of the patient's medical status as determined by the investigator
- Any other medical reason that the study investigator deems appropriate

### 4.3.12 Discontinuation of Individual Patients

When a patient discontinues the study treatment (without reaching a protocol-defined endpoint), the investigator will notify the Principal Investigator as soon as possible (provided, in each case, patient care and safety are not compromised). When a patient discontinues the study treatment, a final visit will be conducted, preferably prior to the initiation of another anticancer therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator or patient's treating physician feel is necessary to treat the patient's condition. Following discontinuation of the study drug, the patient will be treated in accordance with the investigator's/treating physician's best clinical judgment.

At the final visit, the reason(s) for the discontinuation from the study will be recorded and a physical examination, body weight, vital signs measurement, laboratory analyses, performance status, tumor assessment, and an assessment of AEs will be performed as soon as possible after discontinuation from the study treatment. If a patient is discontinued from the study with an ongoing AE or an unresolved clinically significant laboratory result, the site will attempt to provide follow up until a satisfactory clinical resolution of the laboratory result or AE is achieved.

### 4.3.13 Patient Replacement Criteria

If a patient is enrolled but is unable to tolerate ribociclib or to participate in laboratory workup and cardiac studies as well during cycle 1, she would be deemed non-evaluable. In the case of an unexpected trauma or death that is considered unrelated to the underlying solid tumor malignancy, patient would be deemed to be non-evaluable.

### 4.3.14 Discontinuation of the Entire Study

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

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

### 4.3.15 Protocol Deviations

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

# 5 Study Treatments

## 5.1 Allocation to Treatment

Following full assessment and determination that the patient meets all eligibility criteria and has given informed consent for study participation; the investigator or designee will contact the study principal investigator (PI) or designee and request study enrollment. A patient identification number will be assigned, which must be used on all CRF pages and on all documentation and correspondence referencing that patient.

## 5.2 Compliance

Drug accountability will be performed at every visit during the first cycle (Appendix iii). The number of remaining capsules (of ribociclib and letrozole) will be documented and recorded to assess compliance.

The following paragraph is also discussed in the informed consent form. Patient's or their insurance company will have to pay for the prescribed medications as they are part of standard care. However, the first 28-day cycle of their treatment with ribociclib will be paid for through a voucher. Neither the patient nor insurance company would be charged for the first 28-day cycle of ribociclib. This is expected to cover the cost of the ribociclib for the duration of the study. More details about the voucher are available here: https://mprsetrial.mckesson.com/7426//#. If the patient and their physician choose to continue using ribociclib beyond the first cycle then it would lead to added costs for the patient and/or their insurance company.

## 5.3 Drugs

The drugs used in the course of this trial will be ribociclib and letrozole or fulvestrant as well as a luteinizing hormone-releasing hormone (LHRH) agonist (i.e., goserelin, leuprolide) for premenopausal women. These drugs are commercially available drugs and will be prescribed by their oncologist.

### 5.3.1 Ribociclib

Commercially available Ribociclib 600 mg (3 x 200 mg tablets by mouth) QD on days 1 to 21 of a 28-day cycle, followed by 7 days off ribociclib (Days 22 to 28).

### 5.3.2 Fulvestrant

Commercially available fulvestrant will be used. Locally obtained commercial supplies of fulvestrant will be used in accordance with local regulations.

### 5.3.3 Letrozole

Commercially available letrozole will be used. Locally obtained commercial supplies of fulvestrant will be used in accordance with local regulations.

### 5.3.4 Luteinizing hormone-releasing hormone (LHRH) agonist (e.g., goserelin, leuprolide)

Commercially available luteinizing hormone-releasing hormone (LHRH) agonist (goserelin or leuprolide) will be used. Locally obtained commercial supplies will be used in accordance with local regulations only for premenopausal women.

## 5.4 Dose Modifications

- The following dose modifications were developed from the FDA label and supplemented by additional participant-oriented modifications used in previous clinical trials.
- Grading is according to CTCAE Version 5.0.
- All treatment should be discontinued/delayed until the toxicity resolves to Grade 1 or lower, or to baseline if Grade 2 at the time of study entry
- Patients may delay retreatment for up to 28 days to allow the toxicity to resolve. If the toxicity requiring dose interruption has not resolved completely or to CTCAE Grade 1 (or to baseline if Grade 2 at time of study entry) during the maximum 28-day dose interruption period, the patient must permanently discontinue treatment on study
- Patients may restart therapy if toxicities resolve to Grade 1 or lower (or to baseline if Grade 2 at the time of study entry).
- If a dose interruption is required at any point on the study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and weekly blood draws for CBC also will be required for an additional 4 weeks after the AE has been resolved to the specified levels.
- The patient must be referred to a hematologist for further evaluation (1) if frequent transfusions are required or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE Grade 1 or less after 28 days.
- For major surgery while on treatment, up to 28 days of study treatment interruption is allowed.
- All dose interruptions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded.

Table 5: Dose Modification and Management for Interstitial Lung Disease/Pneumonitis

| | | | |
|---|---|---|---|
| Interstitial Lung Disease/Pneumonitis | **Grade 1** (asymptomatic) | **Grade 2** (symptomatic) | **Grade 3** (Severe symptomatic) or **Grade 4** (life-threatening) |
| | No dose interruption or adjustment is | Dose interruption until recovery to Grade $\leq$ 1 then | Discontinue ribociclib. |

| | | | |
|---|---|---|---|
| | required. Initiate appropriate medical therapy and monitor as clinically indicated | consider resuming ribociclib at the next lower dose level*.<br>If Grade 2 recurs, discontinue ribociclib. | |
| *An individualized benefit-risk assessment should be performed when considering resuming ribociclib. | | | |

Table 6: Dose Modification and Management for cutaneous adverse reactions including SCARs

| **Grade 1** (< 10% body surface area (BSA) with active skin toxicity, no signs of systemic involvement) | **Grade 2** (10-30% BSA with active skin toxicity, no signs of systemic involvement) | **Grade 3** (severe rash not responsive to medical management; > 30% BSA with active skin toxicity, signs of systemic involvement present; SJS*) | **Grade 4** (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life threatening consequences; TEN**) |
|---|---|---|---|
| No dose adjustment is required.<br><br>Initiate appropriate medical therapy and monitor as clinically indicated. | | Interrupt ribociclib until the etiology of the reaction has been determined.<br><br>If the etiology is a SCAR, permanently discontinue ribociclib.<br>If the etiology is not a SCAR, interrupt dose until recovery to Grade ≤ 1, then resume ribociclib at the same dose level.<br>If the cutaneous adverse reaction still recurs at Grade 3, resume ribociclib at the next lower dose level. | Permanently discontinue ribociclib. |
| Abbreviations: Severe Cutaneous Adverse Reactions (SCARs); Stevens-Johnson Syndrome (SJS); Toxic Epidermal Necrolysis (TEN)<br>* SJS (Grade 3 and 4) is defined as skin sloughing covering <10% BSA and 10-30% BSA, respectively, with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)<br>** TEN (Grade 4) is defined as skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment). | | | |

Table 7: Dose Modification and Management for QT Prolongation

| | |
|---|---|
| ECGs with QTcF* > 480 ms | • Interrupt ribociclib treatment ms<br>• If QTcF prolongation resolves to < 481 ms, resume treatment at the next lower dose<br>• If QTcF $\geq$ 481 ms recurs, interrupt dose until QTcF resolves to < 481 ms; then resume ribociclib at next lower dose level. |
| ECGs with QTcF* > 500 ms | • Interrupt ribociclib treatment if QTcF greater than 500 ms<br>• If QTcF prolongation resolves to < 481 ms, resume treatment at the next lower dose level.<br>Permanently discontinue ribociclib if QTcF interval prolongation is either greater than 500 ms or greater than 60 ms change from baseline AND associated with any of the following: Torsades de Pointes, polymorphic ventricular tachycardia, unexplained syncope, or signs/symptoms of serious arrhythmia. |
| Electrocardiograms (ECGs) should be assessed prior to initiation of treatment. Repeat ECGs at approximately Day 14 of the first cycle and at the beginning of the second cycle, and as clinically indicated.<br>*QTcF = QT interval corrected by Fridericia's formula. | |

Table 8: Dose Modification and Management for AST or ALT Elevations

| | **Grade 1** (> ULN – 3x ULN) | **Grade 2** (> 3 to 5x ULN) | **Grade 3** (>5 to 20x ULN) | **Grade 4** (> 20x ULN) |
|---|---|---|---|---|
| AST and/or ALT elevations from baseline*, WITHOUT total bilirubin increase above 2x ULN | No dose adjustment required | Baseline* at < Grade 2: Dose interruption until recovery to ≤ baseline grade, then resume ribociclib at same dose level. If Grade 2 recurs, resume ribociclib at next lower dose level<br>Baseline* at Grade 2: No dose interruption | Dose interruption until recovery to ≤ baseline* grade, then resume at next lower dose level.<br>If Grade 3 recurs, discontinue ribociclib. | Discontinue ribociclib |
| Combined elevations in AST and/or ALT WITH total bilirubin increase, in the absence of cholestasis | If patients develop ALT and/or AST > 3 x ULN along with total bilirubin > 2 x ULN irrespective of baseline grade, discontinue ribociclib. | | | |
| Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.<br>*Baseline = prior to treatment initiation. | | | | |

Table 9: Dose Modification and Management for Blood bilirubin increased without AST/ALT increase

| Toxicity/Grade | Recommendations |
|---|---|
| Blood bilirubin increased without AST/ALT increase | |
| **Grade 1**: >ULN - 1.5 x (upper limit of normal) ULN if baseline was normal;<br>> 1.0 - 1.5 x baseline if baseline was abnormal | Maintain dose level with LFTs monitored bi- weekly. |
| **Grade 2:**<br>>1.5 - 3.0 x ULN if baseline was normal;<br>>1.5 - 3.0 x baseline if baseline was abnormal | Dose interruption of ribociclib. If resolved to ≤ grade 1 in ≤ 21 days, then maintain dose level. If resolved to ≤ grade 1 in > 21-28 days or toxicity recurs, then 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, or recovery to ≤ grade 1 is > 28 days, discontinue ribociclib. |
| **Grade 3**: >3.0 - 10.0 x ULN if baseline was normal;<br>>3.0 - 10.0 x baseline if baseline was abnormal | Dose interruption of ribociclib, until resolved to ≤ grade 1, then lower 1 dose level of ribociclib. Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption. If resolved to ≤ grade 1 in > 28 days or toxicity recurs, discontinue ribociclib. |
| **Grade 4**: >10.0 x ULN if baseline was normal;<br>>10.0 x baseline if baseline was abnormal | Discontinue ribociclib. |

Table 10: Dose Modification and Management for Neutropenia

| **Grade 1 or 2** (ANC 1000/mm$^3$ to LLN) | **Grade 3** (ANC 500 to 1000/mm$^3$) | **Grade 3 Febrile Neutropenia** | **Grade 4** (ANC < 500/mm$^3$) |
|---|---|---|---|
| No dose adjustment required | Dose interruption until recovery to Grade ≤ 2. Resume ribociclib at the same dose level. If toxicity recurs at Grade 3, dose interruption until recovery, then resume ribociclib at the next lower dose level. | Dose interruption until recovery of neutropenia to Grade ≤ 2. Resume ribociclib at the next lower dose level. | Dose interruption until recovery to Grade ≤ 2. Resume ribociclib at the next lower dose level. |
| Abbreviations: ANC, absolute neutrophil count; LLN, lower limit of normal. *Grade 3 neutropenia with single episode of fever > 38.3°C (or) above 38°C for more than one hour and/or concurrent infection. | | | |

Table 11. Dose modifications and Management for Thrombocytopenia and Anemia

| Toxicity/Grade | Recommendations |
|---|---|
| Thrombocytopenia (platelet count) | |
| Grade 1: <75,000 mm3 | No dose adjustment required |
| Grade 2: 50-75 mm3 | Dose interruption until recovery to grade ≤1. Re- initiate ribociclib at the same dose. |
| Grade 3: 25-50 mm3 | Dose interruption until recovery to grade ≤1. Re- initiate ribociclib at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤1 and reduces ribociclib to the next lower dose level. |
| Grade 4: >25 mm3 | Dose interruption until recovery to grade ≤1. Re- initiate ribociclib at the next lower dose level. If toxicity recurs at grade 4: discontinue ribociclib. |
| Anemia (hemoglobin) | |
| Grade 1: ≥10.0 – LLN g/dL | No dose adjustment required. |
| Grade 2: ≥8.0 – <10.0 g/dL | No dose adjustment required. |
| Grade 3: <8.0 - >4.9 g/dL, transfusion indicated | Dose interruption until recovery to grade ≤2. Re- initiate ribociclib at the same dose. |
| Grade 4: Life-threatening consequences; urgent intervention indicated | Discontinue ribociclib. |

Table 12: Dose Modification and Management for Other Toxicities that are deemed related and clinically significant by the treating physician*

| **Grade 1 or 2** | **Grade 3** | **Grade 4** |
|---|---|---|

| | | |
|---|---|---|
| No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated | Dose interruption until recovery to Grade $\leq$ 1 then resume ribociclib at same dose level.<br>If Grade 3 recurs, resume ribociclib at the next lower dose level. | Discontinue ribociclib. |
| *Excluding adverse reactions discussed in tables 5-11. | | |

Table 13. Dose Modifications for Toxicities Related to Ribociclib

| | |
|---|---|
| Starting dose | 600 mg |
| First dose reduction | 400 mg |
| Second dose reduction | 200 mg |

## 5.5 Drug Accountability

Ribociclib and letrozole are oral medications, patients will bring the containers to the visits for pill accountability, per section 5.2.

## 5.6 Concomitant Medications

Patients will be instructed to consult the Investigator or other appropriate study personnel before taking any new medications, supplements, or vaccines during the study prescribed by a provider or over the counter medications or supplements-.

Concomitant medications taken within 30 days prior to baseline will be recorded. At each study visit, all concomitant medications taken since the previous visit, including prescription and non-prescription medications, vitamin and mineral supplements, herbal and naturopathic remedies, vaccines, and supportive therapies, will be recorded.

### 5.6.1 Permitted Concomitant Medications

Medications required to treat AEs, manage cancer symptoms, concurrent diseases, and supportive care agents, such as pain medications, antiemetics, and antidiarrheals are allowed. Potential drug interaction between ribociclib and concomitant medications should always be taken into consideration when prescribing such medications. Bisphosphonates and denosumab are allowed.

Prophylactic use of WBC growth factors with ribociclib is not recommended.

Antiemetic therapy can be used according to clinical guidelines for antineoplastic medications with low to minimal emetogenic potential for treatment and/or prevention of nausea and vomiting as a result of study treatment

### 5.6.2 Medications Prohibited

A full list of the medications that are prohibited during study treatment can be found in the appendix 14.4.

Other investigational and anti-neoplastic therapies (including radiation) are prohibited.

Systemic corticosteroid treatment should not be given during the study treatment with ribociclib, except for:

a. Topical applications (e.g. for rash), inhaled sprays (e.g. for obstructive airways diseases), eye drops or local injections (e.g. intra-articular)
b. A short duration (< 5 days) of systemic corticosteroids ≤ to the anti-inflammatory potency of 4 mg dexamethasone (e.g. for chronic obstructive pulmonary disease or as an antiemetic).

### 5.6.3 Medications Not Recommended

In appendix 14.5 there is a list of the medications are not recommended during study treatment and within 14 days prior to the first dose of study medication and for the duration of study treatment. These medications should be excluded if possible. If they must be given, then it will be based on the investigator's judgment.

# 6 Study Procedures

## 6.1 Schedule of Events

Screening assessments are to be conducted within 28 days prior to initiating protocol therapy unless otherwise specified. CBC with differential and biochemical profile (sodium, potassium, calcium, chloride, bicarbonate, BUN, creatinine, AST, ALT, total bilirubin, albumin, alkaline phosphatase) assessments must be done within 28 days prior to initiating protocol therapy, between day 8-16 of cycle 1, and prior to initiation of cycle 2.

Table 14. Study Calendar: Patients will be followed for one cycle

| Study procedure/task | Screening [a] | Treatment cycle is 28 days | End of study [b] |
|---|---|---|---|
| Study day | ≤ 28 days prior to study entry | Cycle 1 Day 8 - 16 | |
| Procedures | | | |
| Eligibility criteria [c] | X | | |
| Informed consent [d] | X | | |
| Clinical visits [e] | X | Per routine clinical practice | |
| Adverse Events | | X | X |
| CYP3A5 Screening [f] | X | | |
| Treatments [g] | | | |
| Ribociclib | | 600 mg PO once daily for 21 days, followed by a 7-day rest period to complete a 28-day treatment cycle | |
| Fulvestrant | | 500 mg IM injection on days 1 and 15 | |
| Letrozole | | 2.5 mg PO daily | |
| Goserelin | | 3.6 mg SQ every 28 days<br>or<br>10.8 mg SQ every 12 weeks | |
| Leuprolide depot | | 3.75 mg IM every 28 days<br>or<br>11.25 mg IM every 12 weeks | |
| Tests | | | |
| Blood draw for pharmacogenomic studies | | X | |
| Serial blood draws for pharmacokinetic studies<br>• Immediately prior to the ribociclib dose, and 0.5hr ± 5min, 1hr ± 5min, 2hr ± 15min, 4hr ± 15min, 6hr ± 15min after the daily dose of ribociclib. | | X | |
| Electrocardiogram [h] | X | X | X |
| CBC with differential and CMP [i] | X | X | X |
| Pregnancy Test [j] | X | | |
| NCI CTCAE PRO questionnaire[k] | X | X | X |
| Adverse event monitoring log | X | X | X |
| Medication adherence PROMIS questionnaire and drug accountability | | X | X |

[a] Screening: All assessments should be performed within 28 days prior to study entry. Study entry will be defined by confirmation of eligibility.

[b] This visit will occur prior to initiation of cycle 2 (e.g., 29th day of the study, plus or minus 3 days)
[c] Eligibility Criteria Evaluation: Patients must meet all of the eligibility criteria reported in the protocol
[d] Informed Consent: Must be obtained prior to undergoing any study-specific procedures.
[e] Clinical Visits: clinical visits will include medical history, vital signs and physical exam and will be conducted as per local practice and as clinically indicated. Physical Examination includes a general clinical examination of major body systems.
[f] To be performed after informed consent and used for screening according to sections 3.6 and 4.3.7. CYP3A5 Screening may be bypassed per Principal Investigator discretion if the necessary number of participants with each phenotype are enrolled (cohort of AA or Black participants - at least 3 poor metabolizers; cohort of NHW participants - at least 3 intermediate or normal metabolizers). If CYP3A5 is already performed it does not need to be repeated within the window of $\leq$ 28 days.
[g] All patients will receive ribociclib plus physician choice endocrine therapy with fulvestrant or letrozole. Luteinizing hormone-releasing hormone (LHRH) agonist (goserelin or leuprolide) will be required for premenopausal women.
[h] To be performed at these times per routine clinical practice and the treating physician: prior to treatment initiation; repeat on day 8-16 of cycle 1, and prior to initiation of cycle 2
[i] To be performed at these times per routine clinical practice and the treating physician: baseline, repeat on day 8-16 of cycle 1, and prior to initiation of cycle 2
[j] To be performed at these times per routine clinical practice and the treating physician: Pregnancy test (serum or urine), required for women of childbearing potential
[k] Questionnaires to be completed within 28 days of C1D1

## 6.2 Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for safety or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Reasons why patients may discontinue or be withdrawn from the protocol may be due to the following:
- AEs
- Intercurrent illness
- Disease progression
- Patient is non-compliant
- Patient is lost to follow-up
- Withdrawal of consent

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcomes, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product, request the patient to

return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

# 7 Assessments

## 7.1 Safety Assessments

Safety assessment will consist of monitoring of all AEs, including serious adverse events (SAEs) at every clinical visit and monitoring of hematology to be performed to check the patient's eligibility at the time of screening, on day 8-16 of cycle 1, and prior to initiation of cycle 2

Other procedures as necessary according to standard of care and in accordance with each site's institutional guidelines will be assessed to monitor for AEs related to the underlying disease, treatment with ribociclib, other endocrine therapy, or supportive therapies.

### 7.1.1 Physical Examination

A full physical examination of all major body systems will be required at screening. Symptom directed physical examinations will be performed as per routine clinical practice during the study. Only physical examination at screening will be recorded on the case report form (CRF).

### 7.1.2 Safety Assessments

Blood tests will include the following:

1) Hematology panel: complete blood count with differential
2) Blood chemistry panel: ALT, ASL, alkaline phosphatase, total bilirubin, serum creatinine

Blood tests will be drawn at the time points described in the study calendar table and analyzed at local laboratories.

A hematology panel (includes complete blood count with differential) will be performed to verify the patient's eligibility at screening, repeat on day 8-16 of cycle 1, and prior to initiation of cycle 2. Laboratory data will be recorded on the CRF.

Blood Chemistry will be performed to verify the patient's eligibility at screening, repeat on day 8-16 of cycle 1, and prior to initiation of cycle 2. Laboratory (blood chemistry and

hematology panels) data will be recorded on the CRF. In the case a laboratory abnormality meets the definition of AE, as determined by the investigator and according to AE reporting, this must be captured on an AE CRF page.

Electrocardiograms will be performed to verify the patient's eligibility at screening, repeat on day 8-16 of cycle 1, and prior to initiation of cycle 2 of treatment with ribociclib. Data will be recorded on the CRF. In the case an electrocardiogram abnormality meets the definition of AE, as determined by the investigator and according to AE reporting, this must be captured on an AE CRF page.

# 8 Adverse Event Reporting

## 8.1 Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

## 8.2 Reporting Period

For SAEs, the active reporting period to the principal investigator begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, through the completion of cycle 1.

AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least one dose of ribociclib through the last patient visit.

Death must be reported if it occurs during the SAE reporting period after the last dose of ribociclib, irrespective of any intervening treatment.

## 8.3 Definition of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Hypersensitivity
- Drug abuse
- Drug dependency

Additionally, they may include the signs and symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug misuse
- Drug interactions
- Medication error
- Occupation exposure
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section in the CRF

Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

### 8.3.1 Medication Errors

Medication errors may result from the administration or consumption of the wrong drug, by the wrong patient, at the wrong time, or at the wrong dosage strength.

Such medication errors occurring to a study participant are to be captured on the medication error CRF which is a specific version of the AE page, and on the SAE form when appropriate.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product
- Potential medication errors or uses outside of what is foreseen in the protocol that does or does not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error should be captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

## 8.4 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or

- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

## 8.5 Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:
- Results in death
- Is life-threatening (immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTC Grade 5 (see Section on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

If an AE meets any of the following criteria, it is to be reported to the DSMC as an SAE:

1) **Death of Patient** An event that results in the death of a patient.
2) **Life-Threatening** An event that, in the opinion of the Investigator, would have resulted in immediate fatality if the medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

3) **Hospitalization** (unless planned for observation, protocol compliance, elective procedures, social reasons) **or**
4) **Prolongation of Hospitalization** An event that results in an admission to the hospital for any length of time or prolongs the patient's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
5) **Congenital Anomaly** An anomaly detected at or after birth, or any anomaly that results in fetal loss.
6) **Persistent or Significant Disability/Incapacity** An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
7) **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

   Dose-limiting toxicities are defined as AEs that are possibly, probably, or definitely related to the therapy (any part of the combination) and would require treatment discontinuation.

## 8.6 Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:
- Rehabilitation facilities
- Hospice facilities
- Respite care (i.e. caregiver relive)
- Skilled nursing facilities
- Nursing homes
- Same-day surgeries

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not an SAE. Examples include:
- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., patient has no place to sleep);
- Administrative admission (e.g., for yearly physical examination);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

## 8.7 Severity Assessment

AEs will be graded according to the National Cancer Institute Common Terminology Criteria (NCI CTC), (Version 5.0). Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

The study Investigator will rate the severity of each AE according to the NCI CTCAE Version 5.0. For AEs not captured by the NCI CTCAE Version 5.0, the following should be used:

1) **Grade 1 (Mild)** The AE is transient and easily tolerated by the patient. No dose adjustment recommended.
2) **Grade 2 (Moderate)** The AE causes the patient discomfort and interrupts the patient's usual activities. Interrupt therapy until grade <1, reinitiate ribociclib at the same dose, if AE reoccurs at grade 2, hold until grade <1, and restart at the next lower dose level.
3) **Grade 3 (Severe):** The AE causes considerable interference with the patient's usual activities. Interrupt therapy until grade <1, reinitiate ribociclib at the same dose, if AE reoccurs at grade 2, hold until grade <1, and restart at the next lower dose level. If toxicity reoccurs grade 3 discontinue permanently.

4) **Grade 4 (Life Threatening)** The AE causes considerable interference with the patient's usual activities and maybe incapacitating or life-threatening. Discontinue ribociclib.
5) **Grade 5 (Severe, Resulting in Death)** The AE resulted in the death of the patient.

## 8.8 Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

## 8.9 Withdrawal Due to Adverse Events

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page. When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

## 8.10 Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the patient. In addition, each study patient will be questioned about AEs.

## 8.11 Reporting Requirements

### 8.11.1 Serious Adverse Events

In the event of an SAE, whether related to study drugs, study procedures or even if not directly related to any study intervention, the study team will notify the Principal

Investigator and Co-Principal Investigators, via email and cc: LCCC-Multicenter-IITs@georgetown.edu within 24 hours of being made aware of the SAE. SAEs should be reported on the FDA Medwatch form.

SAEs should be reported to the IRB, per local IRB guidelines, and to the DSMC, per DSMC reporting guidelines.

#### 8.11.2 Non-Serious Adverse Events

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for the collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used in both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for the collection of SAE information.

# 9 Data Analysis and Statistical Methods

## 9.1 Sample Size, Accrual and, Study Duration

This study is powered to assess the primary outcome (ribociclib in CYP3A5 poor metabolizers vs. CYP3A5 intermediate or normal metabolizers) independently within each race-based cohort. The pharmacokinetic study used to inform the FDA's decision to suggest alternative dosing for patients prescribed a strong CYP3A inhibitor (ritonavir) exhibited a 3.2-fold increase in AUC (15). Genotype may have a lower effect, but the extent of the effect is unclear. We will aim to detect a minimum clinically meaningful change: 2-fold change in AUC, which is less than the fold changes seen in the ritonavir CYP3A drug interaction pharmacokinetic study. In the meantime, data from the same pharmacokinetic study showed the standard deviation of AUC fold change (in $\log_2$ scale) was 0.56. Given that the groups in our study are considered similar, to be conservative, we used the standard deviation of 0.75 in our calculation.

Allelic frequencies for *CYP3A5* are provided from CPIC and PharmGKB and translated to phenotypes via the Hardy-Weinberg equation (32). Based on these frequencies (normal metabolism: 35%; intermediate metabolism: 48%; poor metabolism: 16%), a sample size of 18 would provide 80% power at an $\alpha$=0.05 to detect a 2-fold change in AUC between CYP3A5 poor metabolizers vs. CYP3A5 expressors (i.e., CYP3A5 intermediate or normal metabolism) in African Americans/Blacks. Based on the allelic frequencies for Non-Hispanic Whites (normal metabolism: 0.6%; intermediate metabolism: 14.7%; poor metabolism: 84.6%), a sample size of 18 would also provide 80% power at an $\alpha$=0.05 to detect a 2-fold change in AUC between CYP3A5 poor metabolizers vs. CYP3A5 expressors (i.e., CYP3A5 intermediate or normal metabolism).

Thus, an overall sample size of 36 would provide adequate power to independently test the primary outcome in the two race-based cohorts.

## 9.2 Statistical Analysis Plan

Primary analyses will be performed as follows. Within each race-based cohort, the ribociclib exposure which measured by ribociclib AUC will be summarized by median [Interquartile range, IQR], and two-sample t-test if normality holds or Wilcoxon-Mann-Whitney test will be used to compare AUC between CYP3A5 poor metabolizers and CYP3A5 intermediate or normal metabolizer in each independent race-based cohort. Secondary analyses will be performed as follows. Descriptive statistics will be used to characterize the data profile, frequency and percentages for categorical variables, and mean (SD) or median [IQR] for continuous variables based on the data normalization. Multiple regression will be used to identify variables associated with ribociclib AUC. To best account for any factor that may affect ribociclib exposure, covariates to be assessed include CYP3A5 metabolism status, renal function, liver function, age, race, weight, sex, among others. Any covariates with $P < 0.2$ on univariate analysis will enter the stepwise multiple linear regression model, with $P < 0.05$ considered statistically significant. This methodology will also be used to assess a change in absolute neutrophil count and QTc as the outcome variable. Depending on data distribution, a two-sample t-test or Wilcoxon-Mann-Whitney test will be used for 1) a change (baseline and C1D8-C1D16) in continuous variables (e.g., QTc, absolute neutrophil count) between CYP3A5 poor metabolizers and CYP3A5 intermediate or normal metabolizers, 2) to check the association between a continuous variables and categorical risk factors. Pearson correlation coefficient or Spearman correlation coefficient will be calculated to measure the association between two continuous variables. Fisher's exact test will be used for checking the association between two categorical variables. AEs will be assessed with descriptive statistics and univariate logistic regression will assess the occurrence of specific AEs with pharmacokinetic properties (e.g., AUC, $C_{max}$). The approach from the linear regressions will be adapted to logistic regression to identify covariates associated with the occurrence of grade III or IV neutropenia.

Descriptive analysis of the PRO-CTCAE adverse event log to determine frequency of adverse events by race and by *CYP3A5* genotype.
Descriptive statistics will be used to describe the patients reported outcomes in the survey (see Appendices). As an exploratory analysis, multiple regressions will be used to assess the relationship between patients reported outcomes and other covariates (mentioned above) with ribociclib AUC.

## 9.3 Correlative Studies

The PharmacoScan™ microarray provides data on 4627 markers for each patient. These data serve as a rich opportunity for hypothesis-generating correlative studies with pharmacokinetic properties or AEs. Study designs for exploratory pharmacogenomics are usually conducted as either candidate gene studies or a genome-wide association study (GWAS) (37). This work will be conducted as a candidate gene analysis as the sample size (n = 36) is too limited to attempt a study similar to a GWAS.

Candidate genes will be selected based on biological plausibility. For example, although data around *CYP3A4* are limited (section 1.4), it is a prime candidate gene given overlapping substrate specificity with CYP3A5 and the significant sequence homology (approximately 84%) between *CYP3A4* and *CYP3A5*. Additional candidate genes will be identified based on metabolic pathways, signaling pathways, ribociclib mechanism of action.

A list of genes will be created through a primary literature review and information from the FDA review. Given the pace of discovery work in this field, the list will be generated at or near the completion of the data collection. Prior to the analysis, genes will be ranked so that the stronger candidates are tested with a given outcome first. For example, *CYP3A4* will likely be the first gene assessed for an association with ribociclib AUC with statistical analysis as described in section 9.3 and those similar to other work (38).

Another example of a candidate gene is the *ABCB1* gene which is included in the PharmacoScan™ assay and single nucleotide variations were recently associated with persistent chemotherapy induced alopecia (39). A recent study in our institution showed that the use of scalp cooling in African American/Black women with early stage breast cancer receiving chemotherapy was not effective preventing alopecia; alopecia was prevented in 0/11 patients while previous studies in White populations have reported 50-80% success (40). For this exploratory analysis we aim to assess if this difference could be related to genetic variations and this could potentially be studied in the future with cytotoxic agents associated to alopecia. Depending on how many genes are in the list, we will provide the q-value as well to control the false discovery rate and we may also attempt a learning algorithm such as LASSO or a variant of it to further screen the associated markers

## 9.4 Safety Analysis

Safety data will be summarized for all patients who received one cycle of ribociclib.

## 9.5 Data Safety Monitoring Committee

As this study is an investigator-initiated study utilizing FDA approved agents it is considered a moderate risk study that requires real-time monitoring by the PI and study

team and semiannual reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and with other investigators (when available) and research staff will review the accrual, toxicities, and other protocol issues at weekly protocol meetings and on monthly network disease group teleconferences.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 6 months from the time the first patient is enrolled in the study. Results of the DSMC meetings will be forwarded to the IRB. E-mail notification from the PI will be sent to the DSMC Chair any time there is a major event or issue with the trial affecting patient safety or conduct of the trial. The DSMC Chair has the discretion to have the study reviewed by the DSMC sooner more frequently than every 6 months based on information received.

All SAEs, which are considered unanticipated problems, are required to be reported to the IRB. In addition, all SAEs will be submitted to the DSMC, per DSMC requirements. Based on SAEs, the IRB retains the authority to close the study to further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

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

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

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision.

The rights and privacy of people who participate in a clinical research will be protected at all times. In the event that data are to be used for broader research, it will be de-identified and would not permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual patients. No efforts will be made to identify individual cases, and any shared archive data will not be linked to other identifiable data. The following de-identification and security procedures will be followed to share information with collaborators part of the study:

1) Deletion of 18 HIPAA identifiers
    a. Non-identifiable unique patient ID will be generated
2) Secure netID-based single sign-on (netID is Georgetown's LDAP based secure login system)
3) Users will have to *authenticate* themselves prior to accessing controlled data
4) Furthermore, based on their roles, users will require *authorization* to see specific studies
5) Auditing and security assessments will be performed on a quarterly basis to ensure appropriate de-identification procedures and use of data.

For future studies involving new data types that are not covered in the descriptions above, NIH policy on data sharing will be followed where applicable. For example, Genome Wide Association Studies, if conducted, will comply with *NIH Guidelines* NOT-OD-07-088 (http://grants.nih.gov/grants/gwas/) for data release. Following these guidelines, GWAS data will be submitted to NCBI's dbGAP (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap) or other tools as the NIH's policy on GWAS evolves.

# 10 Quality Control and Quality Assurance

The study site may be subject to review by the IRB or to inspection by appropriate regulatory authorities. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

# 11 Data Handling and Record Keeping

## 11.1 Case Report Forms and Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to an electronic data record. A CRF is required and should be completed for each included patient. Patient data will be entered into the online accessible database. This database is housed at Lombardi-Georgetown but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an online training session so that they may learn how to enroll data into the database. All screening data

should be entered prior to starting therapy, and all ongoing patient data should be entered within 10 business days of each patient visit. The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. Blood chemistry laboratory data during the treatment period, electrocardiograms, and concomitant medications will be collected on the CRF. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts. In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

## 11.2 Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the study records must be transferred to a designee, such as another investigator, or another institution. Investigator records must be kept for a minimum of 2 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

## 11.3 Collaboration with the National Cancer Institute

As described in sections 4.1 and 4.3.7, the NCI is collaborating with GLCCC and MWHC by providing pharmacogenomics and PK testing for the study. The NCI will receive biological samples (e.g., plasma, isolated DNA) in order to perform these assays. In addition, the NCI may receive de-identified data (e.g., age, height, weight, concomitant medications) to assist with the PK and pharmacogenomics analyses. Deidentified data will be encrypted and sent electronically to NCI investigators listed on this protocol.

# 12 Ethics

## 12.1 Institutional Review Board (IRB)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB. All correspondence with the IRB/EC should be retained in the Investigator File.

The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB in writing immediately after the implementation.

## 12.2 Ethical Conduct of the Study

This protocol will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

## 12.3 Patient Information and Consent

All parties will ensure the protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject's actual identity. The informed consent/assent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed, unless a waiver of informed consent has been granted by the IRB. The investigator will retain the original

of each patient's signed consent/assent document.

Participants are compensated for their time, transportation costs, and parking through a flat compensation of $150. This compensation will be available upon completion of the study visit between C1D8-C1D16. For subjects that are seen at the Georgetown CRU, the CRU will provide lunch for the participants during their visit, which is also paid for by the study. At other local sites, the participants will be provided a $10 stipend for a meal.

## 12.4 Risk/Benefit Assessment

### 12.4.1 Risks

All risks have been described in the consent form. Based on the assessments of the risk-to-benefit ratio, the risk level associated with participation in this study is low.

Participants will undergo blood draws in this study. These blood draws will be performed by trained personnel who use appropriate hygiene practices to reduce the risk of infection. Minor discomfort and bruising related to needle insertion are common.

There are risks secondary to study participation related to genetic testing, such as risks related to confidentiality surrounding the genetic information and the chance that the genetic information could in some way expose the study subject to increased risk regarding employment discrimination or that future life, health, disability or long term care insurance providers could potentially use this genetic information to modify the availability or pricing of insurance coverage. These concerns have arisen mainly in regard genetic testing results that are associated with susceptibility to disease risk and are generally less of a concern with pharmacogenomic testing such as that in the proposed study. Moreover, these genetic results are not meant for clinical use and will not be uploaded to the electronic health record or delivered to patients. The consent process will ensure patients are aware that they will not receive genetic results and that the genetic results are intended for research purposes only. Patients who would like to undergo genetic testing are free to do so outside of this research study.

However, in the event this information is inadvertently or mistakenly released, the Genetic Information Nondiscrimination Act (GINA) indicates 1) health insurers may not use individual genetic information to make decisions about eligibility or to set premium amounts, and 2) employers with 15 or more employees may not use genetic information for decisions about hiring, promotion, or employment termination. They may not use individual genetic information when setting the terms of employment.

### 12.4.2 Protections Against Risks

We will prevent or minimize risk through several actions. First, we collect study subject identifying information only when absolutely necessary. Second, participation is always completely voluntary with the right to withdraw at any time. Third, as described in section 11, we have a very rigorous data storage and security plan that minimizes any chances of a data breach.

### 12.4.3 Benefits

There is no direct clinical benefit to patients for participating in this study. In the absence of a direct benefit, the study may advance the fields by provided an increased understanding of ribociclib metabolism, pharmacokinetics, and pharmacogenomics in the treatment of advanced breast cancer.

## 12.5 Reporting of Safety Issues

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable Competent Authority, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the principal investigator should be informed immediately.

In addition, the principal investigator will be notified of any urgent safety measures taken by any investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or ICH GCP that the investigator becomes aware of. Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

a. Emergency Modifications: Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

b. Single Patient/Subject Exceptions: Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the Principal Investigator and the IRB.

c. Other Protocol Deviations/Violations: All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB.

According to the IRB, a protocol deviation is any unplanned variance from an IRB

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

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

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

a. Protocol Deviations: Personnel will report to any data and safety monitoring committee in accordance with their policies. Minor deviations should be summarized and reported to the IRB at the time of continuing review. Major deviations should be summarized and reported to the Regulatory Affairs Coordinator who will submit to the IRB as soon as possible, but not more than 10 calendar days after acquiring information reasonably suggesting that a reportable (major) deviation has occurred.

b. Protocol Violations: Violations should be reported by study personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

## 12.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

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

# 13 References


1. Robinson BN, Newman AF, Tefera E, Herbolsheimer P, Nunes R, Gallagher C, et al. Video intervention increases participation of black breast cancer patients in therapeutic trials. NPJ Breast Cancer. 2017;3:36.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.
3. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747-52.
4. Institute NC. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Mortality - All COD, Aggregated With State, Total U.S. (1969-2017) <Katrina/Rita Population Adjustment December 2019 [Available from: www.cdc.gov/nchs.
5. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687-717.
6. Klijn JG, Blamey RW, Boccardo F, Tominaga T, Duchateau L, Sylvester R, et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol. 2001;19(2):343-53.
7. Bonneterre J, Thurlimann B, Robertson JF, Krzakowski M, Mauriac L, Koralewski P, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol. 2000;18(22):3748-57.
8. Robertson JFR, Bondarenko IM, Trishkina E, Dvorkin M, Panasci L, Manikhas A, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet. 2016;388(10063):2997-3005.
9. Leung BS, Potter AH. Mode of estrogen action on cell proliferative kinetics in CAMA-1 cells. I. Effect of serum and estrogen. Cancer Invest. 1987;5(3):187-94.
10. Malumbres M, Barbacid M. Cell cycle, CDKs and cancer: a changing paradigm. Nat Rev Cancer. 2009;9(3):153-66.
11. Nadia Harbeck FdrP-L, Javier Cortes, Michael Gnant5 Nehmat Houssami, Philip Poortmans, Kathryn Ruddy, Janice Tsang and Fatima Cardoso. Breast cancer. Nature Reviews. 2019;5(66).
12. Tripathy D, Bardia A, Sellers WR. Ribociclib (LEE011): Mechanism of Action and Clinical Impact of This Selective Cyclin-Dependent Kinase 4/6 Inhibitor in Various Solid Tumors. Clin Cancer Res. 2017;23(13):3251-62.
13. Neil A. O'Brien EDT, Raul Ayala, Luo Tong, Shawnt Issakhanian, Ronald Linnartz, Richard S. Finn, Samit Hirawat and Dennis J. Slamon. Abstract 4756: In vivo efficacy of combined targeting of CDK4/6, ER and PI3K signaling in ER+ breast cancer. Cancer research. 2014;74(19).

14. KISQALI. KISQALI (ribociclib) package insert 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209092s000lbl.pdf. Accessed 9/2/2020 [
15. Samant TS, Huth F, Umehara K, Schiller H, Dhuria SV, Elmeliegy M, et al. Ribociclib Drug-Drug Interactions: Clinical Evaluations and Physiologically-Based Pharmacokinetic Modeling to Guide Drug Labeling. Clin Pharmacol Ther. 2020.
16. Aditya Bardia SM, Mariana Chavez-Mac Gregor , Muaiad Kittaneh , Alyssa J. Marino , Alessandro MatanoSuraj Bhansali , Becker Hewes , Javier Cortes. Phase Ib/II study of LEE011, everolimus, and exemestane in postmenopausal women with ER+/HER2-metastatic breast cancer. JCO. 2017;32.
17. Dejan Juric EH, Laura Garcia Estévez, Richard H De Boer, Ingrid Mayer, Mario Campone, Shizuka Asano, Suraj Bhansali, Vickie Zhang, Becker Hewes and Pamela Munster. Abstract P5-19-24: Phase Ib/II study of LEE011 and BYL719 and letrozole in ER+, HER2– breast cancer: Safety, preliminary efficacy and molecular analysis. Cancer research. 2015;75(9).
18. SM Tolaney AF-T, V Boni, T Bachelot, Y-S Lu, M Maur, A Fasolo, M Motta, C Pan, J Dobson, B Hewes and S Chin Lee. Abstract P4-22-12: Ribociclib + fulvestrant in postmenopausal women with HR+, HER2– advanced breast cancer (ABC). Cancer Research. 2017;77(4).
19. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016;375(18):1738-48.
20. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol. 2018;29(7):1541-7.
21. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018;36(24):2465-72.
22. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2020;382(6):514-24.
23. Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018;19(7):904-15.
24. Medicine NUNLo. clinicaltrials.gov 2020 [Available from: https://clinicaltrials.gov/ct2/results?cond=&term=CTLA4&cntry=&state=&city=&dist=.
25. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016;17(4):425-39.
26. Filipa Lynce RZ, Matthew Blackburn, Christopher Gallagher, Olwen Hahn, Maysa Abu-Khalaf, Mahsa Mohebtash, Tianmin Wu, Paula Pohlmann, Asma Dilawari, Shruti Tiwari, Ami Chitalia, Robert Warren, Ming Tan, Ayesha Shajahan-Haq and Claudine Isaacs. Abstract P1-19-20: Safety of palbociclib in African American women with hormone receptor positive HER2 negative advanced breast cancer and benign ethnic neutropenia: PALINA study. Cancer Res. 2020;80.
27. FDA. NDA/BLA Multi-disciplinary Review and Evaluation, KISQALI (ribociclib). 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209092Orig1s000MultidisciplineR.pdf. Accesed 9/2/2020.

28. NIH. NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research 2017. https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm. Accessed 9/2/2020 [
29. Al Hadidi S, Mims M, Miller-Chism CN, Kamble R. Participation of African American Persons in Clinical Trials Supporting U.S. Food and Drug Administration Approval of Cancer Drugs. Ann Intern Med. 2020.
30. Gonzalez FJ CM, Tukey RH. Drug Metabolism. In: Brunton LL, Hilal-Dandan R, Knollmann BC. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. McGraw-Hill N, editor. NY2020.
31. Lamba JK, Lin YS, Schuetz EG, Thummel KE. Genetic contribution to variable human CYP3A-mediated metabolism. Adv Drug Deliv Rev. 2002;54(10):1271-94.
32. Birdwell KA, Decker B, Barbarino JM, Peterson JF, Stein CM, Sadee W, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther. 2015;98(1):19-24.
33. Seibert SR, Schladt DP, Wu B, Guan W, Dorr C, Remmel RP, et al. Tacrolimus trough and dose intra-patient variability and CYP3A5 genotype: Effects on acute rejection and graft failure in European American and African American kidney transplant recipients. Clin Transplant. 2018;32(12):e13424.
34. Flockhart D. Drug interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine 2007. "https://drug-interactions.medicine.iu.edu" Accessed 09/02/2020. [
35. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) Breast Cancer. V 8.2021 ed. Accessed 10/11/2019. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
36. Bao X, Wu J, Sanai N, Li J. Determination of total and unbound ribociclib in human plasma and brain tumor tissues using liquid chromatography coupled with tandem mass spectrometry. J Pharm Biomed Anal. 2019;166:197-204.
37. Walgren RA, Meucci MA, McLeod HL. Pharmacogenomic discovery approaches: will the real genes please stand up? J Clin Oncol. 2005;23(29):7342-9.
38. Iyer L, Hall D, Das S, Mortell MA, Ramirez J, Kim S, et al. Phenotype-genotype correlation of in vitro SN-38 (active metabolite of irinotecan) and bilirubin glucuronidation in human liver tissue with UGT1A1 promoter polymorphism. Clin Pharmacol Ther. 1999;65(5):576-82.
39. Nunez-Torres R, Martin M, Garcia-Saenz JA, Rodrigo-Faus M, Del Monte-Millan M, Tejera-Perez H, et al. Association Between ABCB1 Genetic Variants and Persistent Chemotherapy-Induced Alopecia in Women With Breast Cancer. JAMA Dermatol. 2020.
40. Asma Ali Dilawari PA, Richard Paxman, Ami Chitalia, Christopher Gallagher, Shruti Rakesh Tiwari, Chiranjeev Dash, Lucile L. Adams-Campbell. Scalp cooling to prevent chemotherapy induced alopecia (CIA) in black patients: Differences in efficacy? JCO. 2020;38.

# 14. Appendices

## 14.1. PROMIS Medication Adherence

Medication Adherence

I'd like you to answer the following questions about your breast cancer medicine. Your medication might be called ribociclib or Kisqali. What breast cancer medication will you have in mind as you are answering these questions?

_____

I'll read the responses for these questions, so you won't need a response card.

1. How many times per day are you supposed to take this medicine? Would you say...
   Less than once per day……, 1
   Once per day……..,2
   Twice per day……, 3
   Three or more per day?……. 4

   To what extent do you agree with the following statements?
2. You know how to take this medication as recommended. Would you say you...
   Strongly disagree……..……,1
   Disagree……..……..,2
   Neither agree nor disagree……., 3
   Agree……,4
   Strongly agree?……..,5
3. You understand why you need to take this medicine. Would you say you...
   Strongly disagree……..……,1
   Disagree……..……..,2
   Neither agree nor disagree……., 3
   Agree……,4
   Strongly agree?……..,5
4. You believe it is important to take this medication. Would you say you...
   Strongly disagree……..……,1
   Disagree……..……..,2
   Neither agree nor disagree……., 3

Agree……,4
Strongly agree?……,5

5. You believe the medicine is working. Would you say you...

   Strongly disagree……,1
   Disagree……..,2
   Neither agree nor disagree…….., 3
   Agree……,4
   Strongly agree?……..,5
6. In the past 7 days, you took this medication as recommended. Would you say...
   Never……., 1
   Rarely…….,2
   Sometimes……, 3
   Almost always……,4
   Always?…….,5
7. In the past 7 days, you remembered to take this medication. Would you say...
   Never……., 1
   Rarely…….,2
   Sometimes……, 3
   Almost always……,4
   Always?…….,5
8. In the past 7 days, you did not take this medicine because it caused side effects that bothered you. Would you say...
   Never……., 1
   Rarely…….,2
   Sometimes……, 3
   Almost always……,4
   Always?…….,5
   Please say “Not at all” if you have no side effects.
9. In the past 7 days, you stopped taking this medication because you thought you did not need it. Would you say...
   Never……., 1
   Rarely…….,2
   Sometimes……, 3
   Almost always……,4
   Always?…….,5
10. In the past 7 days, you did not take this medication because of the cost. Would you say...

    Never……., 1
    Rarely…….,2
    Sometimes……, 3
    Almost always……,4
    Always?…….,5
11. In the past 7 days, you are bothered by the side effects of treatment. Would you say...
    Not at all……., 1
    A little bit……..,2
    Somewhat……, 3

Quite a bit…….……,4
Very much?…….,5
Please say “Not at all” if you have no side effects.

12. In the past 7 days, the cost of your medicine has been a financial hardship to you and your family. Would you say...
Not at all…….., 1
A little bit…….……..,2
Somewhat……, 3
Quite a bit…….……,4
Very much?…….,5

## 14.2 Patient Reported Outcomes of CTCAE

# NCI PRO-CTCAE ™ ITEMS

Item Library Version 1.0
English
Form Created on 05 August 2020
As individuals go through treatment for their cancer, they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

| **1a.** In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST? | | | | |
|---|---|---|---|---|
| O None | O Mild | O Moderate | O Severe | O Very severe |
| **1b.** In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities? | | | | |
| O Not at all | O A little bit | O Somewhat | O Quite a bit | O Very much |

| **2a.** In the last 7 days, how OFTEN did you have NAUSEA? | | | | |
|---|---|---|---|---|
| O Never | O Rarely | O Occasionally | O Frequently | O Almost constantly |
| **2b.** In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST? | | | | |
| O None | O Mild | O Moderate | O Severe | O Very severe |

| **3a.** In the last 7 days, how OFTEN did you have VOMITING? | | | | |
|---|---|---|---|---|
| O Never | O Rarely | O Occasionally | O Frequently | O Almost constantly |
| **3b.** In the last 7 days, what was the SEVERITY of your VOMITING at its WORST? | | | | |
| O None | O Mild | O Moderate | O Severe | O Very severe |

| | | | | |
|---|---|---|---|---|
| **4a.** In the last 7 days, how OFTEN did you have BLOATING OF THE ABDOMEN (BELLY)? | | | | |
| O Never | O Rarely | O Occasionally | O Frequently | O Almost constantly |
| **4b.** In the last 7 days, what was the SEVERITY of your BLOATING OF THE ABDOMEN (BELLY) at its WORST? | | | | |
| O None | O Mild | O Moderate | O Severe | O Very severe |

| | | | | |
|---|---|---|---|---|
| **5a.** In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST? | | | | |
| O None | O Mild | O Moderate | O Severe | O Very severe |

| | | | | |
|---|---|---|---|---|
| **6a.** In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)? | | | | |
| O Never | O Rarely | O Occasionally | O Frequently | O Almost constantly |

| | | | | |
|---|---|---|---|---|
| **7a.** In the last 7 days, how OFTEN did you have ARM OR LEG SWELLING? | | | | |
| O Never | O Rarely | O Occasionally | O Frequently | O Almost constantly |
| **7b.** In the last 7 days, what was the SEVERITY of your ARM OR LEG SWELLING at its WORST? | | | | |
| O None | O Mild | O Moderate | O Severe | O Very severe |
| **7c.** In the last 7 days, how much did ARM OR LEG SWELLING INTERFERE with your usual or daily activities? | | | | |
| O Not at all | O A little bit | O Somewhat | O Quite a bit | O Very much |

| | | | | |
|---|---|---|---|---|
| **8a.** In the last 7 days, how OFTEN did you feel a POUNDING OR RACING HEARTBEAT (PALPITATIONS)? | | | | |
| O Never | O Rarely | O Occasionally | O Frequently | O Almost constantly |
| **8b.** In the last 7 days, what was the SEVERITY of your POUNDING OR RACING HEARTBEAT (PALPITATIONS) at its WORST? | | | | |
| O None | O Mild | O Moderate | O Severe | O Very severe |

| | |
|---|---|
| **9a.** In the last 7 days, did you have any RASH? | |
| O Yes | O No |

| |
|---|
| **10a.** In the last 7 days, did you have any HAIR LOSS? |

| | | | | |
|---|---|---|---|---|
| O Not at all | O A little bit | O Somewhat | O Quite a bit | O Very much |

| | | | | |
|---|---|---|---|---|
| **11a.** In the last 7 days, how OFTEN did you have a HEADACHE? | | | | |
| O Never | O Rarely | O Occasionally | O Frequently | O Almost constantly |
| **11b.** In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST? | | | | |
| O None | O Mild | O Moderate | O Severe | O Very severe |
| **11c.** In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities? | | | | |
| O Not at all | O A little bit | O Somewhat | O Quite a bit | O Very much |

| | | | | |
|---|---|---|---|---|
| **12a.** In the last 7 days, how OFTEN did you have ACHING MUSCLES? | | | | |
| O Never | O Rarely | O Occasionally | O Frequently | O Almost constantly |
| **12b.** In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST? | | | | |
| O None | O Mild | O Moderate | O Severe | O Very severe |
| **12c.** In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities? | | | | |
| O Not at all | O A little bit | O Somewhat | O Quite a bit | O Very much |

| | | | | |
|---|---|---|---|---|
| **13a.** In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)? | | | | |
| O Never | O Rarely | O Occasionally | O Frequently | O Almost constantly |
| **13b.** In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST? | | | | |
| O None | O Mild | O Moderate | O Severe | O Very severe |
| **13c.** In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities? | | | | |
| O Not at all | O A little bit | O Somewhat | O Quite a bit | O Very much |

| | | | | |
|---|---|---|---|---|
| **14a.** In the last 7 days, what was the SEVERITY of your VAGINAL DRYNESS at its WORST? | | | | |
| O None | O Mild | O Moderate | O Severe | O Very severe |

| | | | | |
|---|---|---|---|---|
| **15a.** In the last 7 days, how OFTEN did you have HOT FLASHES/FLUSHES? | | | | |
| O Never | O Rarely | O Occasionally | O Frequently | O Almost constantly |
| **15b.** In the last 7 days, what was the SEVERITY of your HOT FLASHES/FLUSHES at their WORST? | | | | |
| O None | O Mild | O Moderate | O Severe | O Very severe |

## 14.3 Medication Diary

**OTHER MEDICATIONS TAKEN**

If you take a daily medication (prescribed or otherwise), please use one line per drug and indicate the start and stop dates under the "Date(s) Taken" section (i.e., 6/2/09 - 6/5/09).

| Drug Name | Dose | Dates Taken | Reason Taken |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

Study Participant Initials _____ Date _____

| FOR STUDY TEAM USE ONLY | |
|---|---|
| Staff Initials: | |
| # pills/caps/tabs dispensed: | # pills/caps/tabs at day 15-21 (PK study): |
| # pills/caps/tabs that should have been taken: | |
| Discrepancy Notes: | |

**DOSING LOG**

Cycle: 1

For each dose take:
3 pills of Ribociclib for 21 days
1 pill of letrozole daily (if applicable)

Please indicate the date, amount taken and any comments.

| | Date | Amount Taken | | Comments |
|---|---|---|---|---|
| | | Ribociclib | Letrozole | |
| Ex: | 6/1/20 | 2 | 1 | vomited hour later |
| Day 1 | | | | |
| Day 2 | | | | |
| Day 3 | | | | |
| Day 4 | | | | |
| Day 5 | | | | |
| Day 6 | | | | |
| Day 7 | | | | |
| Day 8 | | | | |
| Day 9 | | | | |
| Day 10 | | | | |
| Day 11 | | | | |
| Day 12 | | | | |
| Day 13 | | | | |
| Day 14 | | | | |
| Day 15 | | | | |
| Day 16 | | | | |
| Day 17 | | | | |
| Day 18 | | | | |
| Day 19 | | | | |
| Day 20 | | | | |
| Day 21 | | | | |
| Day 22 | | | | |
| Day 23 | | | | |
| Day 24 | | | | |
| Day 25 | | | | |
| Day 26 | | | | |
| Day 27 | | | | |
| Day 28 | | | | |

**Study Participant**
**Self-Administration**
**Study Drug Diary**

Participant Identifier: _____
Protocol #:
Your MD _____ Phone _____
Your RN _____ Phone _____

**STUDY DRUG INSTRUCTIONS:**

**Study Drug A:** Ribociclib
**Study Drug B:** Letrozole

**How Much:** 600 mg
**How Often:** Daily
**When:** Morning

**SYMPTOMS/SIDE EFFECTS**

Please record any side effects experienced during this cycle. Include the date the particular symptom started and when it ended. Please evaluate the severity of the symptom according to the following scale:

**Mild:** Awareness of sign or symptom; easily tolerated and did not affect ability to perform normal daily activities. Symptom did not require medication or therapeutic intervention.

**Moderate:** Significant discomfort which interfered with ability to perform normal daily activities. Symptom was easily resolved with at home medication or simple therapeutic intervention.

**Severe:** Marked discomfort with an inability to carry out normal daily activities. Symptom required new medication and/or therapeutic intervention in order to resolve.

*Please Note:* The severity should reflect the most severe level experienced during the time period.

| Symptom | Start Date | End Date | Severity |
|---|---|---|---|
| | | | |
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## 14.4 Prohibited medications

Prohibited Medications*

| Category | Drug name |
|---|---|
| Strong inhibitors of CYP3A4/5 | Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole |
| Strong inducers of CYP3A4/5 | Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin) , St. John's wort (hypericum perforatum) |
| Substrates of CYP3A4/5 | Alfentanil, apixaban (doses >2.5 mg only), aprepitant, astemizole, cisapride, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin, sirolimus, tacrolimus, terfenadine, thioridazine |
| Medications with a known risk or possible for QT prolongation and/or Torsades de Pointe (TdP) | Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl, mesoridazine, methadone, moxifloxacin, ondansetron (i.v. only), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, sevoflurane, sotalol, sparfloxacin, sulpiride, terfenadine, thioridazine, vandetanib, venlafaxine |
| Herbal medications/preparations or dietary supplements that are strong inhibitors or inducers of CYP3A4/5 or those with a known risk of QT prolongation | Herbal preparations/medications are prohibited throughout the study. These herbal medications include, but are not limited to: St. John’s wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh, and ginseng. Patients should stop using these medications 7 days prior to the first dose of study drug. |

*List applies to formulations of medications that are absorbed systemically

## 14.5 Medications not Recommended

Medications Not Recommended*

| Category | Drug name |
|---|---|
| Moderate CYP3A4/5 inhibitors | Amprenavir, atazanavir, casopitant, cimetidine, darunavir, diltiazem, fosamprenavir, lomitapide, netupitant, tofisopam, verapamil |
| Moderate CYP3A4/5 inducers | Bosentan, efavirenz, etravirine, genistein, lersivirine, modafinil, nafcillin, talviraline |
| Sensitive CYP3A4/5 substrates | Alpha-dihydroergocryptine, almorexant, alpaviroc, apixaban (doses < 2.5 mg only), atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, darifenacin, darunavir, ebastine, eletriptan, eplerenone, felodipine, fluticasone, ivacaftor, lomitapide, lumefantrine, lurasidone, maraviroc, midazolam, perospirone, quetiapine, ridaforolimus, sildenafil, ticagrelor, tilidine, tolvaptan, triazolam, vardenafil, vicriviroc, voclosporin |
| Strong BSEP inhibitors | Bosentan, fusidate, glibenclamide, , sulindac, troglitazone (TGZ-sulfate) |
| MATE1 and OCT2 substrates | Acyclovir, amantadine, amiloride, cephalexin, cephradine, cimetidine, famotidine, fexofenadine, memantine, metformin (also a substrate for OCT1, MATE1, and MATE2K), pindolol, procainamide, ranitidine, varencicline |
| BCRP substrates | Rosuvastatin and sulfasalazine |
| Medications that carry a possible risk for QT prolongation | Alfuzosin, apomorphine, aripiprazole, atazanavir, atomoxetine, bedaquiline, clozapine, dexmedetomidine, dolasetron, eribulin, famotidine, felbamate, fingolimod, foscarnet, gatifloxacin, gemifloxacin, granisetron, iloperidone, isradipine, lithium, mirabegron, mirtazapine, moexipril, norfloxacin, ofloxacin, olanzapine, ondansetron (p.o. only at 4 mg or 8 mg), oxytocin, paliperidone, pasireotide, pipamperone, promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin, sertindole, telavancin, tetrabenazine, tizanidine, tolterodine, vardenafil, ziprasidone |

*List applies to formulations of medications that are absorbed systemically

## 14.6 Adverse event monitoring log (CTCAE 5.0):

| Adverse event | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Baseline | Mid-cycle visit | End of study |
|---|---|---|---|---|---|---|---|
| | | | | | Mark N/A or grade for each visit AND date of onset | | |
| Rash | <10% BSA | 10-30% BSA | Severe rash, >30%, SJS | Any %, requiring antibiotics, TEN | | | |
| Interstitial Lung Disease/ Pneumonitis | Asymptomatic | Symptomatic | Severe Symptomatic | Life threatening | | | |
| Nausea | Loss of appetite without alteration of eating habits | Oral intake decreased without weight loss, dehydration, malnutrition | Inadequate oral intake, hospitalization indicated | N/A | | | |
| Vomiting | Intervention not indicated | Outpatient IV hydration | Tube feeding, TPN, hospitalization | Life threatening | | | |
| Diarrhea | Increase of <4 stools per day | Increase of 4-6 stools per day | >7 stools per day over baseline | Life threatening | | | |
| Constipation | Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema | Persistent symptoms with regular use of laxatives or enemas | Obstipation with manual evacuation indicated; limiting self-care ADL | Life threatening | | | |
| Fatigue | Relived by rest | Not relieved by rest, limiting basic activities of daily living | Limiting self-care | N/A | | | |
| Anorexia | Loss of appetite without alteration in eating habits | Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated | Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated | Life-threatening consequences; urgent intervention indicated | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Alopecia | <50% of normal, only obvious to close inspection | >50% of normal, a wig or hair piece is necessary; psychosocial impact | N/A | N/A | | | |
| Arthralgia | Mild pain | Moderate pain, limiting activities of daily living | Severe pain, limiting self-care | N/A | | | |
| Headache | Mild pain | Moderate pain, limiting activities of daily living | Severe pain, limiting self-care | N/A | | | |
| Hot flush * | Mild | Moderate, limiting activities of daily living | Severe | N/A | | | |
| Other | | | | | | | |
| Other | | | | | | | |
| Other | | | | | | | |

Abbreviations: LLN: lower limit of normal; ULN: upper limit of normal; BSA: body surface area
*No CTCAE

Baseline visit → Completed by _____ Date: _____
Mid-cycle 1 visit → Completed by _____ Date: _____
End of study visit → Completed by _____ Date: _____