CITY OF HOPE
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF MEDICAL ONCOLOGY

TITLE: A Phase IIA Trial Assessing the Tolerability of Ribociclib in Combination with an Aromatase Inhibitor in Patients aged 70 and Older with Hormone Receptor Positive Metastatic Breast Cancer

CITY OF HOPE PROTOCOL NUMBER/PACKET: IRB #17471 Protocol Date: 06/27/18

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SITE: Breast

STAGE (If applicable): Metastatic

MODALITY:

TYPE: Phase 2

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- City of Hope Antelope Valley, CA
- City of Hope Corona, CA
- City of Hope Mission Hills, CA
- City of Hope Rancho Cucamonga, CA
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Clinical Trial Protocol

A Phase IIA Trial Assessing the Tolerability of Ribociclib in Combination with an Aromatase Inhibitor in Patients Aged 70 and Older with Hormone Receptor Positive Metastatic Breast Cancer

Protocol Version Date:	06-27-18
Protocol Version No.:	04
COH Protocol No.:	17471
Sponsor:	City of Hope
Industry Partner:	Novartis
IND #:	Exempt from IND
Agents:	Ribociclib (FDA approved; supplied by Novartis) Aromatase Inhibitors: Anastrozole; exemestane; letrozole (Commercial supply)
Phase:	IIA

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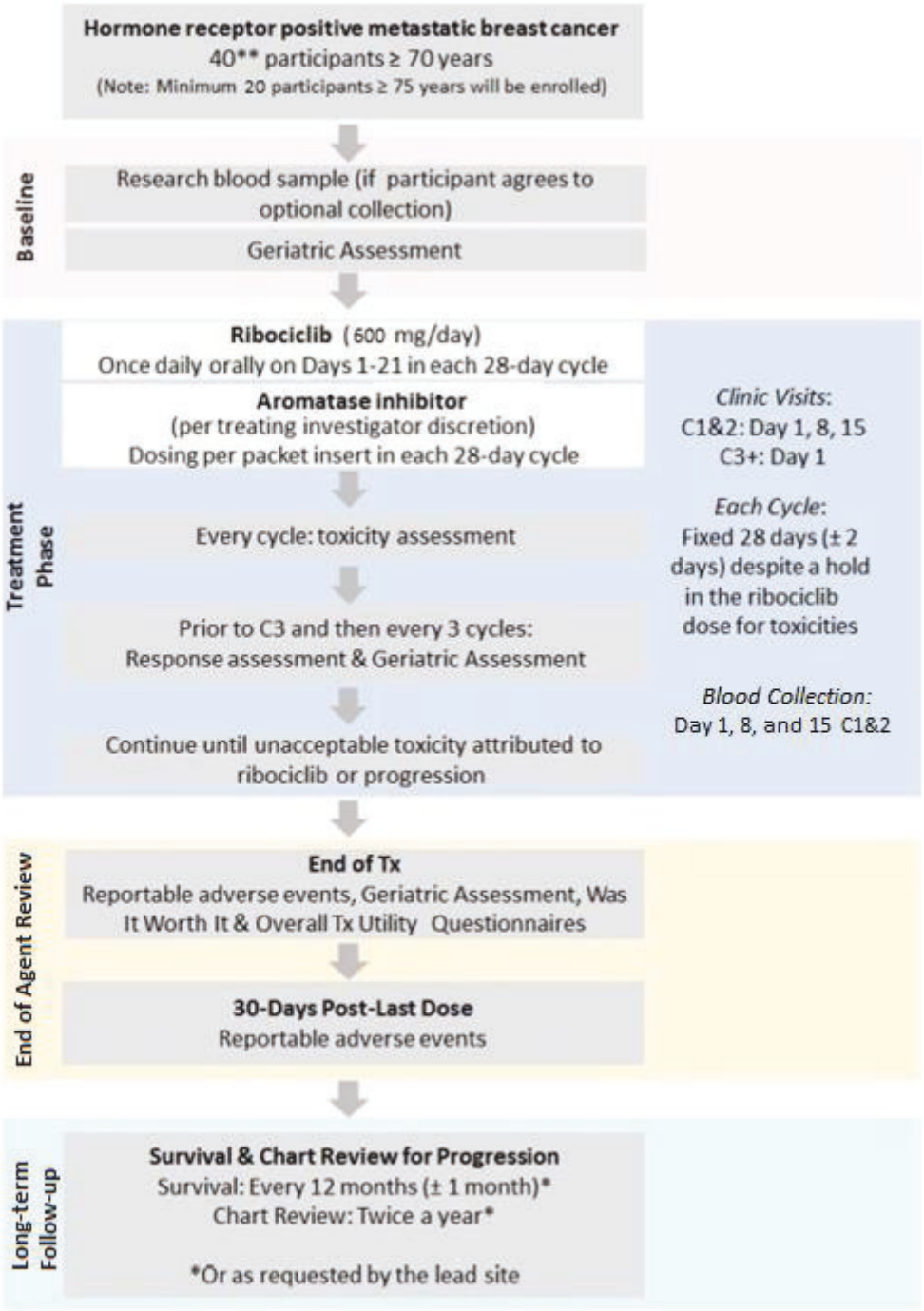
EXPERIMENTAL DESIGN SCHEMA



** Interim safety analysis will be performed after 20 patients have completed 1 cycle of herapy.

PROTOCOL SYNOPSIS

Protocol Title:	
A Phase IIA Trial Assessing the Tolerability of Ribociclib in Combination with an Aromatase Inhibitor in Patients Aged 70 and Older with Hormone Receptor Positive Metastatic Breast Cancer.	
Study Detail:	
Indication(s)	Hormone Receptor Positive Metastatic Breast Cancer
Phase	IIA
Number of subjects	40 evaluable participants ≥ 70 yo (at least 20 participants ≥75 yo)
Estimated Accrual Duration:	24 months
Estimated Study Duration:	55 months
Participating Sites:	City of Hope, Duarte, CA City of Hope Community Practice Sites: • City of Hope South Pasadena • City of Hope Antelope Valley • City of Hope Corona • City of Hope Mission Hills • City of Hope Rancho Cucamonga • City of Hope West Covina Roswell Park Comprehensive Cancer Center, Buffalo NY Wilmot Cancer Institute (University of Rochester), Rochester, NY
Study Agents:	• Ribociclib (Supplied by Novartis) • Aromatase Inhibitors: Anastrozole; exemestane; letrozole (Commercial supply)
Brief Protocol Title for the Lay Public:	Ribociclib in combination with Aromatase Inhibitor in Older Adults
Sponsor:	City of Hope

Rationale for this Study:

Older adults are underrepresented in clinical trials. Despite pronounced changes in drug metabolism, absorption, and distribution with increasing age, limited evidence exists to guide therapy with targeted agents in the older adult population. Evidence now suggests that targeting the CDK/RB pathway has the potential to control ER+ breast cancer progression. To date, clinical data from LEE011 (ribociclib) and PD0332991 (palbociclib) have demonstrated efficacy and tolerable adverse event safety profiles. As the MONALEESA-2 trial demonstrates, the combination of ribloclclib and endocrine therapy is a novel targeted treatment approach for postmenopausal women with hormone receptor positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer. The combination improves progression-free survival compared to endocrine therapy alone. However these studies primarily focused on women less than age 65. For example, the randomized phase II trial (MONALEESA-2) of ribloclclib and letrozole compared to letrozole alone (mean age 62) included only 295 patients study wide aged 65 and older and 373 patients aged less than 65 years study-wide with no published cohort data for enrolled patients over the age of 70. The phase III trial (PALOMA-3) of PD0332991 (mean age 57, respectively) included only 25% of participants age 65 and older, while not reporting on participants aged 75 and older (personal communication with Kellen Meadows, 21 August 2015).

The most common adverse events of ribloclclib in combination with endocrine therapy are neutropenia, leukopenia, and fatigue. In particular, MONALEESA-2 patients receiving the combination ribloclclib and letrozole experienced grade 3 or 4 neutropenia (59.3%), leukopenia (21%), or fatigue (2.4%). In particular, there is a decrease in bone marrow reserve with aging, hence amplifying the potential risk of neutropenia and myelosuppresion. Older adults often have other co-morbid medical conditions which may predispose them to thromboembolism thereby increasing the risk. Because of this, a definitive study in the older adult population will diminish any reservations oncologists may have in prescribing ribociclib with an aromatase inhibitor, and can provide guidance regarding the dosing and toxicity management in older adults.

Study Design:

This study will be an open label, single arm, Phase IIA safety and tolerability study to describe the toxicity profile of ribociclib in combination with an aromatase inhibitor in patients age 70 and older with hormone receptor positive metastatic breast cancer. We plan to study 40 evaluable subjects, stratifying on age such that at least 20 evaluable participants are aged 75 years or older. There will be one interim analysis after 20 evaluable participants have completed one cycle of the drug.

All patients who begin study treatment will be included in the analysis of all clinical endpoints.

Objectives:

Primary objective:

To estimate the safety and tolerability of ribociclib in combination with an aromatase inhibitor in adults aged 70 or older with hormone receptor positive metastatic breast cancer.

Secondary objectives:

1. To describe the full toxicity profile including all grades
2. To estimate the rate of worst grades of myelosuppression (neutropenia, leukopenia, thrombocytopenia, and anemia), neutropenic fever, GI side effects (nausea, diarrhea, decreased appetite, vomiting, stomatitis), fatigue, neuropathy, and thromboembolism
3. To describe rates of dose reductions, dose holds, and hospitalizations
4. To estimate objective response rate and clinical benefit rate as defined by modified RECIST (1.1) criteria
5. To estimate median progression-free and overall survival

6. To determine average plasma steady-state ribociclib C_{trough} concentrations in patients over the age of 70 years

Exploratory objectives:

1. To estimate the rate of adherence to ribociclib
2. To explore factors other than chronologic age that can affect toxicity rates as identified using a cancer-specific geriatric assessment
3. To describe the results of the Was It Worth It (WIWI) and Overall Treatment Utility (OTU) Questionnaires

Endpoints:

Primary:

The primary endpoint is the incidence of grade 2 and above toxicities attributed to ribociclib.

Secondary:

1. All toxicities associated with the combinations as measured by NCI CTCAE v.4.03
2. Dose reductions
3. Dose holds
4. Hospitalizations
5. Response as determined by RECIST (1.1) criteria
6. Progression free survival defined as the time from start of treatment to the first of the following disease events: local/regional/distant recurrence, invasive contralateral breast disease, second primary or death due to any cause.
7. Overall survival defined as the time from start of treatment to death due to any cause
8. Average ribociclib C_{trough} concentrations

Exploratory Endpoints

1. Adherence to ribociclib will be defined as taking 19/21 pills (90%) of their dose of ribociclib.
2. Toxicity Risk Score
3. WIWI response
4. OTU response

Statistical Considerations:

Sample Size Justification:

The sample size is 40 evaluable participants. Participants that receive one dose of treatment will be considered evaluable, anyone that does not receive treatment will be replaced.

Given a sample size of 40 subjects the half-width of the 95% confidence limits for the rate of grade 2 or higher toxicities will be less than or equal to 0.16. For example if we saw a toxicity rate of 0.5 (20 subjects/40) the 95% lower and upper confidence limits would be 0.34 and 0.66, respectively. Further a sample size of 40 will allow us to see a toxicity with a true rate equal to 0.05 in 87 out of 100 trials.

Interim Analysis:

After approximately 20 evaluable subjects have completed at least one full cycle of treatment, the study team will review the data (including the toxicity profile, rates of dose reduction, holds and hospitalizations) and assess if the dose being studied is too high, that it is requiring too many patients, in the opinion of the team, to experience a dose reduction. If so, a reduction of the dose will be considered, otherwise the study will continue to completion at the planned dose.

Analysis Plan:

Rates and associated 95% exact Clopper and Pearson binomial confidence limits will be estimated for 1) grade 2 or higher other toxicities, and 2) dose reductions, dose holds and hospitalizations, and 3) objective response rate (CR+PR) and clinical benefit rate (CR+PR+SD) as determined by RECIST by age strata and overall. Progression free

survival and overall survival will be estimated using the product limit method of Kaplan and Meier/Cox proportional hazards methods by age strata and overall.

Tables will be created to summarize the toxicities and side effects by age strata, course, organ, severity and attribution for all patients. Descriptive statistics will be provided for study participant demographics, number of drug cycles completed, responses from the WIWI Questionnaire and the OTU by age strata and overall. General linear models and graphical methods will be used to explore factors as identified by a cancer-specific geriatric assessment that may be predictive of toxicity/dose reduction, dose holds or hospitalizations.

The relationship between plasma trough and percent drop in neutrophil and platelet counts will be analyzed used linear models methods.

Abbreviated Eligibility Criteria:

Inclusion Criteria

- Hormone receptor positive metastatic breast cancer.
- First or second line endocrine therapy for metastatic disease. One prior line of chemotherapy for metastatic disease is allowed.
- Age: ≥ 70 years and life expectancy > 6 months
- Measurable disease per RECIST (1.1), or bone-only lytic or mixed lytic and blastic lesions that would be accurately assessed by means of computed tomography (CT) or magnetic resonance imaging (MRI).
- The ability to swallow and retain oral medication
- Resolution of all acute toxic effects of prior therapy or surgical procedures to CTCAE Grade ≤ 1 (except alopecia)

Exclusion Criteria

- Untreated brain metastases or symptomatic visceral spread at risk for life-threatening complications
- Concomitant CYP3A strong inhibitors or inducers
- Prior therapy with a CDK inhibitor

Investigational Product Dosage and Administration:

Ribociclib: Administered orally with food on Days 1-21 in each 28-day cycle. Starting dose: 600mg/day.
Aromatase inhibitor: Administered per treating investigator's discretion during each 28-day cycle; dosing should follow the package insert guidelines.

Clinical Observations and Tests to be Performed:

Clinical Observations/ Tests/ Questionnaires: medical history and demographics, physical exams, vital signs, performance status, routine laboratory tests, pill diary assessment, AE assessment, disease assessment, geriatric assessment, Was It Worth It Questionnaire assessment, Overall Treatment Utility assessment. Participants will be followed for survival.

Correlative Biology Studies: From participants who consent to research blood sample collection, a baseline sample of blood will be collected for future studies.

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ABBREVIATIONS

Abbreviation	Meaning
AE	Adverse Event
CFR	Code of Federal Regulations
CICSL	Clinical Immunobiology Correlative Studies Laboratory
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCC	Data Coordinating Center
DSMC	Data & Safety Monitoring Committee
EMR	Electronic Medical Record
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
NCI	National Cancer Institute
OIDRA	Office of IND Development and Regulatory Affairs
PD	Progressive Disease
PI	Principal Investigator
PMT	Protocol Management Team
PR	Partial Response
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SOC	Standard of Care
Tx	Treatment
WIWI	Was It Worth It

1. GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1. Primary Objective

- To estimate the safety and tolerability of the combination of ribociclib and an aromatase inhibitor in adults age 70 or older with hormone receptor positive metastatic breast cancer.

1.2. Secondary Objectives

- To describe the full toxicity profile including all grades
- To estimate the rate of worst grades of myelosuppression (neutropenia, leukopenia, thrombocytopenia, and anemia), neutropenic fever, GI side effects (nausea, diarrhea, decreased appetite, vomiting, stomatitis), fatigue, neuropathy, and thromboembolism
- To describe rates of dose reductions, dose holds, and hospitalizations
- To estimate objective response rate and clinical benefit rate as defined by modified RECIST (1.1) criteria
- To estimate median progression-free and overall survival

1.3. Exploratory Objectives

- To estimate the rate of adherence to ribociclib
- To explore factors other than chronologic age that can affect toxicity rates as identified using a cancer-specific geriatric assessment
- To describe the results of the Was It Worth It (WIWI) and the results of the Overall Treatment Utility (OTU) Questionnaires

2. BACKGROUND

2.1. Introduction/Rationale for Development

This proposal addresses a key research priority of the Cancer and Aging Research Group, National Cancer Institute, National Institute on Aging, and the Institute of Medicine: the assessment of the pharmacology of cancer therapy in older adults. [1, 2] Ribociclib is a novel drug with the potential to change the treatment of metastatic breast cancer- a disease primarily affecting older adults. The combination of ribociclib and endocrine therapy (aromatase inhibitor) is associated with an improvement in progression-free survival (PFS) compared to endocrine therapy alone. [3] The goal of this study is to fill this gap in knowledge by utilizing a phase II design to examine the tolerability of ribociclib and endocrine therapy among older adults aged 70 and older with hormone receptor positive breast tumors. A comprehensive cancer-specific geriatric assessment that includes an evaluation of functional status, other medical conditions, cognitive function, nutritional status, social support, psychological state, and a review of medications will be included, as well as an assessment of adherence.

2.2. Rationale for Studying Cancer Therapy in Older Adults

Aging brings about a progressive decrease in physiologic reserve that affects each individual at a unique pace.[4, 5] The age-related physiological decline in organ systems typically begins in the 3rd decade of life and is not evident at times of rest, but becomes most apparent when the body is stressed.[6] Both cancer and cancer treatment can be considered a physiological stressor, and age-related decreases in physiologic reserve may affect tolerance to cancer treatment.

A number of age-related changes in drug absorption, distribution, metabolism, and excretion may contribute to differences in treatment tolerance between older and younger patients. The absorption of drugs can be affected by decreased gastrointestinal motility, decreased splanchnic blood flow, decreased secretion of digestive enzymes, and mucosal atrophy.[7, 8] With the increased use of oral therapy, medication compliance is an important issue as well.[9] As a person ages, body composition changes, with an increase in body fat and decrease in lean body mass and total body water. The increase in body fat leads to a rise in the volume of distribution for hydrophilic drugs. In the population of older adults with cancer, malnutrition and hypoalbuminemia may result in an increased concentration of drugs that are albumin-bound.[10]

Hepatic mass and blood flow also decrease with age.[4] The impact of the decline in hepatic mass and blood flow on hepatic enzyme function is controversial.[11] In a study of 226 patients, the cytochrome P-450 content in liver biopsy samples decreased by approximately 30% in patients over the age of 70.[12] Renal function also declines with age, and renal insufficiency is common in older adults.[13, 14]

A progressive reduction in the functional reserve of various organ systems may alter the pharmacokinetics of anti-cancer therapies[7, 15] and increase the susceptibility of older individuals to complications of treatment.[12, 14, 18, 19]Normal tissues may be less able to repair the molecular damage caused by antineoplastic agents due to cellular senescence, resulting in greater potential cardiotoxicity, neurotoxicity, mucositis, and hematologic toxicities.[16]

2.3. Factors Other than Chronological Age that Impact Drug Tolerance

Aging is a heterogeneous process. While certain declines in organ function are universal as the human body ages, the rate of this decline and the consequences of this decline on everyday function proceeds at a unique pace in each individual. Therefore, chronologic age tells us relatively little about the specific individual. A more detailed evaluation of an older adult patient is needed in order to capture factors other than chronological age that predict for morbidity and mortality. A comprehensive geriatric assessment may serve this purpose. The comprehensive geriatric assessment includes an evaluation of functional status, co-morbid medical conditions, cognitive function, nutritional status, social support and psychological state, and a review of medications. Conclusions from several studies are emerging regarding the benefits of performing a comprehensive geriatric assessment for older patients with cancer.

1. Factors evaluated in a comprehensive geriatric assessment predict survival;[17]
2. Factors evaluated in a comprehensive geriatric assessment predict toxicity to chemotherapy;[18]
3. A comprehensive geriatric assessment uncovers problems not detected by routine history and physical in initial consultation and follow-up care;[19]
4. Patients undergoing a comprehensive geriatric assessment and intervention based on the results had improved pain control;[20]
5. A comprehensive geriatric assessment and intervention improves an older patient's mental health and well-being.[20]

Consensus guidelines recognize the benefits and recommend the inclusion of a geriatric assessment as part of the evaluation of an older patient.[21]

2.4. Ribociclib

Ribociclib is a cyclin dependent kinase (CDK) 4 and 6 inhibitor which causes cell cycle arrest as the cell travels from G1 phase to S phase [3]. In the absence of ribociclib, these kinases will phosphorylate the retinoblastoma protein (Rb). This phosphorylation causes a release of transcription factors which allows the cell to move through the cell cycle, thus allowing the growth of cancerous cells[3]. When ribociclib inhibits CDK4 and CDK6, the retinoblastoma protein is arrested at the G1 phase, prohibiting "S-phase entry and cell growth" of the cancerous cells [22]. Estrogen-induced proliferation of breast epithelium is further associated with an increased expression of cyclin D1 mRNA and protein. This is consistent with a model of ER+ breast cancer in which receptor activation induces increased cyclin D1 expression, CDK4/6i activation and cell cycle progression. Therefore, targeting the CDK/Rb has great potential to control ER+ breast cancer progression.

2.4.1. Rationale for Combining Ribociclib and Endocrine Therapy

Ribociclib in combination with endocrine therapy compared to endocrine therapy alone improves progression-free survival. Data from the MONALEESA-2 trial demonstrates the efficacy of ribociclib with letrozole in the first line treatment of hormone receptor positive metastatic breast cancer.[23] In this randomized open-label phase III study, 668 women ranging from ages 23-91 had advanced estrogen receptor positive and HER-2 negative breast cancer. The median age of women enrolled was 62 years; all patients had hormone positive disease, and all but 1 patient in each group had HER2-negative disease.[3] These cohorts received either letrozole orally (2.5 mg/day) or received letrozole with ribociclib (600 mg/day for three weeks on and one week off). This dosage and treatment schedule has an acceptable safety profile, lower risk for QT interval prolongation (defined as QTcF), adequate exposures, and preliminary evidence of clinical activity. Three hundred thirty-four patients were assigned to both the ribociclib-letrozole group and to letrozole alone.[3] The median duration of progression-free survival was not reached for the ribociclib and letrozole arm (95% CI, 19.3 to not reached), compared to 14.7 months (95% CI 13.0 to 16.5) for letrozole alone.[3] The rate of locally assessed progression-free survival was significantly higher in the ribociclib group than in the letrozole alone group. After 12 months, the progression free survival rate was 72.8% (95% CI, 67.3 to 77.6) in the ribociclib group compared to 60.9% (95%CI, 55.1 to 66.2) in the letrozole alone group. Common side effects for ribociclib with letrozole were: Grade 3-4 neutropenia (59.3% vs 0.9% in letrozole alone), leukopenia (21% vs 0.6% in letrozole alone), and fatigue (2.4% vs 1% with letrozole). Patients receiving ribociclib with letrozole experienced a pulmonary embolism at a rate of 0.6%. Among patients in the ribociclib and letrozole group, 7.5% discontinued due to adverse events whereas only 2.1% of the letrozole group discontinued the study.

Table 2.4.1a: Common Adverse Reactions in Patients who Received Ribociclib plus Letrozole or Letrozole Alone in MONALEESA-2 Study[3]

	Ribociclib plus Letrozole (N=334)		**Letrozole (N=330)**	
	Grade 3	Grade 4	Grade 3	Grade 4
Any adverse event	221 (66%)	50 (15%)	105 (32%)	3 (1%)
Neutropenia	166 (50%)	32 (10%)	3 (1%)	0
Leukopenia	66 (20%)	4 (1%)	2 (0.6%)	0
Anemia	3 (1%)	1 (0.3%)	4 (1.2%)	0

*Data are in n (%) unless otherwise specified

2.4.2. Age Specific Data from MONALEESA-2 and Other CDK4/6 Inhibitor Trials

Limited evidence exists to guide therapy with ribociclib and endocrine therapy in older adults. In MONALEESA-2, the mean age of patients was 62 with a range from 23-91. In other CDK4/6 inhibitor trials for PD0332991, (PALOMA-3) only 25% of the participants were aged 65 and over. Review of the data obtained from 165 patients in the PALOMA-1 trial, as well as the 521 patients in the PALOMA-3 trial, did not show any apparent differences in systemic exposure related to age. [19]

A subgroup analysis of the efficacy and safety of first-line PD0332991 plus letrozole compared with letrozole alone in patients in the PALOMA-1 study evaluated 165 postmenopausal women. Of the 76 patients aged 65 and older, 37 were treated with PD0332991 and letrozole, and the remainder received letrozole alone. Among patients receiving PD0332991 and letrozole the median PFS for patients aged 65 and over was 26.6 months (95% CI 12.6-NR) in comparison to 7.7 months (95% CI 3.7-10.9) for patients who received letrozole alone. Grade 3-4 neutropenia occurred in 56.8% of patients receiving PD0332991 and letrozole (compared to 2.7% in patients with letrozole alone). In addition, grade 3-4 leucopenia occurred in 29.7% of the patients receiving ribociclib and letrozole, and grade 3-4 fatigue was reported in 10.8% of patients receiving ribociclib and letrozole. Neither of these adverse events occurred in any patients taking letrozole alone.[23]

2.5. Overview and Rationale of Study Design

Ribociclib and endocrine therapy is emerging as a novel treatment for hormone receptor positive metastatic breast cancer. A gap in knowledge specifically exists with regard to the tolerability of this combination in adults aged 70 and over. This is an important research area, since cancer is a disease associated with aging. This Phase II study will evaluate the safety and tolerability of the combination of ribociclib and an aromatase inhibitor in patients aged 70 and over, as well as describe the full toxicity profile, and estimate the objective response rate and clinical benefit, as well as survival. A geriatric assessment and measures of adherence will be included within the study. Overall, our goal is to close this gap in knowledge in older adults with metastatic breast cancer who may derive significant benefit from this novel treatment option.

To further assess treatment efficacy we will ask our participants to answer a short questionnaire that asks, “Was it worth it?” to undergo treatment. Because we know that this question will be largely influenced by the tolerability of this treatment in older adults, it is immensely important for us to determine whether the toxicity of this treatment is deemed “worth it” to extend the lives of older

adults. This is a unique assessment of the benefits and side effects associated with an improvement in progression free survival that could potentially allow patients to make a more informed decision regarding the treatment.

The Was It Worth It (WIWI) questionnaire simply asks three questions “Was it worthwhile to undergo treatment in this research study?”, “If you had to do it over, would you undergo this treatment?”, “Would you recommend this treatment to others?” WIWI also asks the participant to indicate whether their quality of life was affected (improved, stayed the same, or got worse), and what could have been done to improve their treatment experience in this research study. In addition to these standard questions, we are planning to incorporate the question “What made it worth it to undergo this treatment?” in order to determine whether participants have a reason to want to endure potential toxicity for the benefit of progression free survival.

We will also be including a measure of Overall Treatment Utility (OTU) to assess the “objective and subjective measures of anticancer efficacy, tolerability and acceptability.” This is determined using an analysis of clinical benefits in conjunction with an analysis of whether toxicity and serious adverse events affect one’s daily functions. This provides a way to quantify advantages and disadvantages of receiving treatment in this study, as well as an understanding of how a patient aged 70 and older may respond to treatment. OTU is useful in answering the following hypothetical question from the patient’s perspective: “With the benefit of hindsight, are you glad you received treatment?” By including the OTU in this study, researchers and oncologists will be able to better understand the patient’s perspectives regarding the benefits and side effects of treatment, in combination with an assessment of treatment efficacy and toxicity.

3. PARTICIPANT ELIGIBILITY CRITERIA

3.1. Inclusion Criteria

Participants must meet the following criteria upon screening examination to be eligible to participate in the study:

1. Patient has signed the Informed Consent (ICF) prior to any study procedures being performed and is able to comply with protocol requirements.
2. Must be able to swallow ribociclib.

Age Criteria, Life Expectancy and Language Skill

3. Age: ≥ 70 years at time of enrollment
   ≥ 70 to < 74 years OR ≥ 75 years
   - NOTE: A minimum of 20 participants must be ≥ 75 years. The remaining 20 participants may be ≥ 70 to < 74 years OR ≥ 75 years.
4. Subjects must be able to communicate with the investigator and comply with the requirements of the study procedures.

Nature of Illness and Treatment History

5. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer, HER2-negative breast cancer defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+, and metastatic breast cancer.
6. First or second line endocrine therapy for metastatic disease. One prior line of chemotherapy for metastatic disease is allowed.

Laboratory Information

7. Patient has adequate bone marrow and organ function as defined by the following laboratory values at screening:
   a. Absolute neutrophil count ≥1.5 × 10^9 /L
   b. Platelets ≥100 × 10^9 /L
   c. Hemoglobin ≥9.0 g/dL
   d. Patient must have the following laboratory values within normal limits or corrected to within normal limits with supplement before the first dose of study medication:
      - Sodium
      - Potassium
      - Magnesium
      - Total Calcium (corrected for serum albumin)
      - Phosphorous
   e. Serum creatinine <1.5 mg/dL or creatinine clearance ≥50 mL/min
   f. In the absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5 x ULN. If the patient has liver metastases, ALT and AST <5 x ULN
   g. Total bilirubin < ULN; or total bilirubin ≤3.0 x ULN or direct bilirubin ≤1.5 x ULN in patients with well-documented Gilbert's Syndrome.

Cardiac Information

8. Patient with available standard 12-lead ECG with the following parameters at screening (defined as the mean of the triplicate ECGs):
    a. QTcF interval at screening <450msec (using Fridericia's correction)
    b. Resting heart rate 50-90bpm

3.2. Exclusion Criteria

Patients eligible for this study *must not* meet any of the following criteria:

1. Patient received prior treatment with any CDK4/6 inhibitor
2. Patient has a known hypersensitivity to any of the excipients of ribociclib.
3. Patients with a prior malignancy diagnosed within 2 years AND with evidence of disease (except adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer)
4. Patient with concurrent malignancy that is not clinically stable AND needs tumor-directed therapy.
5. Patients with central nervous system (CNS) involvement unless they meet ALL the following criteria:
    a. Untreated brain metastases (e.g., lesions < 1cm) not needing immediate local therapy.
    b. Previously treated brain metastases not needing immediate local therapy.
        - At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment.
        - Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme-inducing anti-epileptic medications for brain metastases.
6. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormalities, including any of the following:
    a. History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 6 months prior to screening.
    b. Documented cardiomyopathy.
    c. Clinically significant cardiac arrhythmias (e.g. ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g. bifascicular block, Mobitz type II and third-degree AV block).
    d. Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
        - Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia.
        - Concomitant use of medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued (within 5 half-lives or 7 days prior to starting study drug) or replaced by safe alternative medication.
        - Inability to determine the QT interval on screening (QTcF, using Fridericia's correction).
    e. Systolic blood pressure (SBP) >160 mmHg or <90 mmHg at screening.
7. Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to starting study drug (see Table 1 for details):
    a. Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges.

   b. That have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.
   c. Herbal preparations/medications, dietary supplements.
   d. Warfarin or other coumadin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), newer anti-coagulation agents such as direct factor Xa inhibitors, or fondaparinux is allowed
8. Patient is currently receiving or has received systemic corticosteroids ≤2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.
   a. The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).
9. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
10. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.).
11. Participation in a prior investigational study within 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer
12. Patient has had major surgery and/or radiotherapy within 14 days prior to receiving study drug or has not recovered from major side effects (tumor biopsy is not considered as major surgery).
13. Patient with a Child-Pugh score B or C.
14. Patient has not recovered from the acute effects of prior systemic therapy (until the toxicity resolves to either baseline or at least Grade 1) except for residual alopecia or peripheral neuropathy.
15. Patient has a history of non-compliance to medical regimen or inability to grant consent.
16. Sexually active males unless they use a condom during intercourse while taking the drug and for 21 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

3.3. Participation of Special Populations

A discussion of the inclusion, exclusion, representation and participation of women, minorities, children, HIV positive individuals and vulnerable populations is provided in Section 17.6.

4. PARTICIPANT ENROLLMENT

NOTE: Sites must meet activation requirements prior to enrolling participants (See the COH Data Coordinating Center (DCC) Supplement).

4.1. Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained. The informed consent process is to be fully documented (see Section 17.4), and the prospective participant must receive a copy of the signed informed consent document.

4.2. Participant Enrollment

4.2.1. COH DCC Availability and Contact Information

Eligible participants will be registered on the study centrally by the DCC at City of Hope. DCC staff are available **between the hours of 8:00 a.m. and 5:00 p.m. PST, Monday through Friday (except holidays).** DCC contact information is as follows:

phone: (626) 256-4673 ext. 83968

e-mail: DCC@coh.org

4.2.2. Slot verification and reservation

Eligible participants are stratified based on age. Designated study staff should call the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject. Slots can only be held for a limited time by an institution.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

4.2.3. Registration Process

To register a participant, the subsequent procedure is to be followed.

1. The participating site's data manager/coordinator/research nurse should contact the DCC via telephone or email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The data manager/coordinator/research nurse should then e-mail copies to DCC@coh.org of the following documents to the DCC:
    - Registration Cover Sheet (Appendix C)
    - Completed Eligibility Criteria List (printed from Section 3.0 of the protocol)

- Source documentation to support eligibility criteria**
- Signed informed consent document
- Signed HIPAA authorization form (if separate from the informed consent document)
- Signed subject's Bill of Rights (COH only)

**For COH participants, provide copies of source documentation only if not readily available as a finalized record in the COH Electronic Medical Record (EMR).

3. After having received all transferred documentation, the DCC will complete and review the documents to verify eligibility, working with the participating site as needed to resolve any missing required source elements. A subject failing to meet all protocol eligibility requirements will not be registered.
4. Once eligibility has been confirmed, DCC staff will register the participant by: assigning a subject accession number, register the subject on study centrally into MIDAS for non-COH participants (the COH CRC will directly accession into MIDAS), and enter the subject into the eCRF system, Medidata RAVE.
5. Once registration has been completed, DCC staff will send a Confirmation of Registration Form, including the participant study number to:
   - the site study team: site PI, treating physician, protocol nurse, CRC and pharmacy
   - the COH sponsor team designees

4.3. Screen Failures and Registered Participants Who Do Not begin Study Treatment

All sites should maintain a screening log of potential participants meeting age criteria who were considered for the study but did not meet eligibility criteria. The log should detail the reason for screen failure.

The DCC is to be notified of all participants who sign consent but do not meet eligibility criteria or do not initiate study treatment. For non-COH sites, the reason for screen failure will be documented in registration coversheet (see Appendix C) and submitted to the DCC.

4.4. Stratification

Participants will be stratified based on age. A minimum of 20 evaluable participants ≥ 75 years must be enrolled. The remaining 20 evaluable participants may be ≥ 70 to < 74 years OR ≥ 75 years.

5. TREATMENT PROGRAM

5.1. Treatment Overview

Participants will be administered protocol therapy consisting of ribociclib in combination with aromatase inhibitor in the outpatient setting.

Participants who end protocol therapy will undergo long-term follow-up (Section 5.1). Windows for all assessments and treatments are detailed in Section 11.0.

5.2. Treatment Cycle Definition and Day Count

A cycle will be a fixed 28 (±2) days in duration (Note: exceptions under certain circumstances are permitted; see Section 6.2.1 (8)).

The cycle day count and cycle count continue despite a hold in ribociclib administration due to toxicities (See Section 6.2.1) - i.e. a cycle may initiate even if ribociclib is being held.

Day 1 safety assessments must be reviewed prior to initiation of ribociclib during a new cycle.

Cycle 1 Day 1 is defined as the first day the participant initiates combined ribociclib and endocrine therapy regimen (See Table 5.3).

5.3. Treatment Plan and Agent Administration

Table 5.3: Treatment regimen

Agent	Starting Dose	Frequency of Administration	Route of Administration
Ribociclib	600 mg/ day	Once daily on Days 1-21 of each 28-day cycle	Orally
Aromatase inhibitor	Per package insert	Per treating investigator's discretion during each 28-day cycle	Per package insert

5.3.1. Ribociclib

Ribociclib should be taken at approximately the same time each day with food. Ribociclib tablets should be swallowed whole.

If applicable, ribociclib may be taken at the same time as endocrine therapy.

If a patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

Management and dose modification associated with ribociclib adverse events are outlined in Section 6.2. ribociclib doses missed for toxicity will not be made up during a cycle.

Participants will be supplied with a Pill Diary (Appendix E) to assess ribociclib compliance.

Ribociclib has been shown to prolong the QT interval in a concentration dependent manner, with mean increase in QTc interval being 22.9 ms (90% CI: 21.6-24.1). Therefore, ECG will be assessed prior to initiation of treatment and patients will only be eligible if QTcF values under <450 msec.

5.3.2. Aromatase inhibitor:

Participants will receive an aromatase inhibitor, according to the package insert and investigator discretion.

Modification in the dose of endocrine therapy due to unacceptable toxicity will occur per treating investigator's discretion.

The type of aromatase inhibitor may be switched at the treating investigator's discretion. Types of aromatase inhibitor includes letrozole, exemestane and anastrozole.

5.4. Duration of Protocol Therapy - Criteria for Ending Protocol Therapy

Participants will receive protocol therapy until one of the below criteria are met:

- Disease progression
- Participant is deemed intolerant to ribociclib because of toxicity, despite dose modification/ delay
- General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator
- Withdrawal of consent for further protocol therapy by the participant (See Section 17.5)

Once participants meet criteria for removal from protocol therapy, the participant should then proceed to End of Treatment and 30-Day-Post Last-Dose visits.

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the medical record and appropriate eCRF. **The COH DCC should be promptly notified of the change in participant status.**

5.5. Long-Term Follow-Up

All participants whose disease had not progressed at the time of end of protocol therapy will undergo **medical chart review for disease progression/response** information until disease progression or the initiation of a new therapy. Medical chart review should occur at least twice annually or as requested by the lead study team.

All participants will be followed for **survival information** by the site and/or by the lead study team designee. If performed by the lead study team, the following information will need to be transferred to the designee in a secure manner: the participant's first and last name, middle initial, social security number, date of birth, and gender. Methods for capturing survival status may include the Social Security Death Index and the National Death Index. Survival analysis will be conducted at least annually or as requested by the lead study team.

5.6. Criteria for Completion of Study Participation

Study participation may conclude when any of the following occur:

- Participant withdrawal (see Section 17.5).

- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for safety, behavioral or administrative reasons

Documentation of the reason for discontinuing study participation and the date effective should be made in the medical record and appropriate eCRF. **The COH DCC should be promptly notified of the change in participant status.**

5.7. Supportive Care, Other Concomitant Therapy, Prohibited Medications

Patients should receive full supportive care during the study, including treatment with antibiotics, antiemetics, blood transfusions, antidiarrheals, and analgesics as appropriate, with the exception of prohibited drugs listed below per institutional policies.

5.7.1. **Prohibited** until end of protocol therapy

End of protocol therapy is when treatment with ribociclib will no longer continue.

- No other investigational therapy should be given to participants
- No anticancer agents other than the study medications administered as part of this study protocol should be given to participants. If such agents are required for a participant then the participant must first be withdrawn from the study.
- Co-medication that may interfere with study results; e.g. immuno-suppressive agents other than corticosteroids, such as systemic cyclosporine and tacrolimus are prohibited during the treatment phase of the study, unless discussed with principal investigator felt to be of low clinical risk to the participant.
- Use of herbal medications may have unknown interactions with the metabolism of the study agents, and therefore are prohibited from use during the treatment phase of the trial.
- Strong CYP3A inhibitors/inducers including St. John's Wort and Grapefruit. Refer to Appendix B for an extensive list.
- Drugs known to cause QT interval prolongation. Refer to Appendix B for an extensive list.
- Hormone replacement therapy, topical estrogens (including any intra-vaginal preparations), megestrol acetate and selective estrogen-receptor modulators (eg, raloxifene).

5.7.2. Use with **caution**

- Medications that are substrates of CYP3A4 with narrow therapeutic indices may need to be reduced when given concurrently with ribociclib.
- Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares.
- Prophylactic use of white blood cell growth factors with ribociclib is not recommended

5.8. Assessments

Refer to the Study Calendar in Section 11.0.

6. ANTICIPATED TOXICITIES AND DOSE DELAY/MODIFICATION

6.1. Anticipated Toxicities

6.1.1. Ribociclib

A list of the adverse events and potential risks associated with ribociclib, as determined by the Package Insert follows (* signifies occurs in ≤ 10%):

Gastrointestinal: Nausea, stomatitis, diarrhea, decreased appetite, vomiting

General disorders and administration site conditions: Fatigue

Hematologic investigations: Abnormal absolute lymphocyte count; decreased lymphocytes, neutropenia, leukopenia, anemia, thrombocytopenia

Infections and infestations: Infection, upper respiratory tract infection*

Musculoskeletal and connective tissue: Weakness

Nervous system: Peripheral neuropathy

Respiratory, thoracic and mediastinal: Epistaxis

Skin and subcutaneous tissue: Alopecia

Vascular: Pulmonary embolism *

6.1.2. Letrozole

A list of the adverse events and potential risks associated with letrozole, as determined by the Package Insert follows (* signifies occurs in > 10%; ** signifies occurs in < 1%):

Cardiac: Myocardial infarction**, chest pain-cardiac**

Gastrointestinal: Nausea, vomiting, constipation*, diarrhea

General disorders and administration site conditions: Fatigue, edema*

Infections and infestations: Urinary tract infection

Injury, poisoning and procedural complications: Fracture

Investigations: Weight gain*, cholesterol high*, weight loss

Metabolism and nutrition: Anorexia

Musculoskeletal and connective tissue: Arthralgia*, myalgia, osteoporosis, weakness*, back pain, chest wall pain

Neoplasms benign, malignant and unspecified (including cysts and polyps): Treatment related secondary malignancy

Nervous system: Headache*, dizziness*, transient ischemic attack**

Psychiatric: Insomnia

Reproductive system and breast: Night sweats*, vaginal hemorrhage, vaginal irritation/ dryness, breast pain

Respiratory, thoracic and mediastinal: Dyspnea*, cough*

Vascular: Hot flashes*, thromboembolic event**

6.1.3. Exemestane

A list of the adverse events and potential risks associated with exemestane, as determined by the Package Insert follows (* signifies occurs in > 10%; ** signifies occurs in < 1%):

Cardiac: Myocardial infarction, angina, myocardial ischemia**

Eye: Visual disturbances

Gastrointestinal: Nausea*, diarrhea, constipation

General disorders and administration site conditions: Fatigue*, edema, increased sweating*, abdominal pain*

Immune system disorders: Allergy

Investigations: Weight gain*

Infections and infestations: Hepatitis

Injury, poisoning and procedural complications: Fractures

Metabolism and nutrition: Increased appetite, anorexia

Musculoskeletal and connective tissue: Arthralgia*, back pain, pain in limb, osteoarthritis, osteoporosis, myalgia

Nervous system: Headache*, dizziness, peripheral neuropathy**, paresthesia

Psychiatric: Insomnia*, depression*, anxiety*

Skin and subcutaneous tissue: Alopecia*

Vascular: Hot flashes*, hypertension*

6.1.4. Anastrozole

A list of the adverse events and potential risks associated with anastrozole, as determined by the Package Insert follows (* signifies occurs in > 10%):

Blood and lymphatic system: Anemia

Cardiac: chest pain-cardiac, myocardial ischemia

Eye: Cataract

Gastrointestinal: Nausea*, vomiting, dyspepsia

General disorders and administration site conditions: Edema limbs*

Infections and infestations: Pharyngitis*, infection, sinusitis, bronchitis, vaginal infection, urinary tract infection, hepatitis, rhinitis

Injury, poisoning and procedural complications: fractures*

Investigations: Weight gain, cholesterol high, Alkaline phosphatase increased, AST increased, ALT increased, bilirubin increased, GGT increased, hypercalcemia, lymphocyte count decreased, weight loss

Immune system disorders: Allergy, anaphylaxis

Musculoskeletal and connective tissue: Weakness*, arthritis*, arthralgia*, pain*, osteoporosis*, back pain*, bone pain*, arthrosis, myalgia

Neoplasms benign, malignant and unspecified (including cysts and polyps): Treatment related secondary malignancy, breast neoplasm

Nervous system: Headache*, dizziness, Ischemia cerebrovascular

Psychiatric: Depression*, insomnia*, anxiety, paresthesia

Reproductive system and breast: Vaginal discharge, breast pain, vaginal hemorrhage

Respiratory, thoracic and mediastinal: Cough*, dyspnea*

Skin and subcutaneous tissue: Rash*, Stevens-Johnson syndrome, erythema multiforme, urticaria, alopecia, pruritus

Vascular: Hot flashes*, hypertension*, lymphedema*, hypotension*, thromboembolic event

6.2. Dose Modifications/ Delays

6.2.1. General Information:

1. The cycle length will remain 28 days (± 2 days) despite a delay in initiating ribociclib on Day 1; endocrine therapy may continue to be administered per the preplanned schedule.
2. Dose holds/reductions of endocrine therapy will occur per treating investigator's discretion.
3. See Table 6.2.1 for criteria to dose modify ribociclib. Dose reductions are as follows:

Table 6.2.1: Ribociclib dose levels

Dose Level	Dose
Starting dose	600 mg/day
First dose reduction	400 mg/day
Second dose reduction	200 mg/day
Third dose reduction	discontinue protocol therapy

Table 6.2.2a: Ribociclib Dose Modification and Management - Hematologic Toxicities

CTCAE v 4.0 Grade	Ribociclib Dose Modifications For Hematologic Toxicities
Grade ≤ 2	Maintain treatment.
Grade 3 (Except febrile neutropenia OR lymphopenia associated with clinical events)	Hold ribociclib until recovery to Grade ≤2. Consider repeating complete blood count monitoring one week later. • Upon recovery Grade ≤2 within 28 days resume therapy at the pre-hold dose. • Permanently discontinue protocol therapy if the toxicity persists for > 28 days.
Grade 3 ANC (<1000 to 500/mm^3) + Fever (≥38.5°C) **OR** **Grade 3 ANC + infection**	Hold ribociclib until recovery to Grade ≤2 (≥ 1000/mm^3). • Upon recovery Grade ≤2 within 28 days resume therapy at the next lower dose. • Permanently discontinue protocol therapy if the toxicity persists for > 28 days.
Grade 4 ANC <500/mm^3 (Except lymphopenia associated with clinical events)	Hold ribociclib until recovery to Grade ≤2. • Upon recovery Grade ≤2 within 28 days resume therapy at the next lower dose. • Permanently discontinue protocol therapy if the toxicity persists for > 28 days.

Table 6.2.2b: Ribociclib Dose Modification and Management- Non-Hematologic Toxicities

	CTCAE v 4.0 Grade	Dose Modifications For Non-Hematologic Toxicities
RELATED to Ribociclib	**Grade ≤ 2**	Maintain treatment.
	Grade ≥3	Hold ribociclib until recovery to Grade ≤1 or baseline. • Upon recovery to Grade ≤1 or baseline within 28 days resume therapy at the next lower dose if medically appropriate at the discretion of the treating physician. • Permanently discontinue protocol therapy if the toxicity persists for > 28 days
NOT-RELATED to Ribociclib	**Grade ≥3**	Treating investigator may hold ribociclib per his/her discretion. Permanently discontinue protocol therapy if the hold is for > 28 days

Table 6.2.2c: Ribociclib Dose Modification and Management- Hepatobiliary Toxicity

	Grade 1 (> ULN-3 x ULN)	Grade 2 (>3-5 x ULN)	Grade 3 (>5-20 x ULN)	Grade 4 (>20 x ULN)
AST and/or ALT Elevations from baseline, WITHOUT increase in total bilirubin above 2 x ULN	No dose adjustment required	**Baseline at < grade 2:** Dose interruption until recovery to ≤ baseline grade, then resume ribociclib at the same dose level. If grade 2 recurs, resume ribociclib at the next dose level. **Baseline at grade 2:** No dose interruption	Dose interruption until recovery to ≤ baseline grade then resume at the next lower dose level. 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 patient develops ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN irrespective of baseline grade, discontinue ribociclib			

Table 6.2.2d: Ribociclib Dose Modification and Management- QT Prolongation

Grade	Dose Modification
For All Grades	1. Check the quality of the ECG and the QT value and repeat if needed. 2. Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If outside of the normal range, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. 3. Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. 4. Check compliance with correct dose and administration of ribociclib. Consider collecting a time matched PK sample; record date and time of last study drug intake
1* QTcF 450-480 ms	Perform steps 1-4 as directed in "For All Grades." No dose adjustment required.
2* QTcF 481-500 ms	Interrupt ribociclib. Perform steps 1-4 as directed in "For all Grades." Perform a repeated ECG within one hour of the first QTcF of ≥ 481 ms. Repeat ECG as clinically indicated until the QTcF returns to < 481 ms, restart ribociclib with dose reduced by 1 dose level. Refer to Table 6.2.1. for dosing schedule. If QTcF ≥ 481 ms recurs, ribociclib should be reduced again by 1 dose level. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 481 ms.
3* QTcF ≥ 501 ms on at least two separate ECGs	Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." Perform a repeat ECG within one hour of the first QTcF of ≥ 501 ms. If QTcF remains ≥ 501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to < 481 ms. • If QTcF returns to < 481 ms, ribociclib will be reduced by 1 dose level. *(Refer to Table 6.2.1 for dosing schedule.)* • If QTcF returns to ≥ 481 ms after performing steps 1-4 as directed in "For All Grades," discontinue ribociclib. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 ms. If QTcF of ≥ 501 recurs, discontinue ribociclib.
4* [QT/QTcF ≥ 501 or > 60 ms change from baseline] and [Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia]	Discontinue ribociclib. Perform steps 1-4 as directed in "For All Grades." • Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms.

*All values refer to the average of the triplicate measurements.

Dose Modification for Use with Strong CYP3A Inhibitors:

- Avoid concomitant use of ribociclib with strong CYp3A inhibitors and consider an alternative concomitant medication with less potential for CYP3A inhbitiion,
- If a strong CYP3A inhibitor must be coadministered, reduce the ribociclib dose to 400 mg once daily.
- If strong inhibitor is discontinued, change the ribociclib dose (after at least 5 half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor.

Dose Modification for Hepatic Impairment

- No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A).

7. SAFETY MONITORING AND REPORTING

7.1 Definitions

7.1.1. Adverse Event (AE)

An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

7.1.1.1 Serious Adverse Event (SAE)

A serious adverse event is any expected or unexpected adverse events that result in any of the following outcomes:

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary malignancy*
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

*Modified from 21 CFR 312.32

7.1.1.2 Unanticipated Problems Involving Risks to Subjects or Others

An unanticipated problem is any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

7.1.1.3 Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events, regardless of seriousness, will be reported.

7.1.2 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, assessing the severity (i.e. grade), expectedness, and attribution of all adverse events.

7.1.2.1 Assessment of Adverse Event Name and Grade

Adverse events will be characterized using the descriptions and grading scales found in The NCI Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0. A copy of the scale can be found at the NCI/CTEP web site. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based on medical judgment and the severity categories of Grade 1 to 5 as defined below:

- Grade 1 (mild) – An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2 (moderate) – An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- Grade 3 (severe) – An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
- Grade 4 (life threatening) – An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
- Grade 5 (fatal) – Death (loss of life) as a result of an event.

7.1.2.2 Assessment of Attribution

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is doubtfully related to the investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions, or concomitant drugs.
- **Definite –** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs, AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

7.1.2.3 Assessment of Expectedness

The following definitions will be used to determine the expectedness of the event:

- **Unexpected**– An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event. *Modified from 21 CFR 312.32 (a)
- **Expected –** An adverse event is expected if it does not meet the criteria for an unexpected event, OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

7.1.3 Reporting of Adverse Events

7.1.3.1 Routine Reporting of Non-Serious Adverse Events by Site Investigators

Routine AE recording will occur via data entry into the study eCRF. Recording of adverse events will begin once the patient is consented and will continue until 30 days after the patient's last dose. Adverse events will be monitored by the Protocol Management Team (PMT). Adverse events that do not meet the criteria of serious OR are not unanticipated problems do not require expedited reporting. AEs reported through expedited processes (i.e. reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

7.1.3.2 Expediting Reporting Requirements of SAEs and UPs by Site Investigators

7.1.3.2.1 Criteria for Reporting SAEs/UPs to the Coordinating Center

Serious Adverse Events meeting the criteria specified below will be reported to the Coordinating Center within **24 hours** of notification that the event occurred.

Adverse events that require expedited reporting include:

- AEs or SAEs that meet the definition of an unanticipated problem
- All deaths that occur within 30 days of active treatment
- All deaths that occur after 30 days of active treatment that are unexpected and possibly, probably, or definitely related to the study agent or procedure
- All serious adverse events, regardless of relationship to study agent or study procedure, that occur within 30 days of the last day of treatment
- All serious adverse events that occurred after 30 days of active treatment/therapy that are considered possibly, probably, or definitely related to the study agent or procedure

Note: Follow-up reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event.

Reportable serious adverse events must be followed until the event is resolved, stabilized, or determined to be irreversible by the participating investigator; for ongoing reportable adverse events that are unrelated to study agent, the follow-up period may end at the 30-days post study-drug assessment. The Coordinating Center should be consulted prior to ending the follow-up of events that have stabilized.

7.1.3.2.2 Non-COH Sites: Procedure for Reporting SAEs/UPs to the COH Data Coordinating Center

1. Sites are to report to their local IRB per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH Data Coordinating Center copies of the IRB submission and corresponding IRB response.
2. Document/describe the SAE/UP on each of the following:
    a. MedWatch 3500A
        i. Downloadable form at http://www.fda.gov/medwatch/getforms.htm
    b. UP/SAE Coversheet
        i. SAE Coversheet is found in Appendix [J]. A modifiable Microsoft Word document is also available from the Data Coordinating Center. An electronic signature on the document will be accepted.
3. Scan and email above documents to DCC@coh.org with the subject title as "IRB # SAE".
    a. All SAE reports received at this account are forwarded immediately to study Principal Investigator, and to Coordinating Center personnel.
    b. While not required, if available and applicable, please also include the local IRB submission for this event in the submission.
4. If an email receipt from Coordinating Center personnel is not received within one working day, please call 626-256-4673 x 83968 and/or email DCC@coh.org.

7.1.3.2.3 COH Investigative Sites: Procedure for Reporting SAEs/UPs to the Coordinating Center

1. Email the following information to DCC@coh.org and msedrak@coh.org.
    a. Participant ID, date the event met criteria for reporting, whether the event meets the definition of serious, whether the event is an unanticipated problem, grade of event, attribution of event, whether the event is a known expected toxicity to study agent.
2. Complete the iRIS AE/UP reporting form per COH reporting timeline.

7.1.3.3 Additional Reporting Requirements of the Study Principal Investigator

7.1.3.3.1 Reporting to COH IRB and DSMC

The study PI (or designee) will report to COH IRB and DSMC via iRIS all reportable serious adverse events that occur at COH and non-COH sites and meet COH IRB and DSMC expedited reporting criteria according to City of Hope's Institutional policy. The study PI will also submit a Protocol Management Team (PMT) report to the COH DSMC at the frequency outlined in Section 3.6. This report will include a review of aggregate adverse event data.

7.1.3.3.2 Reporting to the FDA

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the Medwatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

7.1.3.3.3 Reporting to Participating Investigators

The study PI (or designee) will report all reportable serious adverse events to participating investigators as an IND Safety Report occurring within 30 calendar days of receipt of sponsor (lead site) notification, and indicate whether or not a protocol and/or consent form change is required. A cover letter will indicate the protocol title, the IND#, whether the FDA was informed, and, for non-COH sites, a statement that the report should be submitted to their local IRB for review as an IND safety report if applicable per local IRB policy.

The study PI will also forward to participating sites all IND safety reports received from Novartis, indicating whether a consent form or protocol change is required within 30 days of notification to study PI.

7.1.3.3.4 Reporting to Novartis

All serious adverse events and AESIs (initial and follow-up information) will be reported by the study PI to Novartis within 24 hours of learning of its occurrence per the following guidelines: Novartis Adverse Event Reporting Guidelines (section 7.1).

7.2.0 PROTOCOL DEVIATIONS AND SINGLE SUBJECT EXCEPTIONS

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. Brief interruptions and delays may occasionally be required because of travel delays, airport closures, inclement weather, family responsibilities, security alerts, government holidays, and so forth. Delays can also extend to complications of disease or unrelated medical illnesses not related to disease progression. The PI has the discretion to deviate from the protocol when necessary so long as such a deviation does not threaten patient safety or protocol scientific integrity. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

7.2.1 Definitions

7.2.1.1 Deviation

A deviation is a divergence from a specific element of a protocol that occurred without prior IRB approval. Investigators may deviate from the protocol to eliminate immediate hazard(s) for the protection, safety, and well-being of the study subjects without prior IRB approval.
Examples include, but are not limited to: a) dose adjustments based on excessive patient weight; b) alteration in treatment schedule due to non-availability of the research participant for treatment; and c) laboratory test results which are slightly outside the protocol requirements but at levels that do not affect participant safety.

7.2.1.2 Single Subject Exceptions (SSE)

An SSE is a planned deviation, meaning that it involves circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient. It is a deviation that is anticipated and receives prior approval by the PI and the IRB.

7.2.2 Reporting of Deviations and SSEs

7.2.2.1 Reporting Deviations

For any deviation, the Investigator will notify the COH DSMC and IRB within 5 calendar days of its occurrence via iRIS in accordance with the Clinical Research Protocol Deviation policy.
A list of deviations from all participating sites will be submitted along with the Protocol Management Team (PMT) progress report to the COH DSMC.

For non-COH sites:

- The local IRB and/or DSMC must be notified according to local institutional policies.

- The study Principal Investigator must be notified as soon as practical (within 24 hours of notification of the event) via email to msedrak@coh.org and dcc@coh.org. This email should provide input on the following:
    - Description of the event
    - Impact on participant safety or the safety to others
    - Impact on the study design
    - A corrective and preventative action plan

7.2.2.2 Reporting Single Subject Exceptions

The SSE must be submitted as a "Single Subject Exception Amendment Request" via iRIS in accordance with IRB guidelines and the Clinical Research Protocol Deviation policy. An IRB approved SSE does not need to be submitted as a deviation to the DSMC.

All non-emergency planned deviations from the protocol must have **prior** approval by the Study Principal Investigator, the Site Principal Investigator, COH IRB, and when applicable, the local IRB. In addition, if contractually obligated, the sponsor must also approve the deviation.

7.3.0 STUDY OVERSIGHT, QUALITY ASSURANCE, AND DATA & SAFETY MONITORING

7.3.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

All Investigators agree to:

- Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when necessary to protect the safety, rights or welfare of subjects.
- Personally conduct or supervise the study (or investigation).
- Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
- Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
- Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.

- Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
- Seek IRB and Sponsor approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

7.3.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities as defined in § 21 CFR 312. Subpart D are executed in accordance with federal regulations.

7.3.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, site investigators, collaborating investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) at least monthly to review study status. This review will include, but not be limited to, reportable AEs and UPs, and an update of the ongoing study summary that describes study progress in terms of the study schema. The meeting will be a forum to discuss study related issues including accrual, SAE/AEs experienced, study response, deviations/violations and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed. It is recommended that minutes of these discussions be taken to document the date of these meetings, attendees and the issues that were discussed (in a general format).

7.3.4 Monitoring

Clinical site auditing is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Auditing for this study will be performed by the City of Hope Office of Clinical Trials Auditing and Monitoring (OCTAM).

The site Investigator/Institution will permit the study auditors and appropriate regulatory authorities direct access to the study data and to the corresponding source data and documents to verify the accuracy of this data. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Details of clinical site monitoring are documented in the OCTAM SOP that is provided as a supplement to this document. This document specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Staff from OCTAM will conduct monitoring activities and provide reports of the

findings and associated action items in accordance with the details described in the SOP. Documentation of monitoring activities and findings will be provided to the site study team, the site PI, study PI, and the COH DSMC.

7.3.5 Quality Assurance

The City of Hope Clinical Research Information Support will provide support for this multi-center trial as detailed in the COH DCC Operations Plan provided as a supplement to this document.

7.3.6 City of Hope Data and Safety Monitoring Committee

This is a risk level 3 study as defined in the City of Hope Institutional Data and Safety Monitoring Plan. This determination was made because this study is a Phase IIA trial that is IND Exempt.

The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials that are sponsored by City of Hope. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. The committee reviews the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

The Study Principal Investigator is required to submit periodic status reports (the PMT report) according to the guidelines outlined in the City of Hope Institutional Data and Safety Monitoring Plan. The PMT report will be submitted to the COH DSMC every six months from the date of activation.

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The DSMC will review up-to-date participant accrual; summary of all adverse events captured via routine and expedited reporting; a summary of deviations; any response information; monitoring reports, and summary comments provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. For Phase I studies, a Phase I Tracking Log will be utilized and reviewed by the DSMC to monitor data and safety for dose escalation. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study. Information that raises any questions about participant safety will be addressed with the Principal Investigator, statistician and study team. The PMT report and DSMC recommendations will be circulated to all participating sites for submission to their IRBs, in accordance with NIH guidance.

7.4 Novartis Adverse Event Reporting Guidelines

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

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

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

Pregnancies

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

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

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

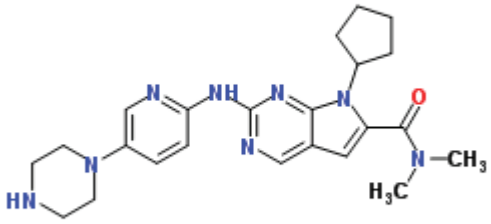
8. AGENT INFORMATION

8.1. Ribociclib

8.1.1. Other Names

Kisqali

8.1.2. Description and Molecular Weight

Structural formula:	
Empirical formula:	$C_{23}H_{30}N_8O$
Molecular weight:	434.254272 g/mol
Chemical Name:	7-Cyclopentyl-N,N-dimethyl-2-{[5-(1-piperazinyl)-2-pyridinyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-6-carboxamid

8.1.3. Mechanism of Action

Inhibitor of cyclin-dependent kinase (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. In vitro, ribociclib reduced cellular proliferation of estrogen receptor (ER)-positive breast cancer cell lines by blocking progression of the cell from G1 into S phase of the cell cycle. Treatment of breast cancer cell lines with the combination of ribociclib and antiestrogens leads to decreased retinoblastoma protein (Rb) phosphorylation, resulting in reduced E2F expression and signaling and increased growth arrest compared to treatment with each drug alone. In vitro treatment of ER-positive breast cancer cell lines with the combination of ribociclib and antiestrogens leads to increased cell senescence, which was sustained for up to 6 days following drug removal. In vivo studies using a patient-derived ER-positive breast cancer xenograft model demonstrated that the combination of ribociclib and letrozole increased the inhibition of Rb phosphorylation, downstream signaling and tumor growth compared to each drug alone.[22]

8.1.4. Pharmacokinetics

Absorption:	Compared to a fasted state, oral administration with a high-fat, high-calorie meal has no effect on the rate and extent of absorption of ribociclib.
Distribution: V_d (mean):	1090 L
Protein binding:	~70%
Metabolism:	Extensively hepatic; Major pathways: Oxidation (dealkylation, C and/or N-acetylation), sulfation, cysteine conjugation, glycosylation and glucuronidation.
Bioavailability:	Mean absolute bioavailability: 46%
Half-life elimination:	32 hours
Time to peak:	1 to 4 hours
Excretion:	Feces. 92% of dose recovered within 22 days; feces is the major route of excretion (69%), with 23% recovered in urine.

8.1.5. Human Toxicity

See Section 6.1.1.

8.1.6. Formulation

Ribociclib is supplied as a 600 mg, 400 mg, or 200 mg doses in assorted blister packs. Each film-coated contains 200 mg of ribociclib free base. Ribociclib is supplied as a light greyish violet, round tablet, curved with beveled edge, debossed with “RIC” on one side and “NVR” on the other. Inactive ingredients present in the tablet include: colloidal silicon dioxide, crospovidine, hydroxypropylcellulose,magnesium stearate, and microcrystalline cellulose.

8.1.7. Storage

The blister packs should be stored at 20^{0}C to 25^{o}C (68^{o}F to 77^{o}F); excursions permitted between 15 to 30^{o}C (59 to 86^{o}F).

8.1.8. Preparation

Ribociclib may be repackaged to provide appropriate capsule quantities to participants. Tabs should not be distributed if broken, cracked or otherwise not intact.

8.1.9. Dose and Administration

See Section 6.2.

8.1.10. Supplier

Study drug is being provided by the drug manufacturer, Novartis.

8.1.11. Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form.

8.1.12. Destruction and Return

Any unused agent at the end of the study, expired agent, and damaged agent will be destroyed according to institutional policies. **Prior** to the destruction of ribociclib, the DCC should be notified and an acknowledgement to proceed from the DCC should be received. Destruction will be documented in the Drug Accountability Record.

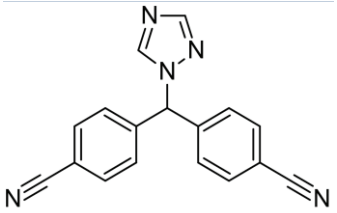
8.2 Letrozole

Please refer to the Package Insert for additional details for letrozole not provided in this section.

8.2.1. Other names

Femara.

8.2.2. Description and Molecular Weight

Structural formula:	
Empirical formula:	$C_{17}H_{11}N_5$
Molecular weight:	285.30 g/mol
Chemical Name:	4-[(4-cyanophenyl)-(1,2,4-triazol-1-yl)methyl]benzonitrile

8.2.3.

Mechanism of Action:

Nonsteroidal competitive inhibitor of the aromatase enzyme system which binds to the heme group of aromatase, a cytochrome P450 enzyme which catalyzes conversion of androgens to estrogens (specifically, androstenedione to estrone and testosterone to estradiol). This leads to inhibition of the enzyme and a significant reduction in plasma estrogen (estrone, estradiol and estrone sulfate) levels. Does not affect synthesis of adrenal or thyroid hormones, aldosterone, or androgens.

8.2.4. Human Toxicity

See Section 6.1.2.

8.2.5. Pharmacokinetics

Absorption:	Rapid and well absorbed; not affected by food
Distribution: V_d:	~1.9 L/kg
Protein binding plasma:	Weak
Metabolism:	Hepatic via CYP3A4 and 2A6 to an inactive carbinol metabolite
Half-life elimination:	Terminal: ~2 days
Time to steady state, plasma	2 to 6 weeks; steady state serum concentrations are 1.5 to 2 times higher than single-dose values
Excretion:	Urine (90%; 6% as unchanged drug, 75% as glucuronide carbinol metabolite, 9% as unidentified metabolites)

8.2.6. Supplier

Letrozole is commercially available.

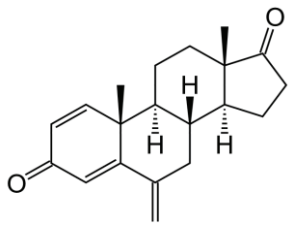
8.3 Exemestane

Please refer to the Package Insert for additional details for exemestane not provided in this section.

8.3.2. Other names

Aromasin

8.3.3. Description and Molecular Weight

Structural formula:	
Empirical formula:	$C_{20}H_{24}O_2$
Molecular weight:	296.403 g/mol
Chemical Name:	6-Methylideneandrosta-1,4-diene-3,17-dione

8.3.4. Mechanism of Action

Exemestane is an irreversible, steroidal aromatase inactivator. It is structurally related to androstenedione, and is converted to an intermediate that irreversibly blocks the active site of the aromatase enzyme, leading to inactivation ("suicide inhibition") and thus preventing conversion of androgens to estrogens in peripheral tissues. Exemestane significantly lowers circulating estrogens in postmenopausal breast cancers where growth is estrogen-dependent.

8.3.5. Human Toxicity

See Section 6.1.3.

8.3.6. Pharmacokinetics

Absorption:	Rapid and moderate (~42%) following oral administration; AUC and C_{max} increased by 59% and 39%, respectively, following a high-fat breakfast compared to fasted state
Distribution:	Extensive into tissues
Protein binding plasma:	90%, primarily to albumin and α_1-acid glycoprotein
Metabolism:	Extensively hepatic; oxidation (CYP3A4) of methylene group, reduction of 17-keto group with formation of many secondary metabolites; metabolites are inactive
Half-life elimination:	~24 hours
Time to peak:	Women with breast cancer: 1.2 hours

Excretion:	Urine (<1% as unchanged drug, 39% to 45% as metabolites); feces (36% to 48%)

8.3.7. Supplier

Exemestane is commercially available.

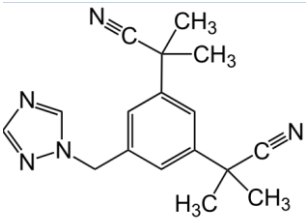
8.4 Anastrozole

Please refer to the Package Insert for additional details for anastrozole not provided in this section.

8.4.2. Other names

Arimidex

8.4.3. Description and Molecular Weight

Structural formula:	
Empirical formula:	$C_{17}H_{19}N_5$
Molecular weight:	293.37 g/mol
Chemical Name:	2-[3-(2-cyanopropan-2-yl)-5-(1,2,4-triazol-1-ylmethyl)phenyl]-2-methylpropanenitrile

8.4.4. Mechanism of Action

Anastrozole is a selective non-steroidal aromatase inhibitor. By inhibiting aromatase, the conversion of androstenedione to estrone, and testosterone to estradiol, is prevented, thereby decreasing tumor mass or delaying progression in patients with tumors responsive to hormones.

8.4.5. Human Toxicity

See Section 6.1.4.

8.4.6. Pharmacokinetics

Onset of estradiol reduction:	70% reduction after 24 hours; 80% after 14 days of daily dosing

Duration of serum estradiol reduction:	6 days
Absorption:	Well absorbed; food reduces the rate but not the overall extent of anastrozole absorption
Protein binding plasma:	40%
Metabolism:	Extensively hepatic (~85%) via N-dealkylation, hydroxylation, and glucuronidation; primary metabolite (triazole) inactive
Half-life elimination:	~50 hours
Time to peak, plasma:	~2 hours without food; 2 to 5 hours with food
Excretion:	Feces; urine (urinary excretion accounts for ~10% of total elimination, mostly as metabolites)

8.4.7. Supplier

Anastrozole is commercially available.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Blood Banking (Optional)

With patient permission obtained (via informed consent), blood (10 mL- green top heparin OR lavender top K+EDTA) will be collected at baseline for future mRNA and DNA isolation and stored in order to be banked for future research. Such studies might include genetic testing to determine how genetics influences chemotherapy toxicity. Samples will be stored between -60°C to -90°C at the COH Clinical Immunobiology Correlative Studies Laboratory (CICSL) until future downstream processing.

Collection, Processing, Labeling and Shipping

Refer to Appendix D1 for collection and to Appendix D2 for shipping (non-COH sites only)

10. RIBOCICLIB PHARMACOKINETICS

10.1 Clinical Pharmacology Objectives

To determine average plasma steady-state ribociclib C_{trough} concentrations in patients over the age of 70 years. Further, we will determine the relationship between average plasma C_{trough} and percent decreases in neutrophil and platelet counts in patients. [24]

10.2 Blood Sample Collection

Blood samples will be collected from a peripheral vein or indwelling venous catheter or by venipuncture. At each time point indicated in the table below, peripheral blood will be collected into a single 10 ml green-top tube (sodium or lithium heparin) to prevent blood clotting. Tubes will be inverted several times and then immediately placed on ice for transportation to the Analytical Pharmacology Core Facility (APCF), the processing laboratory.

Blood samples will be collected at the times indicated in table 10.2.1 below. **Patients will be instructed not to take their ribociclib on these days until after they have had their blood drawn in the clinic.**

Table 10.2 Time Points for Blood Sample Collection for PK Studies

Time Point	Cycle	Day	Date (mm/dd/yy)	Time (hr:min)
Pretreatment	1	1*		
C1D8	1	8		
C1D15	1	15		
C2D1	2	1		
C2D8	2	8		
C2D15	2	15		

*All samples to be drawn prior to the dose of ribociclib on that day.

10.3 Sample Processing

Anti-coagulated whole blood samples (one 10 ml green-top tube) will be processed by centrifugation for 10 minutes at 1500 x g at 4°C. The resulting plasma will be transferred to appropriately labeled polypropylene tubes and frozen at < -70°C until analysis.

10.4 Analytical Method

For analysis of ribociclib in human plasma, a sensitive and selective LC/MS/MS method will be developed and qualified in the Analytical Pharmacology Core Facility at the City of Hope. The method will be based on the published method of Kala et al.[25]

10.5 Pharmacokinetic Data Analysis Methods

Average plasma C_{trough} will be calculated for each subject and the population results will be summarized using standard statistical methods.

11. STUDY CALENDAR

All procedures may increase in frequency if clinically indicated.

Table 11.0 Study Activity Calendar

Evaluations & activities	Screening [a]	Treatment [b]						Off Tx	30-days post-last dose [f]	Long-Term Follow-Up
		Cycles 1			Cycle 2			Cycles 3+			
		Day 1 [c,d]	Day 8	Day 15 [e]	Day 1	Day 8	Day 15	Day 1 [d]			
MD Evaluation	X	X		X	X		X	X	X		
Informed consent [g]	X										
Eligibility criteria [h]	X										
Registration [i]	X										
Medical history [j]	X										
Vital signs [k]	X	X		X	X		X	X	X		
Physical exam [l]	X	X		X	X		X	X	X		
Performance status [m]		X			X			X	X	X	
Hematology	X [n]	X		X	X		X	X	X		
Chemistry (including LFTs)	X [n]	X		X	X		X	X	X		
Lipid Panel	X							X [gg]			
Urinanalysis / BUN	X										

Blood banking sample [p]		X									
Pharmacokinetic blood draw		X	X	X	X	X	X				
Concomitant meds [q]	X	X			X			X	X	X	
AE evaluation [r]	X	X	X	X	X	X	X	X	X	X [s]	
Pill diary [t]		X [t]			X[t]			X [t]	X[hh]		
Geriatric assessment[u]		X[v]						X[w]	X[hh]		
WIWI and OTU x									X[hh]		
Radionuclide Bone Scan, Whole Body	X[y]							X[z]			
CT [aa]	X[y]							X[w]			
ECG (12-lead)	X			X	X		X				
Disease/Response Assessment [bb]								X[w]			
Ribociclib [cc]		Orally once daily on Days 1-21 of each cycle (See Section 5.3)									
AI [cc]		Per treating investigator's discretion. Dosing per package insert in each cycle. (See Section 5.3)									
Chart review dd											X dd
Survival [ee]											X [ee]

a. Screening procedures to be performed within 28 days from start of protocol therapy, except labs which are to be performed within 14 days of start of study agents (footnotes 'n').
b. Treatment will last until unacceptable toxicity or disease progression (see Section 5.4 for more comprehensive list).
c. Cycle 1 Day 1 will be defined as the day the participant initiates the combined ribociclib and endocrine therapy regimen.
d. Each treatment cycle lasts 28 days, with a fixed window of ± 2 days for participant convenience. The cycle duration does not change, even if ribociclib is held (Note: exceptions under certain circumstances are permitted; see Section 6.2). Day 1 safety assessments must be performed and reviewed within 48 hours of initiating ribociclib during a new cycle.
e. Windows for Day 8 and 15 assessments are +/-2 days.
f. A contact/visit for review of adverse events, performance status (see Appendix A), and concomitant medication review, is to be performed at 30 ± 2 days after the last study drug is given. In lieu of a clinic visit, this may be performed via documented phone conversation with a study nurse or clinician. All participants will be followed until resolution or stabilization of all events requiring expedited reporting and occurring during treatment or starting within 30 days of last study drug.
g. Informed consent process to be fully documented (see Section 17.4). Informed consent must occur prior to any research only (non-SOC) screening procedures.
h. Eligibility criteria: refer to Section 3.0. The site will maintain a screen-failure log for all persons screened for eligibility (see Section 4.3).
i. See Section 4.2 for registration process. The DCC must be notified of all persons who sign consent, including screen failures or participants who fail to initiate protocol therapy (see Section 4.3).
j. Medical history: to include any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
k. Vital signs: Weight, heart rate, blood pressure, respiration rate, and temperature. Height required only at baseline.
l. Physical exam to include Clinical Evaluation of Superficial Disease for use in disease evaluation.
m. See Appendix A for Karnofsky performance status.
n. CBC and metabolic panel to be performed within 14 days prior to start of protocol therapy.
o. Metabolic panel: electrolytes, BUN, creatinine, AST, ALT, total bilirubin, total protein, albumin, alkaline phosphatase, and glucose).
p. From participants who consent to research samples only, 10 mL blood sample to be collected in a lavender (K-purple (EDTA) or green (Heparin) top tube, inverted several times, placed on ice and stored at -80°C. See Section 9.1 and Appendix D1.
q. Concomitant medications: All prescription and over-the-counter medications that have been taken within 30 days prior to the first dose of protocol therapy up to 30-day post-last dose will be recorded in the CRFs. See Section 5.7.1 for concomitant medication restrictions.
r. Adverse events (AEs) experienced by participants will be collected and recorded from the pre-treatment Cycle 1 Day 1 safety assessments up to 30 days of the last dose of study medication. See Section 7.0 for reporting guidelines). AEs will be recorded by MD on C1D1, C1D15, C2D1, C2D15, and C3D1. AEs will be recorded by RN on C1D8 and C2D8.
s. The period for collection, recording and reporting of AEs is extended for participant with ongoing adverse events requiring expeditious reporting (see Section 7.3).
t. Ribociclib pill diary: The participant will be given a pill diary (see Appendix E) which will be reviewed for adherence. It will **not be a deviation** if the diary it not returned prior to initiation of the subsequent cycle.
u. Geriatric Assessment (GA) to be administered either via paper (from PDF supplement) or tablet data entry. Duration for completion is usually between 20 and 40 minutes. Appendix F details the GA content, but is not for administration.

v. GA to be administered within seven days of Cycle 1 Day 1 protocol therapy. GA will not be administered for Cycle 2 Day 1.
w. GA and CT to be performed prior to Cycle 3 (± 7 days), then every 3 cycles (± 7 days).
x. Was It Worth It (WIWI) Questionnaire (See Appendix G for content only but not for administration, a separate PDF can be requested from the lead study team) and Overall Treatment Utility (OTU) Questionnaire (See Appendix H).
y. Imaging to be performed within 28 days prior to enrollment.
z. Post-baseline radionucleotide imaging to be performed only as clinically indicated or to confirm complete response.
aa. CT of chest, abdomen, pelvis, any clinically indicated sites of disease, and of bone lesions.
bb. Confirmatory scans following documentation of progression or response will not be required; progression/response will be determined based on results of the single time point. See Section 11.0.
cc. Refer to Section 6.2 for dose modification/ dose delay guidelines.
dd. Medical chart review for disease progression/response will also occur until progression or the initiation of a new therapy at least twice annually or as requested by the lead study team. Post-study new therapy regimens will be collected.
ee. Survival analysis will be conducted by the site and/or by the lead study coordinator at least annually or as requested by the lead study team. All patients will be followed for survival information. The following will be collected: the participant's first and last name, middle initial, social security number, date of birth, and gender. The investigators will utilize the Social Security Death Index and the National Death Index to establish survival status.
ff. ECG to be initiated at baseline mid-cycle of cycle 1 and beginning of cycle 2. Based in observed QT prolongation during treatment, ribociclib may require dose interruption, reduction or discontinuation.
gg. Every 4th cycle.
hh. Off Tx questionnaires to be completed within 30 days of date patient is taken off treatment or before the patient begins a new treatment, whichever occurs first.

12.0 ENDPOINT EVALUATION CRITERIA/MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the new updated international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee version 1.1.[26] Per the new RECIST criteria, as disease response is not the primary endpoint of this trial, confirmatory scans following documentation of progression or response will not be required. Rather, progression/response will be determined based on results of the single scan.

12.1 Definitions

Evaluable for toxicity:

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

Evaluable for objective response:

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

12.2 Disease Parameters

Measurable disease:

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >10mm with conventional techniques (CT, MRI, or caliper measurement) and as >20mm by chest X-ray (if clearly defined and surrounded by aerated lung.) Lymph nodes greater than 10mm on short axis are considered measureable as well. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease:

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm by chest X-ray or <10 mm using CT, MRI or caliper measurement), are considered non-measurable disease. Organomegaly, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI) are all non-measurable.

Bone-Only Disease:

No distant metastases other than in bone.

Target lesions:

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Lymph nodes less than 15mm in the short axis cannot be used as target lesions. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions:

All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment.

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

Clinical lesions:

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

Chest x-ray:

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

Conventional CT and MRI:

These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols such as CT head and neck or MRI brain.

Ultrasound (US):

When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy:

The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers:

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology:

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

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

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Lymph node CR is when the lymph node has decreased to less than 10mm in the short axis.
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (including the baseline scan if that is the smallest), and at least a 5mm increase or the appearance of new lesions.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

12.4.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Incomplete Response/Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. However, unequivocal progression should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances.

12.4.3 Evaluation of Overall Response and Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of measurement criteria on the results of a single timepoint. Response will be determined by radiologist.

Table 12.4.3: Assessment of Best Overall Response Using Target and Non-Target Lesions

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

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as *"symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

12.5. Duration of Response

All response measurements will be from start of treatment to the defined endpoint.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design

This study will be an open label, single arm, Phase IIA safety and tolerability study to describe the toxicity profile of ribociclib in combination with an aromatase inhibitor in patients aged 70 and older with hormone receptor positive metastatic breast cancer. We plan to study 40 evaluable participants. Participants that receive one dose of treatment will be considered evaluable, anyone that does not receive treatment will be replaced. We plant to stratify based on age such that at least 20 participants are aged 75 years or older. There will be one interim analysis after 20 participants have completed one cycle of the drug.

13.1.1 Primary Objective:

To estimate the safety and tolerability of the combination of ribociclib and an aromatase inhibitor in adults age 70 or older with hormone receptor positive metastatic breast cancer

13.1.2 Secondary Objectives:

1. To describe the full toxicity profile including all grades
2. To estimate the rate of worst grades of myelosuppression (neutropenia, leukopenia, thrombocytopenia, and anemia), neutropenic fever, GI side effects (nausea, diarrhea, decreased appetite, vomiting, stomatitis), fatigue, neuropathy, and thromboembolism
3. To describe rates of dose reductions, dose holds, and hospitalizations
4. To estimate objective response rate and clinical benefit rate as defined by modified RECIST (1.1) criteria
5. To estimate median progression-free and overall survival
6. To determine average plasma steady-state ribociclib C_{trough} concentrations in patients over the age of 70 years

13.1.3 Exploratory Objectives

7. To estimate the rate of adherence to ribociclib
8. To explore factors other than chronologic age that can affect toxicity rates as identified using a cancer-specific geriatric assessment
9. To describe the results of the Was It Worth It (WIWI) and Overall Treatment Utility (OTU) Questionnaires

13.1.4 Primary Endpoints

The primary endpoint is the incidence of grade 2 and above toxicities attributed (possible or above) to ribociclib.

13.1.5 Secondary Endpoints

1. All toxicities associated with the combinations as measured by NCI CTCAE v.4.0
2. Dose reductions
3. Dose holds
4. Hospitalizations
5. Response as determined by RECIST criteria
6. Progression free survival defined as the time from start of treatment to the first of the following disease events: local/regional/distant recurrence, invasive contralateral breast disease, second primary or death due to any cause
7. Overall survival defined as the time from start of treatment to death due to any cause
8. To determine average plasma steady-state ribociclib C_{trough} concentrations in patients over the age of 70 years

13.1.6 Exploratory Endpoints

1. Adherent to ribociclib will be defined as taking 19/21 pills (90%) of their dose of ribociclib.
2. Toxicity Risk Score
3. WIWI response
4. OTU response

13.2 Sample Size and Accrual Rate

Given a sample size of 40 evaluable subjects the half-width of the 95% confidence limits for the rate of grade 2 or higher toxicities will be less than or equal to 0.16. For example if we saw a toxicity rate of 0.5 (20 subjects/40) the 95% lower and upper confidence limits would be 0.34 and 0.66, respectively. Further a sample size of 40 will allow us to see a toxicity with a true rate equal to 0.05 in 87 out of 100 trials.

13.3 Interim Analyses

After approximately 20 subjects have completed at least one full cycle of treatment, the study team will review the data (including the toxicity profile, rates of dose reduction, holds and hospitalizations) and assess if the dose being studied is too high, requiring too many patients, in the opinion of the team, to experience a dose reduction. If so, a reduction of the dose will be considered, otherwise the study will continue to completion at the planned dose.

13.4 Analysis Plan

Rates and associated 95% exact Clopper and Pearson binomial confidence limits will be estimated for 1) grade 2 or higher other toxicities, and 2) dose reductions, dose holds and hospitalizations, and 3) objective response rate (CR+PR) and clinical benefit rate (CR+PR+SD) as determined by RECIST. Progression free survival and overall survival will be estimated using the product limit method of Kaplan and Meier/ Cox proportional hazards methods.

Tables will be created to summarize the toxicities and side effects by age strata, course, organ, severity and attribution for all patients. Descriptive statistics will be provided for study participant demographics, number of drug cycles completed, responses from the WIWI Questionnaire and the OTU by age strata and overall. General linear models and graphical methods will be used to explore factors as identified by a cancer-specific geriatric assessment that may be predictive of toxicity/dose reduction, dose holds or hospitalizations.

The relationship between plasma trough and percent drop in neutrophil and platelet counts will be analyzed used linear models methods.

14. DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

14.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Site Investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

14.2 Data Capture Methods and Management

Data for this trial will be collected using Medidata RAVE, City of Hope's electronic capture system. Medidata RAVE is a web based, password protected system that is fully compliant with global regulatory requirements, including 21CRF Part 11 compliant.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

14.3 Case Report Forms/Data Submission Schedule

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

The investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Site Investigator or designee in a timely fashion.

All data will be collected using the electronic data collection system described in Section 14.2, and will be submitted according to the timelines indicated in Table 14.3.

Table 14.3: Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 14 calendar days of treatment administration
Adverse Event Report Forms	Within 14 calendar days of the study visit
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms (concomitant medications, chemistry, hematology etc.)	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of data collection

14.4 Regulatory Records

The investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations. Additional information regarding required documents is provided in the DCC Operations Manual, a supplement to this protocol.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

15.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards

- Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
- Title 21 Part 312 – Investigational New Drug Application
- Title 45 Part 46 – Protection of Human Subjects

- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable institutional research policies and procedures

15.3 Institutional Review Board

In accordance with City of Hope policies, an Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent document will be in the possession of the Investigator. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

The IRB will be informed of revisions to other documents originally submitted for review; serious unexpected or unanticipated adverse experiences occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

Any amendment to the protocol document and accompanying informed consent document/template, as developed and provided by the Study PI, will require review and approval by the IRB before the changes are implemented in the study. The protocol and consent will be reviewed and approved by the COH IRB before submission to a participating site IRB.

15.4 Informed Consent

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Research subjects will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at their hospital or any relationship they have with their hospital.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

Before implementing any study procedure, informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the patient or the patient's legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the patient or patient's legally authorized representative. The original signed consent must be maintained by the Site Investigator and available for inspection sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

15.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies. The COH DCC should be promptly notified of the change in participant status.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures (safety visit) and chart review and survival follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research blood samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

15.6 Special and Vulnerable Populations

15.6.1 Inclusion of Women and Minorities

The study is open to anyone regardless of gender or ethnicity; however, we anticipate that the majority of participants will be female based on the demographics of breast cancer. Efforts will be made to extend the accrual to a representative population in term of ethnicity and race.

15.6.2 Exclusion of Pediatric Patients

Pediatric recipients (children <18 years old of age) are excluded from this study because this study is being conducted in the geriatric population.

15.6.3 Exclusion of HIV Positive Individuals

Persons with HIV are not expressly excluded from this study.

15.6.4 Vulnerable Populations

45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, or economically or educationally disadvantaged persons as vulnerable populations.

Adults lacking capacity to consent are not excluded from participation. This study does not pose additional risks for adults lacking capacity than for the general population. In such instances, informed consent will be sought and documented from the prospective participant's legally authorized representative in agreement with institutional policies and local IRB approval.

15.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with the Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. Source documents provided to coordinating center for the purpose of auditing or monitoring will be de-identified and labeled with the study number, subject ID, and patient initials.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

15.8 Conflict of Interest

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

15.9 Financial Obligations, Compensation, and Reimbursement of Participants

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

The standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The research participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The research participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the research participant were not in a research study.

In the event of physical injury to a research participant resulting from research procedures, appropriate medical treatment will be available at City of Hope to the injured research participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a research participant.

The research participant will not receive reimbursement or payment for taking part in this study.

15.10 Publication/Data Sharing

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

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among City of Hope and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov and results will be reported on ClinicalTrials.gov within 12 months of the estimated or actual completion date of the trial, whichever date is earlier.

16. REFERENCES

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APPENDIX A: KARNOFSKY PERFORMANCE STATUS

Karnofsky Performance Scale	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX B: PROHIBITED MEDICATIONS / MEDICATIONS TO BE USED WITH CAUTION

List of prohibited medications during study drug treatment

Category	Drug Name
Strong CYP3A4/5 inhibitors	Atazanavir/ritonavir, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, ombitasvir/paritaprevir/dasabuvir/ritonavir (VIEKIRA PAK), posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycinvoriconazole
Strong CYP3A4/5 inducers	carbamazepine[3], enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin[3], rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[2,3]
CYP3A4/5 substrates with NTI[1]	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus
Medications with a known risk for QT prolongation[4]	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacine, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sulpiride, sultopride, terlipressin, terodiline, thioridazine, vandetanib
Herbal preparations/ medications	Herbal preparations/medications known as strong inducers or inhibitors of CYP3A4/5 or those with a known risk of QT prolongation are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.
Other investigational and antineoplastic therapies	Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, all SERMS (including raloxifene), biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued study drug.

[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes) or drugs which have <2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood.

[2] Herbal product

[3] P-gp inducer

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

As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI that increases the exposure of ribociclib or the exposure of the QT prolonging drug). A definitive list of drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or Torsades de Pointes (TdP) is available online at qtdrugs.org. Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University "Clinically Relevant" Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

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

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Aprepitant, amprenavir, asafoetida resin (Ferula asafoetida) cimetidine, crizotinib, diltiazem, faldaprevir, imatinib, isavuconazole, netupitant, nilotinib, tofisopam, Schisandra sphenanthera (nan wu wei zi), verapamil
Moderate CYP3A4/5 inducers	Bosentan, dabrafenib, efavirenz, etravirine, genistein,lopinavir[5], modafinil, nafcillin, telotristat
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine, aprepitant, atorvastatin, avanafil, bosutinib,brotizolam, budesonide, buspirone, cobimetinib, darifenacin, dasatininb, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutnib, isavuconazole, ivabradine, ivacaftor, , levomethadyl (LAAM), lomitapide, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, sildenafil, simeprevir, simvastatin, ticagrelor, tilidine, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin
BSEP inhibitors	Alectinib, atorvastatin, bromocriptine, candesartan, clobetasol, clofaziminie, dabigatran, dipyridamole, glyburide, grazoprevir, ledipasvir, mifepristone,pioglitazone, reserpine,rifamycin, simeprevir, telmisartan,timcodar, troglitazone,

	valinomycin, velpatasvir
Medications that carry a possible risk for QT prolongation[2]	Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine , asenapine, atomoxetine, bedaquiline, bendamustine, bortezomib, bosutinib, buprenorphine, cabozantinib, capecitabine, ceritinib, clomipramine, crizotinib,clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, efavirenz, eliglustat, epirubicin, eribulin mesylate, ezogabine(retigabine), famotidine, felbamate, fingolimod, flupentixol, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, ketanserin, lapatinib, lenvatinib, leuprolide, lithium, melperone, midostaurin, mifepristone, mirabegron, mirtazapine, moexipril/HCTZ, necitumumab, nicardipine, nilotinib, norfloxacin, nortriptyline, nusinersen, ofloxacin, osimertinib, oxytocin, paliperidone, palonosetron, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, perphenazine, pilsicainide, pimavanserin, pipamperone, promethazine, prothipendyl, rilpivirine, risperidone, romidepsin, sertindole, sorafenib, sunitinib, tamoxifen, tipiracil/trifluridine, tizanidine, tolterodine, toremifene,trimipramine, tropisetron, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone
MATE1/2 substrates[3]	Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topotecan, varenicline
OCT1/2 substrates[4]	Amantadine, 6-beta-hydroxycortisol, carboplatin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, oxyplatin, oxybutynin, phenformin, picoplatin, pilsicainide, pindolol, ranitidine, sorafenib, tropisetron, trospium, umeclidinium,, and zidovudine
BCRP substrates	Daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, tenofovir, topotecan, venetoclax

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

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

[3] MATE1 and MATE2 share considerable substrate specificity.

[4] OCT1 and OCT2 share considerable substrate specificity.

[5] Lopinavir is prohibited when combined with ritonavir (see Table 14-1)

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

APPENDIX C: REGISTRATION COVERSHEET

COH IRB 17471: ***A Phase IIa Trial Assessing the Tolerability of Ribociclib in Combination with an Aromatase Inhibitor or in Patients Aged 70 and Older with Hormone Receptor Positive Metastatic Breast Cancer.***

Data Coordinating Center:
City of Hope
1500 Duarte Road
Duarte, CA 91010
Tel: 626-256-4673 x 83968
Email: DCC@coh.org (use #secure# in subject line)

Principal Investigator
Name:
Address:

Phone:
Fax:
e-mail:

CRA/Study Coordinator:	Contact Number:
Patient's Initials: (F M L):	Institution:
Medical Record No:	Investigator/Treating Physician:
Patient's DOB:	IRB approval valid until (date):
Sex: _____Male _____Female	Date Informed Consent Signed:
	Projected start date of treatment:

Race		Ethnicity		Method of Payment:_____	
	Black		Hispanic	Codes:	
	Caucasian		Non-Hispanic	**01** Private	**06** Military or Veterans Adm. sponsored
	Asian		Other_____	**02** Medicare	**07** Self-pay (no insurance)
	American Indian			**03** Medicare & private ins.	**08** No means of payment (no insurance)
	Native Hawaiian/Pacific Islander			**04** Medicaid	**09** Unknown
	Other_____ _____			**05** Medicaid & Medicare	

Reason for Screen Failure:

Reason for Failing to Initiate Protocol Therapy:

APPENDIX D-1: BLOOD BANKING COLLECTION FORM (OPTIONAL)

Patient MRN (COH Only):	Patient Initials (F, M, L):
Institution:	

Sample Collection:

1. A 10 mL baseline sample should be collected from consenting patients.
2. Label each sample with the participants' initials, study ID number, date of collection, and sample collection time.
3. A green top heparin OR a lavender top K+EDTA tube should be used for collecting the sample.
4. After collection, gently invert the tube several times (at least 4 times) and place on ice.
5. **For COH-Duarte Campus**:
    - Samples placed on ice may be taken immediately to CICSL in Shapiro (room 1042) on the day of collection; arrangements should be made ahead of time with Vivi Tran (email: vtran@coh.org or ext. 62634). Samples will then be frozen at -60°C to -90°C at CICSL.
6. **For COH Community Practices**:
    - Store samples in a -60°C to -90°C freezer. Frozen -60°C to -90°C samples should be taken on dry ice to the Clinical Immunobiology Correlative Studies Laboratory (CICSL) in Shapiro (room 1042).
7. **For Non-COH sites**:
    - Store in a -60°C to -90°C freezer until shipment. Refer to Appendix D-2 for shipping details.

Sample #	Schedule	Collected Volume	Tube Type Used (Select One)	Time of Collection	Date of Collection
1	**Day 1**: Prior to protocol therapy	_____ mL	Sodium heparin Lithium heparin K_2EDTA K_3EDTA	____:____ AM/ PM	____/____/____

A copy of this form should be maintained by the institution and a copy should accompany the sample to CICSL.

CRA/Study Coordinator:	Contact Number:
CRA/Study Coordinator Signature:	Date:

APPENDIX D-2: BLOOD BANKING SHIPPING DETAILS- NON-COH SITES

Follow the requirements for the proper packaging and shipping of biomedical material found in 42 CFR Part 72 - Interstate Shipment of Etiologic Agents Centers for Disease Control and Prevention, Office of Health and Safety, Biosafety Branch site.

1. Samples should be shipped at the request of the lead COH study team.
2. If applicable, samples should be batched if multiple participants are recruited at the site.
3. Ship samples on **Monday to Thursday** via **overnight FedEx on dry ice**. There should be enough dry ice to last for at least 72 hours in the shipment.
4. Do not ship on either a Friday, weekend or a holiday.
5. Sites should request pre-paid shipping labels from Vani Katheria (vkatheria@coh.org).
6. **Prior to shipment**:
    a. Send pending shipping notifications to Vivi Tran (vtran@coh.org) and copy Vani Katheria (vkatheria@coh.org).
7. **On the day of shipment**:
    a. Include a copy of Appendix D-1 with the shipment.
    b. Ship to the below address:

        City of Hope
        Attn: Vivi Tran,
        CICSL Core Laboratory,
        Shapiro Bldg, Rm 1044,
        Beckman Research Institute of the City of Hope
        1500 E. Duarte Road
        Duarte, CA 91010-3000.
        Tel: 626-256-4673 ext 62634.
        Email: vtran@coh.org

    c. Email the FedEx tracking number to Vivi Tran (vtran@coh.org) and copy Vani Katheria (vkatheria@coh.org).

APPENDIX E: RIBOCICLIB PILL DIARY

Study Accession #:	Patient Initials (F, M, L):
Institution:	Cycle #:

Ribociclib should be taken **once every day for 21 days by mouth.** Ribociclib should be taken **at approximately the same time each day.** If you miss or vomit a dose do not make up the missed/ vomited dose that day; instead take the ribociclib dose the next day at the regularly scheduled time. Ribociclib pills should be swallowed whole.

Record all side effects, missed ribociclib doses, supplements and other medication you are taking in the Pill Diary.

Bring the study drug bottle to every clinic visit to show _____.
At the **end of each cycle**, please return this diary and study drug bottle to_____.

How to fill the Pill Diary (Example Only)

To be filled in by the institution
Cycle #: 1 *Cycle Start Date: 9/7/2016*

Ribociclib Dose: 125 mg/ day *Take: 1 pill per day*

To be filled in by the patient			***# of pills taken***	***Comments***
				Side effects, supplements, other medication, missed doses
Day	***Date***	***Time***		
1	*9/7/16*	*8:20 am/pm*	*1*	*Nausea. Muscle pain.*
2	*9/8/16*	*8:20 am/pm*	*1*	*Vomited the pill but did not take an extra pill today.*

Cycle #: _____ Cycle Start Date: _____

Ribociclib Dose: _____ mg/ day Take: _____ pill per day

Week 1			**# of pills taken**	**Comments**
				Side effects, supplements, other medication, missed doses
Day	**Date**	**Time**		
1		___:___ am/pm		
2		___:___ am/pm		
3		___:___ am/pm		
4		___:___ am/pm		
5		___:___ am/pm		
6		___:___ am/pm		
7		___:___ am/pm		

Ribociclib Dose: _____ mg/ day Take: 1 pill per day

Week 2			**# of pills taken**	**Comments**
				Side effects, supplements, other medication, missed doses
Day	**Date**	**Time**		
8		___:___ am/pm		
9		___:___ am/pm		
10		___:___ am/pm		
11		___:___ am/pm		

12		___:___ am/pm		
13		___:___ am/pm		
14		___:___ am/pm		

Ribociclib Dose: _____ mg/ day Take: 1 pill per day

Week 3			**# of pills taken**	**Comments**
Day	**Date**	**Time**		***Side effects, supplements, other medication, missed doses***
15		___:___ am/pm		
16		___:___ am/pm		
17		___:___ am/pm		
18		___:___ am/pm		
19		___:___ am/pm		
20		___:___ am/pm		
21		___:___ am/pm		

Rest Week

Week 4			**# of pills taken**	**Comments**
Day	**Date**	**Time**		***Side effects, supplements, other medication, missed doses***
22		Do not take Ribociclib this week.		
23				
24				

25			
26			
27			
28			

Participant Signature *(please sign at the end of the cycle when submitting your diary)* _____	**Date:** ____/_____/_____

Nurse Signature _____	**Date:** ____/_____/_____

APPENDIX F-2: GERIATRIC ASSESSMENT SURVEY

Completed via touchscreen computer survey (preferable) or paper assessment forms. A PDF version formatted to collect information will be provided to participating sites.[27]

Patient Questionnaire

Responsible person name (*Physician, Nurse, or CRA*) _____
Assessment Period (as applicable to this study) □ Pre-treatment □□ Cycle # □ End of Treatment

Patient Instructions: If you are unable to complete the questionnaire, a member of your health care team will assist you. Please do not have a family member complete the questionnaire for you.

□ **Mark box with an "X", if form was not completed at specified timepoint and specify reason:**

(Mark one with an X.) □ Patient refused □ Patient withdrew consent □ Not done

□ Other, specify _____

(For assessment date, record approximate date form was to be completed.)

A. BACKGROUND INFORMATION

1. What is the highest grade you finished in school? *(Mark one with an X.)*

□ Less than 9 years of school
□ Some high school (9-11 years)
□ High school graduate, or GED
□ Some college or technical school
□ College degree graduate
□ Graduate degree
□ Post graduate education, but no higher degree
□ I prefer not to answer

2. What is your marital status? *(Mark one with an X.)*

□ Married
□ Domestic partnership
□ Widowed
□ Divorced
□ Separated
□ Never married
□ I prefer not to answer

3. With whom do you live? *(Mark all that apply with an X.)*

□ Spouse / partner
□ Girlfriend / boyfriend
□ Children aged 18 years or younger
□ Children aged 18 years or older
□ Parents/ parents-in-law
□ Live alone
□ Others, specify: _____
□ Other relative, specify: _____

4. What is your current employment status? *(Mark one with an X.)*

□ Employed ≥ 32 hours per week
□ Employed ≤ 32 hours per week
□ Homemaker
□ Disabled
□ On medical leave
□ Unemployed
□ Retired
□ Student full-time
□ Student part-time
□ Other, specify: _____

5. How old are you? __ years old

6. What is your race?

□ White □ Asian
□ Black or African American □ Native Hawaiian or Other Pacific Islander
□ Native Indian or Alaskan Native □ Unknown

7. What is your ethnicity?

□ Hispanic or Latino □ Non-Hispanic □ Unknown

B. DAILY ACTIVITIES*

PATIENT INSTRUCTIONS: Indicate your response by marking an X in one box per question.

1. Can you use the telephone…
   - □ Without help, including looking up and dialing
   - □ With some help (can answer phone or dial operator in an emergency, but need a special phone or help in getting the phone number or dialing)
   - □ Completely unable to use the telephone

2. Can you get to places out of walking distance…
   - □ Without help (can travel alone on busses, taxis, or drive your own car)
   - □ With some help (need someone to help you or go with you when traveling)
   - □ Completely unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance

3. Can you go shopping for groceries or clothes (assuming you have transportation) …
   - □ Without help (taking care of all shopping needs yourself, assuming you have transportation)
   - □ With some help (need someone to go with you on all shopping trips)
   - □ Completely unable to do any shopping

4. Can you prepare your own meals…
   - □ Without help (plan and cook full meals yourself)
   - □ With some help (can prepare some things but unable to cook full meals yourself)
   - □ Completely unable to prepare any meals

5. Can you do your housework…
   - □ Without help (can clean floors, etc.)
   - □ With some help (can do light housework but need help with heavy work)
   - □ Completely unable to do any housework

6. Can you take your own medicines…
   - □ Without help (in the right doses at the right time)
   - □ With some help (able to take medicine if someone prepares it for you and/or reminds you to take it)
   - □ Completely unable to take your medicines

7. Can you handle your own money…
   - □ Without help (write checks, pay bills, etc.)
   - □ With some help (manage day-to-day buying but need help with managing your checkbook and paying your bills)
   - □ Completely unable to handle money

* OARS IADL [28]

C. PHYSICAL ACTIVITIES*

1. The following items are activities you might do during a typical day. Does your health limit you in these activities? **(*Mark an X in the box on each line that best reflects your situation.*)**

Activities	Limited a lot	Limited a little	Not limited at all
a. Vigorous activities such as: running, lifting heavy objects, participating in strenuous sports	□	□	□
b. Moderate activities such as: moving a table, pushing a vacuum cleaner, bowling, or playing golf	□	□	□
c. Lifting or carrying groceries	□	□	□
d. Climbing several flights of stairs	□	□	□
e. Climbing one flight of stairs	□	□	□
f. Bending, kneeling, or stooping	□	□	□
g. Walking more than a mile	□	□	□
h. Walking several blocks	□	□	□
i. Walking one block	□	□	□
j. Bathing or dressing yourself	□	□	□

* MOS, Physical Functioning Scale [29]

D. CURRENT HEALTH RATING*

Which one of the following phrases best describes you at this time? *(Mark one with an X.)*

□ Normal, no complaints, no symptoms of disease
□ Able to carry on normal activity, minor symptoms of disease
□ Normal activity with effort, some symptoms of disease
□ Care for self, unable to carry on normal activity or do active work
□ Require occasional assistance but able to care for most of personal needs
□ Require considerable assistance for personal care
□ Disabled, require special care and assistance
□ Severely disabled, require continuous nursing care

* Patient KPS[30]

E. FALLS

How many times have you fallen in the last 6 months? □□□

F. YOUR HEALTH

1. Your General Health*

Patient Instructions: Do you have any of the following illnesses at the present time, and if so, how much does it interfere with your activities: **Not at all, Somewhat or A Great Deal?** *(Mark an X in the box that best reflects your answer.)*

				If you have this illness: How much does it interfere with your activities?		
Illness	**No**	**Yes**		**Not at all**	**A little**	**A great deal**
a. Other cancers or leukemia	□	□	→	□	□	□
b. Arthritis or rheumatism	□	□	→	□	□	□
c. Glaucoma	□	□	→	□	□	□
d. Emphysema or chronic bronchitis	□	□	→	□	□	□
e. High blood pressure	□	□	→	□	□	□
f. Heart disease	□	□	→	□	□	□
g. Circulation trouble in arms or legs	□	□	→	□	□	□
h. Diabetes	□	□	→	□	□	□
i. Stomach or intestinal disorders	□	□	→	□	□	□
j. Osteoporosis	□	□	→	□	□	□
k. Chronic liver or kidney disease	□	□	→	□	□	□
l. Stroke	□	□	→	□	□	□
m. Depression	□	□	→	□	□	□

* OARS IADL[28]

2. How is your eyesight (with glasses or contacts)? *(Mark one with an X.)*
   - □ Excellent
   - □ Good
   - □ Fair
   - □ Poor
   - □ Totally blind

   If fair, poor, or totally blind, how much does it interfere with your activities?

   ☐ Not at all □ Somewhat □ A great deal

3. How is your hearing (with a hearing aid, if needed)? *(Mark one with an X.)*
   - □1 Excellent

□2 Good
□3 Fair
□4 Poor
□5 Totally deaf

If fair, poor, or totally deaf, how much does it interfere with your activities?

☐ Not at all ☐ Somewhat ☐ A great deal

4. Do you have any other physical problems or illnesses (other than listed in questions 1-4) at the present time that seriously affect your health?

□ No

□ Yes, specify: [ ]

If yes, how much does this interfere with your activities? *(Mark one with an X.)*

□ Not at all □ Somewhat □ A great deal

* OARS IADL[28]

G. NUTRITIONAL STATUS

1. Have you lost weight involuntarily over the past 6 months?

□ No
□ Yes

If yes, how much?
□□□ pounds

2. What is your weight now?
□□□ pounds
3. What was your weight 6 months ago?
□□□ pounds

Notation for Study Build Team: If a medication form is being used for the main study, this medication form does not need to be included in the Patient Questionnaire.

How many medications (either prescribed or over-the-counter), herbs, or vitamins do you currently take?

____

Please list all prescribed or over-the-counter medicines, herbs, or vitamins you are currently taking (doses not necessary).

1. [ ]
2. [ ]
3. [ ]
4. [ ]
5. [ ]
6. [ ]

7.

8.

9.

10.

11.

12.

13.

14.

15.

H. HEALTH QUESTIONNAIRE*

INSTRUCTIONS: These questions are about how you have been feeling within the past month. Please mark an "X" in the box on each line that best reflects your situation.

How much of the time during the past two weeks:	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
1. has your daily life been full of things that were interesting to you?	□	□	□	□	□	□
2. did you feel depressed?	□	□	□	□	□	□
3. have you felt loved and wanted?	□	□	□	□	□	□
4. have you been a very nervous person?	□	□	□	□	□	□
5. have you been in firm control of your behavior, thoughts, emotions, feelings?	□	□	□	□	□	□
6. have you felt tense or high-strung?	□	□	□	□	□	□
7. have you felt calm and peaceful?	□	□	□	□	□	□
8. have you felt emotionally stable?	□	□	□	□	□	□
9. have you felt downhearted and blue?	□	□	□	□	□	□

10. have you felt restless, fidgety, or impatient?	☐	☐	☐	☐	☐	☐
11. have you been moody, or brooded about things?	☐	☐	☐	☐	☐	☐
12. have you felt cheerful, light-hearted?	☐	☐	☐	☐	☐	☐
13. have you been in low or very low spirits?	☐	☐	☐	☐	☐	☐
14. were you a happy person?	☐	☐	☐	☐	☐	☐
15. did you feel you had nothing to look forward to?	☐	☐	☐	☐	☐	☐
16. have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
17. have you been anxious or worried?	☐	☐	☐	☐	☐	☐

* MHI-17 [29]–

I. SOCIAL ACTIVITIES*

1. During the past 4 weeks, how much time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

2. Compared to your usual level of social activity, has your social activity during the past 6 months decreased, stayed the same, or increased because of a change in your physical or emotional condition?
- ☐ Much less socially active than before
- ☐ Somewhat less socially active than before
- ☐ About as socially active as before
- ☐ Somewhat more socially active as before
- ☐ Much more socially active than before

3. Compared to others your age, are your social activities more or less limited because of your physical health or emotional problems?
- ☐ Much more limited than others
- ☐ Somewhat more limited than others
- ☐ About the same as others
- ☐ Somewhat less limited than others
- ☐ Much less limited than others

* MOS, Social Activities [29]

J. SOCIAL SUPPORT*

INSTRUCTIONS: People sometimes look to others for companionship, assistance or other types of support. How often is each of the following kinds of support available to you if you need it? (*Mark an X in the box on each line that best reflects your situation.*)

		None of the Time	A Little of the Time	Some of the Time	Most of the Time	All of the Time
1.	Someone to help you if you were confined to bed.	□	□	□	□	□
2.	Someone you can count on to listen to you when you need to talk.	□	□	□	□	□
3.	Someone to give you good advice about a crisis.	□	□	□	□	□
4.	Someone to take you to the doctor if needed.	□	□	□	□	□
5.	Someone to give you information to help you understand a situation.	□	□	□	□	□
6.	Someone to confide in or talk to about yourself or your problem.	□	□	□	□	□
7.	Someone to prepare your meals if you were unable to do it yourself.	□	□	□	□	□
8.	Someone whose advice you really want.	□	□	□	□	□
9.	Someone to help you with daily chores if you were sick.	□	□	□	□	□
10.	Someone to share your most private worries and fears with.	□	□	□	□	□
11.	Someone to turn to for suggestions about how to deal with a personal problem.	□	□	□	□	□
12.	Someone who understands your problems.	□	□	□	□	□

* MOS Social Support Survey [31]

K. SPIRITUALITY/RELIGION

Directions: Please answer the following questions about your religious beliefs and/or involvement. (Please mark an "X" in the box on each line that best reflects your situation.)

1. How often do you attend church, synagogue, or other religious meetings?

   ☐ More than once per week
   ☐ Once a week
   ☐ A few times a month
   ☐ A few times a year
   ☐ Once a year or less
   ☐ Never

2. How often do you spend time in private religious activities, such as prayer, meditation, or Bible study?
   ☐ More than once a day
   ☐ Daily
   ☐ Two or more times per week
   ☐ Once a week
   ☐ A few times a month
   ☐ Rarely or never

The following section contains 3 statements about religious belief or experience. Please mark the extent to which each statement is true or not true for you.

3. In my life, I experience the presence of the Divine (i.e., God).
   - ☐ Definitely true of me
   - ☐ Tends to be true
   - ☐ Unsure
   - ☐ Tends *not* to be true
   - ☐ Definitely *not* true

4. My religious beliefs are what really lie behind my whole approach to life.
   - ☐ Definitely true of me
   - ☐ Tends to be true
   - ☐ Unsure
   - ☐ Tends *not* to be true
   - ☐ Definitely *not* true

5. I tried hard to carry my religion over into all other dealings in my life.
   - ☐ Definitely true of me
   - ☐ Tends to be true
   - ☐ Unsure
   - ☐ Tends *not* to be true
   - ☐ Definitely *not* true

*DUREL: Duke University ReligionIndex [32]

L. YOUR FEELINGS*

1. Do you often feel sad or depressed? □ No □ Yes

2. How would you describe your level of anxiety, on average? Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.

0	1	2	3	4	5	6	7	8	9	10
No anxiety										Anxiety as bad as It can be

*Mahoney et al., 1994; LASA [33]

M. QUESTIONS CONCERNING THE QUESTIONNAIRE

1. Were there any questions difficult to understand? □ No □ Yes
   If Yes, which questions were they?

2. Was the time it took to answer all the questions too long, just right or too short?
   - □ Too short → How long would you have liked the questionnaire to be? □□ minutes
   - □ Just right
   - □ Too long → How long would you have liked the questionnaire to be? □□ minutes

   Which items would you remove?

3. Did you find any of the questions upsetting? □ No □ Yes

   If Yes, which questions were they?

Could you tell me why they were upsetting?

4. Do you think the questionnaire left out any questions that were important to ask?

Thank you for your participation.

APPENDIX F-2: GERIATRIC ASSESSMENT: HEALTHCARE PROFESSIONAL QUESTIONNAIRE

Completed via touchscreen computer survey (preferable) or paper assessment forms. A PDF version formatted to collect information will be provided to participating sites.

I. This form completed by: *(Mark all that apply with an X.)* Assessment Period (as applicable to this study)
□ Physician □ Nurse □ CRA □ Pre-treatment □□ Cycle # □ End of Treatment

□ **Mark box with an "X", if form was not completed at specified timepoint and specify reason:**
(Mark one with an X.) □ Patient refused □ Patient withdrew consent □ Not done
□ Other, specify _____
(For assessment date, record approximate date form was to be completed.)

II. FUNCTIONAL STATUS

A. KPS (Healthcare professional rated*)
Please rate your assessment of patient's Karnofsky Performance Status as of date this form is completed. *(Scale is listed below.)*
___ %

%	CRITERIA
100	Normal: no complaints; no evidence of disease.
90	Able to carry on normal activity; only minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, but unable to carry on normal activity or do active work.
60	Requires occasional assistance, but is able to care for most personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization is indicated although death not imminent.
20	Very sick; hospitalization necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead.

* Physician KPS[34]

B. Timed “Up and Go”*

INSTRUCTIONS: The timed “Up and Go” measures, in seconds, the time it takes for an individual to stand up from a standard arm chair (approximate seat height of 46 cm [approximately 1.5 ft]), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair, and sit down again. The subject wears his/her regular footwear and uses their customary walking aid (none, cane, walker, etc.) No physical assistance is given. The subject starts with his back against the chair, his arm resting on the chair’s arm, and his walking aid in hand. He is instructed that on the word “go”, he is to get up and walk at a comfortable and safe pace to a line on the floor 3 meters (approximately 10 feet) away, turn, and return to the chair and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a wrist watch with a second hand or a stop-watch can be used to time the performance.

Time to perform “Up and Go” □□.□ seconds

* Timed “Up and Go” [35]

III. COGNITION ***This section is only completed Pretreatment and at the end of treatment***

6-ITEM ORIENTATION-MEMORY-CONCENTRATION TEST**						
	Patient's Response	**Maximum errors**	**Score**		**Weight**	**Final score**
1. What year is it now? [without looking at a calendar]	□□□□	1	□□	x	4 =	□□
2. What month is it now? [without looking at a calendar]	□□	1	□□	x	3 =	□□
Memory Phrase: Repeat this phrase after me: 'John Brown, 42 Market Street, Chicago'						
3. About what time is it? [within 1 hour – without looking at your watch]	□□:□□	1	□□	x	3 =	□□
4. Count backwards 20 to 1.		2	□□	x	2 =	□□
5. Say the months in reverse order.		2	□□	x	2 =	□□
6. Repeat the Memory Phrase.		5	□□	x	2 =	□□
			TOTAL SCORE: □□			

Scoring: For items 1 to 3, the response is either correct (score 0) or incorrect (score 1). For items 4 to 6, add one point for each error (item 4 and 5 maximum error is 2; for item 6, maximum error is 5); total all scores in "Final Score" column. Data from participants found to have gross cognitive impairment as determined by the Orientation-Memory-Concentration Score ≥11 will be excluded from the analysis. Maximum score = 28.
** OMC[36]

IV. SCORING ***This section is only applicable if OMC-Test is completed Pretreatment and Post treatment***

Did the patient score ≥11 on the 6-Item Orientation-Memory-Concentration Test?

□ No
□ Yes (**If yes, notify the patient's treating physician.)**

This question is only applicable to question #1 in "Section K. Your Feelings" from the Patient Questionnaire.

1. How did the patient answer the question "Do you often feel sad or depressed?" in the Patient Questionnaire *(Section K)*?

No
Yes **(If yes, notify the patient's treating physician.)**

V. NUTRITION

What is the patient's height? (*from patient's chart*) □□□ cm
What is the patient's current weight? (*from patient's chart*) □□□ kg
What was the patient's weight approximately 6 months ago? *(from patient's chart or patients self report)* □□□ kg
Calculated Body Mass Index: □□.□
Percent Unintentional Weight Loss: □□.□%

VI. QUESTIONS REGARDING THE QUESTIONNAIRES

A. Were any of the questionnaires in the "Geriatric Assessment – Healthcare Professional Questionnaire" difficult for you to administer?
□Yes □No

If no, please proceed to the next question.
If yes, please indicate which questionnaire was difficult to administer? *(Mark all that apply with an X.)*
□ KPS Healthcare Professional Rated (page 1)
□ Timed Up and Go (page 2)
□ 6-Item Orientation-Memory-Concentration Test (page 2)
□ Other: Please specify _____

B. Were any of the questionnaires in the "Geriatric Assessment – Patient Questionnaire" difficult for the patient to complete?
□Yes □No

If no, please proceed to the next question. If yes, please indicate which questionnaire(s) was difficult for the patient to complete? *(Mark all that apply with an X.)*
□ Background Information (page 1)
□ Daily Activities (page 2-3)
□ Physical Activities (page 3)
□ Current Health Rating (page 4)
□ Falls (page 4)
□ Your Health (page 4-5) *(Mark all that apply with an X.)*
□ 1. Your general health (page 4-5)
□ 2. Medications (page 6)
□ Your Mood (page 7-8)
□ Social Activity (page 9)
□ Social Support (page 10)

C. Was the patient able to complete "Geriatric Assessment – Patient Questionnaire" on his/her own?
□Yes □No
If no, why? *(Mark all that apply with an X.)*
□ Not literate (does not read or write)
□ Visual problem
□ Fatigue
□ Questions too difficult (above the patient's reading ability)
□ Other: specify_____

D. Length of time to complete both the Patient and Healthcare Professional Questionnaires
Length of time to complete healthcare professional questionnaire □□□ minutes
Length of time to complete patient questionnaire □□□ minutes
Total length of time to complete both questionnaires □□□ minutes

Completed by: _____ Date form completed: □□ / □□ / □□□□
(Last name, First name) *M M D D Y Y YY*

APPENDIX G: WAS IT WORTH IT (WIWI) QUESTIONNAIRE

A PDF version formatted to collect information will be provided to participating sites.

Patient MRN (COH Only):	Patient Initials (F, M, L):
Institution:	

Undergoing cancer treatment is a personal choice and an individual experience. We would like to get feedback on your experience following cancer treatment.

Directions: Please answer each question by circling Y (for yes), N (for no), or U (for Uncertain).

Was it worthwhile for you to undergo cancer treatment?	Y	N	U
If you had to do it over, would you undergo cancer treatment?	Y	N	U
Would you recommend this cancer treatment to others?	Y	N	U

Overall, did your quality of life change by undergoing cancer treatment? (Circle one response)

It improved It stayed the same It got worse

Overall how was your experience following cancer treatment? (Circle one response)

Better than I expected The same as I expected Worse than I expected

If there was one thing that could have been done to improve your experience following cancer treatment, what would it be?

APPENDIX H: OVERALL TREATMENT UTILITY (FOR CLINICIAN ONLY)

Patient MRN (COH Only):	Patient Initials (F, M, L):
Institution:	

OTU is a novel clinical outcome measure incorporating objective and subjective measures of anticancer efficacy, tolerability, and acceptability, assessed at the end of protocol therapy and condensed into a simple 3 point score.

OTU may be regarded as asking the clinician: "With the benefit of hindsight, are you glad you gave this treatment?" and asking the patient: "With the benefit of hindsight, are you glad you received it? OTU is scored as good, intermediate or poor, corresponding to "yes", "uncertain" or "no" replies to these questions.

To score the OTU, the patient is assessed at the end of protocol therapy (see Section 10.0) using the following criteria:

1) **Clinical benefit?** Categorized as:
    a. Both radiologically progression- free (RECIST response or stable disease) and no clinical deterioration as assessed by treating consultant
    b. Either radiologically progression- free (RECIST progressive disease) or clinical deterioration as assessed by treating consultant
2) **Tolerable and acceptable?** Categorized as:
    a. All of the following:
        No SAE or SUSAR attributed to treatment
        No episodes of grade ≥3 non-hematological toxicity
        Patient response to "How much has your treatment interfered with your normal daily activities" is not "Very much"
        Patient response to "How worthwhile do you think your treatment has been?" is not "Not at all"
    b. Any of the following:
        An SAE or SUSAR (suspected unexpected serious adverse reaction) attributed to treatment
        An episode of grade ≥3 non-hematological toxicity
        Patient response to "How much has your treatment interfered with your normal daily activities" is "Very much"
        Patient response to "How worthwhile do you think your treatment has been?" is "Not at all"

Scoring (tick one):

Good OTU: Patient is alive and scores 1a/2a
Intermediate OTU: Patient is alive and scores 1a/2b or 1b/2a
Poor OTU: Patient is alive and scores 1b/2b, or patient is dead

Authorized Investigator Name:	
Signature:	Date:

APPENDIX I: LIST OF SUPPLEMENTAL MATERIALS

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

COH DCC Operations Manual- This document will serve as guidance as to the responsibilities of the Data Coordinating Center, as well as those of the participating sites.

COH Office of Clinical Trial Auditing and Monitoring (OCTAM) SOP

COH DSMC Committee Charter

APPENDIX J: SAE/UP REPORTING COVERSHEET

NOTIFICATION OF UNANTICIPATED PROBLEM/SERIOUS ADVERSE EVENT

For Use by Participating Institutions Only

THIS FORM ALONG WITH A COPY OF THE MEDWATCH 3500 OR IRB REPORTING FORM MUST BE **EMAILED** TO DCC@COH.ORG WITHIN 24 HOURS OF KNOWLEDGE OF ONSET OF SERIOUS ADVERSE EVENT OR UNANCTICIPATED PROBLEM

COH IRB #17471- Participating Site IRB # _____

From:	Date:
Phone No.:	Email:
Reporting Investigator:	
Event:	
Participant ID:	Institution:
Date Event Met Reporting Criteria (as defined in protocol):	

Type of Report:	☐ Initial ☐ Follow-up
CTCAE Grade:	☐ G1/mild ☐ G2/moderate ☐ G3/severe ☐ G4/life threatening ☐ G5
Attribution to **Ribociclib:**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Attribution to **endocrine therapy**:	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Historical/Known Correlation to **Ribociclib**:	☐ Expected ☐ Unexpected
Historical/Known Correlation to **endocrine therapy**:	☐ Expected ☐ Unexpected
Meets Definition of Serious AE:	☐ Serious ☐ Non-serious
Meets Definition of Unanticipated Problem:	☐ UP ☐ Not a UP
Has the event been reported to the following institution's IRB?	☐ No ☐ Yes; Date:_____/____/_____

Authorized Investigator Signature:	Date:____/____/____