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PROTOCOL GOG-3026

STUDY TITLE: A Phase II Trial of Ribociclib (LEE011) plus Letrozole in Women with Recurrent Low-Grade Serous Carcinoma of the Ovary, Fallopian Tube or Peritoneum

PROTOCOL VERSION #	4.0
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Table of Contents

ABBREVIATIONS & DEFINITIONS

Term	Abbreviation	Definition
Dose-Limiting Toxicity	DLT	Describes side effects of a drug or other treatment that are serious enough to prevent an increase in dose or level of that treatment. (DLTs are defined before beginning the trial and are protocol-specific.)
Maximum Tolerated Dose	MTD	The highest dose of a drug or treatment that does not cause unacceptable side effects. The MTD is determined in clinical trials by testing increasing doses on different groups of people until the highest dose with acceptable side effects is found.
Overall Survival	OS	The length of time from either the date of diagnosis or the start of treatment for a disease, that patients diagnosed with the disease are still alive.
Progression-Free Survival	PFS	The length of time during and after the treatment of a disease that a patient lives with the disease but it does not get worse.
Time to Progression	TTP	The length of time from the date of diagnosis or the start of treatment for a disease until the disease starts to get worse or spread to other parts of the body.
Clinical Benefit Rate	CBR	Summation of response rate and stable disease rate

Reference: National Cancer Institute (NCI) Dictionary of Cancer Terms
http://www.cancer.gov/dictionary

PROTOCOL SYNOPSIS

Protocol Title	**A Phase II Trial of Letrozole + Ribociclib in Women with Recurrent Low-Grade Serous Carcinoma of the Ovary, Fallopian Tube or Peritoneum**
Targeted Patient Population	Histologically confirmed diagnosis of low-grade serous carcinoma of ovary, fallopian tube or peritoneum. Patients may have been treated with unlimited prior therapies excluding aromatase inhibitors. Patients must have measurable disease.
Study Design	This is an open-label, multi-institution activity phase II trial. Eligible subjects with recurrent low-grade serous carcinoma who sign informed consent will receive the combination of letrozole and Ribociclib until disease progression or until they experience significant adverse events. <u>Safety Lead-in</u> A review of safety will occur after the first 6-10 patients are treated and complete one cycle (including starting cycle 2 within the DLT constraints outlined in Section 4.6) or have a DLT prior to completing the first cycle. Within the safety lead-in, patients who do not have a DLT and who do not complete cycle 1 will be replaced.
Treatment Schema	Letrozole will be administered at a dose of 2.5 mg by mouth daily. Ribociclib will be administered at a dose of 600 mg by mouth daily for 21 days followed by 7 days off treatment. Treatment will be until progression or toxicity.
Objectives	**Primary Objective:** To determine the response rate of patients receiving the combination of letrozole + Ribociclib. **Secondary Objective(s):** To determine the clinical benefit (CR, PR, and SD) rate of patients receiving the combination of letrozole + Ribociclib. To determine the nature, frequency, and maximum degree of toxicity associated with this combination using CTCAE v5.0.

	To determine the progression-free survival of women receiving the combination of letrozole + Ribociclib. To determine the overall survival of women receiving the combination of letrozole + Ribociclib. **Exploratory Objective(s):** 1. To determine the expression of estrogen receptor (ER), progesterone receptor (PR), and proliferative index (ki-67) and their correlation with response and clinical benefit. 2. To determine genomic signatures associated with response and clinical benefit of the combination of letrozole + Ribociclib.
Expected Number of Patients	19-51
Expected Number of Centers	25
Expected Duration of the Protocol	22 months
Inclusion Criteria	Patients eligible for inclusion in this study must meet all of the following criteria: 1. Patient has signed the Informed Consent (ICF) prior to any screening procedures being performed and is able to comply with protocol requirements. 2. Age $\geq$ 18 years at time of study entry. 3. Willingness and ability to comply with study and follow-up procedures. 4. Histological confirmation of diagnosis of low-grade serous carcinoma of ovary, fallopian tube or peritoneum; Original diagnosis of de novo low-grade serous carcinoma or Original diagnosis of serous borderline tumor with subsequent diagnosis of low-grade serous carcinoma. • In order to prevent inclusion of patients with high-grade serous carcinoma, diagnosis of low-grade serous carcinoma will be verified as part of screening review by a gynecologic pathologist. Tissue for confirmation can be from primary tumor or recurrence.

	5. Patient must have recurrent, measurable disease by RECIST v1.1. 6. There are no restrictions on number of prior therapies. 7. Patient cannot have previously received a prior cyclin dependent kinase inhibitor (CDKi). **Patients who were treated with letrozole or another aromatase inhibitor for other indications must have not taken the drug for 6 months prior to initiating letrozole for this trial and may not have progressed on treatment**. 8. Patients must not have remaining ovarian function to be included. In women who have at least one retained ovary, menopause must be confirmed with laboratory confirmation. Women who have ovarian function are eligible but must be placed on hormonal suppression. Menopause must be confirmed with laboratory confirmation, to include an estradiol level as this is assessed within 8 weeks of patient having been on tamoxifen. 9. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2 10. Resolution of all acute toxic effects of prior therapy or surgical procedures to National Cancer Institute (NCI) CTCAE Grade ≤ 1. Patients with grade 1 taxane-induced neuropathy, any grade alopecia, amenorrhea, or other toxicities not considered a safety risk for the patient as per investigator's discretion are eligible. 11. Patient has adequate bone marrow and organ function as defined by the following laboratory values at screening: • Absolute neutrophil count ≥1.5 × 10^9/L • Platelets ≥100 × 10^9/L • Hemoglobin ≥9.0 g/dL • Potassium, total calcium (corrected for serum albumin), magnesium, sodium and phosphorus within normal limits for the institution or corrected to within normal limits with supplements before first dose of study medication

	• INR ≤1.5 (unless patient is receiving permitted anticoagulants and the INR is within the therapeutic range of intended use for that anticoagulant within 7 days prior to the first dose of study drug). Serum creatinine <1.5 mg/dL or creatinine clearance ≥50 mL/min • In the absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5 x ULN. If the patient has liver metastases, ALT and AST <5 x ULN • Total bilirubin < ULN; or total bilirubin ≤3.0 x ULN or direct bilirubin ≤1.5 x ULN in patients with well-documented Gilbert's Syndrome. 12. Patient with available standard 12-lead ECG with the following parameters at screening: • QTcF interval at screening <450msec (using Fridericia's correction) • Resting heart rate 50-90bpm 13. Must be able to swallow ribociclib and letrozole capsules/tablets. 14. Patients receiving tamoxifen or toremifene must have washout period of 5 half-lives prior to randomization.
Exclusion Criteria	Patients eligible for this study must not meet any of the following criteria: 1. Patient has a known hypersensitivity to any of the excipients of ribociclib or letrozole. 2. Patient has a concurrent malignancy or malignancy within 3 years prior to starting study drug, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer. Patients with known brain metastases are excluded. 3. Patients with central nervous system (CNS) involvement unless they meet ALL of the following criteria:

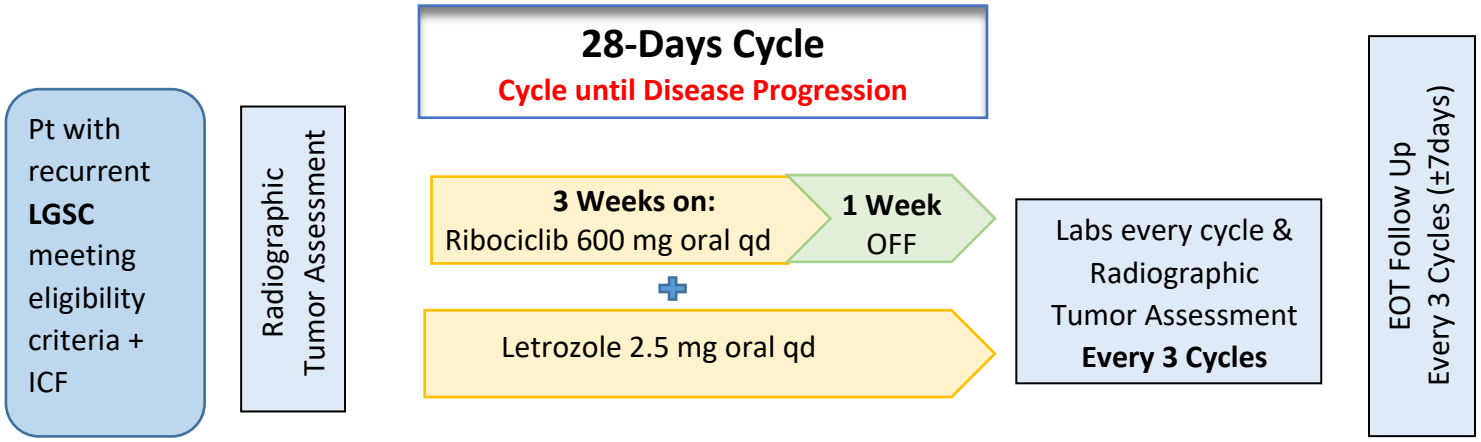
	• At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment • Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases. 4. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). 5. Patient has a known history of HIV infection (testing not mandatory). 6. 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.). 7. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormalities, 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) • 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 idiopathic sudden death or congenital long QT syndrome, or any of the following: o Risk factors for Torsades de Pointe (TdP) including uncorrected hypocalcemia, hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia. o 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 o Inability to determine the QT interval on screening (QTcF, using Fridericia's correction) o Systolic blood pressure (SBP) >160 mmHg or <90 mmHg at screening 8. Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to starting study drug (see Table 1 for details): • Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges • That have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5 • Herbal preparations/medications, dietary supplements. 9. Participation in other studies involving investigational drug(s) within 30 days prior to randomization or within 5 half-lives of the investigational product (whichever is longer) or participation in any other type of medical research judged not to be scientifically or medically compatible with this study. If the patient is enrolled or planned to be enrolled in another study

	that does not involve an investigational drug, the agreement of Novartis study medical lead is required to establish eligibility. 10. Patient is currently receiving warfarin or other coumadin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH) or fondaparinux is allowed. Direct-Acting Oral Anticoagulants (DOACS) are permitted. 11. Patient is currently receiving or has received systemic corticosteroids ≤2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment. The following uses of corticosteroids are permitted: a short duration (<5 days) of systemic corticosteroids; any duration of topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular) 12. Patient who has received radiotherapy ≤4 weeks or limited field radiation for palliation ≤2 weeks prior to starting study drug, and who has not recovered to grade 1 or better from related side effects of such therapy (exceptions include alopecia) and/or in whom ≥25% of the bone marrow (Ellis, 1961) was irradiated. 13. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects (tumor biopsy is not considered as major surgery). 14. Patient with a Child-Pugh score B or C. 15. Patients who are pregnant or breastfeeding. 16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception throughout the study and for 3 weeks after study drug discontinuation. Highly effective contraception methods include: • Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and

	withdrawal are not acceptable methods of contraception • Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment . Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. 17. Current use of food or drugs known to be potent CYP3A4 inhibitors, drugs known to be potent CYP3A4 inducers, and drugs that are known to prolong the QT interval unless the prohibited concomitant medication can be replaced by other drugs of less potential to inhibit or induce CYP3A4 or prolong QT interval (See Appendix C for Prohibited Concomitant Medications). 18. Patients whose tumors contain both low-grade serous carcinoma (LGSC) and high-grade serous carcinoma (HGSC) 19. Patients with history of haemopoietic stem cell or bone marrow transplant.

PROTOCOL SCHEMA



1.0 BACKGROUND

1.1 Low-Grade Serous (LGSC) Carcinoma of the Ovary/Peritoneum

Serous carcinoma represents the most common histologic subtype of epithelial ovarian cancer. After almost 20 years of analysis and refinement, investigators proposed a binary grading system for serous carcinoma to replace the FIGO 3-tier grading system and subsequently found it to be highly reproducible with excellent interobserver and intraobserver agreement (1-3). Since 2004, this grading system has been widely accepted and integrated into the 2014 World Health Organization classification of ovarian cancer. Concomitantly, several studies indicated that ovarian serous tumors of low malignant potential and low-grade serous carcinoma (LGSC) exist on a continuum and have molecular signatures and clinical behaviors distinct from high-grade serous carcinoma (4-12). Thus, LGSC may occur de novo or following a diagnosis of serous tumor of low malignant potential.

Our multidisciplinary team has been at the forefront of clinical and translational research of LGSC in elucidating its molecular biology and genetics (13-20) and in describing its clinical behavior (21-28). Compared with high-grade serous carcinoma, LGSC is associated with younger age at diagnosis, relative chemoresistance, and prolonged overall survival (median OS = 101.7 months) (22, 23, 25-27). However, despite its relatively good prognosis, over 70% of women with stage II-IV disease will develop recurrent disease. This observation combined with LGSC's relative chemoresistance underscores the critical need for identifying novel therapies.

Over the past few years, our investigators have led efforts to identify novel therapies, including hormonal therapy (see below), MEK inhibitors, and anti-angiogenesis therapy (13, 29-31). In addition, there is a NRG Oncology international phase II/III trial, "A randomized phase II/III study to assess the efficacy of trametinib (GSK1120212) in patients with recurrent or progressive low-grade serous ovarian cancer or peritoneal cancer," which has thus far accrued 200 patients over 37 months.

1.2 The similarity of LGSC to ER+ Breast Cancer

Low-grade serous carcinoma shares several characteristics with luminal breast cancer: 1) extremely high frequency of ER expression (> 80%), 2) significant clinical benefit from hormonal therapies in the maintenance and recurrent settings (clinical benefit > 70%; median PFS = 7.4 months), and 3) significantly worse outcome in women < 35 years old (19, 27, 30-32).

In breast cancer, ribociclib has been shown to have anti-tumor activity in HR-positive pre-clinical tumor xenograft models. In addition, ribociclib combined with letrozole has synergistic effects with sustained tumor control in PIK3CA-wildtype, ER-positive breast cancer models.

1.3 Rationale for Studying the Combination of Ribociclib + Letrozole

Gershenson et al. reported 64 women with recurrent low-grade serous carcinoma who received 89 separate hormonal therapy regimens. The objective response rate was 9%, and an additional 62% had stable disease. Of the 50 patients in the study for whom tissue was available for immunostaining, all had positive ER expression. In the most recent study using hormonal therapy for low-grade serous carcinoma, Gershenson et al. reported on 203 women with stage II-IV low-grade serous carcinoma who underwent primary cytoreductive surgery followed by platinum-based chemotherapy (30). The 70 women who received hormonal maintenance therapy had a significantly improved PFS compared to the 133 women who underwent observation (median PFS, 64.9 vs. 26.4 mos; P < .001). Based on information indicating relative chemoresistance and response to hormonal therapies in women with low-grade serous carcinoma, physicians are increasingly replacing conventional chemotherapy with hormonal therapy in the first-line, maintenance, and recurrent settings.

Ribociclib is an orally active potent and highly selective reversible inhibitor of CDK4 and CDK6. The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase.

1.4 Pre-Clinical Data

The effect of ribociclib on pRb phosphorylation, BrdU uptake and cell cycle progression was assessed in more than 40 cell lines derived from hematological malignancies, esophageal cancer, liposarcoma, colon cancer, melanoma, non-small cell lung cancer, pancreatic cancer, and breast cancers. In 13 pRb-positive breast cancer cell lines, ribociclib inhibited pRb phosphorylation with an average IC_{50} value of 0.413 µM (range: 0.06 to 1.20 µM). Similarly, ribociclib interfered with G1 to S phase cell cycle progression in these cells as determined by either BrdU uptake or FACS analysis with an average IC_{50} value of 0.43 µM (range: 0.07 to 0.89 µM). In contrast, in lineage-matched pRb-negative cell lines no effect of ribociclib on either pRb phosphorylation or cell cycle progression was observed [RD-2009-50759]. Thus, ribociclib is able to impact cell cycle progression in cell lines derived from a variety of tumor types that harbor a diversity of genetic alterations in a manner dependent on intact pRb.

Ribociclib was further tested in a panel of 47 breast cancer cell lines with known ER status. ER+ breast cancer cell lines were most sensitive to ribociclib, with 16 of the 18 cell lines showing IC50s < 1 µM, while the majority (21 out of 29) of the ER-negative cell lines had IC50s > 1 µM. These data suggest that the majority of ER+ breast cancer cells are dependent on CDK-4/6 signaling for proliferation (O'Brien et al 2014)[RD-2016-00052].

1.5 Phase I/II Data of Ribociclib in Combination with Letrozole in Advanced Breast Cancer

Study CLEE011X2107 is a phase Ib, multicenter study of the combination of ribociclib and/or alpelisib with letrozole in adult patients with advanced HR+ breast cancer. The primary

endpoints of the study are to estimate the MTD(s) and/or RP2D(s) for the 3 combinations: ribociclib + letrozole, alpelisib + letrozole, ribociclib + alpelisib + letrozole. The dose escalation part for ribociclib + letrozole; alpelisib + letrozole and ribociclib + alpelisib+ letrozole combination has been completed and patients were also enrolled on dose expansion for these doublet and triplet combinations.

1.6 Doublet ribociclib + letrozole

Forty-seven patients have been enrolled **(cut-off date: 02-May-2017)** to receive ribociclib (600 mg) + letrozole (2.5 mg). The median age of patients was 60 (range: 38–76) years, all the patients were female, and the distribution of ECOG performance status of 0/1 at baseline was 28/19 patients, respectively. Thirty-seven patients were discontinued from the study (29 due to progressive disease, 5 due to physician decision, 2 due to adverse events, and 1 due to subject decision) and 10 patients were still ongoing.

Two patients experienced as DLT a grade 4 neutropenia. The RDE for ribociclib + letrozole is ribociclib 600 mg 3 weeks on/1 week off schedule and letrozole 2.5 mg.

All patients experienced at least one AE. The most frequent AEs (≥10%), regardless of grade, causality, were: neutropenia (74.5%); nausea (51.1%); diarrhea (40.4%); fatigue (38.3%); arthralgia (31.9%); alopecia (29.8%); anemia (27.7%); back pain, constipation, cough, vomiting (25.5% for each); asthenia, hot flush, rash (23.4% for each); alanine aminotransferase increased, aspartate aminotransferase increased, headache, urinary tract infection (21.3% for each); decreased appetite, dry skin (19.1% for each); neutrophil count decreased, pain in extremity, pruritus, stomatitis, white blood cell count decreased (17.0% for each); abdominal pain, dry eye, oropharyngeal pain (12.8% for each); abdominal pain upper, anxiety, hyperglycemia, insomnia, leukopenia, musculoskeletal pain, myalgia, neck pain, pyrexia, and upper respiratory tract infection (10.6% for each).

1.7 Key efficacy results for the combination of ribociclib + letrozole:

As of 02 May 2017, the best overall response as per local investigator/radiology reports among 47 patients treated with ribociclib + letrozole was complete response (CR) in two patients (4.3%) and partial response (PR) in 12 patients (25.5%). The overall response rate (ORR) was 29.8%; the clinical benefit rate (CBR) was 59.6%. Seven patients (14.9%) had progressive disease (PD).

1.8 Randomized Phase II and Phase III Data of Ribociclib in Combination with Letrozole in Advanced Breast Cancer

Study CLEE011A2301 is a phase III, multicenter study of the combination of ribociclib or placebo with letrozole in postmenopausal women with HR+, HER2-negative advanced (metastatic or loco regionally recurrent) breast cancer who have not received prior therapy for advanced disease. The study met its primary objective at the pre-planned interim analysis;

ribociclib in combination with letrozole demonstrated statistically significant benefit over placebo in combination with letrozole in prolonging PFS based on investigators assessments.

In total, 668 patients were randomized; 334 patients each to the ribociclib plus letrozole arm and the placebo plus letrozole arm. Median duration of follow up at the second overall survival interim analysis (data cut-off 02-Jan-2017) was 26.4 months.

As of 04-Jan-2017 data cut-off date, 219 (32.8%) patients overall remained on treatment and the proportion of patients continuing to receive treatment in the ribociclib plus letrozole arm was higher than in placebo plus letrozole arm (39.2% vs. 26.3%, respectively). Disease progression was the primary reason for treatment discontinuation and was more frequent in the placebo plus letrozole arm compared to the ribociclib plus letrozole arm (60.8% vs. 39.8%). Adverse events led to the discontinuation of study treatment in 35 patients (5.2%): 27 patients (8.1%) in ribociclib plus letrozole arm and 8 patients (2.4%) in placebo plus letrozole arm.

As of 04-Jan-2017 cut off date, the majority of patients experienced at least one AE in both treatment groups (99.1% vs. 97.6%); the most commonly (≥ 30%) reported AEs in ribociclib plus letrozole group, irrespective of causality were: neutropenia (64.1%), nausea (53.3%), fatigue (41.3%), diarrhea (38.3%), alopecia (34.4%), vomiting (33.5%), and arthralgia (33.2%). AEs where a higher proportion of ribociclib plus letrozole-treated patients reported events (and where there was a ≥ 10% difference to the placebo plus letrozole group) included: neutropenia (+59.3%), nausea (+22.7%), decreased neutrophil count (+20.4%), alopecia (+18.3%), decreased white blood cell count (+16.8%), vomiting (+16.8%), anemia (+14.9%), diarrhea (+13.8%), leukopenia (+12.9%), increased ALT (+12.9%), increased AST (+11.7%), and rash (+10.7%). The incidence of SAEs was 25.4% and 15.5% in the ribociclib plus letrozole and placebo plus letrozole arms, respectively. Twenty-eight patients (8.4%) from the ribociclib plus letrozole group experienced SAEs that were considered by the Investigator to be related to study treatment. The most frequently reported SAE in the ribociclib plus letrozole arm, irrespective of causality, was pneumonia in 6 patients (1.8%). Febrile neutropenia was reported as suspected in 3 patients (0.9%).

Permanent discontinuations due to AEs were reported in 16.8% of patients receiving ribociclib plus letrozole and 3.9% in patients receiving placebo plus letrozole. The most common AEs leading to treatment discontinuation of ribociclib in patients receiving ribociclib plus letrozole were ALT increased (4.5%), AST increased (2.7%), vomiting (2.4%) based on data cut off of 4 Jan 2017.

AEs led to study drug interruptions in 251 patients (75.1%) in ribociclib + letrozole arm and 57 patients (17.3%) in placebo + letrozole arm. Neutropenia was the reason for ribociclib interruption in 140 patients (41.9%), vomiting in 22 (6.6%), nausea in 18 (5.4%), and diarrhea in 16 (4.8%) patients. Dose reductions due to AEs occurred in 160 (47.9%) patients in ribociclib

arm, most often due to neutropenia (83 patients, 24.9%), and in 10 patients (3.0%) in placebo arm.

In general, the overall incidence of AEs was similar to that seen at the first interim analysis, with no new or unexpected toxicities observed. All events were reversible and managed with dose interruption/reduction.

There were 10 on treatment deaths (7 [2.1%] in the ribociclib group and 3 (0.9%) in the placebo group). Two patients in the ribociclib group died from the progression of underlying breast cancer; the remaining 5 deaths in the ribociclib group were due to acute respiratory failure (2 patients), pneumonia, sudden death and death from an unknown cause. The case of sudden death was considered to be related to ribociclib and occurred on day 11 in cycle 2 in association with grade 3 hypokalemia (treated with oral potassium supplements) and a grade 2 prolongation in the QT interval on day 1 of cycle 2. The patient who died from an unknown cause received ribociclib for 4 days before withdrawing consent and discontinuing the study treatment; her death was reported 19 days later and was not considered to be related to ribociclib by the investigator. In the placebo arm, two (2) deaths were attributed to breast cancer and one was due to a subdural hematoma.

1.9 Key efficacy results:

Study A2301 met its primary objective at the primary analysis (29 Jan 2016 data cut off), with compelling evidence of clinical benefit in patients with HR+, HER2-negative advanced breast cancer. A 44.4% estimated risk reduction in ribociclib plus letrozole treated patients was evident in the primary PFS endpoint as per investigator assessment (HR=0.556, 95% CI: 0.429, 0.720; one sided p-value =3.29×10-6). Results were consistent across the subgroups of age, race, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, bone only metastasis disease. Updated PFS analyses (02 Jan 2017 data cut off) demonstrated continued treatment benefit for patients receiving ribociclib + letrozole vs placebo + letrozole (hazard ratio=0.568; 95% CI: 0.457–0.704; p=9.63×10–8; Figure 5-2). Median PFS was prolonged by 9.3 months, from 16.0 months (95% CI: 13.4–18.2) in the placebo + letrozole arm to 25.3 months (95% CI: 23.0–30.3) in the ribociclib + letrozole arm. The 24-month PFS rates were 54.7% in ribociclib plus letrozole arm vs 35.9% in the placebo plus letrozole arm. As of 02-Jan-2017 cut off, overall survival data remain immature, with 15.0% vs 19.8% of patient deaths in the ribociclib plus letrozole vs placebo plus letrozole arm (hazard ratio=0.746; 95% CI: 0.517–1.078; p=0.059).

Improved ORR of 42.5% versus 28.7% and CBR of 79.9% vs 73.1% were for the ribociclib plus letrozole arm relative to placebo plus letrozole arm. The median time to response was not achieved in either treatment arm. Median duration of response is 26.7 months (95% CI: 24.0, NE) with ribociclib + letrozole versus 18.6 months (95% CI: 14.8, 23.1) with placebo + letrozole.

The ORR (54.5% vs. 38.8%) and CBR (80.2% vs. 71.8%) in the subgroup of patients with measurable disease at baseline were consistent with the primary analysis results.

1.10 FDA Approval

Ribociclib was approved by the FDA on March 13, 2017 for use in combination with an AI for post-menopausal, hormone receptor positive, Her-2/neu negative recurrent breast cancer, based on findings from the phase III MONALEESA-2 trial. In that study, the combination of ribociclib and letrozole reduced the risk of progression or death by 44% compared with letrozole plus placebo in the first-line setting for HR+/HER2- advanced breast cancer (HR, 0.556; 95% CI, 0.43-0.72; P <.0001).

1.11 Study Agent

Ribociclib (formerly LEE011) is an orally bioavailable, highly selective small molecule inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6). Ribociclib has been approved by the United States Food and Drug Administration (U.S. FDA) and the European Commission as an initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor based on a randomized, double-blind, placebo-controlled, international clinical trial (MONALEESA-2). Additional marketing authorizations are under review by health authorities. Additional phase III clinical trials for the treatment of hormone receptor positive (HR+) breast cancer patients, as well as several other phase I or II clinical studies are being conducted.

1.12 Post-marketing experience

Kisqali® (Ribociclib) in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer was approved by the FDA on 13 March 2017, and by the European Commission on 22-Aug-2017. Other health authority reviews are currently ongoing. Additional marketing approvals are expected on an ongoing basis.

Kisqali® is commercially available as 200 mg film coated tablets in 3 presentations – 63 tablets, 42 tablets and 21 tablets. On 04-May-2017 the FDA also approved the Kisqali Femara Co-pack for the same indication. The Co-pack contains both Kisqali and 26 day supply of Femara (letrozole) tablets.

1.13 Other Agent(s)

Letrozole is a highly potent, orally active non-steroidal competitive inhibitor of the aromatase enzyme system. It effectively inhibits the conversion of androgens to estrogens both in vitro and in vivo. It is indicated both as first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic

breast cancer as well as for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

Letrozole was initially studied at doses of 0.1mg to 5.0mg daily in six non-comparative Phase I/II trials in 181 postmenopausal estrogen/progesterone receptor positive or unknown advanced breast cancer patients previously treated with at least antiestrogen therapy. Patients had received other hormonal therapies and also may have received cytotoxic therapy. Eight (20%) of forty patients treated with letrozole 2.5mg daily in Phase I/II trials achieved objective tumor response (complete or partial response).

A randomized, double-blinded, multinational trial compared Letrozole 2.5mg with tamoxifen 20mg in 916 postmenopausal patients with locally advanced (Stage IIIB or loco-regional recurrence not amenable to treatment with surgery or radiation) or metastatic breast cancer. Time to progression (TTP) was the primary endpoint of the trial. Letrozole was superior to tamoxifen in TTP and rate of objective tumor response.

1.14 Rationale

Based on encouraging results in women with advanced hormone-receptor-positive breast cancer, a clinical trial for women with recurrent low-grade serous carcinoma is warranted. Furthermore, such a trial would have great appeal to women with recurrent low-grade serous carcinoma, a cohort with limited therapeutic options. Although low-grade serous carcinoma is a rather uncommon histologic subtype, prolonged overall survival results in a relatively high prevalence.

1.15 Gender and Ethnicity

This study will be open to women, including members of any minority groups and their subpopulations.

2.0 OBJECTIVES

2.1 Primary Objective

1. To determine the proportion of patients who have objective tumor response (complete or partial) within one year from start of study treatment as assessed by RECIST 1.1 in patients with recurrent low-grade serous carcinoma of the ovary, fallopian tube or peritoneum treated with the combination of ribociclib + letrozole.

2.2 Secondary Objectives

1. To examine the proportion of patients who have clinical benefit (complete response [CR], partial response [PR], or stable disease [SD]) in patient with recurrent low-grade serous carcinoma of the ovary, fallopian tube or peritoneum treated with the combination of ribociclib + letrozole.
2. To estimate the nature, frequency, and maximum degree of toxicity associated with this combination using CTCAE v5.
3. To estimate the progression-free survival of women receiving the combination of ribociclib + letrozole.
4. To estimate the overall survival of women receiving the combination of ribociclib + letrozole.

2.3 Exploratory Objectives

1. To determine the expression of Rb, estrogen receptor (ER), progesterone receptor (PR), and proliferative index (ki-67) and their correlation with response and clinical benefit.

2. To determine genomic signatures associated with response and clinical benefit of the combination of ribociclib + letrozole. (Note: for the exploratory objectives, no additional tissue biopsy will be required. We will test the recurrent tumor if available. If not we will test the primary tumor).

2.4 Endpoints

2.4.1 Primary endpoints

1. Objective Response rate as determined by RECIST 1.1.

2.4.2 Secondary endpoints

1. Clinical benefit (CR, PR, SD) rate.

2. Toxicity using CTCAE v5.0.

3. Progression-free survival

4. Overall survival

2.4.3 Exploratory endpoints

1. Expression of ER, PR, and ki-67 and their correlation with response and clinical benefit.
2. Genomic signatures and their correlation with response and clinical benefit.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Patient has signed the Informed Consent (ICF) prior to any screening procedures being performed and is able to comply with protocol requirements.
2. Age $\geq$ 18 years at time of study entry.
3. Willingness and ability to comply with study and follow-up procedures.
4. Histological confirmation of diagnosis of low-grade serous carcinoma of ovary, fallopian tube or peritoneum; Original diagnosis of de novo low-grade serous carcinoma or Original diagnosis of serous borderline tumor with subsequent diagnosis of low-grade serous carcinoma
    - In order to prevent inclusion of patients with high-grade serous carcinoma, diagnosis of low-grade serous carcinoma will be verified as part of a screening review by a gynecologic pathologist. Tissue for confirmation can be from primary tumor or recurrence.
5. Patient must have recurrent, measurable disease by RECIST v1.1.
6. There are no restrictions on number of prior therapies.
7. Patient cannot have previously received a prior cyclin dependent kinase inhibitor (CDKi). **Patients who were treated with letrozole or another aromatase inhibitor for other indications must have not taken the drug for 6 months prior to initiating letrozole for this trial and may not have progressed on treatment**.
8. Patients must not have remaining ovarian function to be included. In women who have at least one retained ovary, menopause must be confirmed with laboratory confirmation. Women who have ovarian function are eligible but must be placed on hormonal suppression. Menopause must be confirmed with laboratory confirmation, to include an estradiol level as this is assessed within 8 weeks of patient having been on tamoxifen.
9. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2
10. Resolution of all acute toxic effects of prior therapy or surgical procedures to National Cancer Institute (NCI) CTCAE Grade ≤ 1. Patients with grade 1 taxane-induced neuropathy, any grade alopecia, amenorrhea, or other toxicities not considered a safety risk for the patient as per investigator's discretion are eligible.

11. Patient has adequate bone marrow and organ function as defined by the following laboratory values at screening:
    a. Absolute neutrophil count ≥1.5 × 10^9/L
    b. Platelets ≥100 × 10^9/L
    c. Hemoglobin ≥9.0 g/dL
    d. Potassium, total calcium (corrected for serum albumin), magnesium, sodium and phosphorus within normal limits for the institution or corrected to within normal limits with supplements before first dose of study medication
    e. INR ≤1.5 (unless patient is receiving permitted anticoagulants and the INR is within the therapeutic range of intended use for that anticoagulant within 7 days prior to the first dose of study drug).
    f. Serum creatinine <1.5 mg/dL or creatinine clearance ≥50 mL/min
    g. In the absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5 x ULN. If the patient has liver metastases, ALT and AST <5 x ULN
    h. Total bilirubin < ULN; or total bilirubin ≤3.0 x ULN or direct bilirubin ≤1.5 x ULN in patients with well-documented Gilbert's Syndrome.
12. Patient with available standard 12-lead ECG with the following parameters at screening:
    a. QTcF interval at screening <450msec (using Fridericia's correction)
    b. Resting heart rate 50-90bpm
13. Must be able to swallow ribociclib and letrozole capsules/tablets.
14. Patients receiving tamoxifen or toremifene must have washout period of 5 half-lives prior to randomization.

3.2 Exclusion Criteria

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

1. Patient has a known hypersensitivity to any of the excipients of ribociclib or letrozole.
2. Patient has a concurrent malignancy or malignancy within 3 years prior to starting study drug, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer. Patients with known brain metastases are excluded.
3. Patients with central nervous system (CNS) involvement unless they meet ALL of the following criteria:
    a. At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment
    b. Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases.
4. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).

5. Patient has a known history of HIV infection (testing not mandatory).
6. 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.).
7. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormalities, including any of the following:
    a. History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 6 months prior to screening
    b. History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    c. Documented cardiomyopathy
    d. Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
    e. 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)
    f. Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
        i. Risk factors for Torsades de Pointe (TdP) including uncorrected hypocalcemia, hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia.
        ii. 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
        iii. Inability to determine the QT interval on screening (QTcF, using Fridericia's correction)
        iv. Systolic blood pressure (SBP) >160 mmHg or <90 mmHg at screening
8. Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to starting study drug (see Table 1 for details):
    a. Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges
    b. That have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5
    c. Herbal preparations/medications, dietary supplements.
9. Participation in other studies involving investigational drug(s) within 30 days prior to randomization or within 5 half-lives of the investigational product (whichever is longer) or

participation in any other type of medical research judged not to be scientifically or medically compatible with this study. If the patient is enrolled or planned to be enrolled in another study that does not involve an investigational drug, the agreement of the Novartis study medical lead is required to establish eligibility.

10. Patient is currently receiving warfarin or other coumadin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH) or fondaparinux is allowed. Direct-Acting Oral Anticoagulants (DOACs) are permitted.
11. Patient is currently receiving or has received systemic corticosteroids ≤2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment. The following uses of corticosteroids are permitted: a short duration (< 5 days) of systemic corticosteroids; any duration of topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).
12. Patient who has received radiotherapy ≤4 weeks or limited field radiation for palliation ≤2 weeks prior to starting study drug, and who has not recovered to grade 1 or better from related side effects of such therapy (exceptions include alopecia) and/or in whom ≥25% of the bone marrow (Ellis, 1961) was irradiated.
13. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects (tumor biopsy is not considered as major surgery).
14. Patient with a Child-Pugh score B or C.
15. Patients who are pregnant or breastfeeding
16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception throughout the study and for 3 weeks after study drug discontinuation. Highly effective contraception methods include:
    - Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

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

17. Current use of food or drugs known to be potent CYP3A4 inhibitors, drugs known to be potent CYP3A4 inducers, and drugs that are known to prolong the QT interval (see Appendix C for Prohibited Concomittant Medications).
18. Patients whose tumors contain both low-grade serous carcinoma (LGSC) and high-grade serous carcinoma (HGSC).
19. Patients with history of haemopoietic stem cell or bone marrow transplant.

4.0 STUDY DESIGN

This is an open-label, multi-institution, phase II trial. Eligible subjects with recurrent low-grade serous carcinoma who sign informed consent will receive the combination of letrozole and Ribociclib until disease progression or until they experience significant adverse events.

Table 1. Dose and Treatment Schedule

Agent	Dose	Route	Schedule
Ribociblib	600 mg	Capsules/tablets for oral use	Daily for 21 days then 7 days off
Letrozole	2.5 mg	Capsules for oral use	Daily

**Doses as appropriate for assigned dose level.

- Letrozole will be administered at a dose of 2.5 mg by mouth daily with continuous treatment until progression or unacceptable toxicity. The dose of letrozole will not be modified.
- Ribociclib will be administered at a dose of 600 mg by mouth daily for 21 days followed by 7 days off treatment. Treatment will be until progression or unacceptable toxicity.

4.1 TREATMENT PLAN: Ribociclib

Ribociclib will be supplied by Novartis or its designee in the form of 200 mg hard gelatin capsules or tablets as individual patient supply packaged in bottles. Storage conditions are described in the medication label.

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

Ribociclib will be administered as a flat-fixed dose of 600 mg daily, and not by body weight or body surface area.

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

Ribociclib must be taken as follows:

- Patients should be instructed to take the ribociclib capsules/tablets with a large glass of water (~250 ml) at the same time each day.
- Ribociclib can be taken without regard to meals; however dietary habits around the time of dosing should be as consistent as possible throughout the study
- Patients should be instructed to swallow the ribociclib capsules/tablets whole and not to chew, crush or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Patients must avoid consumption of grapefruit, grapefruit hybrids, pummelos, star-fruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medication, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.
- No herbal or dietary supplements are permitted, due to potential interactions with ribociclib; multivitamins are allowed.

4.2 TREATMENT PLAN: Letrozole

Letrozole is formulated as tablets of 2.5 mg and supplied in bottles. The dose of letrozole is one 2.5 mg tablet administered orally once daily. The oral single dose of ribociblib should be taken together with the daily dose of letrozole 2.5 mg as per schedule below.

4.3 Treatment Dispensation, Compliance and Accountability

4.3.1 Ribociclib will be provided and dispensed by the pharmacy. Study medication will be supplied in an open label fashion. Patients will self-administer both medications at home.

4.3.2 Patients will be instructed to take the study medication at an approximately consistent time each day.

The use of a patient pill calendar (See Appendix C) during study therapy will be utilized by the patient and the treating clinic to help promote and monitor compliance with Ribociclib and letrozole.

4.4 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 following lists 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 (v05, release date: 2015), 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 (www.qtdrugs.org).

4.5 AGENTS (DRUG FORMULATION AND PROCUREMENT)

4.5.1 Investigational Agent: **Ribociclib**

Ribociclib will be supplied by Novartis or its designee in the form of 200 mg hard gelatin capsules or tablets as individual patient supply packaged in bottles. Storage conditions are described in the medication label.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded. Ribociclib will be administered as a flat-fixed dose (e.g. 400 mg or 600 mg daily), and not by body weight or body surface area.

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

Refer to the Ribociclib Investigator's Brochure (IB) for more information. IB requests should be sent via email to GOGRegulatory@gog.org with **GOG-3026 Request for IB** in the subject line.

4.5.1.1 Source and Pharmacology: Also known by its tradename Kisqali® and its clinical trials name LEE011, is a kinase inhibitor indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer

4.5.1.2 Adverse Events and Drug Interactions

Most common adverse reactions (incidence ≥ 20%) are neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache and back pain.

See **Appendix D** for prohibited concomitant medications

Drugs known to prolong QT interval: Avoid concomitant use of drugs known to prolong QT interval such as anti-arrhythmic medicines.

4.5.1.3 Guidelines for Administration

Ribociclib must be taken as follows:

- Patients should be instructed to take the ribociclib capsules/tablets with a large glass of water (~250 ml) at the same time each day.
- Ribociclib can be taken without regard to meals; however dietary habits around the time of dosing should be as consistent as possible throughout the study
- Patients should be instructed to swallow the ribociclib capsules/tablets whole and not to chew, crush or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Patients must avoid consumption of grapefruit, grapefruit hybrids, pummelos, star-fruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medication, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.

- No herbal or dietary supplements are permitted, due to potential interactions with ribociclib; multivitamins are allowed.

4.5.1.4. Drug Supply and Storage

Please refer to the Regulatory Manual for Drug Ordering Instructions and Forms.

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the medication label. Medication labels will comply with the legal requirements of each country and be printed in the local language.

Study Drug Compliance and Accountability

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

4.5.2 Commercial Agent: Letrozole

4.5.2.1 Refer to the FDA-approved package insert for more information: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=82b77d74-085f-45ac-a7dd-1f5c038bf406

4.5.2.2

Source and Pharmacology: Also known by its tradename Femara®, letrozole is an aromatase inhibitor indicated for adjuvant treatment of postmenopausal women with breast cancer.

4.5.2.3 Adverse Events and Drug Interactions

The most common adverse reactions (greater than 20%) were hot flashes, arthralgia; flushing, asthenia, edema, arthralgia, headache, dizziness, hypercholesterolemia, sweating increased, bone pain; and musculoskeletal.

4.5.2.4 Guidelines for Administration

Letrozole tablets are taken orally without regard to meals.

Recommended dose: 2.5.mg once daily.

Patients with cirrhosis or severe hepatic impairment: 2.5 mg every other day

4.5.2.5 Supplier: Letrozole will be supplied by Novartis or its designee. Please refer to the Regulatory Manual for drug ordering instructions and forms.

4.6 Safety Lead-in

A review of safety will occur after the first 6-10 patients are treated and complete one cycle (including starting cycle 2 within the DLT constraints below) or have a DLT prior to completing the first cycle. Within the safety lead-in, patients who do not have a DLT and who do not complete cycle 1 will be replaced.

A dose limiting toxicity (DLT) is defined as an AE or clinically significant abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment with ribociclib and meets any of the criteria included in the table below. NCI CTCAE version 5.0 should be used for all grading.

Criteria for Defining Dose-Limiting Toxicities

Toxicity	**DLT Criteria**
Hematology	CTCAE grade 4 neutropenia lasting more than 7 consecutive days
	CTCAE grade 4 thrombocytopenia
	CTCAE grade 3 thrombocytopenia with bleeding
	CTCAE grade 3 or 4 febrile neutropenia
ECG QT interval	QTc interval ≥501 ms on at least 2 separate ECGs
Cardiac	Cardiac toxicity ≥ CTCAE grade 3 Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or Troponin ≥ CTCAE grade 3
Gastro-intestinal	≥ CTCAE grade 3 vomiting ≥48 hours despite optimal anti-emetic therapy ≥ CTCAE grade 3 diarrhea ≥48 hours despite optimal anti-diarrhea treatment
Hepato-biliary	≥ CTCAE grade 2 total bilirubin for more than 7 consecutive days ≥ CTCAE grade 3 total bilirubin ≥ CTCAE grade 2 ALT with a ≥grade 2 bilirubin elevation of any duration in the absence of liver metastases ≥ CTCAE grade 3 ALT for >4 consecutive days CTCAE grade 4 ALT or AST Grade 4 serum alkaline phosphatase >7 consecutive days
Renal	≥ CTCAE grade 3 serum creatinine

ILD/pneumonitis	≥ CTCAE grade 3
Any drug-related death	
Non-hematologic events	≥ CTCAE grade 3, except for the exclusions noted below:
Exceptions to DLT criteria	Grade 3 alopecia
	<5 days of CTCAE grade 3 fatigue
	Grade 3 fever or infection without neutropenia <5 days duration
	Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant
CTCAE version 5.0 should be used for grading. Optimal therapy for vomiting and diarrhea should be based on institutional guidelines with consideration of the prohibited medications listed in these protocol guidelines.	

4.7 TREATMENT/ DOSE MODIFICATIONS

4.7.1 Ribociclib - Dose Modification Guidelines

Management of severe or intolerable adverse reactions requires temporary dose reduction and/or interruption of ribociclib therapy. For patients who do not tolerate the dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment.

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

4.7.1.1 Ribociclib Dose Adjustment/Management Recommendation for Hematological Adverse Reactions

Toxicity/Grade	**Dose Adjustment and Management Recommendations**
Thrombocytopenia	
Grade 1(≥75 x10^9/L)	No dose adjustment required.

Grade 2 (≥50 x 10^9/L – <75 x 10^9/L)	Dose interruption until recovery to grade <2 Re-initiate ribociclib at the same dose.
Grade 3 (≥25 x 10^9/L - <50 x 10^9/L)	Dose interruption until recovery to grade <2. 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(<25 x 10^9/L)	Dose interruption until recovery to grade <2. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 4: discontinue ribociclib
Absolute neutrophil count (ANC)	
Grade 1 (≥1.5 x10^9/L)	No dose adjustment required.
Grade 2 (≥1.0 - <1.5 x 10^9/L)	No dose adjustment required.
Grade 3 (≥0.5 - <1.0 x 10^9/L)	Dose interruption until recovery to ≥ 1.0 x 10^9/L. Re-initiate ribociclib at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to ≥1.0 x 10^9/L. If resolved in ≤7 days, then maintain dose level. If resolved in >7 days, then reduce ribociclib dose to the next lower dose level.
Grade 4 (<0.5 x 10^9/L)	Dose interruption until recovery to ≥1.0 x 10^9 /L. Re-initiate ribociclib 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.

Febrile neutropenia	
Grade 3 ANC <1.0 x 10^9/L with a single temperature of >38.3 ºC (101 ºF) or a sustained temperature of ≥38 ºC (100.4 ºF) for more than one hour	Dose interruption until improvement of ANC ≥1.0 x 10^9 /L and no fever. Restart at the next lower dose level. If febrile neutropenia recurs, discontinue ribociclib.
Grade 4	Discontinue ribociclib.

Life-threatening consequences; urgent intervention indicated	
Anemia (Hemoglobin)	
Grade 1 (≥10.0 – LLN g/dL)	No dose adjustment required.
Grade 2 (≥8.0 – <10.0 g/dL)	No dose adjustment required.
Grade 3 (<8.0 g/dL)	Dose interruption until recovery to grade <2. Re-initiate ribociclib at the same dose.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.

4.7.1.2 Recommendations for Ribociclib Dose Modification in Case of Hepatic Toxicities

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 1 (> ULN – 1.5 x ULN) (confirmed 48 to 72hrs later)	Maintain dose level with LFTs monitored every two weeks
Grade 2 (>1.5 – 3.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ grade 1 in ≤21 days, then maintain dose level If resolved to ≤ grade 1 in >21 days or toxicity recurs, then reduce 1 dose level Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions, discontinue ribociclib
Grade 3 (>3.0 – 10.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ grade 1 in ≤21 days, lower 1 dose level of ribociclib Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption If resolved to ≤ grade 1 in >21 days or toxicity recurs, discontinue ribociclib
Grade 4 (>10.0 x ULN)	Discontinue ribociclib

Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤1 x ULN) due to hemolysis or Gilbert Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
AST or ALT	
AST or ALT without bilirubin elevation >2 x ULN	
Same grade as baseline or increase from baseline grade 0 to grade 1 (confirmed 48 to 72 hrs later)	No dose adjustment required with LFTs monitored per protocol if same grade as baseline or every two weeks in case of increase from baseline grade 0 to 1
Increase from baseline grade 0 or 1 to grade 2 (>3.0 – 5.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ baseline value in ≤21 days, then maintain dose level If resolved to ≤ baseline value in >21 days or toxicity recurs, then reduce 1 dose level Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions or recovery to ≤ baseline value is >28 days, discontinue ribociclib
Increase from baseline grade 0 or 1 to grade 3 (>5.0 – 20.0 x ULN)	Dose interruption of ribociclib until resolved to ≤ baseline value, then lower 1 dose level of ribociclib Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption If recovery to ≤ baseline value is >28 days, discontinue ribociclib If toxicity recurs, discontinue ribociclib

Increase from baseline grade 2 to grade 3 (>5.0 – 20.0 x ULN)	Dose interruption of ribociclib until resolved to ≤ baseline value, then lower 1 dose level of ribociclib Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity reoccurs after 2 dose reductions or recovery to ≤ baseline value is > 28 days, discontinue ribociclib
Grade 4 (>20.0 x ULN)	Discontinue ribociclib
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 total bilirubin >2 x ULN without evidence of cholestasis **or** 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
Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, and alcohol intake.	

Additional Follow-up for Hepatic Toxicities

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

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

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

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

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

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

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

Hepatic toxicity monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin, direct and indirect bilirubin, alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), creatine kinase, 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 retesting 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 preexisting 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 7.02), and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

4.7.1.3 Dose Modification Guidance in Case of QT Prolongation

Grade	**Dose Modification**
For All Grades	1. Check the quality of the ECG and the QT value and repeat if needed. 2. Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If outside of the normal range, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. 3. Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. 4. Check compliance with correct dose and administration of ribociclib. Consider collecting a time matched PK sample; record date and time of last study drug intake
1 QTcF 450-480 ms	Perform steps 1-4 as directed in "For All Grades." No dose adjustment required.
2 QTcF 481-500 ms	Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." Perform a repeat ECG within one hour of the first QTcF of ≥ 481 ms. Repeat ECG as clinically indicated until the QTcF returns to < 481 ms, Restart ribociclib with dose reduced by 1 dose level. Refer to Section 4.7.1 for dosing schedule. If QTcF ≥ 481 ms recurs, ribociclib should be reduced again by 1 dose level. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 481 ms.
3 QTcF ≥ 501 ms on at least two separate ECGs	Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." Perform a repeat ECG within one hour of the first QTcF of ≥ 501 ms. If QTcF remains ≥ 501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to < 481 ms. • If QTcF returns to < 481 ms, ribociclib will be reduced by 1 dose level. Refer to Section 4.7.1 for dosing schedule. • If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in "For All Grades," discontinue ribociclib. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 ms If QTcF of ≥ 501 ms recurs, discontinue ribociclib.
4 [QT/QTcF ≥ 501 or > 60 ms change from baseline] and [Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia]	Discontinue ribociclib. Perform steps 1-4 as directed in "For All Grades." • Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms.

4.7.1.4 Dose Adjustment and Management Recommendation for ILD/pneumonitis (CTCAE v4.03)

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

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

4.7.1.5 Guidance for Management of All Other Adverse Reactions

Consider performing an analysis of serum potassium, calcium, phosphorus, and magnesium for all adverse reactions that are potentially associated/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.

Ribociclib Dose Adjustment and Management Recommendation for All Other Adverse Reactions

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

4.7.1.6 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.

4.7.1.7 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. Please consult the list of prohibited medications and the list of use with caution medications for further guidance.

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 nondrug therapies section of the patient record.

Bisphosphonates and denosumab

Adjuvant bisphosphonate/denosumab therapy is allowed per local and ASCO guidelines. Bisphosphonates and denosumab are permitted for the treatment of osteoporosis and prevention of skeletal related events for patients with bone metastases. Chronic concomitant bisphosphonate/denosumab therapy for the prevention of bone metastasis is not permitted.

Hematopoietic growth factors

Hematopoietic growth factors may be used according to ASCO guidelines.

Selective radiotherapy

Selective radiotherapy is permitted. It should not be delivered to a target lesion Cumulative courses of RT should not encompass > 25% of irradiated bone marrow. No dose modification of study treatment is needed during selective radiotherapy.

Permitted concomitant therapy requiring caution

Medications to be used with caution during ribociclib and [If applicable: and co-treatment] in this study are listed below (see Table 2). This list is not comprehensive and is only meant to be used as a guide. These medications should be excluded from patient use if possible. If they must be given, then use with caution and consider a ribociclib interruption if the concomitant medication is only needed for a short time.

- Moderate inhibitors or inducers of CYP3A4/5
- 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 risk for QT prolongation

Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to lead to induction of CYP3A enzymes, thereby potentially increasing the risk of reducing ribociclib drug exposure to subtherapeutic levels. Systemic corticosteroid treatment should not be given during the study, except for:

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

Prohibited concomitant therapy

The following medications are prohibited during study treatment in the study (see Table 1). 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
- Other investigational and antineoplastic therapies not part of the study
- 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.

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.

For complete information, refer to the ribociclib (LEE011) Investigator's Brochure and other drug package insert. See **Appendix C** for information on possible interactions with other drugs.

4.7.2 Letrozole - Dose Modification Guidelines

Toxicity Site	Observation	Management
Bone Effects	Use of Letrozole may cause decreases in bone mineral density (BMD)	Consideration should be given to monitoring BMD
Grade 3-4 hypercholesterolemia	Hypercholesterolemia was reported in 52.3% of letrozole patients and 28.6% of tamoxifen patients.	Consideration should be given to monitoring serum cholesterol.
Subjects with cirrhosis and severe hepatic impairment		Reduce dose to 2.5mg every other day

5.0 PATIENT ENTRY/RANDOMIZATION PROCEDURE

Regulatory Requirements: Please see the Regulatory Manual for site requirements prior to screening and enrollment of patient.

Patient Entry and Registration: The GOG Partners' IRT System (https://partners.gog.org) will be used for patient registration following the completion of the Pathology Screening (see Section 6.1 for instruction for obtaining a Screening ID).

6.0 Study Parameters

6.1 Pre-Treatment Evaluations (Screening)

The following must be collected/ performed within 28 days prior to Cycle 1, day 1 of treatment. Clinical and laboratory evaluations performed as part of routine standard of care do not need to be repeated if performed within the appropriate window.

- Voluntary, written, dated, and signed informed consent must be obtained before any study specific procedures are performed (with the exception of certain imaging assessments if meeting the criteria defined in this section).
- Radiographic tumor assessments that were performed before the signing of the informed consent form as routine procedures (but within 28 days prior to study enrollment) do not need to be repeated and may be used as baseline assessments, as long as:
    - The tests were performed per the method requirements outlined in the Tumor Assessment Requirement Flowchart, the Efficacy Assessments sections.
    - Appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes
- Complete medical history and disease treatment history.
- UPT in WOCBP
- ECOG PS
- Baseline AE assessment
- Physical exam with vital signs
- Labs: CMP, CPK, CBC with differential (diff), Uric acid, Urinalysis
- ECG
- Tumor assessment – CT chest, abdomen, and pelvis, or MRI
- Concomitant medication
- CA-125
- Lipid panel (total cholesterol, HDL, LDL, triglycerides) fasting preferred
- Coagulation (PT and INR)
- Submission of an H&E stained slide for pathology review to confirm eligibility.
- Obtain a Screening ID (format: XXXX-3026-YYYY) from the GOG Partners' IRT System (https://partners.gog.org).
- Print IRT Screening Confirmation
- Send H&E stained slide (labeled with Screening ID) along with a completed copy of the Digital Pathology Screening Form (Appendix E) and printout of the IRT Screening Confirmation to:

  GOG 3026 Pathology Review
  Biopathology Center
  Nationwide Children's Hospital
  700 Children's Dr, WA1340

Columbus, OH 43205
Phone: (614) 722-2865

- Receive results of pathology review via email to registrar patient.
- If pathology review results indicate patient is eligible (and all other eligibility criteria are met), return to the GOG Partners' IRT System to complete patient registration. Once completed, proceed to Rave for patient data entry.
- If pathology review results indicate patient is not eligible, no further action is required in the GOG Partners' IRT System.

Special Note Regarding the Safety Lead-In
For the Safety Lead-in portion, the assigned Screening ID also serves as a slot reservation. These reservations are not transferrable to other patients, and if the patient is not enrolled within the required timeframe, the reservation is cancelled and the slot is then made available to other patients and sites. If all slots for the lead-in are reserved, including existing enrollments, patients can be added to a waiting list. Patients on the waiting list can begin the pathology screening process noted above, but may be unable to be enrolled during the Safety Lead-in if accrual is met in the interim.

To mitigate the risk of over-accrual, the number of active screening patients will be limited in that the sum of patients enrolled and active screening patients cannot exceed the total for phase or study accrual. If a patient in screening is found to not be eligible, or has elected to seek other treatment, this information should be reported in the IRT system as soon as possible. Any "stale" screening patient records will be marked as inactive after 30 days to help in the monitoring of accrual.

Treatment should be initiated within 7 days of registration.

Please refer to the Regulatory Manual for more information regarding the safety lead-in.

6.2 Evaluations on Treatment

Collection of Concomitant Medications and Adverse Events (AEs) should occur throughout the study, as described. Pre-treatment (Screening) evaluations do not need to be repeated if within 28 days of Cycle 1 Day 1.

Day 1 (±3 days)

- History and physical exam with vital signs
- Labs: CMP, CPK, CBC with differential (diff), Uric acid, Urinalysis
- If WOCBP, pregnancy test within 3 days of treatment for Cycle 1 only
- AEs

- ECG (if clinically indicated)
- Study drugs to be taken daily at the same time every day for 21-consecutive days.
- CA-125
- Lipid panel (total cholesterol, HDL, LDL, triglycerides) fasting preferred
- Coagulation (PT and INR)

Day 21 (±3 days)

- Ribociclib –start of 1-week off period.
- Letrozole – Continue taking through the week off period of Ribociclib.

6.3 Off-Treatment Evaluations (End of Treatment or EOT visit)

The end of treatment visit will be performed as soon as possible but no later than 4 weeks (i.e., 28 days) ± 7 days from last dose of investigational product and prior to the initiation of any new anticancer therapy.

6.4 Follow-up Evaluations

After discontinuation of study treatment, post-study survival status (including post study anticancer therapies) will be collected approximately every 3 months for the first two years and then every six months for the next three years. from the last dose of study treatment. Telephone contact is acceptable.

If patient comes off study treatment prior to progression, continue tumor measurements and radiologic evaluations on schedule until progression or initiation of a subsequent cancer therapy. Toxicity assessments will be continued until resolution or return to baseline. Patients will be followed after last drug dose until toxicity resolution or return to baseline, until progression if patient withdraws before progressive disease, or until study withdrawal if it occurs before this time.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (i.e., for photographed or palpable lesions) documented disease progression as per RECIST v1.1 definitions will continue to have tumor assessment performed during the follow-up visits every 3 months (± 7 days) from the date of starting protocol therapy until disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first.

6.5. Schedule of Assessments

	Screening Phase[a]	**Treatment Phase: 28-day cycles[f]**					**Post Treatment Follow up Phase [e]**
Visit Name	Screening	Cycle 1*	Cycle 2	Cycle 3	Cycle 4 - n	End of Treatment	
Treatment Days	Prior to Day 1	1	1	1	1		
Physical Assessments							
History & Physical Exam with vital signs	X	X	X	X	X		
Review of Concomitant Medications	Continuous – up to 30 days after last dose of study treatment						
Performance Status	X						
Laboratory Assessments							
Hematology: CBC	X	X	X[g]	X[g]	X[g]	X	
Chemistry (including LFTs): K, Ca, Mg, Na, P, CPK, Uric Acid, AST, ALT, total bilirubin, BUN	X	X	X	X	X	X	
Coagulation: PT and INR	X	X	X	X	X	X	
Lipid Panel: Total cholesterol, HDL, LDL, triglycerides (fasting preferred)	X	X			X[h]		
CA-125	X	X	X	X	X		X

	Screening Phase[a]	Treatment Phase: 28-day cycles[f]					Post Treatment Follow up Phase [e]
Visit Name	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4 - n	End of Treatment	
Urinalysis	X	X	X	X	X	X	
Urine Pregnancy Test (WOCBP only)	X	X					
Cardiac Assessments							
ECG (12-Lead)[j]	X	X[i]	X[i]	As clinically indicated			
Safety & Imaging							
Toxicity Assessment/Adverse Events	Continuous						
Tumor Imaging[b]	X			X[d]			X
H&E for Pathology Review[c]	X						
Survival Follow Up							X

Legend:

* Pre-treatment (Screening) evaluations do not need to be repeated if within 28 days of Cycle 1 Day 1.

a. Within 28 days of first dose of letrozole + ribociclib

b. CT or MRI of chest, abdomen, and pelvis

c. H&E stained slide must be submitted for pathology review to confirm eligibility

d. Every 3 cycles

e. The end of treatment visit will be performed as soon as possible but no later than 4 weeks (i.e., 28 days) ± 7 days from last dose of investigational product and prior to the initiation of any new anticancer therapy. After discontinuation of study treatment, post-treatment follow-up, including survival status, will be collected every 3 months for the first 2 years and then every 6 months for 3 year for a total of 5 years. Telephone contact is acceptable. If patient comes off study treatment prior to progression, continue tumor measurements and radiologic evaluations on schedule until disease progression or initiation of a subsequent cancer therapy. Toxicity assessments continue until resolution or return to baseline. Patients who discontinue study treatment for reasons other than disease progression should have tumor assessments performed during follow-up visits every 3 months until disease progression, initiation of new anticancer therapy or discontinuation from participation on study.

f. Due to scheduling, these visits may occur +/- 3 days from the required time point. Additionally, it may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the Investigator or in order to accommodate patient/physician scheduling logistics.

g. Must be performed within 3 days of re-treatment.

h. Every 4th cycle

i. Predose and 2-4 hours postdose at investigator's discretion if clinically indicated.

j. For patients with QTcF ≥ 481 ms at any time, interrupt study treatment and follow the procedures described in the "Ribociclib Dose Modification section". If treatment is resumed, repeat ECGs 7 days and 14 days after dose resumption (and then as clinically indicated). During subsequent cycles, perform predose ECG for every cycle starting at cycle 6, and predose and 2-4 postdose starting at cycle 9 and every 3rd cycle thereafter.

7.0 PATHOLOGY/BIOSPECIMEN REQUIREMENTS

7.1 Pathology Review for Confirmation of Eligibility

This protocol requires a digital pathology review to confirm eligibility.

Regardless of whether the patient's original diagnosis was ovarian or peritoneal serous tumor of low malignant potential or low-grade serous carcinoma, eligible patients include those with recurrent low-grade serous carcinoma of the ovary, fallopian tube or peritoneum.

One H&E stained slide from the recurrent tumor (obtained at secondary surgery, prior biopsy, or SOC image-guided fine needle/core biopsy) or from the original diagnostic specimen documenting low-grade serous carcinoma must be obtained from the pathology department and sent by overnight courier at the institution's expense to the Biopathology Center:

GOG 3026 Pathology Review
Biopathology Center
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

A completed copy of the Digital Pathology Screening Form (Appendix E), printout of the IRT Screening Confirmation, and a copy of the corresponding pathology report must be submitted with the H&E. All items shipped must be labeled with the Screening ID (format: XXXX-3026-YYYY; see Section 6.1 for details). Slides must also be labeled with the surgical pathology accession number and block number from the corresponding pathology report.

7.2 Protocol for digital review of pathology slides

The representative H&E stained slide will be scanned at the Biopathology Center into a tissue review database. A gynecologic pathologist will be provided the case for central prospective review using VIPER (Virtual Imaging for Pathology Education and Research). The institution will be notified of patient eligibility by email within five business days of:

(1) receipt at the Biopathology Center of the
   a. H&E,
   b. corresponding pathology report,
   c. completed Digital Pathology Screening Form (Appendix E), and
   d. printout of the IRT Screening Confirmation; and
(2) pathologist review.

Failure to send the required materials and/or improper labelling could delay the results review.

7.3 Translational Research

Next generation sequencing will be performed on all pre-treatment tissue specimens. These results will be correlated to response and clinical benefit. In addition, we will evaluate estrogen receptor (ER) signaling and correlate these findings with response.

Specimen Requirements

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions are required to submit the patient's translational research specimens as outlined below (unless otherwise specified). **Refer to Appendix F for details.**

Required Specimen (Specimen Code)	Collection Time Point	Ship To
FFPE Tumor Tissue (Submit at least one tumor type – Listed in order of preference)		
Archival FFPE Recurrent Primary (FRP01) or Recurrent Metastatic (FRM01) Tumor[1] 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment	Biopathology Center within 8 weeks of registration[2]
Archival FFPE Primary (FP01) or Metastatic (FM01) Tumor[1] 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to all treatment	
Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s) and frozen[3]	Prior to starting study treatment	Biopathology Center within 1 week of registration[2]

1 A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the Biopathology Center.
2 Biopathology Center / Protocol GOG 3026, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org
3 Do not use glass blood collection tubes.

7.4 Laboratory Testing

7.41 Hormone Receptor Immunohistochemistry

Unstained sections of formalin-fixed, paraffin-embedded (FFPE) tumor will be used for hormone receptor (e.g., estrogen receptor [ER]-alpha, ER-beta, progesterone receptor [PR]-alpha, PR-beta, G protein-coupled ER [GPR-30]) immunohistochemistry (IHC).

7.42 Mutation Analysis

Unstained sections of FFPE tumor and DNA extracted from whole blood will be used for mutational analysis (e.g., PTEN, PIK3CA, KRAS, CTNNB1 [beta-catenin], Rb).

7.43 Next-Generation Sequencing (NGS)

Unstained sections of FFPE tumor will be used for next-generation sequencing (NGS) mutational analysis.

8.0 Evaluation Criteria

8.1 Antitumor Effect – Solid Tumors

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

In the present study, tumors will be re-evaluated by CT scan of the chest, abdomen, and pelvis every 12 weeks during treatment and at least 4 weeks after the first observation of a complete or partial response. After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated every 12 weeks.

8.1.1 Definitions

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

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

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

Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

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

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

8.1.2 Methods for Evaluation of Measurable Disease

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

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

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

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

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

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. **For these reasons, the GOG will not allow PET-CT use for RECIST 1.1 response criteria.**

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

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

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

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

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

CA-125 (Ovarian, fallopian tube and primary peritoneal cancer trials): CA-125 cannot be used to assess response or progression in this study. If CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response. Specific guidelines for CA-125 response (in recurrent ovarian cancer) have been published [JNCI 96:487-488, 2004]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria that are to be integrated with objective tumor assessment for use only in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

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

It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measurable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease versus progressive disease, as an effusion may be a side effect of the treatment.

8.1.3 Response Criteria

8.1.3.1 Evaluation of Target Lesions

Response Criteria - Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the

	sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
Clinical Benefit	CR+PR+SD Progression-free survival

8.1.3.2 Evaluation of Non-Target Lesions

Response Criteria - Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Not evaluable (NE)	When at least one non-target lesion is not evaluated at a particular time point

8.1.3.3 Evaluation of Biomarkers

If serum CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

Progression **cannot** be based upon biomarkers, such as serum CA- 125, for this study.

8.1.3.4 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease):

Evaluation of Overall Response

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later.

8.1.4 Frequency of Tumor Re-evaluation

In the present study, tumors will be re-evaluated by CT scan of the chest, abdomen, and pelvis every 12 weeks during treatment and at least 4 weeks after the first observation of a complete or partial response. After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated every 12 weeks.

8.1.5 Date of Progression

Date of progression is defined as the first day when the RECIST (version 1.1) criteria for PD are met. CA 125 (GCIG) progression alone is **not** sufficient for progression to be defined.

8.1.6 Reporting of tumor response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death from malignant disease, early death from toxicity, early death from other cause or unknown (not assessable, insufficient data).

Early death is defined as any death occurring before the first per protocol time point of tumor re-evaluation. The responsible investigator will decide if the cause of death is malignant disease, toxicity, or other cause.

Patients for whom response is not confirmed will be classified as "unknown" unless they meet the criteria for stable disease (or the criteria for partial response in case of an unconfirmed complete response). Patients' response will also be classified as "unknown" if insufficient data were collected to allow evaluation per these criteria. See table above for further detail.

8.1.7 Duration of Response

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

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

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

8.1.8 Progression-free survival: Progression-free survival (PFS) is defined as the duration of time from study entry to time of progression or death or the date of last contact, whichever occurs first.

8.1.9 Overall Survival

Overall survival is defined as the time from study entry to time of death or date of last contact.

9.0 DURATION OF STUDY

9.1 In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient withdraws consent for the study,
- Patient non-compliance with the protocol,
- Death,
- Pregnancy, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

9.1.1 If patient comes off study treatment prior to progression, continue tumor measurements and radiologic evaluations on schedule until progression or initiation of a subsequent cancer therapy. Toxicity assessments will be continued until resolution or return to baseline. Patients will be followed after last drug dose until toxicity resolution or return to baseline, until progression if patient withdraws before progressive disease, or until study withdrawal if it occurs before this time.

9.1.2 All patients will be treated (with completion of all required case report forms) until disease progression or study withdrawal. Patients will then be followed every three months for the first two years and then every six months for the next three years. Patients will be monitored for delayed toxicity and survival for this 5-year period with Follow-Up Forms submitted to the GOG Statistical and

Data Center, unless consent is withdrawn. Follow-Up Forms will no longer be required if the study is terminated prior to the completion of the 5-year follow-up period.

9.1.3 A patient is considered off study therapy when the patient has progressed or died, a non-protocol drug or therapy (directed at the disease) is initiated or all study therapy is totally discontinued. Report all treatment received on Cycle Drug Information Forms and adverse events on Adverse Event Forms up until the patient qualifies as being off study therapy.

10.0 Study Monitoring and Reporting Procedures

10.1 Adverse Event Reporting

10.1.1 Definitions

Adverse Event (AE): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Progression of disease is considered the natural development of cancer in this study; therefore it is not considered as an adverse event.

Suspected Adverse Reaction (SAR): Adverse event for which there is a reasonable possibility that the investigational drug caused the adverse event (i.e., attribution to study drug of possible, probable, or definite).

Serious Adverse Event (SAE): An adverse event or suspected adverse reaction is considered "serious" if in the view of either the Investigator or sponsor, it results in any of the following outcomes:

1) Death,
2) A life-threatening adverse event,
3) Inpatient hospitalization or prolongation or existing hospitalization,
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 that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate 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.

Unexpected Adverse Event: An adverse event is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed.

10.1.2 GOG Reporting Requirements:

All investigators and ultimately the protocol Principal Investigator (PI) have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the study drug. It is the responsibility of the investigator to supply the medical documentation needed to support expedited AE reports in a timely manner. Investigators **MUST** immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is reasonable possibility that the drug caused the event (21 CFR 312.64(b)). Please refer to Section 10.15 for reporting procedures.

Information regarding AEs and SAEs will be collected from the time of informed consent until 30 days from the last dose administered.

When possible, adverse events should be described in terms of a change in the baseline status or with a diagnosis or summary term rather than as individual symptoms. The Investigator is responsible for reporting SAEs to the appropriate Institutional Review Board (IRB) or other committees in accordance with local institutional and IRB policies.

10.1.3 Criteria for Determining Adverse Event Severity:

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting.

10.1.4 Criteria for Determining Adverse Event Causality:

The following attribution categories will be used in assessing the relationship between the AE and the study drug:

RELATIONSHIP	**ATTRIBUTION**	**DESCRIPTION**
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly **NOT** related* to the intervention
	Unlikely	The AE *is **doubtfully related*** to the intervention
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

10.1.5 SAE Reporting to GOG and Novartis:

The investigator must report to GOG any serious adverse event, whether or not considered drug-related, within 24 hours of any site personnel becoming aware of the event. Please see the Data Management Manual for instructions for submitting SAE reports to GOG in Medidata Rave.

The GOG Regulatory Compliance Department will forward all SAE reports to Novartis within 24 hours of first awareness.

10.2 GOG Data Management Forms

The Case Report Forms (CRFs) noted in the Data Management Form Manual must be submitted through the Medidata Rave Electronic Data Entry System (www.imedidata.com). All amendments to CRFs must also be submitted through Medidata Rave.

Please refer to the Data Management Form Manual.

10.3 Safety Monitoring for Safety Lead-In

The formal safety monitoring process for the safety lead-in for this protocol includes bi-weekly teleconferences which will be scheduled with participating sites to discuss the patients enrolled on the safety lead-in. The site investigator or MD delegate is required to participate on the calls. In addition, it is recommended that the responsible Clinical Research Coordinator participate as well.

During the teleconference, each patient's drug doses, treatment delays, abnormal blood counts, and AEs/SAEs as documented on the Case Report Forms (CRFs) in Medidata Rave. The CRF data should be updated prior to each call. Sites should be prepared to discuss the following topics for each enrolled patient:

- Drug dosing (including total number of cycles)
- Treatment delays
- Dose modifications
- Adverse Events, Serious Adverse Events, DLTs
- Abnormal laboratory values
- Response evaluations
- Number of potentially eligible patients awaiting study

Please refer to the Regulatory Manual for more information regarding the safety lead-in.

11.0 Statistical Considerations

The intent of this this study is to assess the anti-tumor activity of the combination of letrozole + ribociclib in women with recurrent low-grade serous carcinoma of the ovary, fallopian tube or peritoneum measured by objective tumor response. This is a single-arm, open-label phase II study with a safety lead-in using an optimal flexible 2-stage design (33).

The targeted accrual for the first stage of the study will be 23 eligible and evaluable patients but permitted to range from 19 to 26 for administrative reasons. The cumulative targeted accrual for the second stage will be 48 eligible and evaluable patients but permitted to range from 44 to 51 for administrative reasons.

11.1 Study endpoints

11.1.1 Primary endpoints

The frequency of objective tumor response as assessed by RECIST 1.1.

11.1.2 Secondary endpoints

The frequency of clinical benefit (CR, PR, or SD).

The frequency and severity of adverse events as assessed by CTCAE v5.0.

Progression-free survival

Overall survival

11.1.3 Exploratory endpoints

Measurements of expression of ER, PR, and ki-67 and objective tumor response and clinical benefit.

Measurements of genomic signatures and objective tumor response and clinical benefit.

11.2 Anticipated annual accrual is approximately 31-39 patients based on GOG-0239.

The accrual duration will take approximate 7-9 months for the first stage without suspension of safety lead-in and 8-10 months for the second stage, separately. Additionally, the evaluation of patients with complete/partial response takes at least 16 weeks, and it can take even longer to evaluate patients with stable disease to determine whether they respond or not. Therefore, the duration for completion of primary endpoint will be approximately 13-15 months from activation of the study for the first stage, and 14-16 months from activation of the second stage for the second stage if the study advances to the second stage.

11.3 Study plan

Safety lead-in

The purpose of the safety lead-in phase is not to identify the MTD of the combination regimen. Rather it is being conducted to assure the safety of this regimen in the population of interest through the determination of cycle 1 DLTs. Patients will be dichotomized as either experiencing at least one DLT in cycle 1 (including delays in cycle 2 administration) or experiencing no DLTs at all in cycle 1.

After six patients have received a full cycle of treatment and are observed for the whole first cycle, the safety of the regimen will be assessed based on the dose limiting toxicities (DLTs) listed in Section 4.6. At most ten patients will be accrued before this safety evaluation takes place, and if necessary, accrual will be suspended at 10 patients in order to do this evaluation.

The probability of DLT (θ) will be assessed using a Bayesian interpretation of θ, in which θ is considered to be a random variable with a probability distribution. We combine the data observed in our trial with a prior probability distribution for θ to obtain a posterior distribution for θ. The DLT data is binomially distributed (DLT yes/no). The conjugate prior for the binomial distribution is the beta distribution, so we assume the prior for θ, $f(\theta)$, to be Beta(α, β). We specify our prior to have $\alpha=2$ and $\beta=6$ which reflects the belief that the θ for the regimen is most likely around 0.1 to 0.25. Our interested target for the probability of DLT is 0.25.

Let n be the number of DLT-evaluable patients (i.e., had a DLT or treated for a full cycle), and x be the number of patients experiencing DLTs. The posterior for θ at the end of the safety lead-in is thus Beta(α + x, β + n − x). Consideration will be given to stopping the study if Pr(θ > 0.25|x, n) > 0.5, which corresponds to stopping if the number of patients with DLTs is greater or equal to critical value, r, i.e., 2 or more out of 6 or 7 patients, or 3 or more out of 8-10 patients. Table 11.1 shows the posterior probabilities of θ exceeding the target of 0.25 at the end of safety lead-in and corresponding critical values. These critical values are guidelines, but clinical judgment will be exercised, taking into account the nature of the toxicities and the likelihood of the toxicity being related to treatment.

Table 11.1: Posterior Probabilities of θ [Pr(DLT)] Exceeding the Target of 0.25 and Corresponding Critical Values for Consideration of Stopping for Toxicity

x / n	Pr(θ > 0.25|x,n)										
	0	1	2	3	4	5	6	7	8	9	10
6	0.13	0.33	0.58	0.79	0.92	0.98	0.99				
7	0.10	0.28	0.52	0.74	0.89	0.96	0.99	1.00			
8	0.08	0.24	0.46	0.69	0.85	0.94	0.98	1.00	1.00		
9	0.06	0.20	0.41	0.63	0.81	0.92	0.97	0.99	1.00	1.00	
10	0.05	0.16	0.35	0.57	0.77	0.89	0.96	0.99	1.00	1.00	1.00

Phase II

The intent of this study is to assess the anti-tumor activity of the combination of letrozole + ribociclib measured by objective tumor response. Tumor response is dichotomized as response (i.e., complete or partial response) vs. non-response (i.e., stable disease, progressive disease, or unknown) and is assumed to have a Bernoulli distribution with a probability equal to π. Given a sample size, the number of tumor responses is binomially distributed with a given sample size and probability equal to π. Statistically, the evaluation of the study regimen efficacy measured by tumor response will be formulated through hypothesis testing via tumor response.

If combination proposed here has a true response rate of 10% or less, it would be considered of little clinical significance. Alternatively, if the true response rate were at least 25%, further investigation would be clearly indicated. Therefore, the primary hypotheses for this study can be formulated as follow:

$$H0: \pi \leq 0.10,$$

$$H1: \pi \geq 0.25,$$

where π is the probability of true tumor response, H0 is the null hypothesis and H1 is the alternative hypothesis. An optimal flexible two-stage design will be implemented to evaluate the primary hypotheses with average type I and type II error rates at 0.1 level, respectively (33). This design has early stopping guidelines that intends to limit patient accrual to inactive treatments and it permits the actual number of patients entered in each stage to vary slightly in order to

accommodate the challenges of coordinating a multicenter clinical trial while maintaining the levels of average type I and type II errors.

We will target an accrual of 23 eligible and evaluable patients in the first stage of this study, but in practice permit accrual to range from 19 to 26 patients due to administrative coordination. If there are more than 2 out of 19-25, or 3 out of 26 patients responding (complete or partial response) and medical judgment indicates, accrual to the second stage of the trial will be initiated. Otherwise, the study will be stopped and the treatment regimen will be classified as clinically uninteresting. If the study advances to the second stage, then an overall study accrual of 48 eligible and evaluable patients will be targeted, but permitted to range from 44 to 51 patients for administrative reasons. If more than 6 out of 44-45 patients respond or 7 out of 46-51 patients respond then the regimen will be considered worthy for additional investigation.

Under the assumed accrual ranges of 19 to 26 (stage 1) and 44 to 51 (cumulatively after stage 2), if the true probability of response is 10% (H0), then this study has a 64% probability of early termination and a probability of 10% of incorrectly declaring the study regimen interesting; if the true probability of tumor response is 25%, then the study has a 90% chance of correctly classifying the study regimen as being interesting.

The following table summarizes the accrual and decision guideline.

Stage of Accrual	Targeted Cumulative Accrual	Limits of Actual Accrual	Max Number of Responses to Reject Study Regimen
1	23	19-26	2/(19-25), 3/26
2	48	44-51	6/(44-45), 7/(46-51)

11.4 Secondary and exploratory analyses

Secondary analyses

The proportion of patients who have clinical benefit will be calculated and an estimate of 90% confidence interval will be provided.

The frequency and maximum severity of acute adverse events will be tabulated graded by CTCAE v5.0.

Kaplan-Meier median estimates and graphs will be used to describe PFS and OS survival functions.

Exploratory analyses

Summary statistics (and graphs where it is appropriate) will be done for exploratory biomarker endpoints.

Appropriate methods will be implemented to explore the associations of biomarkers with the response and clinical benefit, e.g., Spearman's correlation coefficient for interval/ordinal type of

biomarker measurements with response or clinical benefit, chis-squared test for nominal type of biomarker measurements with response or clinical benefit.

The purpose of exploratory objective is to explore and possibly generate hypotheses for future study. Therefore there will be no adjustment for multiple tests.

11.5 Only those patients who are deemed "ineligible" or who receive no therapy will be eliminated from the analysis. All patients who receive any therapy will be evaluated for both treatment efficacy and toxicity. While on occasion, circumstances may prevent the determination of treatment efficacy, such patients will be included in the analysis and labeled as "unknown". This category will be listed and be reflected in the calculation of the response rate.

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APPENDIX A: PERFORMANCE STATUS SCALES

PERFORMANCE STATUS CRITERIA					
ECOG (Zubrod)		**Karnofsky**		**Lansky**	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort, some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of, and less time spent in, play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to a bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.
5	Dead	0	Dead	0	Dead

As published in Am J Clin Oncol: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655. The Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

APPENDIX B: NYHA CLASSIFICATION OF HEART DISEASE

New York Heart Association (NYHA) classification of heart disease

Table 1: NYHA Classification of Heart Disease

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

APPENDIX C: PROHIBITED MEDICATIONS DURING STUDY DRUG TREATMENT

Table 1. List of prohibited medications during study drug treatment

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

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

[2] Herbal product

[3] P-gp inducer

[4] The list provided is as of December 2019.Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.

As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI that increases the exposure of ribociclib or the exposure of the QT prolonging drug). A definitive list of drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or Torsades de Pointes (TdP) is available online at qtdrugs.org.

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

Table 2. List of medications to be used with caution during study drug treatment

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Aprepitant, amprenavir, asafoetida resin (Ferula asafoetida) cimetidine, crizotinib, diltiazem, faldaprevir, imatinib, isavuconazole, netupitant, nilotinib, tofisopam, Schisandra sphenanthera (nan wu wei zi), verapamil
Moderate CYP3A4/5 inducers	Bosentan, dabrafenib, efavirenz, etravirine, genistein,lopinavir[5], modafinil, nafcillin,telotristat
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine, aprepitant, atorvastatin, avanafil, bosutinib,brotizolam, budesonide, buspirone, cannabinoids[6], cannabidiol[6], cobimetinib, darifenacin, dasatininb, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutnib, isavuconazole, ivabradine, ivacaftor, , levomethadyl (LAAM), lomitapide, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, sildenafil, simeprevir, simvastatin, ticagrelor, tilidine, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin
BSEP inhibitors	Alectinib, atorvastatin, bromocriptine, candesartan, clobetasol, clofaziminie, dabigatran, dipyridamole, glyburide, grazoprevir, ledipasvir, mifepristone,pioglitazone, reserpine,rifamycin, simeprevir, telmisartan,timcodar, troglitazone, valinomycin, velpatasvir
Medications that carry a possible risk for QT prolongation[2]	Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine , asenapine, atomoxetine, bedaquiline, bendamustine, bortezomib, bosutinib, buprenorphine, cabozantinib, capecitabine, ceritinib, clomipramine, crizotinib,clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, efavirenz, eliglustat, epirubicin, eribulin mesylate, ezogabine(retigabine), famotidine, felbamate, fingolimod, flupentixol, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, ketanserin, lapatinib, lenvatinib, leuprolide, lithium, melperone, midostaurin, mifepristone, mirabegron, mirtazapine, moexipril/HCTZ, necitumumab, nicardipine, nilotinib, norfloxacin, nortriptyline, nusinersen, ofloxacin, osimertinib, oxytocin, paliperidone, palonosetron, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, perphenazine, pilsicainide, pimavanserin, pipamperone, promethazine, prothipendyl, rilpivirine, risperidone, romidepsin, sertindole, sorafenib, sunitinib, tamoxifen, tipiracil/trifluridine, tizanidine, tolterodine, toremifene,trimipramine, tropisetron, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone
MATE1/2 substrates[3]	Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topotecan, varenicline
OCT1/2 substrates[4]	Amantadine, 6-beta-hydroxycortisol, carboplatin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, oxali platin, oxybutynin, phenformin, picoplatin, pilsicainide, pindolol, , ranitidine, sorafenib, tropisetron, trospium, umeclidinium,, , and zidovudine
BCRP substrates	Daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, tenofovir, topotecan, venetoclax

[1] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.[2] The list provided is as of January 2018. Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.

[3] MATE1 and MATE2 share considerable substrate specificity.

[4] OCT1 and OCT2 share considerable substrate specificity.

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

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

Category	Drug Name

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

APPENDIX D- PATIENT PILL CALENDAR:

Patient Name: _____Date of first dose on calendar: _____

Patient Study ID: _____Cycle #:_____

- Complete one form for each cycle of treatment
- You will take Ribociclib once a day for 21 days followed by 7 days off. You will take Letrozole once a day every day.
- Please bring this form and your bottles of Letrozole and Ribociclib each time you return for an appointment

Day	Date	Time of Ribociclib Dose	Dose taken	Time of Letrozole Dose	Dose taken	Comments
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
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28						

BIOPATHOLOGY CENTER
DIGITAL PATHOLOGY SCREENING FORM

One H&E stained slide from the recurrent tumor (obtained at secondary surgery, prior biopsy, or SOC image-guided fine needle/core biopsy) or from the original diagnostic specimen documenting low-grade serous carcinoma must be sent for determination of eligibility by digital pathology review.

The H&E, along with a completed copy of this form, corresponding pathology report, and printout of the IRT Screening Confirmation must be shipped by overnight courier at the institution's expense to:

GOG 3026 Pathology Review
Biopathology Center
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: (614) 722-2865

Protocol **GOG 3026**

PATIENT INFORMATION

Screening ID _____

Patient Initials _____

SPID _____

Block # _____

Date Collected _____

REQUESTING SITE

Institution Name _____

Contact for Questions Regarding Submission

Name _____

Phone _____

Email _____

APPENDIX F - TRANSLATIONAL RESEARCH BIOSPECIMEN PROCEDURES

I. Requesting Translational Research Biospecimen Kits

One single chamber kit will be provided per patient for the collection and shipment of frozen whole blood.

Sites can order kits online via the Kit Management link (https://ricapps.nationwidechildrens.org/KitManagement). Each site may order two kits per protocol per day (daily max = 6 kits).

Please contact the Biopathology Center if you need assistance (Email: BopPhone: 866-464-2262).

Be sure to plan ahead and allow time for kits to be shipped by ground transportation. Kits should arrive within 3-5 business days.

Note: Unused materials and kits should be returned to the Biopathology Center. A pre-paid shipping label for the return of unused supplies and kits may be obtained via the Kit Management system. Select "Empty Kit" for package contents when returning unused kits.

II. Archival FFPE Tissue Shipped to the Biopathology Center

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (e.g., recurrent, primary, metastatic). Only one block may be submitted per tissue type.

- **Recurrent** tumor should be collected prior to the patient receiving any study treatment. Recurrent tumor collected from the site of primary disease should be labeled **recurrent primary (FRP01)**. Recurrent tumor collected from a site other than the site of primary disease (e.g., lymph node) should be labeled **recurrent metastatic (FRM01)**.
- Archival **primary (FP01)** and **metastatic (FM01)** tumor should be collected prior to the patient receiving any treatment.

Mandatory FFPE Biospecimen Requirement

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm) must be submitted. All tissue sections must be cut sequentially from one block.

Labeling FFPE Tissue

A waterproof permanent marker or printed label should be used to label each translational research tissue biospecimen with:

patient ID (XXXX-3026-YYYY)
patient ID (XXXX-3026-YYYY)
specimen code (see above)
collection date (mm/dd/yyyy)
surgical pathology accession number
block number

Note: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

Required Documentation
All FFPE tissue should be submitted with the following documentation:
- Corresponding pathology report or Pathology Verification Form (Appendix H)
- FFPE Materials Verification Form (Appendix G)
- Translational Research – FFPE Submission Form (printout of form completed in Rave)

III. Whole Blood Shipped to the Biopathology Center
1. Label the lavender/purple top (EDTA) collection tube(s) as described below. Multiple tubes may be used to collect the required amount. **Do not use glass blood collection tubes.**
2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.
4. Immediately freeze the whole blood in an upright position in a -70°C to -80°C freezer or by direct exposure with dry ice until ready to ship. If a -70°C to -80°C freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

Labeling Whole Blood
A waterproof permanent marker or printed label should be used to label each translational research whole blood biospecimen with:

patient ID (XXXX-3026-YYYY)
specimen code (WB01)
collection date (mm/dd/yyyy)

Required Documentation
All whole blood should be submitted with the following documentation:
- Translational Research – Whole Blood Submission Form (printout of form completed in Rave)

IV. Shipping Translational Research Biospecimens
- Translational research biospecimens must not be shipped until after patient registration.
- The required documentation must be included for each translational research biospecimen.
- All translational research biospecimens should be shipped to:

  Biopathology Center / Protocol GOG-3026
  Nationwide Children's Hospital
  700 Children's Dr, WA1340
  Columbus, OH 43205
  Phone: 614-722-2865
  FAX: 614-722-2897
  Email: BPCBank@nationwidechildrens.org

A. FFPE Tissue Shipped to the Biopathology Center
FFPE tissue and all required documentation should be shipped using your own container at your own expense to the Biopathology Center (address above). **Do not ship FFPE tissue for Saturday delivery.**

B. Whole Blood Shipped to the Biopathology Center

Frozen whole blood should be shipped using the biospecimen kit provided to the Biopathology Center (address above). If including frozen whole blood from more than one patient in a kit, each whole blood specimen should be placed in a separate zip-lock bag.

Frozen biospecimens should be shipped **Monday through Thursday for Tuesday through Friday delivery**. Do not ship frozen biospecimens on Friday or the day before a holiday. Note: Saturday delivery is not available for frozen biospecimens.

Frozen biospecimens should be stored in an ultra-cold freezing/storage space (i.e., ultra-cold ≤-70^{o}C freezer, liquid nitrogen, or direct exposure with dry ice) until the biospecimens can be shipped.

Shipping Frozen Translational Research Biospecimens in a Single Chamber Kit

1. Pre-fill the kit chamber about 1/3 full with dry ice.
2. Place the frozen biospecimens from patient in a separate zip-lock bag.
3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing both envelopes.
4. Place the Tyvek envelope containing the frozen biospecimens into the kit and fill the chamber to the top with dry ice.
5. Insert a printout of the Rave-completed Translational Research – Whole Blood Submission Form for each whole blood biospecimen.
6. Place the cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner chamber.
7. Print a pre-paid FedEx air bill using the Kit Management link (https://ricapps.nationwidechildrens.org/KitManagement/). Attach the air bill.
8. Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.
9. Arrange for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

APPENDIX G – BIOPATHOLOGY CENTER FFPE MATERIALS VERIFICATION FORM

This form should be completed by the person in the pathology department who provides the FFPE materials to the requestor. ***Please return this form, along with the FFPE materials, to the requestor.*** *The requestor must include this completed form with the shipment of FFPE materials.*

REQUIRED FFPE MATERIALS

- **One** of the following tumor types must be submitted:
  - Archival **recurrent primary (FRP01)** or **recurrent metastatic (FRM01)** tumor – i.e., collected prior to study treatment.
  - Archival **primary (FP01)** or **metastatic (FM01)** tumor – i.e., collected prior to any treatment.
- Every attempt should be made to provide an FFPE block; however, if a block cannot be provided on a permanent basis, then 20 unstained slides (10 charged [5µm] and 10 uncharged [10µm]) must be submitted.
- All tissue sections must be cut sequentially from **one** block.

PATIENT INFORMATION (to be completed by person requesting FFPE materials)

Study ID: _____

FFPE MATERIALS (to be completed by person preparing FFPE materials)

Surgical Pathology #: _____ **Block #:** _____ **Date Collected:** __ __ / __ __ / __ __ __ _

Tissue Type: □ Recurrent Primary (FRP01) □ Recurrent Metastatic (FRM01)

□ Primary (FP01) □ Metastatic (FM01)

Site: □ Ovary □ Fallopian Tube □ Peritoneum

□ Other, specify _____

Materials Prepared	Count	Thickness (µm)
Block		**Not Applicable**
Charged slides		
Uncharged slides		

_____ _____

Name of person preparing materials Date

APPENDIX H - BIOPATHOLOGY PATHOLOGY VERIFICATION FORM

A copy of the corresponding pathology report must be shipped with all tissue biospecimens sent to the Biopathology Center.

If a pathology report is not available, a copy of the radiology report or operative report from the tissue collection procedure in addition to a completed copy of this appendix (i.e., Pathology Verification from) **must** also be submitted to the Biopathology Center.

Note: If this information is not provided with the tissue biospecimen, then the tissue will not be accepted by the Biopathology Center.

Please have the Pathologist responsible for signing out this patient's case complete the following:

Study ID: _____

Date of Procedure (mm/dd/yyyy): _____

Tissue Type (circle one): **Recurrent Primary** **Recurrent Metastatic**

Primary **Metastatic**

Site Tissue Taken From: _____

Diagnosis: _____

Recurrent disease documented by: _____

I agree that this tissue may be released for research purposes only and that the release of this tissue will not have any impact on the patient's care.

_____ _____

Pathologist's Signature Date

_____

Pathologist's Printed Name