Mayo Clinic Cancer Center

Phase 2 Trial of Ribociclib (LEE011) and Letrozole in ER Positive Relapsed Ovarian Cancer, Fallopian Tube Cancer, Primary Peritoneal Carcinomas and Endometrial Cancers

Study Chairs: Gerardo Colon-Otero, MD
Mayo Clinic
4500 San Pablo Road
Jacksonville, FL 32224
904/953-2000
904/953-2315 (FAX)

Study Cochairs: [redacted]

Statistician: [redacted]

√Study contributor(s) not responsible for patient care

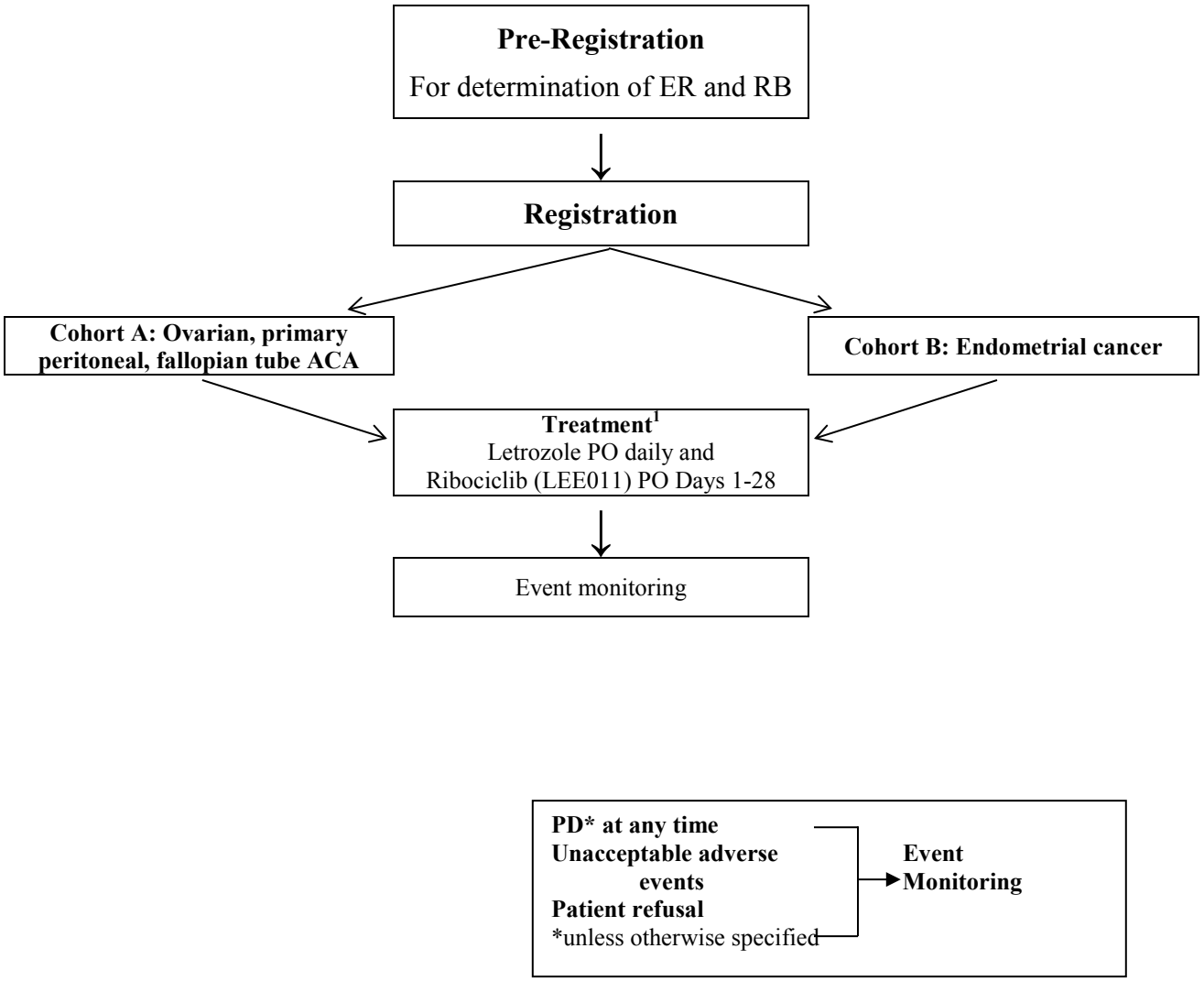
Drug Availability
Commercial Agents: None
Drug Company Supplied: Ribociclib (LEE011), Letrozole (IND 128473)

Document History	**(Effective Date)**
Activation	08July2016
Addendum 1	20January2017
Addendum 2	04April2017
Addendum 3	12March2018
Addendum 4	21August2018
Addendum 5	14March2019

Table of Contents

Phase 2 Trial of Ribociclib (LEE011) and Letrozole in ER Positive Relapsed Ovarian Cancer, Fallopian Tube Cancer, Primary Peritoneal Carcinomas and Endometrial Cancers 1
Table of Contents 2
Schema 3
1.0 Background 4
2.0 Goals 7
3.0 Patient Eligibility 9
4.0 Test Schedule 12
5.0 Grouping Factors 13
6.0 Registration Procedures 13
7.0 Protocol Treatment 15
8.0 Dosage Modification Based on Adverse Events 17
9.0 Ancillary Treatment/Supportive Care 30
10.0 Adverse Event (AE) Reporting and Monitoring 32
11.0 Treatment Evaluation Using RECIST Guideline 38
12.0 Descriptive Factors 44
13.0 Treatment/Follow–up Decision at Evaluation of Patient 44
14.0 Body Fluid Biospecimens - None 45
15.0 Drug Information 45
16.0 Statistical Considerations and Methodolology 51
17.0 Pathology Considerations/Tissue Biospecimens 56
18.0 Records and Data Collection Procedures 58
19.0 Budget 59
20.0 Key References: 60
Appendix I ECOG PERFORMANCE STATUS 62
Appendix II MEDICATION DIARY 63
Appendix III CONCOMITANT MEDICATIONS 64

Schema



[1] Cycle length=28 days ±3 days

Generic name: Letrozole Mayo abbreviation: LETROZ Availability: Novartis	Generic name: Ribociclib Mayo abbreviation: LEE011 Availability: Novartis

1.0 Background

1.1 There is a need for additional effective treatment of relapsed ovarian, fallopian tube, primary peritoneal carcinomas and endometrial cancers. These tumors are collectively the third most common cause of all cancer deaths in women.

1.2 Estrogen receptor (ER) positivity has been observed in 38-60% of all ovarian cancers (1,2). Ninety percent of all borderline ovarian tumors express ER (3). Aromatase is expressed by 33-81% of ovarian cancers (6). Estrogen receptor positivity is seen in 80 % of all endometrial cancers, more commonly in the low grade endometrioid tumors (23). Expression of aromatase has been observed in 67% of all endometrial cancers (15,16).

1.3 At least three phase 2 trials of aromatase inhibitors in metastatic endometrial cancer have been reported in the literature (13, 14, 26). In a GOG trial of anastrozole reported by Rose et al, a 9% response rate was observed (2 PR and 2 stable disease) in 23 patients with recurrent/metastatic endometrial cancer not exposed to cytotoxic chemotherapy (13). The 2 responses lasted 13 and 18 months and both patients responding had grade 2 tumors. In this trial, the median progression free survival was 1 month and the median duration of anastrozole treatment was 4 weeks. In the second trial reported by Ma et al for the NCIC, letrozole was given to 32 postmenopausal women with recurrent endometrial cancers who had received at the most one prior progestational agent and no prior chemotherapy for metastatic disease. A 9.4% response rate and 39% stable disease was observed. A median progression -free survival of 6.7 months was observed in the subset with stable disease (13). Among 19 patients with available tissue in the second trial, ER positivity and PR positivity was seen in 86% of the cases. Only 2 of these 19 patients had a response, both having a partial response and both been ER and PR positive tumors. Seventy percent of the patients treated in the trial of Ma et al had not received prior hormonal treatment. The response rates seen in this trial were similar to the response rate seen with single agent tamoxifen or single agent progestational agents in recurrent endometrial cancers (13).The third trial was reported by Lindemann et al for the Nordic Society of Gynecologic Oncology on the use of exemestane in patients with advanced, persistent or recurrent endometrial cancer (26). In this trial, 51 patients with advanced or recurrent endometrial cancer with measurable disease were treated with exemestane 25 mg daily. Estrogen receptor positivity was defined as 2+ staining in 10% or more of the cancer cells. There were no responses noted in 11 evaluable patients with ER negative disease. Among 40 patients with ER positive disease, responses were seen in 4 patients (10% response rate) with 2 patients achieveing a complete response.. An additional 25% of patients (10/40 patients) had stable disease after 6 months of treatment, for a 35% benefit ratio after 6 months of treatment. All patients who responded to treatment had long lasting remissions (over 55 months and 23 months for the 2 patients who achieved a CR and 25.6 and 26.6 months among the patients who achieved PR).

1.4 At least eight phase 2 clinical trials evaluating aromatase inhibitors have been completed on relapsed ovarian cancer. These studies showed a variable level of activity with a response rate ranging from 0-35% and stable disease noted in 20-42%. (4-6).

1.5 Bowman et al reported in 2002 the largest phase 2 trial of letrozole in relapsed ovarian cancer. A total of 60 patients were treated. The authors observed a significant correlation between ER and PR expression in the tumors and benefit from treatment (prolongation of time to progression, CA-125 responses) (7). CA-125 responses (greater than 50% decreases in baseline levels) were noted in 8% of the patients. Median time to progression was 12 weeks for the whole group. Stable disease at 12 weeks was noted in 17% of the patients with a median time to progression of 35 weeks for this subset (7). The authors concluded that there seems to be a subset of ovarian cancers that may benefit from letrozole therapy and that this subset is characterized by higher expression of estrogen and progesterone receptors.

1.6 Clinical data from Dr. Colon-Otero's practice is also consistent with the presence of a subset of relapsed ovarian cancer patients who may obtain long term benefits from aromatase inhibitor therapy. Six patients with relapsed ovarian cancer cared for by Dr. Colon-Otero had responses to aromatase inhibitors lasting for 1 year to over 13 years after progressing on multiple chemotherapy regimens. Two of the patients had a grade 1 papillary serous carcinoma, 2 patients had high grade endometrioid carcinomas and 2 had high grade papillary serous carcinomas. ER and PR data was available in 2/6 patients and was positive on both of them.

1.7 Additional data also suggest that response rates to aromatase inhibitors are higher in patients with borderline ovarian tumors, which have a higher level of expression of estrogen receptors (8-9).

1.8 A trial of everolimus and letrozole in endometrial cancer demonstrated significant activity of this combination (27). All patients had received up to 2 prior chemotherapy regimens. A 32% response rate (11/35 evaluable patients) was observed including a 25% CR rate (9 patients). Forty percent of the evaluable patients experienced clinical benefit at 16 weeks (CR, PR or stable disease; CBR). Sixty five percent of the ER positive endometrioid tumors had clinical benefit (13/20 patients). All 7 cases with serous histology had progressive disease but only 2 of these tumors were ER positive.

1.9 In post-menopausal women with metastatic breast cancer, resistance to aromatase inhibitor therapy is associated with activation of the cyclin kinase pathway. The addition of a cyclin kinase inhibitor (palbociclib, PD0332991) to letrozole in a randomized phase 2 trial for patients with previously untreated ER positive metastatic breast cancer was associated with a significant prolongation of disease free survival (11). A total of 165 patients were studied with an increase in PFS

from 7.5 months to 26 months noted in the group treated with the combination of palbociclib (PD0332991) and letrozole (11).

1.10 Ribociclib (LEE011) is an oral inhibitor of CDK 4/6 that induces dephosphorylation of Rb and G1 cell cycle arrest in cancer cells. First in human trials showed a tolerable dose of 600 mg PO daily or 900 mg PO daily for 3 of 4 weeks as well as a dose of 400 mg daily (12, 19). Multiple phase 1 studies of ribociclib as a single agent or in combination with multiple other agents including letrozole have been completed and/or are ongoing. For example, Study CLEE011A2115C is an ongoing, Phase 1B dose-escalation study, followed by a Phase 2 single-arm study of the combination of ribociclib and letrozole in poetmenopausal women with ER positive, HER2 negative metastatic breast cancer. As of August 6, 2015, 12 patients were treated with 400 mg ribociclib and letrozole as proposed in this study, with 9 patients completing Cycle 1. At the time of data cut-off dat, 2 SAEs have been reported including 1 case of hepatic function abnormalities and 1 case of elevated serum creatinine.We will use the 400 mg PO daily dose for this proposed trial.

1.11 The p16-CDK4/6-Rb pathway regulates cell cycle progression from G1-S. Given the mechanism of action of ribociclib (LEE011), RB expression is a pre-requisite for ribociclib anti-neoplastic effects. Lack of expression of p16 and expression of RB correlate with response to cyclin kinase inhibitors in general although no correlation between biomarker expression and response was noted by Lin et al in the postmenopausal breast cancer trial of letrozole and palbociclib (PD0332991)(18). In a xenotropic model of glioblastoma multiforme, Ling et al describes that response to cyclin kinase inhibitor (PD0332991) correlated with the presence of wild type RB, the lack of amplification of CDK4 and the lack of p16-INK4a expression (17).

1.12 In ovarian cancer, Dong et al found that 71% of the tumors expressed pRb (20). In endometrial cancer, loss of Rb expression is a rare event, present in only 4 out of 70 cases studied by Niemann et al (21,22, 24). Deletion of p16 with associated expression of Rb is not present in endometrial hyperplasia but has been seen in 26% of cases of endometrial cancers evaluated by Koh et al and this phenotype correlates with higher grade tumors (25).

1.13 In view of the above findings, it is conceivable that inhibition of the cyclin kinase pathway in ER positive ovarian cancers and endometrial cancers may lead to synergism when administered concomitantly with aromatase inhibitors. The proposed pilot study will evaluate the response rate and progression free survival of patients with relapsed estrogen receptor positive ovarian cancer and relapsed estrogen receptor positive endometrial cancers treated with letrozole and ribociclib (LEE011).

1.14 A phase 2 trial of everolimus and letrozole in relapsed ER positive ovarian cancer by Colon-Otero et al just completed acrual. Primary endpoint of this trial was the

demonstration that mTOR inhibition with everolimus given together with letrozole will significantly prolong the time to progression and lead to an increase in the percentage of patients without progressive disease at 12 weeks of treatment (PFS12) (a PFS12 greater than 45%) compared to historical controls of letrozole alone (which had shown a PFS12 of 20%). Preliminary analysis of the first 16 patients enrolled in the trial showed that the primary endpoint was met with 69% percent of the patients not progressing at 12 weeks. This study also demonstrated the feasibility of developing PDX models from CT guided biopsy specimens on these patients as planned on this proposed study. These results support the concept that some of the proven effective interventions to circumvent resistance to aromatase inhibitor therapy in ER positive breast cancer, like mTOR inhibition and cyclin kinase inhibition, may also be effective in other ER positive tumors like ovarian cancer.

2.0 Goals

2.1 Primary objective:

Demonstrate if the combination of letrozole and ribociclib (LEE011) leads to a higher percentage of patients who are progression free at 12 weeks (PFS 12) as compared with that observed in prior studies with single agent letrozole.

2.2 Secondary objectives

2.21 Demonstrate if the combination of letrozole and ribociclib (LEE011) leads to a higher CA-125 response rate in patients with relapsed ER positive ovarian cancers and endometrial cancers as compared to that observed in previously reported single agent letrozole studies.

2.22 Other secondary endpoints will consist of median progression-free survival (PFS), overall survival (OS), the confirmed response rate, and adverse events.

2.3 Correlative Research

2.31 Identify molecular biomarkers associated with a response to treatment with letrozole and ribociclib (LEE011) (in patients with relapsed ovarian carcinomas and endometrial cancers).

2.32 Develop PDX avatars on tumors from participants for possible future translational study evaluating a potential correlation between responses in the PDX model to patients' responses.

2.321 For proposed future patient derived xenograft experiments, response to therapy is tumor volumes measured by ultrasound; this measurement exhibit a standard deviation in the range of 10 to 25% of the tumor volume. Taking the high end of the standard deviation, for each model we anticipate 5 animals per group (control or letrozole + ribociclib) will give us approximately 80% power to determine a 50% difference in tumor volume (57% difference for 4 animals). Thus, 10 animals/model will be adequate for this comparison. To explore whether the responsiveness of

tumors to letrozole + ribociclib is not due to either agent alone, additional cohorts of 5 animals treated with letrozole and 5 animals treated with riboccilcib, will also be treated for a total of 20 animals/model. However, formal comparisons will only be made between control and combination therapy, and thus no penalties for multiple comparisons will be assessed. The study endpoint is 28 days following treatment initiation. “Response” will be defined as tumors with at least a 50% reduction in tumor volume at study end. “Unresponsive” will be defined as tumors with less than 10% tumor volume reduction at study end. Intermediate values will be defined as “Stable”. Tumor growth curves will be plotted graphically and notated to indicate the outcome status of the originating patients. End of study tumor volumes will be correlated with outcome status of the originating patient in an exploratory fashion.

The preclinical combinatorial data will be compared to patient clinical trial outcome data to determine if the avatar models match clinical findings related to tumor responsiveness to therapy. If so, numerous directions may be taken that could include profiling tumor tissues to identify biomarkers for responsiveness or utilizing the avatar models to explore other therapeutic alternatives to nonresponders.

2.322 Should these exploratory studies demonstrate a correlation of benefit on protocol therapy to a specific “ribociclib/letrozole DNA response signature”, after discussions with the Sponsor and co-investigators, the study will be amended to enroll an additional cohort of patients that are screened and demonstrated to be ‘positive’ for the putative response signature to validate these findings.

3.0 Patient Eligibility

3.1 Pre-Registration- Inclusion Criteria

3.11 Ability to understand and the willingness to sign a written informed consent document.

3.12 Age ≥18 years and post-menopausal.

3.13 Histologically confirmed recurrent ovarian, fallopian tube or primary peritoneal carcinoma or endometrial cancer in post-menopausal women.
NOTE: Pure clear cell and pure mucinous carcinomas are ineligible. Platinum sensitive, platinum resistant and platinum refractory disease are eligible. No limitations in the number of prior regimens.

3.14 Patient has disease amenable to biopsy and is agreeable to undergo a biopsy.
NOTE: Under unusual circumstances, submission of ascites material may be acceptable if a biopsy is not possible. This exception will require approval by one of the study Principal Investigators.

3.15 Willing to provide tissue samples for ER and RB staining (see Sections 6.2 and 17.1).

3.2 Registration – Inclusion Criteria

3.21 Measurable disease by RECIST criteria as defined in Section 11.0.

3.22 Tumors must stain positive for estrogen receptor positive (≥10%) by IHC.

3.23 ECOG Performance Status (PS) 0, 1, or 2 (Appendix I)

3.24 The following laboratory values obtained ≤21 days prior to registration.

- Absolute neutrophil count (ANC) ≥1000/mm^3
- Platelet count ≥100,000/mm^3
- Hemoglobin ≥9.0 g/dL
- Total bilirubin ≤1 x ULN; or total bilirubin ≤3.0 x ULN with direct bilirubin ≤1.5 x ULN in patients with well-documented Gilbert's Syndrome.
- Aspartate transaminase (AST) ≤2.5 x ULN (≤5x ULN in patients with liver metastasis)
- INR ≤2
- Creatinine ≤1.5 mg/dL
- Potassium, total calcium (corrected for serum albumin), magnesium, sodium and phosphorus ≤ULN (or corrected to ≤ULN with supplements prior to registration)

3.25 Ability to swallow study medication

3.26 Provide informed written consent.

3.27 Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.28 Willing to provide tissue samples for correlative research purposes (see Sections 6.0 and 17.0).

3.3 Registration – Exclusion Criteria

3.31 Patients who have central nervous system (CNS) involvement unless they meet ALL of the following criteria:
- ≥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.

3.32 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.).

3.33 Clinically significant, uncontrolled heart disease or cardiac repolarization abnormalities and/or recent events including any of the following:
- History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 6 months prior to screening
- History of documented congestive heart failure (New York Heart Association functional classification III-IV)
- Documented cardiomyopathy
- Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) at screening
- 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), long QT syndrome or family history of long QT syndrome
- Idiopathic sudden death or congenital long QT syndrome
- 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)
  NOTE: QTcF, using Fridericia's correction, is QT/RR^0.33 where RR=60/Heart Rate.
- Systolic blood pressure (SBP) >160 mmHg or <90 mmHg at screening
- Bradycardia (heart rate <50 at rest), by ECG or pulse, at screening
- Tachycardia (heart rate >110 at rest), by ECG or pulse at screening

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

3.35 Patient is currently receiving any of the following medications and cannot be discontinued ≤7 days prior to starting study drug (see Appendix III, as well as Section 7.6 and Table 5-7 of Ribociclib Investigator's Brochure for details):

known strong inducers or inhibitors of CYP3A4/5 including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges or that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5 or herbal preparations/medications or dietary supplements

3.36 Patient is currently receiving or has received systemic corticosteroids within ≤2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.
NOTE: 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)

3.37 Patient has received radiotherapy ≤4 weeks or limited field radiation for palliation ≤2weeks prior to starting study drug, and who has not recovered to Grade 1 or better from related side effects of such therapy (exceptions include alopecia) and/or in whom ≥30% of the bone marrow was irradiated.

3.38 Patient has had major surgery ≤14 days prior to registration or has not recovered from major side effects (tumor biopsy is not considered as major surgery).

3.39a Known to be HIV positive (testing not mandatory).

3.39b Patient has a known hypersensitivity to any of the excipients of ribociclib including peanut and soy.

3.39c Patient is currently receiving warfarin or other coumarin-derived anticoagulant for treatment, prophylaxis or otherwise. **NOTE:** Therapy with dabigatran, heparin, low molecular weight heparin (LMWH) or fondaparinux is allowed.

3.39d Participation in a prior investigational study within 30 days prior to enrollment or ≤5 half-lives of the investigational product, whichever is longer

3.39e Patient has not recovered from all toxicities related to prior anticancer therapies to NCI-CTCAE version 4.0 Grade <3
(Exception to this criterion: patients with any grade of alopecia or neuropathy are allowed to enter the study).

3.39f Patient with a Child-Pugh score B or C.

3.39g 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 significant small bowel resection).

3.39h Prior therapy for ovarian or uterine cancer with ribociclib or an aromatase inhibitor (letrozole, anastrozole or exemestane).

3.39i Patient has received systemic chemotherapy ≤3 weeks prior to registration.

4.0 Test Schedule

Tests and procedures			Active Monitoring Phase		
	Pre-Registration	**≤21 days prior to registration**	**During Cycle 1-2 (every 14 days)** ±3 days	**Prior to Cycle 3 and beyond (every 28 days** ±3 days)[8] **(Prior to Cycle 4 for tumor measurements and CA-125)**	**End of Treatment**
History and exam,Wt, PS		X	X	X	X
Adverse event assessment*		X	X	X	X
Patient Medication Diary (Appendix II)[2] collected at the end of each cycle			X	X	X
Hematology group (HgB, WBC, PLT, ANC)		X	X[5]	X[5]	X
Chemistry group (creatinine, Na, K, P, Total bili, alk phos, AST, ALT)		X	X[6]	X[6]	X
Serum Magnesium		X	X[6]	X[6]	
PT/INR		X			
Lipid panel		X		X[1]	X
Urinalysis		X			
Chest x-ray (in addition to CT chest)		X			
ECG[7,R]		X	X[7]	X	X
ECHO[R]		X	As clinically indicated		
CA-125[1]		X		X[1]	X
Tumor Measurements: CT or MRI of the chest, abdomen and pelvis[1]		X		X[1]	X[3]
Tumor biopsies [4,R]		X			
ER/PR/RB status from archived tissue if available (If archived not readily available, status must be collected off fresh tissue biopsy)	X				

1. As assessed by examination or imaging studies (CT scans and/or MRI as indicated). Use same imaging throughout the study. Tumor measurements by imaging studies and serum CA-125 levels (if abnormal at baseline) to be performed every 12 weeks (at baseline, at 12 weeks, at 24 weeks, etc). No need to obtain imaging studies or CA-125 levels before Cycle 4 (12 weeks). Lipid panel every 12 weeks.
2. The diary must begin the day the patient starts taking the medications and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.
3. Except in case of discontinuation from treatment due to progression, tumor assessment at EOT is not necessary if the previous evaluation was done within 6 weeks of EOT.
4. Tumor biopsies must be collected after registration and confirmation of ER and RB positive status and prior to starting treatment, unless a fresh biopsy is needed for determination of ER and RB positive status. Patients should only have one biopsy procedure for this study. If patient receives fresh biopsy

procedure to determine ERand RB status, then tissue for correlative studies should be obtained at that time.

5. Check weekly per protocol if toxicity until toxicity resolves or as clinically indicated.
6. Obtain also potassium, calcium, phosphorus and magnesium levels in the event of prolongation of QT interval of any level and in the event of toxicities that can be associated with electrolyte imbalance (diarrhea, nausea, other cardiac toxicities). Levels will need to be checked regularly until they normalize. See Section 8.0.
7. A standard 12-Lead ECG is recommended at baseline, Cycle 1 Day 1 if ≥7 days from baseline and at Cycle 1 Day 15 and Cycle 2 Day 1and 15. Cycle 3-6 the ECG will be obtained on Day 1. For patients with QTcF ≥481 ms at any time, follow the procedures described in the "Ribociclib Dose Modification section", Section 8.0. After 2 years of treatment, ECGs will be done every 3 cycles.
8. After 2 years of treatment, Clinical evaluations/test and blood tests can be obtained locally by an oncologist and mailed/faxed to Mayo Clinic. Patients must return to every 3 cycles for follow-up at Mayo Clinic.
   *After 2 years of treatment, adverse events will also be assessed every 3 cycles during the patients follow-up at Mayo Clinic.

R Biopsies and Creation of Avatar will be Research funded.

5.0 Grouping Factors

Tumor Type (Cohort):
Cohort A: Ovarian, primary peritoneal, fallopian tube ACA vs. Cohort B: Endometrial cancer
NOTE: Collected at Registration (Step 2) Only

6.0 Registration Procedures

6.1 Pre-Registation (Step 1)

6.11 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration application. The registration application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration application are available on the MCCC web page (http://hsrwww.mayo.edu/ccs/training) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm that the process has been successfully completed prior to release of the study agent. Patient registration via the registration application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office (507) 284-2753. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 Prior to accepting the pre-registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient pre-registration eligibility

- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information.

6.13 Pre-registration tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.2 Registration (Step 2)

6.21 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, call the MCCC Registration Office at (507) 284-2753 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.22 Correlative Research
A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19c and 17.1).

6.23 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.
In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.
When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.24 Prior to accepting the registration, registration application will verify the following:

- IRB approval at the registering institution
- Patient eligibility

6.25 Treatment cannot begin prior to registration and must begin ≤7 days after registration.

6.26 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.27 All required baseline symptoms (see Section 10.6) must be documented and graded.

6.28 Treatment on this protocol must commence at Mayo Clinic Rochester or Mayo Clinic Florida or Mayo Clinic Arizona under the supervision of a medical oncologist.

6.29 Study drug is available on site.

7.0 Protocol Treatment

7.1 Pre-Registration

Patients with recurrent ovarian, fallopian tube or primary peritoneal carcinoma or endometrial cancer will be pre-registered to facilitate RB testing required for eligibility.

Tissue samples (see Section 17.0) will be sent to:

[redacted]

RB results will be returned to the requesting study coordinator within 5 days so that the patient can be registered and enter the trial in a timely manner.

7.2 Treatment Schedule

Agent	Dose Level	Route	ReRx
RIBOCICLIB	200 mg CAPS, 2 PO daily (400 mg daily)	PO	Every28 days ±3 days
LETROZOLE	2.5 mg TABS, 1 PO daily	PO	Every 28 days±3 days

7.3 Return to treating institution

For this protocol, the patient must return to the consenting institution for evaluation at the indicated times.

If patient is tolerating therapy without toxicity after 2 years of treatment, the patient may be seen by their local oncologist (if outside of Mayo).

7.4 Treatment by local medical doctor (LMD)

If patient is tolerating therapy without toxicity after 2 years of treatment, the patient may be seen by their local oncologist (if outside of Mayo). Clincal evaluations/tests and blood tests can be obtained locally per the test schedule and mailed/faxed to Mayo clinic. Patient would need to return to Mayo Clinic every 3 cycles. All unused study drug must be returned and all study drug must be accounted for. A 3-month supply of study drug will be provided every 3 cycles.

7.5 Drug administration

Ribociclib will be administered as a flat-fixed dose (e.g. 400 mg daily), and not by body weight or body surface area. Letrozole will also be administered as a fixed dose.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose. **NOTE: There are no specific dose modifications for letrozole unless indicated in the tables below.**

ALERT: **ADR reporting may be required for some adverse events (See Section 10).**

Table 8.1 Dose Levels

(Based on Adverse Events in Tables 8.2-8.3)

Dose Level	RIBOCICLIB	LETROZOLE
0*	400 MG PO DAILY	2.5 MG PO DAILY
-1	400 MG PO DAILY (Days 1-21 Q 28 days)	2.5 MG PO QOD
-2	200 MG PO DAILY (Days 1-21 Q 28 days)	N/A

*Dose level 0 refers to the starting dose. N/A=not applicable

Table 8.2 Dose Modifications

NOTE: Cycles will be 28 (±3) days in length. Day 1 of each cycle will begin with the administration of letrozole regardless of the ribociclib dosing based on adverse event. Omitted doses will not be made up. This table will be used for both Day 1 (retreatment AEs) and Days 2-28 (interval AEs) for Ribociclib.

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified*** ← ←

CTCAE System/Organ/Class (SOC)	GRADE	ADVERSE EVENT	AGENT	ACTION**
INVESTIGATIONS	Grade 2	Platelet count decreased <75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9/L)	RIBOCICLIB	Omit until recovery to Grade ≤1 Re-initiate ribociclib at the same dose

CTCAE System/Organ/Class (SOC)	GRADE	ADVERSE EVENT	AGENT	ACTION**
INVESTIGATIONS	Grade 3	Platelet count decreased (<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10e9 /L)	RIBOCICLIB	Omit until recovery to Grade ≤1 Re-initiate ribociclib at the same dose level •If toxicity recurs at Grade 3: temporary dose interruption until recovery to Grade ≤1 and reduce ribociclib to the next lower dose level
	Grade 4	Platelet count decreased (<25,000/mm^3; <25.0 x 10e9 /L)	RIBOCICLIB	Omit until recovery to Grade ≤1 Re-initiate ribociclib at the next lower dose level •If toxicity recurs at Grade 4: discontinue ribociclib
	Grade 3	Neutrophil count decreased (≥0.5 - <1.0 x 10^9/L)	RIBOCICLIB	Omit until recovery to >1.0 x 10^9/L Re-initiate ribociclib at the same dose level. •If toxicity recurs at Grade 3: temporary dose interruption until recovery to ≥1.0 x 10^9/L. If resolved in ≥7 days, reduce ribociclib dose to the next lower dose level. If resolved in ≤7 days, resume ribociclib at same dose level
	Grade 4	Neutrophil count decrease (<0.5 x 10^9/L)	RIBOCICLIB	Omit until recovery to >1.0 x 10^9/L Re-initiate ribociclib at the next lower dose level •If toxicity recurs at Grade 4: temporary dose interruption until recovery to ≥1.0 x 10^9/L and reduce ribociclib at the next lower dose level

CTCAE System/Organ/Class (SOC)	GRADE	ADVERSE EVENT	AGENT	ACTION**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Grade 3	Febrile neutropenia ANC <1.0 x 10^9/L with [a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour]	RIBOCICLIB	Omit until improvement of ANC ≥1.0 x 10^9/L and no fever Restart at the next lower dose level •If febrile neutropenia recurs, discontinue ribociclib
	Grade 4	Febrile neutropenia Life-threatening consequences; urgent intervention indicated	RIBOCICLIB	Discontinue
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Grade 3	Anemia Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	RIBOCICLIB	Omit until recovery to Grade ≤2 Re-initiate ribociclib at the same dose
	Grade 4	Anemia Life-threatening consequences; urgent intervention indicated	RIBOCICLIB	Discontinue

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no further adverse events >Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time, in the following cycles. This applies to both ribociclib and letrozole.

NOTE: At the investigator discretion ribociclib or letrozole may be continued if one agent is discontinued due to adverse events.

8.3 Recommendations for ribociclib and letrozole dose modifications in case of hepatic toxicities

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←

8.31 Blood Bilirubin Increased

CTCAE System/Organ/Class (SOC)	Grade	ADVERSE EVENT	AGENT	ACTION**
BASED ON INTERVAL ADVERSE EVENT				
INVESTIGATIONS	Grade 1 (>ULN – 1.5 x ULN) (confirmed 48 to 72hrs later)	BLOOD BILIRUBIN INCREASED	RIBOCICLIB and LETROZOLE	Maintain dose level with LFTs monitored bi-weekly
	Grade 2 (>1.5 – 3.0 x ULN)			Omit ribociclib and letrozole If resolved to ≤Grade 1 in ≤28 days, then maintain dose level If resolved to ≤Grade 1 in >28 days or toxicity recurs, then reduce 1 dose level If toxicity recurs after two dose reductions,discontinue ribociclib and letrozole and go to event monitoring
	Grade 3 (>3.0 – 10.0 x ULN)			Omit ribociclib and letrozole If resolved to ≤Grade 1 in ≤28 days, lower 1 dose level of ribociclib If resolved to ≤Grade 1 in >28 days or toxicity recurs, discontinue ribociclib and letrozole
	Grade 4 (>10.0 x ULN)			Discontinue ribociclib and letrozole
AT TIME OF RETREATMENT				
INVESTIGATIONS	Grade 1 (>ULN – 1.5 x ULN) (confirmed 48 to 72hrs later)	BLOOD BILIRUBIN INCREASED	RIBOCICLIB and LETROZOLE	Maintain dose level with LFTs monitored bi-weekly

CTCAE System/Organ/Class (SOC)	Grade	ADVERSE EVENT	AGENT	ACTION**
INVESTIGATIONS	Grade 2 (>1.5 – 3.0 x ULN)	BLOOD BILIRUBIN INCREASED	RIBOCICLIB and LETROZOLE	Hold ribocicliband letrozole If resolved to ≤Grade 1 in ≤28 days, then maintain dose level If resolved to ≤Grade 1 in >28 days or toxicity recurs, then reduce 1 dose level If toxicity recurs after two dose reductions,discontinue Ribociclib and letrozole and go to event monitoring
	Grade 3 (> 3.0 – 10.0 x ULN)			Hold ribocicliband letrozole If resolved to ≤ grade 1 in ≤ 28 days, lower 1 dose level of ribociclib If resolved to ≤ grade 1 in > 28 days or toxicity recurs, discontinue ribociclib and letrozole
	Grade 4 (> 10.0 x ULN)			Discontinue ribociclib and letrozole
Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤ 1 x ULN) due to hemolysis or Gilbert Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.				

8.32 Alanine Aminotransferase or Aspartate Aminotransferase Increased

CTCAE System/Organ/Class (SOC)	Grade	ADVERSE EVENT	AGENT	ACTION**
BASED ON INTERVAL ADVERSE EVENT				
INVESTIGATIONS	Same grade as baseline or increase from baseline Grade 0 to Grade 1 (confirmed 48 to72 hrs later)	ALANINE AMINOTRANSFERASE INCREASED AND	RIBOCICLIB and LETROZOLE	Maintain dose level with LFTs monitored bi-weekly

CTCAE System/Organ/Class (SOC)	Grade	ADVERSE EVENT	AGENT	ACTION**
INVESTIGATIONS	Increase from baseline to Grade 2 (>3.0 – 5.0 x ULN)	ASPARTATE AMINOTRANSFERASE INCREASED		Omit ribociclib and letrozole If resolved to ≤Grade 1 in ≤28 days, then maintain dose level If resolved to ≤Grade 1 in >28 days or toxicity recurs, then reduce 1 dose level Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions,discontinue Ribociclib and letrozole and go to event monitoring
	Increase from baseline to Grade 3 (>5.0 – 20.0 x ULN)			Omit ribociclib and letrozole If resolved to ≤Grade 1 in ≤28 days, lower 1 dose level of ribociclib Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption If resolved to ≤Grade 1 in >28 days or toxicity recurs, discontinue ribociclib and letrozole
	Grade 4 (>20.0 x ULN)			Discontinue ribociclib and letrozole
AT TIME OF RETREATMENT				
INVESTIGATIONS	Same grade as baseline or increase from baseline Grade 0 to Grade 1 (confirmed 48 to72 hrs later)	ALANINE AMINOTRANSFERASE INCREASED AND	RIBOCICLIB and LETROZOLE	Maintain dose level with LFTs monitored bi-weekly

CTCAE System/Organ/Class (SOC)	Grade	ADVERSE EVENT	AGENT	ACTION**
	Increase from baseline grade 0 or 1 to Grade 2 (>3.0 – 5.0 x ULN) or from baseline Grade 2 to Grade 3 (>5.0 – 20.0 x ULN)	ASPARTATE AMINOTRANSFERASE INCREASED		Hold ribociclib and letrozole If resolved to ≤Grade 1 in ≤28 days, then maintain dose level If resolved to ≤Grade 1 in >28 days or toxicity recurs, then reduce 1 dose level If toxicity recurs after two dose reductions,discontinue Ribociclib and letrozole and go to event monitoring
	Increase from baseline Grade 0 or 1 to Grade 3 (>5.0 – 20.0 x ULN)			Hold ribociclib and letrozole If resolved to ≤Grade 1 in ≤28 days, lower 1 dose level of ribociclib If resolved to ≤Grade 1 in >28 days or toxicity recurs, discontinue ribociclib and letrozole
	Grade 4 (>20.0 x ULN)			Discontinue ribociclib and letrozole
AST or ALT and concurrent Bilirubin				
For patients with normal ALT or AST or total bilirubin at baseline: AST or ALT ≥Grade 2 combined with (>3 x ULN) in patients with normal values at baseline and total bilirubin >2 x ULN without evidence of cholestasis or AST or ALT ≥Grade 3 (>5 x ULN) in patients with Grade 1 or 2 at baseline, and total bilirubin >2 x ULN For patient with elevated AST or ALT or total bilirubin at baseline: baseline: [AST or ALT >2 x baseline AND >3.0x ULN] OR [AST or ALT 8.0x ULN]- whichever is lower-combined with [total bilirubin 2x baseline AND >2.0 x ULN]				Discontinue ribociclib and letrozole
Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, and alcohol intake.				

8.4 Additional follow-up for hepatic toxicities

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

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

• For patients with normal ALT or AST or TBIL value at baseline: AST or ALT >3.0 x ULN combined with TBIL >2.0 x ULN

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

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

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

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

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

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

• Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or return to normal values.

• Obtaining a more detailed history of current symptoms.

• Obtaining a more detailed history of prior and/or concurrent diseases, including history of any pre-existing liver conditions or risk factors.

• Obtaining a history of concomitant drug use (including non-prescription medications, herbal and dietary supplements), alcohol use, recreational drug use, and special diets.

• Ruling out acute viral hepatitis types A, B, C, D, and E; hepatotropic virus infections (CMV, EBV or HSV); autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.

• Obtaining a history of exposure to environmental chemical agents.

Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).

• Considering gastroenterology or hepatology consultations.

• Assessing cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure as possible etiologies for liver dysfunction.

• Liver biopsy as clinically indicated to assess pathological change and degree of potential liver injury.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant", thus met the definition of SAE (Section 8.2.17.02), and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

8.5 Dose modification guidance for ribociclib in case of QTcF prolongation

Grade	Dose Modification
For all grades	1. Check quality of the ECG and the QTcF value and repeat if needed 2. Perform an analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If below the lower limit of normal, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. 3. Review concomitant medication usage for the potential to inhibitCYP3A4 and/or to prolong the QTcF-interval. 4. Check compliance with correct dose and administration of ribociclib
1 QTcF 450-480 ms	Perform steps 1-4 as directed in "For All Grades." No dose adjustment required.
2 QTcF 481-500 ms	Omit ribociclib. Perform steps 1-4 as directed in the "For All Grades" section above. Perform a repeat ECG one hour after the first QTcF of ≥481ms. Repeat ECG as clinically indicated until the QTcF returns to < 481 ms. Restart ribociclib with dose reduced by 1 dose level. • If QTcF ≥481 ms recurs, ribociclib should be reduced again by 1 dose level (please refer to the dosing schedule table) • Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patient who has therapy interrupted due to QTcF ≥481 ms

3 QTcF ≥501 ms on at least two separate ECGs	Omit ribociclib. Perform steps 1-4 as directed in the "For All Grades" section above. • **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 clinically indicated until the QTcF returns to <481 ms. • If QTcF returns to <481 ms, ribociclib should be reduced by 1 dose level. (Please refer to the dosing schedule table) • If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in the "For All Grades" section above, discontinue ribociclib. **Repeat ECGs 7 days and 14 days after dose resumption for any patient who has therapy interrupted due to QTcF ≥501 ms** • If QTcF of ≥501 ms recurs, discontinue ribociclib
4 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 the "For All Grades" section above. • Obtain local cardiologist or qualified specialist consultation and repeat cardiac monitoring as indicated until the QtcF returns to <481 ms

Additional follow-up for QTcF prolongation

In case of QTcF prolongation regardless of the grade:

- Perform an analysis of serum potassium, calcium, phosphorus, and magnesium, and if below lower limit of normal, correct with supplements to within normal limits.
- Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT-interval.
- Check compliance with correct dose and administration of ribociclib.

8.6 Ribociclib and letrozole dose adjustment and management recommendation for all other adverse reactions

Grade	Dose Adjustment and Management Recommendations
1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
2	Dose interruption until recovery to Grade ≤1. Initiate appropriate medical therapy and monitor.

	Re-initiate ribociclib and letrozole at the same dose. If the same toxicity recurs at Grade 2, interrupt ribociclib and letrozole until recovery to Grade ≤1. Re-initiate ribociclib at the next lower dose level.
3	Dose interruption until recovery to Grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate ribociclib and letrozole at the next lower dose level If toxicity recurs at Grade 2: temporary dose interruption until recovery to Grade ≤1 and reduce ribociclib and letrozole dose to the next lower dose level If toxicity recurs at Grade 3, discontinue ribociclib and letrozole
4	Discontinue ribociclib and letrozole and treat with appropriate medical therapy.

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

8.7 Adjustment of Starting Dose in Special Populations

Renal impairment

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

Patients with baseline renal impairment are excluded from the study (serum creatinine >ULN or creatinine clearance <50 mL/min). Patients who experience renal impairment of Grade 2 or higher during the treatment period should discontinue treatment and should be followed for safety assessments.

Elderly

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

Concomitant Medications

Permitted concomitant therapy

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

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

Bisphosphonates and denosumab

Bisphosphonates and denosumab are allowed as indicated.

Hematopoietic growth factors

Hematopoietic growth factors may be used according to ASCO guidelines.

Palliative radiotherapy

Palliative radiation is permitted if done solely for bone pain relief. It should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow. No dose modification of study treatment is needed during palliative radiotherapy.

Permitted concomitant therapy requiring caution

Refer to the ribociclib (LEE011) Investigator's Brochure, Section 7.6 and Table 5-7, as well as Appendix III of protocol for information on possible interactions with other drugs.

Medications to be used with caution during ribociclib and letrozole in this study are listed below (see Appendix III). This list is not comprehensive and is only meant to be used as a guide. These medications should be excluded from patient use if possible. If they must be given, then use with caution and consider a ribociclib interruption if the concomitant medication is only needed for a short time (see Appendix III):

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

Prohibited concomitant therapy

The following medications are prohibited during study treatment in the study (see Section 7.6 and Table 5-7 of ribociclib IB and Appendix III). This list is not comprehensive and is only meant to be used as a guide:

- Strong inhibitors or inducers of CYP3A4/5
- Substrates of CYP3A4/5 with a narrow therapeutic index
- Medications that carry a known risk for QT prolongation
- Herbal medications/preparations, dietary supplements (except for vitamins) including but not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications and dietary supplements at least 7 days prior to first dose of study treatment.
- Other investigational and antineoplastic therapies not part of the study

Drugs with QT prolongation

As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI that increases the exposure of ribociclib or the exposure of the QT prolonging drug). 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 www.qtdrug.org.

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

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO) Update of Recommendation for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol 2006; 24:3187-3205, 2006.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide (for grade 1-2 diarrhea). The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 Concomitant medications: Patients must be instructed not to take any medications (over-the-counter or other products) during the protocol treatment period without prior consultation with the investigator. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) taken within 28 days of starting study treatment through the 30-day safety follow up visit should be reported on the CRF.

9.51 Concomitant Medications

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

The lists in Appendix III are not comprehensive and are only meant to be used as a guide. The lists are based on the Oncology Clinical Pharmacology guidance, Drug-Drug Interaction and Co-medication Consideration Database (v05,release date: 29 Oct 2015)2), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction Table (http://medicine.iupui.edu/clinpharm/ddis/main-table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation

/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (http://www.druginteractioninfo.org/). For current lists of medications that may cause QT prolongation and/or torsades de pointes (TdP), refer to the CredibleMeds® website (https://crediblemeds.org/www.qtdrugs.org).). Please contact the medical monitor with any questions.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting.

Routine Reporting

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.6.
- Routine AE reporting for Phase 3 clinical studies using an investigational agent/intervention and a commercial agent in combination must be reported as defined by the general guidelines provided by sponsors, Groups, Cancer Centers, or Principal Investigators. See Section 10.6.

Expedited Reporting

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to Section 10.4 for specific AE reporting requirements or exceptions.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch.
- An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

10.4 Expedited Reporting Requirements for IND/IDE Agents

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.

6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 10.41 of the protocol.

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional instructions:

1. Submit form MedWatch 3500A to the FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, by fax at [redacted] or online at: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

2. **All events must be reported to Novartis Pharmaceuticals DS&E Department [redacted] within 24 hours of learning of its occurrence.** This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

3. Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, using Mayo Expedited Event Report form [redacted] o the MCCC Regulatory Affairs Unit(RAU) Risk Information Specialist, who will determine and complete IRB reporting. TheRAU will submit to the MCCC SAE Coordinator

10.41 Special Situations for Expedited Reporting

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report may not be required for specific Grade 1, 2 and 3 Serious Adverse Events where the AE is **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supercede the standard Expedited Adverse Event Reporting Requirements:

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.
General disorders and administrations site conditions	Fatigue	≤Grade 4
Gastrointestinal Disorders	Mucositis oral	≤Grade 4

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

10.5 Other Required Reporting

10.51 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.52 Death

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benigh, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.52 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE be reported. Three options are available to describe the event:
    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
    - Myelodysplastic syndrome (MDS)
    - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.53 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.6 Required Routine Reporting

Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Gastrointestinal Disorders	Diarrhea	X	X
	Mucositis oral	X	X
Investigations	Alanine aminotransferase increased	X	X
	Aspartate aminotransferase increased	X	X
	Blood bilirubin increased	X	X
General disorders and administration site conditions	Fatigue	X	X
Investigations	Electrocardiogram QT corrected interval prolonged	X	X

10.61 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.611 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.612 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.613 Grade 5 AEs (Deaths)

10.6131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.62 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation Using RECIST Guideline

Eligible patients for this trial have to have measurable diseasebasedon RECIST v1.1 criteria

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) . Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations:

For the purposes of this study, patients should be reevaluated every 12 weeks.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are considered measurable disease.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

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

addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT or MRI imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.33 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 12 weeks (see Section 11.44).

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

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the

opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes
Non-measurable sites of disease (Section 11.22) are classified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to <1.0 cm.
  c. Normalization of tumor biomarkers.
- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).
- Progression (PD): At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph

node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.

b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
  c. Normalization of tumor biomarkers
- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes and/or maintenance of tumor marker level above the normal limits.
- Progression (PD): At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion

and target lymph node status. It must be representative of overall disease status change.)

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following table:

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the MCCC protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to

symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

Platinum Type: Refractory (PD while on initial platinum based therapy) vs. Resistant (PD within 6 months of completion of platinum based therapy) vs. Sensitive (PD beyond 6 months of platinum based therapy)

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who develop PD while receiving therapy will go off treatment and be followed for survival in the event monitoring phase (see Section 18.0).

13.2 Patients who go off protocol treatment for reasons other than PD will go off treatment and be followed per Section 18.0 in the event monitoring phase.

13.3 Patients who are in CR, PR or SD will continue on therapy until progression, toxicity or until the treating physician and the patient decide to stop treatment. After they go off treatment, they will be followed in event monitoring per section 18.0.

13.4 Patients who develop non-CNS PD at any time should go off treatment and be followed in event monitoring (see section 18.0). These patients should be treated with alternative chemotherapy if their clinical status is good enough to allow further therapy.

13.5 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.6 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the

patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.7 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens - None

15.0 Drug Information

15.1 Investigational Study Treatment (Ribociclib)

15.11 **Background**: Ribociclib is an orally bioavailable, highly selective small molecule inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) that induces G1 arrest at sub-micromolar concentrations in a variety of retinoblastoma protein (pRb)-positive cancer cells *in vitro*.

15.12 **Formulation**: The ribociclib drug product is planned for oral administration. The available clinical forms are hard gelatin capsules (10 mg, 50 mg and 200 mg), film-coated tablets (50 mg and 200 mg) and an oral solution (30 mg/mL). The capsules only contain the drug substance; there are no excipients. The film-coated tablets consist of drug substance and compendial quality microcrystalline cellulose, hydroxypropylcellulose, crospovidone, colloidal silicon dioxide and magnesium stearate. The film-coating is a mix of compendial quality polyvinyl alcohol, titanium dioxide, iron oxides, talc, lecithin and xanthan gum. The oral solution consists of ribociclib succinate in water with an orange flavoring agent and the compendial excepients citric acid, methylparaben, potassium sorbate, and sodium saccharin.

15.13 **Preparation and storage**: The shelf life of the drug product is established based on ongoing stability studies and may be extended during the clinical study. The capsules and film-coated tablets are packaged in HDPE bottles. The oral solution is provided as 100 mL in 180 mL brown glass bottles. A press-in bottle adapter and oral dosing syringe are also provided in the administration kit. Refer to the clinical labels for current shelf-life, in-use and storage conditions for the capsules, film-coated tablets and oral solution.

15.14 **Administration:** Ribociclib should be taken with a large glass of water (~250 mL) at the same time each day. Ribociclib can be taken without regard to meals. Swallow the capsules or film-coated tablets whole, and do not chew, crush, or open them. Avoid consumption of grapefruit, Seville oranges or products containing the juice of each. Orange juice is allowed.

15.15 **Pharmacokinetic information**:
Absorption – Rapidly absorbed with median Tmax ranging from 1 to 4 hours.

Distribution – Steady state was generally reached by Day 8 and mean half-life ranged from 15.9 to 32.6 hours.

Metabolism – Ribociclib underwent extensive hepatic metabolism via CYP3A4 in humans based on in vitro and in vivo studies. Following oral administration of a single 600 mg dose of ribociclib in humans (CLEE011A20102), the primary metabolic pathways for ribociclib involved (dealkylation, C and/or N-oxygenation, oxidation (-2H)) and combinations thereof. Phase II conjugates of ribociclib involved N-acetylation, sulfation, cysteine conjugation, glycosylation and glucuronidation. Ribociclib was the major circulating drug-derived entity in plasma. No major unique human metabolites were found in plasma.

Excretion – The half-life for ribociclib is 32 hours. Ribociclib is mainly eliminated via hepatic clearance, with renal clearance playing a lesser role.

15.16 **Potential Drug Interactions**: Based on *in* vitro data, ribociclib is primarily metabolized by CYP3A4. Based on clinical data, ritonavir (a strong CYP3A4 inhibitor) and rifampicin (a strong CYP3A4 inducer) markedly increased and decreased ribociclib exposure, respectively. Therefore, drugs that are strong inhibitors or inducers of CYP3A4 should not be co-administered with ribociclib. Patients who receive medications that are moderate inhibitors or inducers of CYP3A4/5 should be observed for signs of overexposure or potential reduced efficacy of ribociclib, respectively.

Examples of strong CYP3A4 inhibitors include: boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, and voriconazole.

Examples of strong CYP3A4 inducers include: avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), and St. John's wort.

Based on clinical data, ribociclib is a moderate inhibitor of CYP3A4 activity. Therefore, drugs with narrow therapeutic windows that are CYP3A4/5 substrates should not be coadministered with ribociclib. Patients taking drugs that are sensitive substrates of CYP3A4/5 that do not have a narrow therapeutic index should be observed for signs of overexposure of the concurrent medication.

Examples of CYP3A4/5 substrates with narrow therapeutic windows include: alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, and terfenadine.

Co-administration of ribociclib with other drugs that inhibit BSEP may result in intrahepatic cholestasis and hepatic toxicity. Therefore known BSEP inhibitors should be used with caution during treatment with ribociclib. Additionally, caution is recommended with co-administration of sensitive substrates of the renal transporters, MATE1 and OCT2, and with sensitive substrates of BCRP. Examples of BSEP inhibitors: bosentan, fusidate, glibenclamide, lovastatin, sulindac, troglitazone (TGZ-sulfate). Examples of MATE1 and OCT2 substrates: acyclovir, amantadine, amiloride, cephalexin, cephradine, cimetidine, famotidine, fexofenadine, memantine, metformin (also a substrate for OCT1, MATE1, and MATE2K), pindolol, procainamide, ranitidine, and varencicline. Examples of BCRP substrates: rosuvastatin and sulfasalazine.

Prolongation of the QT interval has been observed with ribociclib. Caution should be exercised with all medications that are known to produce this effect. Those known to have a strong signal will be prohibited and others are to be used with caution. Particular attention should be paid to drugs with a possible risk of QT prolongation that are also CYP3A4 substrates. Concurrent administration of these medications with ribociclib may lead to additive QT effects due to CYP3A4 inhibition ribociclib.

15.17 **Known potential toxicities**:

Common known potential toxicities, ≥10%:
Central Nervous System: Headache, isomnia
Dermatologic: Rash, maculopapular rash, alopecia, pruritus
Gastrointestinal: Nausea, vomiting, diarrhea, stomatitis, constipation, abdominal pain, decreased appetite
General Disorders: Asthenia, fatigue, peripheral edema, pyrexia
Hematologic: Anemia, leukopenia, lymphopenia, neutropenia
Hepatic: AST/ALT increased, blood bilirubin increased
Infections: Urinary tract infection
Musculoskeletal: Back Pain
Respiratory: Dyspnea

Less common known potential toxicities, 1% - <10%:
Cardiovascular: Electrocardiogram QT prolongation, syncope
Dermatologic: Erythema
Eye: Lacrimation increased, dry eye
Gastrointestinal: Dysgeusia, dyspepsia, weight decreased
Hematologic: Thrombocytopenia, febrile neutropenia
Hepatic: Drug induced liver injury, hepatocellular injury, hepatotoxicity, hepatic failure
Metabolic: Hypocalcemia, hypokalemia, hypophosphatemia
Renal: Blood creatinine increased
Respiratory, Thoracic, Mediastinal: Epistaxis

15.18 **Drug procurement:** Novartis will provide ribociclib free of charge to study participants for use in this trial. Each participating site will order/monitor drug supply.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.19 Nursing Guidelines

1. There are numerous drug to drug interactions with this agent. Assess patient's medication list including over the counter agents and refer to section 15.16 for a list of classes of drugs to avoid or use with caution while patient is receiving ribociclib.
2. Monitor ECG per protocol. Agent is known to cause QT prolongation. Use with caution with other agents know to prolong the QT interval.
3. Rash is a known side effect. Instruct patient to report any rash or pruritis to the study team.
4. Gastrointestinal side effects are common, including nausea, vomiting, diarrhea, and stomatitis/mucositis. Manage symptomatically and monitor for effectiveness.
5. Monitor CBC w/differential. Cytopenias have been commonly seen.
6. Monitor renal function and encourage hydration.
7. Rarely patients may experience elevated LFTs. Monitor liver function and report any increased LFT's to the treating physician.
8. Agent may cause headaches and insomnia. Manage symptomatically and monitor for effectiveness.
9. Pyrexia, asthenia may be seen. Manage symptomatically and as necessary with dose reductions/holds per protocol guidelines.

15.2 Letrozole for Oral Administration (Femara®)

15.21 **Background**: Letrozole is a 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. This leads to inhibition of the enzyme and a significant reduction in plasma estrogen levels. Letrozole does not affect synthesis of adrenal or thyroid hormones, aldosterone, or androgens. Patients treated with letrozole do not require glucocorticoid or mineralocorticoid replacement therapy.

15.22 **Formulation**: Letrozole is available for oral administration as 2.5 mg tablets.

15.23 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store letrozole at room temperature of 77°F (25°C); excursions permitted to 59°F to 86°F (15°C to 30°C).

15.24 **Administration:** Refer to the treatment section for specific administration instructions. Administer orally with or without food.

15.25 **Pharmacokinetic information**:
Distribution: V_d: ~1.9 L/kg
Protein binding: weak
Metabolism: Hepatic via CYP3A4 and CYP2A6 into an inactive carbinol metabolite
Half-life elimination: Terminal: ~ 2 days
Excretion: Urine (90%; 6% as unchanged drug, 75% as glucuronide carbinol metabolite, 9% as unidentified metabolites)

15.26 **Potential Drug Interactions**:
Cytochrome P450 Effect: Substrate of CY2A6 (minor) CYP3A4 (minor). **Inhibitor** of CYP2A6 (strong), CYP2C19 (weak)
Increased Effect/Toxicity: CYP2A6 substrates, methadone, vitamin K antagonists (eg, warfarin)
Decreased Effect: digoxin, tegafur, vitamin K antagonists (eg, warfarin)

15.27 **Known potential adverse events:** Consult the package insert for the most current and complete information.
Common known potential toxicities, >10%:
Cardiovascular: Edema
Central nervous system: Headache, dizziness, fatigue
Endocrine & metabolic: Hypercholesterolemia, hot flashes
Gastrointestinal: Nausea, weight gain, constipation
Neuromuscular & skeletal: Weakness, arthralgia, arthritis, bone pain, back pain, bone mineral density decreased/osteoporosis, bone fracture
Respiratory: Dyspnea, cough
Miscellaneous: Diaphoresis, night sweats

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Chest pain, hypertension, chest wall pain, peripheral edema, cerebrovascular accident including hemorrhagic stroke, thrombotic stroke, thromboembolic event including venous thrombosis, thrombophlebitis, MI, angina, transient ischemic attack
Central nervous system: Insomnia, pain, anxiety, depression, vertigo, somnolence
Dermatologic: Rash, alopecia, pruritis
Endocrine & metabolic: Breast pain, hypercalcemia
Gastrointestinal: Diarrhea, vomiting, weight loss, abdominal pain, anorexia, dyspepsia
Genitourinary: Urinary tract infection, vaginal bleeding, vaginal dryness, vaginal hemorrhage, vaginal irritation
Neuromuscular & skeletal: Limb pain, myalgia
Ocular: Cataract
Renal: Renal disorder
Respiratory: Pleural effusion
Miscellaneous: Infection, influenza, viral infection, secondary malignancy

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Anaphylactic reaction, angioedema, arterial thrombosis, cardiac failure, carpal tunnel syndrome, endometrial cancer, endometrial hyperplasia, endometrial proliferation, erythema multiforme, hepatitis, leukopenia, memory impairment, stomatitis, tachycardia, thrombocytopenia, toxic epidermal necrolysis, trigger finger

15.28 **Drug procurement:** Novartis will provide letrozole free of charge to study participants for use in this trial. Each participating site will order/monitor drug supply.

15.29 **Nursing guidelines**

15.291 Manage hot flashes with non-hormonal interventions (ie: venlafaxine XR 75 mg daily).

15.292 Manage pain (arthralgias). Instruct patient to report unrelieved pain.

15.293 May take with food if needed for nausea. Instruct patient to report unrelieved nausea or vomiting.

15.294 Assess for changes in bowel patterns. Manage diarrhea or constipation with non-prescription drugs. Tell patients to report unrelieved diarrhea or constipation.

15.295 If patient experiences difficulty breathing or sudden onset chest pain, instruct them to seek emergency medical attention immediately.

15.296 Monitor for signs of edema, instruct patient to report any swelling in legs, feet, or hands.

15.297 Drug procurement: Commercially available.

16.0 Statistical Considerations and Methodolology

16.1 Overview

This study will be a single-arm phase II study to determine the initial clinical benefit of letrozole in combination with ribociclib in patients with ovarian cancer (Cohort A) or endometrial cancer (Cohort B).. The primary endpoint will be the percentage of patients alive and progression-free at the 12 week-timepoint (PFS12) assessed in each cohort separately. The null hypothesis will be set at a 20% for PFS12, the rate observed by Bowman et al in a phase 2 trial of letrozole in ovarian cancer (7). The treatment of letrozole and ribociclib will be deemed worthy of further investigation if 45% or more of patients are alive and progression-free at 12 weeks. Secondary endpoints will consist of CA-125 response, progression-free survival (PFS), overall survival (OS), confirmed response rate, and adverse events. These endpoints will be assessed in each cohort separately. In addition, this study will also assess a couple translational endpoints as well.

16.11 Primary Endpoint:

The primary endpoint of this trial is the proportion of patients alive and progression-free at 12 weeks (PFS12). All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for PFS12. Patients who go off treatment early (prior to 12 weeks) will be considered as failures.

16.12 Sample Size:

The one-stage study design is fully described in Section 16.2. 19 evaluable patients will be accrued to each of the 2 cohorts of this phase II study unless undue toxicity is encountered. We anticipate accruing an additional patient per arm to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, maximum accrual is expected to be 20 patients per cohort (40 patients total). To account for patients that are consented and do not meet full eligibility criteria, we anticipate having to consent and screen 80 patients to achieve the maximum accrual of 40 patients.

16.13 Accrual Time and Study Duration:

The anticipated accrual rate is approximately3-4 patients per month. Therefore, the accrual period for this phase II study is expected to be approximately 12 months. The final analysis can begin approximately 20 months after the trial begins, i.e. as soon as the last patient has been followed for 12 weeks plus time for data entry and clean-up.

16.2 Statistical Design

16.21 Decision Rule: For each cohort separately, the largest PFS12 rate where the proposed treatment regimen would be considered ineffective in this population is 20% (7), and the smallest PFS12 rate that would warrant subsequent studies with the proposed regimen in this patient population is

45%. The following one-stage design uses 19 evaluable patients per arm to test the null hypothesis that the true PFS12 rate in this patient population is at most 20% (7).

16.211 Final Analysis Decision Rule (full 19 eligible patients): Enter 19 evaluable patients in each cohort. If 6 or fewer patients are alive and progression-free at 12 weeks, we will consider this regimen ineffective in this patient population. If 7 or more patients are alive and progression-free, we may recommend further testing of this regimen in subsequent studies in this patient population.

16.212 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients is discussed in Section 16.35.

16.213 Data and Safety Monitoring:

The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The trial is monitored continually by the study team who are notified of every grade 4 and 5 event in real time. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office. Any safety issues requiring protocol changes are communicated through protocol amendments.

Adverse Event Stopping Rule: Based on previous experience with this disease, we expect approximately 30% of patients to experience Grade 4+ adverse events. If at any time, 4 of the initial 10 patients or 40% of all patients (i.e., when accrual is greater than 10 patients), have experienced any Grade 4 or 5 adverse event (at least possibly related to the study treatment), accrual to the study will be suspended to allow for a full review of the data. Each grade 5 event will be reviewed on a case by case basis in a real time fashion to determine whether study accrual should be suspended. After consideration by the study team [ie, Study Chair(s), Statistician, Operations Office, etc] and consultation with representatives at the primary Internal Review Board (IRB) affiliated with the Operations Office, a decision will be made as to whether and how the study will proceed.

16.22 Power and Significance Level: Assuming that the number of PFS12 successes is binomially distributed, the significance level is 7% when the true PFS12 rate is 20% and the power is 83% when the true PFS12 rate is 45%.

16.23 Other Considerations: Toxicity, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan

16.31 Primary Endpoint: The proportion of PFS12 successes will be estimated by the number of successes divided by the total number of evaluable patients. Ninety-five percent confidence intervals for the true success proportion will be calculated according to the exact binomial method.

16.32 Definitions and Analyses of Secondary Endpoints (Note: These endpoints will be analyzed separately for each cohort).

16.321 CA-125 response: The key secondary endpoint of the study will be a CA-125 response, defined as a 50% or greater reduction in baseline CA-125. The null hypothesis will be set at CA-125 response rate of 8.3%, based on the response of single agent letrozole, as reported by Bowman et al (7). The treatment of letrozole and ribociclib will be considered promising, based on CA-125, if the observed CA-125 response rate is 30% or more. This will require at least 6 CA-125 responders in 19 evaluable patients.

16.322 Progression-Free survival (PFS) is defined as the time from registration to the first of either disease progression or death from any cause. Patients who receive the study drug, but then never return for an evaluation will be censored on their last follow-up date. PFS will be estimated using the method of Kaplan-Meier.

16.323 Overall survival (OS) is defined as the time from registration to death from any cause. OS will be estimated using the method of Kaplan-Meier.

16.324 The confirmed response rate will be estimated using RECIST 1.1 criteria. A confirmed tumor response is defined to be either a CR or PR.. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response. Patients who go off study early before having a tumor assessment performed will be considered a failure.

16.33 Adverse Events: All patients that have intitiated treatment will be considered evaluable for adverse event (AE) analyses. The maximum grade for each type of AE will be recorded for each patient, and frequency tables will be reviewed to determine AE patterns. AEs will be analyzed separately by cohort.

16.34 Translational Endpoints for xenograft experiments: Xenograft will be created on each patient with plans for the following future translational

experiments.For patient derived xenograft experiments, response to therapy is based on tumor volumes measured by ultrasound; this measurement exhibits a standard deviation in the range of 10 to 25% of the tumor volume. Taking the high end of the standard deviation, for each model we anticipate 5 animals per group (control or letrozole + ribociclib) will give us approximately 80% power to determine a 50% difference in tumor volume (57% difference for 4 animals), with a 2-sided significance level of 0.05. Thus, 10 animals/model will be adequate for this comparison. To explore whether the responsiveness of tumors to letrozole + ribociclib is not due to either agent alone, additional cohorts of 5 animals treated with letrozole and 5 animals treated with ribociclib, will also be treated for a total of 20 animals/model. However, formal comparisons will only be made between control and combination therapy, and thus no penalties for multiple comparisons will be assessed. The study endpoint is 28 days following treatment initiation. “Response” will be defined as tumors with at least a 50% reduction in tumor volume at study end. “Unresponsive” will be defined as tumors with less than 10% tumor volume reduction at study end. Intermediate values will be defined as “Stable”. Tumor growth curves will be plotted graphically and notated to indicate the outcome status of the originating patients. End of study tumor volumes will be correlated with outcome status of the originating patient as well. In addition, this study will identify molecular biomarkers associated with a response to treatment with letrozole and ribociclib in patients with relapsed ovarian and endometrial carcinomas. Finally, we will determine if response rates to letrozole and ribociclib in PDX avatars correlate to responses noted in the patients. For these additional analyses, the Fisher’s Exact test will be used to measure the associations. All of these translational endpoints are considered exploratory and hypothesis generating due to the small proposed sample size for this study.

16.35 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals as though they were accrued for the final analysis.

16.4 Inclusion of Women and Minorities

16.41 This study will be available to all eligible women, regardless of race or ethnic origin.

16.42 There is no information currently available regarding differential effects of this regimen in subsets defined by race or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.43 Based on prior studies involving similar disease sites, we expect about 20% of patients will be classified as minorities by race and all will be women. Expected sizes (per study design) of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	4	0	4
Not Hispanic or Latino	36	0	36
Ethnic Category: Total of all subjects	40	0	40
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	4	0	4
Black or African American	4	0	4
Native Hawaiian or other Pacific Islander	0	0	0
White	32	0	32
Racial Category: Total of all subjects	40	0	40

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Pathology Considerations/ Correlative Study	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Pre-registration	Registration (prior to start of treatment)	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Immunohistochemistry for pathology review and ER, PR status if archival tissue is not available a new biopsy must be obtained	Archived tissue for eligibility	Paraffin embedded	3 unbaked, unstained slides at 5 microns 15 positively charged slides at 5 microns	X		Yes	N/A.
RB status must be obtained: if archival tissue is not available a new biopsy must be obtained (Section 17.2)	Mandatory	Paraffin embedded	5 slides, 1 H&E, plus 4 unstained slides @ 5 microns	X		No	Ambient using kit from Clarient
Confirmation (will not change eligibility if different from archived) of IHC for ER, PR status for patients with archival tissue (Section 17.3)	Mandatory	Paraffin embedded	1 core biopsy		X	Yes	N/A.
Fresh tumor biopsies for creation of Tumor Avatar (Section 17.4)	Mandatory	Fresh Specimen	5 core specimens		X	Yes	On ice cold McCoy medium transported on ice to [redacted] Lab in Rochester MN

NOTE: Each patient will have one (1) biopsy procedure for this study. If tissue is needed for pre-registration for ER/PR/RB confirmation, then all other biopsy tissue should be obtained at the same time.

17.2 Diagnostic Slides from Original and /or Recurrent Tissue

17.21 Study Coordinator will complete Pre-Registration Tissue Submission and enter in remote data entry system.

17.22 Slides from original and/or recurrent tumor tissue will be sent to Clarient (a NeoGenomics company) for RB evaluation via kits provided by Clarient.
NOTE: If archival tissue is not available, a biopsy will need to be performed to obtain tissue prior to sending to Clarient (see Section 17.3).

17.23 Send 5 slides (1 H&E plus 4 unstained slides @ 5 microns) to:

[redacted]

17.24 Clarient will email real time results to requesting coordinator within 5 working days and copy Study Data Manager and Principal Investigator to facilitate study entry. (If not already done, Study Coordinator must forward email to Data Manager and PI prior to registering patient.)

17.25 Clarient will provide summary data to PI and Statistician at two timepoints.

17.3 Correlative Tissue Collection

Fresh tissue biopsy- Tissue biopsy of disease is required for study participation, outside of contingencies outlined in Section 5.4. Under ultrasound or CT, using an 18 guage needle, if available (or at Radiology discretion), a fresh tissue biopsy will be obtained. Upon scheduling of the procedure, the study coordinator will contact the research lab contact of [redacted] (for Rochester patients) to alert them to be coordinate the expeditious recovery of tumors samples.

The first core received will be placed in standard formalin solution for tumor confirmatory H & E staining and confirmation or determination of ER, PR, RB status.

An additional 5 core samples are requested for research.

- DO NOT PLACE IN FORMALIN
- Core will be collectively placed directly into ice cold McCoy Medium supplied to the radiology suites.

  Upon completion of the procedure, the samples procured in Florida and Arizona will be send by FedEx on ice to the [redacted] laboratory:

[redacted]

- Samples procured in Rochester will be picked up in the Radiology suite by the [redacted] lab contact.
- Upon receipt of samples from both locations, tumor cores will be minced, pooled and directly injected intraperitoneally into SCID mice in the [redacted] Laboratory, per the relevant IACUC protocol maintained by the [redacted] Lab.

17.4 Potential additional translational studies:

[redacted] has approximately 300 Avatar models of ovarian cancer cases that could be tested for RB, P16 and ER, PR, and Cyclin D expression. Ten tumors that stain positive for RB and ER and negative for P16 could be tested for the efficacy of the combination of letrozole and ribociclib as well as 10 tumors that do not stain with those biomarker features. Genomic analysis for the identification of genetic changes associated with response in the Avatar tumors could be pursued. Analysis of the tumors once resistance occurs for identification of genomic changes associated with resistance to ribociclib (LEE011) could be pursued as well.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

18.11 Pre-Registration Material(s)

Case Report Form (CRF)	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Pre-Registration Screening Failure	Complete only if patient is NOT registered after she is pre-registered
Pathology materials	See Section 17.0 (for central review, eligibility, etc. confirmation prior to Registration)

18.12 Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study	≤14 days after registration
Adverse Event - Baseline	
RECIST Measurement - Baseline	
Research Tissue Submission - Baseline (see Section 17.0)	
End of Active Treatment/Cancel Notification	Submit ≤14 days after registration if withdrawal/refusal occurs prior to beginning protocol therapy

18.13 Test Schedule Material(s)

CRF	**Active-Monitoring Phase**	
	At each evaluation during treatment	At end of treatment
Evaluation/Treatment	X	X
Nadir/Adverse Event	X	X

CRF	Active-Monitoring Phase	
	At each evaluation during treatment	At end of treatment
RECIST Measurement	X	X
End of Active Treatment/Cancel Notification		X
ADR/AER	At each occurrence (see Section 10.0)	

18.14 Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q.3 months until PD	At PD	After PD q. 6 mos.	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 2 years after registration, no further follow-up is required.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: ECGs, baseline ECHO and AVATAR studies and research biopsies.

19.3 Study drugs provided: Ribociclib and letrozole

20.0 Key References:

1. Kommoss F, Pfisterer J, Thome M et al. Steroid receptors in ovarian carcinoma: immunohistochemical determination may lead to new aspects. Gynecol Oncol 1992;47:317–22. ExternalResolverBasic Bibliographic Links [Context Link]
2. Rao BR, Slotman BJ. Endocrine factors in common epithelial ovarian cancer. Endocr Rev 1991;12:14–26. ExternalResolverBasic Bibliographic Links [Context Link]
3. Abu-Jawdeh GM, Jacobs TW, Niloff J, Cannistra SA. Estrogen receptor expression is a common feature of ovarian borderline tumors. Gynecol Oncol 1996;60:301–7. [Context Link]
4. Papadimitriou CA, Markaki S, Siapkaras J et al. Hormonal therapy with letrozole for relapsed epithelial ovarian cancer. Long-term results of a phase II study. Oncology 2004;66:112–7. ExternalResolverBasic Bibliographic Links [Context Link]
5. Bowman A, Gabra H, Langdon SP et al. CA125 response is associated with estrogen receptor expression in a phase II trial of letrozole in ovarian cancer: identification of an endocrine-sensitive subgroup. Clin Cancer Res 2002;8:2233–9. ExternalResolverBasic Bibliographic Links [Context Link]
6. Li YF, Hu W, Fu SQ, Li JD, Liu JH, Kavanagh JJ: Aromatase inhibitors in ovarian cancer: Is there a role? International Journal of Gynecological Cancer. 18 (4): 600-614, 2008.
7. Bowman A, Gabra H, Langdon SP et al. CA125 response is associated with estrogen receptor expression in a phase II trial of letrozole in ovarian cancer: identification of an endocrine-sensitive subgroup. Clin Cancer Res 2002;8:2233–9. ExternalResolverBasic Bibliographic Links [Context Link]
8. Kavanagh JJ, Hu W, Fu SQ et al. Anti-tumor activity of letrozole in patients with recurrent advanced low malignant potential or low grade serous ovarian tumors. J Clin Oncol (2007 ASCO Annual Meeting Proceedings, Chicago, IL) 2007;25: No. 185 (Abstract 5582). [Context Link]
9. Lee EJ, Deavers MT, Hughes JI, Lee JH, Kavanagh JJ. Metastasis to sigmoid colon mucosa and submucosa from serous borderline ovarian tumor: response to hormone therapy. Int J Gynecol Cancer 2006;16(Suppl. 1):295–9. [Context Link]
10. S. Mabuchi, D. A. Altomare, M. Cheung, et al., "RAD001 inhibits human ovarian cancer cell proliferation, enhances cisplatin-induced apoptosis, and prolongs survival in an ovarian cancer model," Clinical Cancer Research, vol. 13, no. 14, pp. 4261–4270, 2007.
11. Finn et al: Abstract S1-6, SABCS 2012
12. 17.Novartis, data on file.
13. Rose PG, Brunetto VL, Vanle L, et al. A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2000;78(2):212-216.
14 Ma BB, Oza A, Eisenhauer E, et al. The activity of letrozole in patients with advanced or recurrent endometrial cancer and correlation with biological markers: a study of the National Cancer Institute of Canada Clinical Trials Group. Int J Gynecol Cancer. 2004;14(4):650-658.
15. Bulun SE, Zeitoun K, Sasano H, Simpson ER. Aromatase in aging women. Semin Reprod Endocrinol 1999;17:349—58
16. Sasano H, Harada N. Intratumoral aromatase in human breast, endometrial, and ovarian malignancies. Endocr Rev 1998;19:593—607.
17. Ling Cen, Brett L. Carlson, Mark A. Schroeder, Jamie L. Ostrem, Gaspar J. Kitange, Ann C. Mladek, Stephanie R. Fink, Paul A. Decker, Wenting Wu, Jung-Sik Kim, Todd Waldman, Robert B. Jenkins, and Jann N. Sarkaria : p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells Neuro-Oncology 14(7):870–881, 2012.
18. Dean et al. Cell Cycle 2012;11:2756-2761
19. Infante JR, Shapiro GI, Witteveen PO, Gerecitano JF, Ribrag V, Chugh R, et al. Phase 1 multicenter, open label, dose-escalation study of LEE011, an oral inhibitor of cyclin-dependent kinase 4/6, in patients with advanced solid tumors or lymphomas. Mol Cancer Ther 2013;12: A276.

20. Dong Y, Walsh MD, McGuckin MA, Cummings MC, Gabrielli BG, Wright GR et al. (1997). Int J Cancer 74: 407–415.
21. Semczuk A, Schneider-Stock R, Miturski R, Skomra D, Tomaszewski J, Roessner A et al. (2000). Pathol Res Pract 196: 41–46.
22. G Scambia1, S Lovergine2 and V Masciullo1,2: RB family members as predictive and prognostic factors in human cancer. Oncogene (2006) 25, 5302–5308. doi:10.1038/sj.onc.1209620
23. Reid-Nicholson M, Iyengar P, Hummer AJ et al: Immunophenotypic diversity of endometrial adenocarcinomas: implications for differential diagnosis. Modern Pathology (2006) 19, 1091–1100. doi:10.1038/modpathol.3800620;
24. Niemann TH1, Yilmaz AG, McGaughy VR, Vaccarello L.: Retinoblastoma protein expression in endometrial hyperplasia and carcinoma.. Gynecol Oncol. 1997 May;65(2):232-6.
25. Koh VM1, Shi YX, Tang QH.: P16 and retinoblastoma protein expression in endometrial carcinoma and clinical significance. Eur J Gynaecol Oncol. 2011;32(3):309-15.
26. Lindemann K, Malander S, Christensen RD et al: Examestane in advanced or recurrent endometrial carcinoma: a prospective phase II study by the Nordic Society of Gynecologic Oncology (NSGO). BMC Cancer. 2014 Feb 5;14:68. doi: 10.1186/1471-2407-14-68.
27. Slomovitz BM, Jiang Y, Yates MS et al: Phase 2 study of everolimus and letrozole in patients with recurrent endometrial cancer.

Appendix I ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat html

Appendix II MEDICATION DIARY

Name _____ Study No.MC1561
Patient No. _____

Patient Instructions

- Please indicate on the calendar below *every* day that you take your study medication by placing the dose taken on the line under the date.
- If you miss a dose, place a check "**0**" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- Bring ***all*** bottles and any unused study medication along with this diary when you return for your next appointment.
- Ribociclib should be taken at the same time every day, either with or without food. The capusles or tablets should be swallowed whole with a glass of water. The capsules or tablets should not be chewed or crushed. If the pills are thrown up, this should be noted on your diary but you should not take another pill until your next scheduled dose.
- You should avoid eating foods high in fat, avoid drinking grapefruit juice, and avoid eating Seville (sour) oranges and grapefruit while on this study.

Study Drug	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date							
Ribociclib							
Letrozole							

Study Drug	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date							
Ribociclib							
Letrozole							

Study Drug	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date							
Ribociclib							
Letrozole							

Study Drug	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Date							
Ribociclib							
Letrozole							

Date:_____ Participant Signature_____

Area Below To Be Completed only by Coordinator

Number of pills returned Study Coordinator Initials

Date_____ Discrepancy Yes____ No_____

Appendix III CONCOMITANT MEDICATIONS

List of prohibited medications during study drug treatment

Category	Drug Name	
Strong CYP3A4/5 inhibitors	Atazanavir/ritonavir Boceprevir (Victrelis) Clarithromycin (Biaxin) Cobicistat (Tybost) Conivaptan (Vaprisonl) Danoprevir/ritonavir Eltegravir/ritonavir Grapefruit juice Indinavir/ritonavir Itraconazole (Sporanox, Onmel) Ketoconazole (Nizoral, Xolegel, Extina) Lopinavir/ritonavir Mibefradil (Posicor)	Nefazodone (Serzone) Nelfinavir (Viracept) Ombitasvir/paritaprevir/dasabuvir/ritonavir (VIEKIRA PAK) Posaconazole (Noxafil) Ritonavir (Norvir) Saquinavir (Invirase) Saquinavir/ritonavir Telaprevir (Incivek) Telithromycin (Ketek) Tipranavir/ritonavir Troleandomycin (Triocetin, Tekmisin) Voriconazole (Vfend)
Strong CYP3A4/5 inducers	Carbamazepine (Tegretol, Carbatrol, Equetro, Epitol) Lumacaftor Mitotane (Lysodren) Phenobarbital (Luminol) Phenytoin (Dilantin, Dilantin-125, Phenytek, Cerebyx)	Rifabutin (Mycobutin) Rifampin (or rifampicin; Rifadin)[3] St. John's wort (hypericum perforatum)[3]
CYP3A4/5 substrates with NTI[1]	Alfentanil (Alfenta) Astemizole (Hismanal) Cisapride (Prepulsid, Propulsid) Cyclosporine (Neoral, Sandimmune, Restasis, Gengraf) Diergotamine Dihydroergotamine (DHE 45, Migranal) Ergotamine (Ergomar) Fentanyl (Duragesic, Abstral, Subsys, Ionsys, Sublimaze)	Pimozide (Orap) Quinidine (Quinaglute, Quinidex) Sirolimus (Rapamune) Tacrolimus (Protopic, Prograf, Hecoria)
Medications with a known risk for QT prolongation[4]	Amiodarone (Cordarone, Nexterone, Pacerone) Anagrelide (Agrylin) Arsenic trioxide Astemizole (Hismanal) Azithromycin (Zithromax, AzaSite, Zmax)	Ibutilide (Corvert) Levofloxacin (Levaquin, Quixin, Iquix) Levomethadyl (OrLAAM, LAAM) Ibutilide, Levofloxacin, Levomepromazine, Levosulpiride

Category	Drug Name
	Chlorpromazine (Thorazine, Largactil) Cilostazol (Pletal) Ciprofloxacin (Cipro, Cetraxal, Ciloxan, Proquin) Cisapride (Prepulsid, Propulsid) Citalopram (Celexa) Clarithromycin (Biaxin) Disopyramide (Norpace) Dofetilide (Tikosyn) Domperidone (Motilium) Donepezil (Aricept) Dronedarone (Multaq) Droperidol (Inapsine) Erythromycin (Ilotycin, Staticin, Ery-tab, Ery-Ped, Pce, Erythra-Derm, T-Stat, Ery, E.e.s., Erygel, Eryped, Eryc, Akne-mycin) Escitalopram (Lexapro) Flecainide (Tambocor) Fluconazole (Diflucan) Halofantrine (Halfan) Haloperidol (Haldol) Methadone (Diskets, Methadose, Dolophine) Moxifloxacin (Avelox, Vigamox, Moxeza) Ondansetron (Zofran, Zuplenz) Papaverine HCl (intra-coronary) Pentamidine (NebuPent, Pentam) Pimozide (Orap) Procainamide (Pronestyl, Procan-SR, Procanbid) Propofol (Diprivan) Quinidine (Quinaglute, Quinidex) Sevoflurane (Ultane, Sojourn) Sotalol (Betapace, Sotylize, Sorine) Sparfloxacin (Spacin, Zagam, Zagam Respipac) Sulpiride (Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Prometar, Sulpor)Sultopride, Terlipressin, Terodiline Thioridazine (Mellaril, Melleril) Vandetanib (Caprelsa)
Herbal preparations/ medications	Herbal preparations/medications are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort Kava Ephedra (ma huang) Gingko biloba Dehydroepiandrosterone (DHEA) Yohimbe Saw palmetto Ginseng Patients should stop using these herbal medications 7 days prior to first dose of study drug.
Other investigational and antineoplastic therapies	Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued study drug.

Category	Drug Name
[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes) or drugs which have<2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood. [2] Herbal product [3] P-gp inducer [4] The list provided is as of January 2018.Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list. 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 permitted medications requiring caution during study drug treatment

Category	Drug Name	
Moderate CYP3A4/5 inhibitors	Aprepitant	Imatinib
	Amprenavir (Agenerase)	Isavuconazole
	Asafetida resin (Ferula asafetida)	Netupitant (Akynzeo)
	Cimetidine (Tagamet)	Nilotinib
	Crizotinib	Schisandra sphenanthera (na wu wei zi)
	Darunavir (Prezista)	Tofisopam (Emandaxin, Grandaxin, Sériel)
	Diltiazem (Cardizem, Dilt-cd, Dilacor, Tiazac)	Verapamil (Covera-HS, Calan, Verelan, Isoptin)
	Faldaprevir	
Moderate CYP3A4/5 inducers	Bosentan (Tracleer)	Lopinavir[5]
	Dabrafenib	Modafinil (Provigil)
	Efavirenz (Sustiva, Atripla)	Nafcillin
	Etravirine (Intelence)	Telotristat
	Genistein	

Category	Drug Name	
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine (Almirid, Cripar) Aprepitant Atorvastatin (Lipitor) Avanafil (Stendra, Spedra) Bosutinib (Bosulif) Brotizolam (Lendormin) Budesonide (Entocort, Pulmicort, Ucens) Buspirone (Buspar) Cobimetinib Darifenacin (Enablex) Dasatininb, Ebastine (Evastin, Kestine, Ebastel, Aleva, Ebatrol) Eletriptan (Relpax) Eplerenone (Inspra) Felodipine (Plendil) Fluticasone (Cutivate) Grazoprevir Ibrutinib Isavuconazole Ivabradine Ivacaftor (Kalydeco) Levomethadyl (LAAM) Lomitapide (Juxtapid) Lovastatin	Lumefantrine (or benflumetol; Coartem) Lurasidone (Latuda) Maraviroc (Selzentry, Celsentri) Midazolam Midostaurin Naloxegol Neratinib Nisoldipine Perospirone (Lullan) Quetiapine (Seroquel) Ridaforolimus (Deforolimus) Sildenafil (Viagra, Revatio) Simeprevir Simavastatin Ticagrelor (Brilinta) Tilidine (Tilidin, Valoron, Valtran) Tolvaptan (Samsca) Triazolam (Halcion) Ulipristal Vardenafil (Levitra, Staxyn) Venetoclax Vicriviroc Voclosporin (Luveniq)

Category	Drug Name	
Strong BSEP inhibitors	Alectinib Atorvastatin Bromocriptine Candesartan Clobetasol Clofaziminie Dabigatran Dipyridamole Glyburide Grazoprevir Ledipasvir Mifepristone Pioglitazone Reserpine Rifamycin Simeprevir	Telmisartan Timcodar Troglitazone (TGZ-sulfate, Rezulin, Resulin, Romozin, Noscal) Valinomycin Velpatasvir
Medications that carry a possible risk for QT prolongation[2]	Alfuzosin (Uroxatral) Apomorphine (Apokyn) Aripiprazole (Abilify) Artenimol+piperaquine Asenapine Atomoxetine (Strattera) Bedaquiline (Sirturo) Bendamustine Bortezomib Bosutinib Buprenorphine Cabozantinib Capecitabine Ceritinib Clomipramine Clozapine (Clozaril, FazaClo) Crizotinib Cyamemazine (cyamepromazine) Dabrafenib Dasatinib Degarilix Delamanid Desipramine Dexmedetomidine (Precedex) Dolasetron (Anzemet)	Ketanserin Lapatinib Lenvatinib Leuprolide Lithium Melperone Midostaurin Mifepristone Mirabegron Mirtazapine Moexipril/HCTZ Necitumumab Nicardipine Nilotinib Norfloxacin Nortriptyline Nusinersen Ofloxacin (Floxin, Ocuflox) Osimertinib Oxytocin (Pitocin, Syntocinon) Paliperidone (Invega) Palonosetron Prothipendyl Rilpivirine (Edurant) Risperidone (Risperdal)

Category	Drug Name	
	Efavirenz	Romidepsin
	Eliglustat	Sertindole (Serdolect, Serlect)
	Epirubicin	Sorafenib
	Eribulin mesylate (Halaven)	Sunitinib
	Ezogabine (retigabine)	Tamoxifen
	Famotidine (Pepcid, Fluxid, Select)	Tipiracil/Trifluridine
	Felbamate (Felbatol)	Tizanidine (Zanaflex)
	Fingolimod (Gilenya)	Tolterodine (Detrol)
	Flupentixol	Toremifene
	Gemifloxacin (Factive)	Trimipramine
	Granisetron (Sancuso, Granisol)	Tropisetron
	Hydrocodone-ER	Vardenafil (Levitra, Staxyn)
	Iloperidone (Fanapt)	Vemurafenib
	Imipramine (melipramine)	Venlafaxine
	Isradipine (Dynacirc)	Vorinostat
	Lithium (Lithobid, Lithane)	Ziprasidone (Geodon)
	Mirabegron (Myrbetriq, Betmiga)	
	Mirtazapine (Remeron)	
	Moexipril (Univasc)	
	Norfloxacin (Noroxin)	
	Panabinostat	
	Pasireotide (Signifor)	
	Pazopanib	
	Perflutren lipid microspheres	
	Perphenazine	
	Pilsicainide	
	Pimavanserin	
	Pipamperone (Dipiperon, Dipiperal, Piperonil, Piperonyl, Propitan)	
	Promethazine (Phenergan, Phenadoz, Promethegan)	
MATE1/2 substrates[3]	Acyclovir	
	Cephalexin	
	Cimetidine	
	Fexofenadine	
	Ganciclovir	
	Glycopyrronium	
	Metformin	
	Pindolol	
	Plisicainide	
	Ranitidine	
	Topotecan	
	Varenicline	

Category	Drug Name	
MATE1 and OCT1/2 substrates[3]	Amantadine (Symmetrel) 6-Beta-hydroxycortisol Carboplatin Cisplatin Cephalexin (Keflex) Cephradine (Cefradine) Lamivudine Linagliptin	Memantine (Namenda) Metformin Oxyplatin Oxybutynin Phenformin Picoplatin Pilsicainide Pindolol (Visken) Ranitidine (Zantac, Select) Sorafenib Tropisetron Trospium Umeclidinium Zidovudine
BCRP substrates	Danunorubicin Dolutegravir Doxorubicin Hematoporphyrin Imatinib Methotrexate Mitoxanthrone Pitavastatin Rosuvastatin (Crestor) Sulfasalazine (Azulfidine) Irinotecan Ethinyl Estradiol Simvastatin Sulfasalazine Sofosbuvir Tenofovir Topotecan Venetoclax	

Category	Drug Name
[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. 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.	