University Health Network

# FORMULARY MONOGRAPH

*The Clinical Evaluation of letrozole and ribociclib (Kisqali Femara Co-Pack Kit)*

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## I. EXECUTIVE SUMMARY

The CDK inhibitors have been studied in women with advanced or metastatic breast cancers that are HER2-negative and ER-positive, or HR-positive. Currently, there are 3 CDK inhibitors approved by the FDA. Ribociclib is the 2nd of the three CDK inhibitors to be approved and, like the other newer agents, have little clinical literature to effectively evaluate their overall efficacy. The National Comprehansive Cancer Network (NCCN) guidelines for post-memnopausal women with recurrent or metastatic cancer (ER- or PR-+, either HER2, _ or +) have been updated to include 2 of the 3 CDK Inhibitors, palbociclib and ribociclib. Both are recommended as a Category 1, first-line treatment option. The treatment guidleines do not recommend one CDK over the other. The NCCN states systemic treatment or metastatic or recurrent cancer prolongs survival and can improve quality of life.

Published data for ribociclib includes its use only with letrozole. As such, ribociclib is aavailable packaged with letrozole as a "copack." The dosing regimen for ribociclib is 21 days on therapy, followed by 7 days off. Ribociclib requires more toxicity-related dose adjustments than palbociclib.

The CDK inhibitors are effective and meet safety thresholds for indicated uses. All CDK inhibitors, including ribociclib, had frequent, and often severe, neutropenia (Grade 3 or greater in more than 60% of the clinical trial cases). Dose reductions for QT prolongation, neutropenia, and ALT and/or AST are recommended in the ribociclib package insert. Other frequent adverse events included leukopenia, anemia and GI events. No safety information is provided for use in pregnancy; therefore, contraception should be used during and after treatment.

Additional clinical trials are on-going for ribociclib for its use in metastatic or recurring breast cancer, as well as other cancer types.

## II. DISEASE STATE SUMMARY

Breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast. Every year about 180,000 cases of invasive breast cancer and 40,000 deaths will occur in the United States. In addition, about 2000 men

will be diagnosed with breast cancer. Epithelial malignancies of the breast are the most common cause of cancer in women (excluding skin cancer), accounting for about one-third of all cancer in women. As a result of improved treatment and earlier detection, the mortality rate from breast cancer has begun to decrease very substantially in the United States.

Once metastatic disease is suspected, careful evaluation of the primary disease history, current symptoms, and existing comorbid diseases is essential. The history of the primary disease should include a review of the initial presentation, stage of disease, histology, hormone receptor and *HER2*/neu status, nuclear grade, and treatment modalities employed. Knowledge of the initial tumor type may yield clues about the sites of disease as well as its biology. For instance, infiltrating ductal carcinoma most commonly involve the lungs, pleura, liver, and brain. Infiltrating lobular carcinoma may metastasize to unusual sites such as the bone marrow, meninges, peritoneum, and retroperitoneal structures, such as the ureters[5].

If possible, a biopsy of the metastatic or recurrence site is required to confirm the histologic type, as well as ER, PR, and *HER2*/neu status, because there is some evidence of significant discordance in the receptor status between the time of diagnosis of the primary tumor and the time of diagnosis of metastasis[6,7]. Changes in ER status occur in 14.5% to 40% of cases, whereas changes in *HER2* expression/amplification range from 0% to 37%[8]. Pathologic confirmation is also essential in patients suspected of having metastases if the clinical presentation or course is not typical. Such relapse scenarios include single-lesion metastasis, unusual metastatic sites, and long DFI. Solitary lesions should always be biopsied because of the possibility that the lesion may not be not malignant or may be caused by a second different primary malignancy. This occurs in up to 10% of patients with solitary lesions and would have a direct impact on the treatment selection.

Determining the ER, PR, and HER2 status of the tumor at the time of diagnosis of early breast cancer and, if possible, at the time of recurrence is critical, both to gauge a patient's prognosis and to determine the best treatment regimen. In addition to ER status and PR status, the rate at which tumor divides (assessed by an immunohistochemical stain for Ki-67) and the grade and differentiation of the cells are also important prognostic factors. These markers may be obtained on core biopsy or surgical specimens, but not reliably on FNA cytology. Patients whose tumors are hormone receptor-positive tend to have a more indolent disease course than those whose tumors are receptor-negative. Moreover, treatment with an anti-hormonal agent is an essential component of therapy for hormone-receptor positive breast cancer at any stage. While up to 60% of patients with metastatic breast cancer will respond to hormonal manipulation if their tumors are ER-positive, less than 5% of patients with metastatic, ER-negative tumors will respond.

Another key element in determining treatment and prognosis is the amount of the *HER2* oncogene present in the cancer. HER2 overexpression is measured by an immunohistochemical assay that is scored using a numerical system: 0 and 1+ are considered negative for overexpression, 2+ is borderline/indeterminate, and 3+ is overexpression. In the case of 2+ expression, fluorescence in situ hybridization (FISH) is recommended to more accurately assess *HER2* amplification. Guidelines for the interpretation of *HER2* results by IHC and FISH have been published by the College of American Pathologists. According to these guidelines, a tumor is positive for HER2 amplification if one of the two criteria is met: (1) dual-probe HER2/CEP17 ratio is 2.0 or more or (2) dual-probe HER2/CEP17 ratio is less than 2.0 with an average HER2 copy number 6.0 signals per cell or greater. If the dual-probe HER2/CEP17 ratio is less than 2.0 with an average HER2 copy number of 4.0 to 5.9 signals per cell, this is equivocal. The presence of HER2 amplification and overexpression is of prognostic significance and predicts the response to trastuzumab. Occasionally, a tumor has an indeterminate HER2 result by both immunohistochemistry and FISH testing. The College of American Pathologists guidelines provide direction for further analysis in this situation.

Individually these biomarkers are predictive and thus provide insight to guide appropriate therapy. Moreover, when combined they provide useful information regarding risk of recurrence and prognosis. In general, tumors that lack expression of HER2, ER, and PR ("triple negative") have a higher risk of recurrence and metastases and are associated with a worse survival compared with other types. Neither endocrine therapy nor HER2-targeted agents are useful for this type of breast cancer, leaving chemotherapy as the only treatment option. In contrast, patients with early stage, hormone receptor–positive breast cancer may not benefit from the addition of chemotherapy to hormonally targeted treatments. Several molecular tests have been developed to assess risk of recurrence and to predict which

patients are most likely to benefit from chemotherapy. Oncotype DX (Genomic Health) evaluates the expression of 21 genes relating to ER, PR, HER2, and proliferation in a tumor specimen and categorizes a patient's risk of recurrence (recurrence score) as high, intermediate, or low risk. In addition to providing prognostic information, the test also has predictive value since studies have shown that patients in the high-risk category are most likely to respond to chemotherapy. This test is primarily indicated for ER-positive, lymph node-negative tumors but at least one study has shown that it may also have value in node-positive tumors. Centralized testing for ER, PR, *HER2* and Ki67 by standard immunohistochemical techniques is able to provide as much prognostic information as Oncotype DX. Mammaprint (Agendia) is an FDA-approved 70-gene signature assay that is available for evaluating prognosis. This test classifies patients into good and poor prognostic groups to predict clinical outcome and may be used on patients with hormone receptor positive or negative breast cancer. Several other assays are in development to better stratify patients based on risk assessment.

Despite great advances in the treatment of MBC, this condition remains largely incurable, with a median survival of 2 to 3 years. The therapeutic concepts in MBC have changed with the realization that breast cancer is a conglomerate of several molecularly defined subtypes, each with a distinct prognosis, clinical course, and sensitivity to existing therapeutics. Treatment for MBC has dramatically evolved, incorporating new hormonal therapies, cytotoxic agents, and monoclonal antibodies. Refinements of chemotherapy with different combinations of newer agents along with modulating agents and growth factor support have allowed further advancement in the treatment of MBC. Despite great enthusiasm for targeted therapies, these agents have exhibited modest activity when used as single agents. A better understanding of the molecular biology of signaling pathways and the discovery of new biomarkers will help select patients who benefit from specific treatments.

## III. DISEASE TREATMENT SUMMARY

Hormonally driven breast cancer may be particularly sensitive to inhibition of cell cycle regulatory proteins, called cyclin dependent kinases (CDK). A phase II randomized study evaluating letrozole with or without an oral CDK 4/6 inhibitor (palbociclib) for the first-line treatment of postmenopausal women with hormone receptor–positive advanced breast cancer demonstrated a striking and highly significant doubling of progression-free survival with palbociclib compared to the control arm. The 2016 results from the phase III confirmatory study (PALOMA-2) in the first-line setting confirmed a significant 10-month improvement in progression-free survival associated with the use of palbociclib plus letrozole. Moreover, results from the phase III PALOMA-3 study showed the addition of palbociclib to fulvestrant in *pretreated* patients with ER-positive metastatic breast cancer more than doubled progression-free survival. Palbociclib in combination with letrozole is FDA-approved for patients with previously untreated ER-positive HER2-negative metastatic breast cancer; palbociclib in combination with fulvestrant is FDA-approved for patients whose advanced disease has progressed after hormonally targeted therapy. FDA-approved ribociclib, another CDK 4/6 inhibitor, in combination with letrozole for first-line metastatic hormone receptor–positive breast was shown to significantly improve progression-free survival in a phase III clinical trial (MONALEESA-2). In general, palbociclib and ribociclib are well tolerated; however, they are associated with grade 3/4 neutropenia; thus, monitoring patients closely is required. A third CDK4/6 inhibitor, abemaciclib, was recently approved for HR-positive, HER2-negative advanced or metastatic breast cancer in combination with fulvestrant (in women with disease progression following endocrine therapy) or as monotherapy (in women with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting).

# IV. HIGHLIGHTS OF PRESCRIBING INFORMATION

## Packager

Novartis Pharmaceuticals Corporation

## Indications and usage

KISQALI FEMARA CO-PACK, a co-packaged product containing ribociclib, a kinase inhibitor, and letrozole, an aromatase inhibitor, is indicated 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.

## Dosage and administration

KISQALI FEMARA CO-PACK tablets are taken in combination orally with or without food.

- KISQALI recommended starting dose: 600 mg orally (three 200 mg tablets) taken once daily for 21 consecutive days followed by 7 days off KISQALI treatment.
- KISQALI dose interruption, reduction, and/or discontinuation may be required based on individual safety and tolerability.
- FEMARA: 2.5 mg (one tablet) continuously for a 28-day cycle.

## Dosage forms and strengths section

Tablets:

- KISQALI: 200 mg
- FEMARA: 2.5 mg

## Contraindications

None.

## Warnings and precautions

- QT interval prolongation: Monitor electrocardiograms (ECGs) and electrolytes prior to initiation of treatment with KISQALI. Repeat ECGs at approximately Day 14 of the first cycle and at the beginning of the second cycle, and as clinically indicated. Monitor electrolytes at the beginning of each cycle for 6 cycles, and as clinically indicated.
- Hepatobiliary toxicity: Increases in serum transaminase levels have been observed. Perform Liver Function Tests (LFTs) before initiating treatment with KISQALI FEMARA CO-PACK. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.
- Neutropenia: Perform Complete Blood Count (CBC) before initiating therapy with KISQALI FEMARA CO-PACK. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.
- Embryo-Fetal toxicity: Can cause fetal harm when administered to pregnant women. Advise women of child-bearing potential of the potential risk to a fetus and to use effective contraception during therapy.

## Adverse reactions

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

## Drug interactions

- CYP3A4 Inhibitors: Avoid concomitant use of KISQALI FEMARA CO-PACK with strong CYP3A inhibitors. If strong inhibitors cannot be avoided, reduce KISQALI dose.
- CYP3A4 Inducers: Avoid concomitant use of KISQALI FEMARA CO-PACK with strong CYP3A inducers.
- CYP3A substrates: The dose of sensitive CYP3A substrates with narrow therapeutic indices may need to be reduced when given concurrently with KISQALI FEMARA CO-PACK.
- Drugs known to prolong QT interval: Avoid concomitant use of drugs known to prolong QT interval such as anti-arrhythmic medicines.

## Use in specific populations

Lactation: Advise not to breastfeed.

## Overdosage

There were no known cases of overdose with ribociclib and letrozole in Study 1. General symptomatic and supportive measures should be initiated in all cases of overdose where necessary.

## Clinical pharmacology

Ribociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signaling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb).

In vitro, ribociclib decreased pRb phosphorylation leading to arrest in the G1 phase of the cell cycle and reduced cell proliferation in breast cancer cell lines. In vivo, treatment with single agent ribociclib in a rat xenograft model with human tumor cells led to decreased tumor volumes which correlated with inhibition of pRb phosphorylation.

Letrozole is a nonsteroidal competitive inhibitor of the aromatase enzyme system by competitively binding to the heme of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues. In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens (primarily androstenedione and testosterone) to estrone and estradiol. The suppression of estrogen biosynthesis in peripheral tissues and in the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

In vivo studies, using patient-derived estrogen receptor positive breast cancer xenograft models, combination of ribociclib and antiestrogen (e.g. letrozole) resulted in increased tumor growth inhibition compared to each drug alone.

Ribociclib

Cardiac Electrophysiology
Serial, triplicate ECGs were collected following a single dose and at steady-state to evaluate the effect of ribociclib on the QTc interval in patients with advanced cancer. A pharmacokinetic-pharmacodynamic analysis included a total of 267 patients treated with ribociclib at doses ranging from 50 to 1200 mg, including 193 patients treated with ribociclib 600 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval. The estimated mean change from baseline in QTcF was 22.9 ms (90% CI: 21.6, 24.1) at the mean observed $C_{max}$ at steady-state following administration at the recommended 600 mg dose [see Warnings and Precautions (5.1)].

Letrozole

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg FEMARA (letrozole) suppress plasma concentrations of estradiol, estrone, and estrone sulfate by 75% to 95% from baseline with maximal suppression achieved within two-three days. Suppression is dose-related, with doses of 0.5 mg and higher giving many values of estrone and estrone sulfate that were below the limit of detection in the assays. Estrogen suppression was maintained throughout treatment in all patients treated at 0.5 mg or higher.

Letrozole is highly specific in inhibiting aromatase activity. There is no impairment of adrenal steroidogenesis. No clinically-relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose of FEMARA 0.1 mg to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1, 0.25, 0.5, 1, 2.5, and 5 mg did not indicate any attenuation of aldosterone or cortisol production. Glucocorticoid or mineralocorticoid supplementation is, therefore, not necessary.

No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0.1, 0.5, and 2.5 mg single doses of FEMARA or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1 mg to 5 mg. This indicates that the blockade of estrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH were not affected by letrozole in patients, nor was thyroid function as evaluated by TSH levels, T3 uptake, and T4levels.

Ribociclib exhibited over-proportional increases in exposure (peak plasma concentrations ($C_{max}$) and area under the time concentration curve (AUC)) across the dose range of 50 mg to 1200 mg following both single dose and repeated doses. Following repeated 600 mg once daily administration, steady-state was generally achieved after 8 days and ribociclib accumulated with a geometric mean accumulation ratio of 2.51 (range 0.972 to 6.40).

Letrozole's terminal elimination half-life is about 2 days and steady-state plasma concentration after daily 2.5 mg dosing is reached in 2-6 weeks. Plasma concentrations at steady state are 1.5 to 2 times higher than predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2.5 mg. These steady-state levels are maintained over extended periods, however, and continuous accumulation of letrozole does not occur.

Absorption and Distribution

Ribociclib

The time to reach $C_{max}$ ($T_{max}$) following ribociclib administration was between 1 and 4 hours.

Binding of ribociclib to human plasma proteins in vitro was approximately 70% and independent of concentration (10 to 10,000 ng/mL). Ribociclib was equally distributed between red blood cells and plasma with a mean in vivo blood-to-plasma ratio of 1.04. The apparent volume of distribution at steady-state (Vss/F) was 1090 L based on population PK analysis.

Food Effect: Compared to the fasted state, oral administration of a single 600 mg dose of KISQALI film-coated tablet with a high-fat, high-calorie meal (approximately 800 to 1000 calories with ~50% calories from fat, ~35% calories from carbohydrates, and ~15% calories from protein) had no effect on the rate and extent of absorption of ribociclib ($C_{max}$ GMR: 1.00; 90% CI: 0.898, 1.11; $AUC_{inf}$ GMR: 1.06; 90% CI: 1.01, 1.12) .

Letrozole

Letrozole is rapidly and completely absorbed from the gastrointestinal tract and absorption is not affected by food. It is metabolized slowly to an inactive metabolite whose glucuronide conjugate is excreted renally, representing the major clearance pathway. About 90% of radiolabeled letrozole is recovered in urine.

Letrozole is weakly protein bound and has a large volume of distribution (approximately 1.9 L/kg).

Metabolism and Elimination/Excretion

Ribociclib

In vitro and in vivo studies indicated ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of radio-labeled ribociclib to humans, the primary metabolic pathways for ribociclib involved oxidation (dealkylation, C and/or N-oxygenation, oxidation (-2H)) and combinations thereof. Phase II conjugates of ribociclib Phase I metabolites involved N-acetylation, sulfation, cysteine conjugation, glycosylation and glucuronidation. Ribociclib was the major circulating drug-derived entity in plasma (44%). The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803,

N-demethylation), and M1 (secondary glucuronide), each representing an estimated 9%, 9%, and 8% of total radioactivity, and 22%, 20%, and 18% of ribociclib exposure. Clinical activity (pharmacological and safety) of ribociclib was due primarily to parent drug, with negligible contribution from circulating metabolites.

Ribociclib was extensively metabolized with unchanged drug accounting for 17% and 12% in feces and urine, respectively. Metabolite LEQ803 was a significant metabolite in excreta and represented approximately 14% and 4% of the administered dose in feces and urine, respectively. Numerous other metabolites were detected in both feces and urine in minor amounts (≤ 3% of the administered dose).

The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63% CV) and the geometric mean apparent oral clearance (CL/F) was 25.5 L/hr (66% CV) at steady-state at 600 mg in patients with advanced cancer. The geometric mean apparent plasma terminal half-life (T1/2) of ribociclib ranged from 29.7 to 54.7 hours and geometric mean CL/F of ribociclib ranged from 39.9 to 77.5 L/hr at 600 mg across studies in healthy subjects.

Ribociclib is eliminated mainly via feces, with a small contribution of the renal route. In 6 healthy male subjects, following a single oral dose of radio-labeled ribociclib, 92% of the total administered radioactive dose was recovered within 22 days; feces was the major route of excretion (69%), with 23% of the dose recovered in urine.

Letrozole

Metabolism to a pharmacologically-inactive carbinol metabolite (4,4'methanol-bisbenzonitrile) and renal excretion of the glucuronide conjugate of this metabolite is the major pathway of letrozole clearance. Of the radiolabel recovered in urine, at least 75% was the glucuronide of the carbinol metabolite, about 9% was two unidentified metabolites, and 6% was unchanged letrozole.

In human microsomes with specific CYP isozyme activity, CYP3A4 metabolized letrozole to the carbinol metabolite while CYP2A6 formed both this metabolite and its ketone analog. In human liver microsomes, letrozole inhibited CYP2A6 and inhibited CYP2C19, however, the clinical significance of these findings is unknown.

Specific Populations

Patients with Hepatic Impairment

Ribociclib

Based on a pharmacokinetic trial in patients with hepatic impairment, mild (Child-Pugh class A) hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (Child-Pugh class B; geometric mean ratio [GMR]: 1.50 for $C_{max}$; 1.32 for $AUC_{inf}$) and severe (Child-Pugh class C; GMR: 1.34 for $C_{max}$; 1.29 for $AUC_{inf}$) hepatic impairment. Based on a population pharmacokinetic analysis that included 160 patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib, further supporting the findings from the dedicated hepatic impairment study.

Letrozole

The effect of hepatic impairment on FEMARA exposure in noncirrhotic cancer patients with elevated bilirubin levels has not been determined.

In a study of subjects with mild to moderate non-metastatic hepatic dysfunction (e.g., cirrhosis, Child-Pugh classification A and B), the mean AUC values of the volunteers with moderate hepatic impairment were 37% higher than in normal subjects, but still within the range seen in subjects without impaired function.

In a pharmacokinetic study, subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh classification C, which included bilirubins about 2-11 times ULN with minimal to severe ascites) had twofold increase in exposure (AUC) and 47% reduction in systemic clearance. Breast cancer patients with severe hepatic impairment are thus expected to be exposed to higher levels of letrozole than patients with normal liver function receiving similar doses of this drug [see Clinical Pharmacology (12.3)].

Patients with Renal Impairment

Ribociclib

The pharmacokinetics of ribociclib in patients with severe renal impairment (eGFR < 30 mL/min/1.73m$^2$) is unknown. Mild (60 mL/min/1.73m$^2$ ≤ eGFR < 90 mL/min/1.73m$^2$) and moderate (30 mL/min/1.73m$^2$ ≤ eGFR < 60 mL/min/1.73m$^2$) renal impairment had no effect on the exposure of ribociclib based on a population PK analysis.

Letrozole

In a study of volunteers with varying renal function (24-hour creatinine clearance: 9 to 116 mL/min), no effect of renal function on the pharmacokinetics of single doses of 2.5 mg of FEMARA was found. In addition, in a study of 347 patients with advanced breast cancer, about half of whom received 2.5 mg FEMARA and half 0.5 mg FEMARA, renal impairment (calculated creatinine clearance: 20 to 50 mL/min) did not affect steady-state plasma letrozole concentrations.

Additional pharmacokinetic information on ribociclib:

The pharmacokinetics of ribociclib was investigated in patients with advanced cancer following oral daily doses ranging from 50 mg to 1200 mg. Healthy subjects received single oral doses of 400 or 600 mg or repeated daily oral doses (8 days) at 400 mg.

Effect of Age, Weight, Gender, and Race

Population PK analysis showed that there are no clinically relevant effects of age, body weight, gender, or race on the systemic exposure of ribociclib.

Drug Interaction Studies

Drugs That Affect Ribociclib Plasma Concentrations

CYP3A inhibitors: A drug interaction trial in healthy subjects was conducted with ritonavir (a strong CYP3A inhibitor). Compared to ribociclib alone, ritonavir (100 mg twice a day for 14 days) increased ribociclib $C_{max}$ and $AUC_{inf}$ by 1.7-fold and 3.2-fold, respectively, following a single 400 mg ribociclib dose. $C_{max}$ and AUC for LEQ803 (a prominent metabolite of LEE011, accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively. A moderate CYP3A4 inhibitor (erythromycin) is predicted to increase ribociclib $C_{max}$ and AUC by 1.3-fold and 1.9-fold, respectively.

CYP3A inducers: A drug interaction trial in healthy subjects was conducted with rifampicin (a strong CYP3A4 inducer). Compared to ribociclib alone, rifampicin (600 mg daily for 14 days) decreased ribociclib $C_{max}$ and $AUC_{inf}$ by 81% and 89%, respectively, following a single 600 mg ribociclib dose. LEQ803 $C_{max}$ increased 1.7-fold and $AUC_{inf}$ decreased by 27%, respectively. A moderate CYP3A inducer (efavirenz) is predicted to decrease ribociclib $C_{max}$ and AUC by 37% and 60%, respectively.

Drugs That Are Affected By KISQALI

CYP3A4 and CYP1A2 substrates: A drug interaction trial in healthy subjects was conducted as a cocktail study with midazolam (sensitive CYP3A4 substrate) and caffeine (sensitive CYP1A2 substrate). Compared to midazolam and caffeine alone, multiple doses of ribociclib (400 mg once daily for 8 days) increased midazolam $C_{max}$ and $AUC_{inf}$ by 2.1-fold and 3.8-fold, respectively. Administration of ribociclib at 600 mg once daily is predicted to increase midazolam $C_{max}$ and AUC by 2.4-fold and 5.2-fold, respectively. The effect of multiple doses of 400 mg ribociclib on caffeine was minimal, with $C_{max}$ decreased by 10% and $AUC_{inf}$ increased slightly by 20%. Only weak inhibitory effects on CYP1A2 substrates are predicted at 600 mg ribociclib once daily dose.

Gastric pH-elevating agents: Coadministration of ribociclib with drugs that elevate the gastric pH was not evaluated in a clinical trial; however, altered ribociclib absorption was not identified in a population PK analysis and was not predicted using physiology based PK models.

Letrozole: Data from a clinical trial in patients with breast cancer and population PK analysis indicated no drug interaction between ribociclib and letrozole following coadministration of the drugs.

Anastrozole: Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and anastrozole following coadministration of the drugs.

Exemestane: Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and exemestane following coadministration of the drugs.

In vitro Studies

Effect of ribociclib on CYP enzymes: In vitro, ribociclib was a reversible inhibitor of CYP1A2, CYP2E1 and CYP3A4/5 and a time-dependent inhibitor of CYP3A4/5, at clinically relevant concentrations. In vitro evaluations indicated that KISQALI has no potential to inhibit the activities of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 at clinically relevant concentrations. It has no potential for time-dependent inhibition of CYP1A2, CYP2C9, and CYP2D6, and no induction of CYP1A2, CYP2B6, CYP2C9 and CYP3A4 at clinically relevant concentrations.

Effect of ribociclib on transporters: In vitro evaluations indicated that KISQALI has a low potential to inhibit the activities of drug transporters P-gp, OATP1B1/B3, OCT1, MATEK2 at clinically relevant concentrations. KISQALI may inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations.

Effect of transporters on ribociclib: Based on in vitro data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of ribociclib at therapeutic doses.

### How supplied/Storage and handling section

KISQALI FEMARA CO-PACK is dispensed in a carton for a total of 28 days of therapy.

Each carton contains individual ribociclib and letrozole drug products as follows:

KISQALI (ribociclib) Tablets:

200 mg tablets.

Light greyish violet, round, curved with beveled edge, debossed with “RIC” on one side and “NVR” on the other side.

FEMARA (letrozole) Tablets:

2.5 mg tablets.

Dark yellow, round, slightly biconvex, with beveled edges, imprinted with the letters “FV” on one side and “CG” on the other side.

KISQALI FEMARA CO-PACK Cartons:

- NDC 0078-0923-61 - 3 Blister packs, containing 21 tablets (200 mg per tablet) (600 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA
- NDC 0078-0916-61 - 3 Blister packs, containing 14 tablets (200 mg per tablet) (400 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA
- NDC 0078-0909-61 - 1 Blister pack, containing 21 tablets (200 mg per tablet) (200 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA

Store KISQALI FEMARA CO-PACK at 20°C to 25°C (68°F to 77°F). Store in the original package.

## V. PUBLISHED EVIDENCE REVIEWED

## Literature Comparison Table

| [ref] | Citation | Evidence Grade | Intervention | N | Duration | Population | Design | Endpoints | Results/Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Hortobagyi GN - 2016 | 1a | Ribociclib 600 mg daily in 4-week cycles plus letrozole 2.5 mg daily (n=334) Placebo plus letrozole 2.5 mg daily (n=334) | N = 668 | Treatment period: day of the first dose to disease progression, unacceptable toxicity, death, or discontinuation of treatment for other reasons | Postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer who had not received prior treatment | DB MC Phase III RCT | Primary Progression Free Survival (PFS) Secondary Overall Survival (OS) Safety | Primary: Median PFS: not reached (95% CI, 19.3 months to not reached) in the ribociclib/letrozole group vs 14.7 months (95% CI, 13.0 to 16.5) in the placebo/letrozole group (HR, 0.56; 95% CI, 0.43 to 0.72; p<0.001) Rate of PFS at 18 months: 63% ribociclib vs 42.2% placebo Secondary: OS: data not available Safety: Common grade 3/4 AEs: neutropenia (59.3% with ribociclib/letrozole vs 0.9% with placebo/letrozole), leukopenia (21.0% with ribociclib/letrozole vs 0.6% with placebo/letrozole) |
| 2 | Curigliano G - 2016 | 1b | 2.5mg/day letrozole alone (n=4) 2.5mg/day letrozole with 400mg/day ribociclib (n=6) 2.5mg/day letrozole with 600mg/day ribociclib (n=4) | N = 14 | 14 days | postmenopausal women (median age of 65) with resectable, HR+, human epidermal growth factorreceptor 2-negative (HER2-) early BC | MC RCT | Primary Assess the difference in antiproliferative marker Ki67 from baseline to time of surgery Secondary Assessment of safety, tolerability, and PK Evaluation of PD markers related to ribociclib activity in BC | 13 patients completed (93%) Primary: Study was prematurely terminated due to low patient enrollment in July, 2014 Secondary All AEs were mild to moderate w no associated Grade 3/4 AEs Following dosing, both ribociclib and letrozole were rapidly absorbed. Cmax w/I 2-4 hrs. Plasma concentration increased 2-3 fold from Day 1 to Day 14. |

# VI. THERAPEUTIC EFFICACY

## Summary of Published Literature

The CDK inhibitors have been studied in women with advanced or metastatic breast cancers that are HER2-negative and ER-positive, or HR-positive. Currently, there are 3 CDK inhibitors approved by the FDA. Ribociclib is the 2nd of the three CDK inhibitors to be approved and, like the other newer agents, have little clinical literature to effectively evaluate their overall efficacy.

The combination of ribociclib and letrozole has been studied in postmenopausal women The time of Progression Free Survival (PFS) was significantly improved with ribociclib plus letrozole compared to letrozole alone when used first-line. It is important to note the final PFS with ribociclib plus letrozole could not be determined because the trial was terminated early due to lack of enrollment.

Overall survival (OS) with ribociclib plus letrozole could not be determined due to length of trials. Progression Free Survival (PFS) is a commonly used proxy, but is controversial as a replacement for OS, which is the gold standard.

There are no studies directly comparing ribociclib to other effective agents, including other CDK inhibitors.

# VII. REFERENCES


1. Karuturi M, Valero V, Chavez-MacGregor M. Metastatic Breast Cancer. In: Kantarjian HM, Wolff RA. eds. *The MD Anderson Manual of Medical Oncology, 3e* New York, NY: McGraw-Hill
2. Hortobagyi GN et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med. 2016 Nov 3;375(18):1738–48
3. Freedman RA, Tolaney SM, 11/04/2017, Efficacy and safety in older patient subsets in studies of endocrine monotherapy versus combination therapy in patients with HR+/HER2- advanced breast cancer: a review., Breast cancer research and treatment,
4. Sonke GS, Hart LL, Campone M, Erdkamp F, Janni W, Verma S, Villanueva C, Jakobsen E, Alba E, Wist E, Favret AM, Bachelot T, Hegg R, Wheatley-Price P, Souami F, Sutradhar S, Miller M, Germa C, Burris HA, 10/22/2017, Ribociclib with letrozole vs letrozole alone in elderly patients with hormone receptor-positive, HER2-negative breast cancer in the randomized MONALEESA-2 trial., Breast cancer research and treatment,
5. Polk A, Kolmos IL, Kümler I, Nielsen DL, 01/23/2017, Specific CDK4/6 inhibition in breast cancer: a systematic review of current clinical evidence., ESMO open, Vol. 1, Issue 6, Pages e000093
6. Xu H, Yu S, Liu Q, Yuan X, Mani S, Pestell RG, Wu K, 04/24/2017, Recent advances of highly selective CDK4/6 inhibitors in breast cancer., Journal of hematology & oncology, Vol. 10, Issue 1, Pages 97
7. Corona SP, Ravelli A, Cretella D, Cappelletti MR, Zanotti L, Dester M, Gobbi A, Petronini PG, Generali D, 02/24/2017, CDK4/6 inhibitors in HER2-positive breast cancer., Critical reviews in oncology/hematology, Vol. 112, Pages 208-214
8. López-Tarruella S, Jerez Y, Márquez-Rodas I, Echavarria I, Martin M, 07/31/2017, Ribociclib for the treatment of advanced hormone receptor-positive, HER2-negative breast cancer., Future oncology (London, England), Vol. 13, Issue 24, Pages 2137-2149
9. Bilgin B, Sendur MAN, Şener Dede D, Akıncı MB, Yalçın B, 07/25/2017, A current and comprehensive review of cyclin-dependent kinase inhibitors for the treatment of metastatic breast cancer., Current medical research and opinion, Vol. 33, Issue 9, Pages 1559-1569
10. 11/03/2016, Ribociclib Lengthens Breast Cancer Survival., Cancer discovery, Vol. 6, Issue 12, Pages 1299
11. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, Campone M, Blackwell KL, André F, Winer EP, Janni W, Verma S, Conte P, Arteaga CL, Cameron DA, Petrakova K, Hart LL, Villanueva C, Chan A, Jakobsen E, Nusch A, Burdaeva O, Grischke EM, Alba E, Wist E, Marschner N, Favret AM, Yardley D, Bachelot T, Tseng LM, Blau S, Xuan F, Souami F, Miller M, Germa C, Hirawat S, O'Shaughnessy J, 11/03/2016, Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer., The New England journal of medicine, Vol. 375, Issue 18, Pages 1738-1748
12. Roskoski R, 03/16/2016, Cyclin-dependent protein kinase inhibitors including palbociclib as anticancer drugs., Pharmacological research, Vol. 107, Pages 249-275

# APPENDIX

## Relevant Clinical Trials

| Status | Study | Conditions | Interventions |
|---|---|---|---|
| Recruiting | A Study Assessing Efficacy & Safety of Ribociclib in Patients With Advanced Well/Dedifferentiated Liposarcoma | Liposarcomas, Dedifferentiated; Liposarcoma - Well Differentiated; Liposarcoma; Mixed Type; Soft-Tissue Sarcoma | Drug: Ribociclib |
| Recruiting | Ribociclib (LEE011) in Preoperative Glioma and Meningioma Patients | Glioblastoma Multiforme; Meningioma | Drug: Ribociclib |
| Recruiting | Early-Phase Study to Assess Inhibitor Ribociclib in Patients With Recurrent Glioblastoma or Anaplastic Glioma | Glioblastoma; Glioma | Drug: Ribociclib |
| Recruiting | Phase I Evaluating the Combination of Ribociclib+Capecitabine in Locally Advanced/Metastatic Breast Cancer HER2 Negative | Breast Cancer | Drug: Combination of ribociclib + capecitabine |
| Recruiting | Study of Ribociclib (LEE011), Everolimus, and Letrozole, in Patients With Advanced or Recurrent Endometrial Carcinoma | Malignant Neoplasms of Female Genital Organs; Endometrial Carcinoma | Drug: Ribociclib; Drug: Everolimus; Drug: Letrozole |
| Recruiting | Ribociclib + PDR001 in Breast Cancer and Ovarian Cancer | Metastatic Hormone-Receptor-Positive (HR+) Breast Cancer; HER2-Negative Breast Cancer; Metastatic Epithelial Ovarian Cancer | Drug: Ribociclib; Drug: PDR001; Drug: Fulvestrant |
| Recruiting | Ribociclib (Ribociclib (LEE-011)) With Platinum-based Chemotherapy in Recurrent Platinum Sensitive Ovarian Cancer | Ovarian Cancer; Fallopian Tube Cancer; Peritoneal Carcinoma | Drug: ribociclib; Drug: Paclitaxel; Drug: Carboplatin |
| Recruiting | Ribociclib and Doxorubicin in Treating Patients With Metastatic or Advanced Soft Tissue Sarcomas That Cannot Be Removed by Surgery | Metastatic Angiosarcoma; Metastatic Epithelioid Sarcoma; Metastatic Fibrosarcoma; Metastatic Leiomyosarcoma; Metastatic Liposarcoma; Metastatic Malignant Peripheral Nerve Sheath Tumor; Metastatic Synovial Sarcoma; Metastatic Undifferentiated Pleomorphic Sarcoma; Myxofibrosarcoma; Pleomorphic Rhabdom | Drug: Doxorubicin; Drug: Ribociclib |
| Completed | Study of Safety and Efficacy in Patients With Malignant Rhabdoid Tumors (MRT) and Neuroblastoma | Malignant Rhabdoid Tumors (MRT), Neuroblastoma | Drug: LEE011 |
| Recruiting | LEE001 and Chemoembolization In Patients With Advanced Hepatocellular Carcinoma | Hepatocellular Carcinoma | Drug: LEE011; Procedure: Chemoembolization |
| Recruiting | Ribociclib (LEE011) Rollover Study for Continued Access | Continued Access to Study Treatment(s), Cancers With a Mass, Bulky Tumor, Nodule, Lump, Advanced Cancer, Advanced Solid Tumors, Advanced Solid Malignancies | Drug: LEE011 |
| Recruiting | Letrozole Plus Ribociclib or Placebo as Neo-adjuvant Therapy in ER-positive, HER2-negative Early Breast Cancer | Breast Cancer | Drug: Letrozole; Drug: Ribociclib; Drug: Placebo |
| Recruiting | Phase II Trial of Ribociclib and Everolimus in Advanced Dedifferentiated Liposarcoma (DDL) and Leiomyosarcoma (LMS) | Soft Tissue Sarcoma | Drug: Ribociclib; Drug: Everolimus |
| Recruiting | Adjuvant Ribociclib With Endocrine Therapy in Hormone Receptor+/HER2- High Risk Early Breast Cancer | Breast Cancer | Drug: Ribociclib; Drug: Placebo; Drug: Adjuvant endocrine therapy |

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| Recruiting | Enzalutamide With and Without Ribociclib for Metastatic, Castrate-Resistant, Chemotherapy-Naive Prostate Cancer That Retains RB Expression | Hormone-Resistant Prostate Cancer; Metastatic Prostate Carcinoma; Prostate Carcinoma Metastatic in the Bone; Stage IV Prostate Cancer | Drug: Enzalutamide; Drug: Ribociclib |
| Recruiting | A Study of LEE011 With Everolimus in Patients With Advanced Neuroendocrine Tumors | Neuroendocrine Tumors | Drug: LEE011; Drug: everolimus |
| Recruiting | Ribociclib and Bicalutamide in AR+ TNBC | Triple Negative Breast Cancer | Drug: ribociclib; Drug: ribociclib; Drug: Bicalutamide |
| Completed | Evaluation of Hepatic Function Impairment on the Pharmacokinetics of LEE011 | Normal Hepatic Function; Impaired Hepatic Function | Drug: LEE011 |