Clinical Cancer Research

FDA Approval: Ribociclib for the Treatment of Postmenopausal Women with Hormone Receptor–Positive, HER2-Negative Advanced or Metastatic Breast Cancer

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Abstract

On March 13, 2017, the FDA approved ribociclib (KISQALI; Novartis Pharmaceuticals Corp.), a cyclin-dependent kinase 4/6 inhibitor, in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)–positive, HER2-negative advanced or metastatic breast cancer. The approval was based on a randomized, double-blind, placebo-controlled, international clinical trial (MONALEESA-2). A total of 668 patients were randomized to receive either ribociclib plus letrozole (n = 334) or placebo plus letrozole (n = 334). An improvement in progression-free survival (PFS) was observed in patients receiving ribociclib plus letrozole compared with patients receiving placebo plus letrozole [HR = 0.556; 95% confidence interval (CI), 0.429–0.720]. Overall response rate (ORR) in patients with measurable disease was 52.7% (95% CI, 46.6–58.9) in the ribociclib plus letrozole arm and 37.1% (95% CI, 31.1–43.2) in the placebo plus letrozole arm. Overall survival data were immature. The most common adverse reactions observed in 20% or more of patients taking ribociclib were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache, and back pain. This article summarizes FDA decision-making and data supporting the approval of ribociclib. *Clin Cancer Res; 24(13); 2999–3004. ©2018 AACR.*

See related commentary by Spring and Bardia, p. 2981

Introduction

Advanced or metastatic breast cancer is a serious and life-threatening disease. In 2017, it is estimated that approximately 40,000 women will die of breast cancer in the United States (1). For postmenopausal patients with hormone receptor (HR)–positive, HER2-negative advanced or metastatic breast cancer, available endocrine-based therapies include aromatase inhibitors (letrozole, anastrozole, and exemestane), which are commonly used interchangeably, as well as tamoxifen and fulvestrant (2). These endocrine-based therapies provide a median progression-free survival (PFS) or median time to progression of approximately 9 to 12 months (2). Patients ultimately develop resistance and disease progression and receive multiple additional therapies, including many lines of chemotherapies that are associated with considerable toxicity. Therefore, improving on endocrine-based therapies represents an unmet medical need. The FDA granted accelerated approval to palbociclib, an inhibitor of cyclin-dependent kinase (CDK) 4 and 6, in this setting in 2014 (3) based on results of the PALOMA-1 study (4) and more recently regular approval in 2017 based on the confirmatory PALOMA-2 trial (5). Here, we present the FDA rationale for the approval of ribociclib in combination with an aromatase inhibitor for the treatment of postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer.

Chemistry

The chemical name of ribociclib succinate is butanedioic acid-7-cyclopentyl-*N*,*N*-dimethyl-2-{[5-(piperazin-1-yl) pyridin-2-yl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (1/1). Ribociclib is supplied in 200-mg tablets for oral administration.

Nonclinical Pharmacology and Toxicology

Ribociclib is a small-molecule kinase inhibitor targeting CDK4 and 6. Ribociclib had a greater *in vitro* potency for kinase inhibition of CDK4/cyclin D1 (IC_{50} = 8 nmol/L) compared with CDK6/cyclin D3 (IC_{50} = 39 nmol/L). In contrast, palbociclib did not appear to be selective for inhibiting CDK4/cyclin D1 (IC_{50} = 11 nmol/L) kinase activity *in vitro* compared with CDK6/cyclin D2 (IC_{50} = 15 nmol/L). The impact of differences in target selectivity for CDK4 versus CDK6 on efficacy in patients is unclear. Repeat-dose toxicology studies with daily administration of oral ribociclib for 27 weeks in rats and 39 weeks in dogs were conducted.

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doi: 10.1158/1078-0432.CCR-17-2369

Major target organs of toxicity included liver (vacuolation of biliary epithelia), testes (seminiferous tubule degeneration), epididymis (epithelial vacuolation, luminal cellular debris, and hypospermia), thymus (involution), and lymph nodes (lymphoid depletion). The effects of ribociclib on the male reproductive organs, the thymus, the lymph nodes, and the bone marrow are likely related to the primary pharmacologic activity of inhibiting CDK4/6 activity. At exposures (AUC) similar to those in patients receiving 600-mg ribociclib, QTc interval prolongation was observed in dogs. Ribociclib also induced premature ventricular contractions (PVC) in a dog that had approximately 5 times the exposure in patients at the recommended dose of 600 mg based on C_{max}. The mechanism of QTc prolongation is unclear; however, QTc prolongation does not appear to be a consequence of CDK4/6 inhibition based on available data. Reactive metabolites of ribociclib formed *in vitro* bound to a range of cellular proteins to form adducts in human liver microsomes and human, rat, or dog hepatocytes. No further follow-up studies were conducted to characterize these drug–protein adducts. Although these reactive hepatic metabolites provide a potential mechanism of the hepatobiliary toxicity observed in animals and patients administered ribociclib, there is no definitive evidence that they are related.

Ribociclib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay or an *in vivo* rat bone marrow micronucleus assay. On the basis of its mechanism of action and effects in animal developmental and reproductive toxicity studies, ribociclib can cause fetal harm if administered to a pregnant woman.

Clinical Pharmacology

The time to reach C_{max} (T_{max}) following ribociclib administration was between 1 and 4 hours. The geometric mean apparent plasma clearance was 25.5 L/hour, and the geometric mean plasma elimination half-life was 32 hours (range, 8–98 hours) at steady state at 600-mg once-daily dosing. Ribociclib showed no clinically significant food effect. Ribociclib is metabolized primarily by CYP3A.

Additional data submitted during the review demonstrated no clinically relevant drug interaction between the approved aromatase inhibitors (letrozole, anastrozole, or exemestane) and ribociclib, further supporting the extension of the indication. These data included interim pharmacokinetic and safety analyses from an open-label, phase Ib dose-finding study, of which one arm is evaluating ribociclib plus exemestane in patients with $ER^+/HER2^-$ advanced breast cancer who were resistant to prior letrozole or anastrozole therapy. In addition, the applicant submitted data from the anastrozole and ribociclib/placebo arms of MONALEESA-7, a double blind, phase III trial in premenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease.

Ribociclib can prolong the QT interval in a concentration-dependent manner, with mean increase in QTc interval exceeding 20 ms at 600-mg once-daily dosing. On the basis of exposure–response relationship for QT prolongation and simulation of exposure data, an alternative dosing regimen, such as 300 mg twice daily or 400 mg once daily, could potentially reduce the QT prolongation risk. However, only the 600-mg dose was studied in the study supporting approval, and exposure–response relationships for efficacy could not be established due to the lack of data (only 13% of patients in the MONALEESA-2 trial had valid predose pharmacokinetic samples). A postmarketing requirement (PMR) to study the effect of an alternative dosing regimen on safety and efficacy, after evaluation of ECG, pharmacokinetic, and efficacy data from the ongoing phase III MONALEESA-3 (CLEE011F2301) and MONALEESA-7 (CLEE011E2301) studies in advanced/metastatic breast cancer was agreed to with the applicant. An additional PMR was agreed upon to determine an appropriate dose of ribociclib in patients with severe renal impairment.

Clinical Trial Design

The approval of ribociclib was based on the MONALEESA-2 trial, an international, multicenter, randomized, double-blind, placebo-controlled, phase III study evaluating the efficacy and safety of treatment with ribociclib plus letrozole versus placebo plus letrozole in postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer who received no prior therapy for their advanced or metastatic disease. Patients who received (neo) adjuvant therapy for breast cancer were eligible. If the prior neo (adjuvant) therapy included letrozole or anastrozole, the disease-free interval had to be >12 months from the completion of treatment until randomization. Patients who received $\leq$14 days of letrozole or anastrozole for advanced disease prior to randomization were also allowed. Any prior (neo) adjuvant anticancer therapy had to be stopped at least 5 half-lives or 7 days before randomization (whichever was longer). Eligible patients were randomized in a 1:1 ratio to either ribociclib (600 mg once daily, days 1–21 in a 28-day cycle) plus letrozole (2.5 mg once daily, continuous) or placebo (once daily, days 1–21 in a 28-day cycle) plus letrozole (2.5 mg once daily, continuous). Randomization was stratified by the presence or absence of liver or lung metastases. Study treatment continued until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason. Patients in the placebo-plus-letrozole arm were not allowed to cross over to the ribociclib-plus-letrozole arm at the time of progression.

The primary efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST, with secondary endpoints of overall survival (OS), overall response rate (ORR), and retrospective PFS analysis by blinded independent central review (BICR). A preplanned efficacy analysis occurred at 243 total progression events or 80% of the planned events for the final analysis.

Efficacy Results

Demographics and disease characteristics are summarized in Table 1. All enrolled patients in MONALEESA-2 were female. All patients had positive estrogen and/or progesterone receptor status. With respect to prior antineoplastic therapy, the two treatment arms were also generally well-balanced; 46.6% had received chemotherapy and 51.3% had received hormonal therapy in the neoadjuvant or adjuvant setting. The major efficacy outcome measure was investigator-assessed PFS, which at the preplanned interim efficacy analysis, demonstrated an HR of 0.556 [95% confidence interval (CI), 0.429–0.720; one-sided P value < 0.0001] in favor of ribociclib plus letrozole. Median PFS in the ribociclib-plus-letrozole arm was not reached (95% CI, 19.3–not reached), and median PFS in the placebo-plus-letrozole

Table 1. Demographics and disease characteristics in the primary efficacy analysis

	Ribociclib plus letrozole $n = 334$	Placebo plus letrozole $n = 334$
Age in years		
Mean (SD)	61.4 (11.0)	61.9 (10.5)
Median (min–max)	62 (23–91)	63 (29–88)
Age category (*n*, %)		
<65 years	184 (55.1)	189 (56.6)
≥65 years	150 (44.9)	145 (43.4)
Race (*n*, %)		
Caucasian	269 (80.5)	280 (83.8)
Asian	28 (8.4)	23 (6.9)
Black	10 (3.0)	7 (2.1)
Native American	1 (0.3)	0
Pacific Islander	1 (0.3)	0
Other	12 (3.6)	8 (2.4)
Unknown	13 (3.9)	16 (4.8)
ECOG Performance Status (*n*, %)		
0	205 (61.4)	202 (60.5)
1	129 (38.6)	132 (39.5)
Region (*n*, %)		
Europe	150 (44.9)	146 (43.7)
North America	108 (32.3)	121 (36.2)
Asia	35 (10.5)	33 (9.9)
Latin America	7 (2.1)	7 (2.1)
Other	34 (10.2)	27 (8.1)
Stage at initial diagnosis (*n*, %)		
0	7 (2.1)	6 (1.8)
I	55 (16.5)	48 (14.4)
II	99 (29.3)	107 (32.0)
III	58 (17.4)	62 (18.6)
IV	115 (34.4)	108 (32.3)
Unknown	0	3 (0.9)
Missing	1 (0.3)	0
Stage at time of study entry (*n*, %)		
III	1 (0.3)	3 (0.9)
IV	333 (99.7)	331 (99.1)
Medication: hormonal therapy setting[a]		
Adjuvant	175 (51.8)	166 (49.7)
Neoadjuvant	0	4 (1.2)
Palliative	19 (5.7)	20 (6.0)
Prevention	3 (0.9)	2 (0.6)
Other	23 (6.9)	18 (5.4)
Current extent of disease (metastatic sites; *n*, %)		
Breast	8 (2.4)	11 (3.3)
Bone marrow	0	2 (0.6)
Bone	246 (73.7)	244 (73.1)
Bone only	69 (20.7)	78 (23.4)
Visceral	197 (59.0)	196 (58.7)
Liver	59 (17.7)	73 (21.9)
Lung	153 (45.8)	150 (44.9)
Other	22 (6.6)	18 (5.4)
Skin	15 (4.5)	10 (3.0)
Lymph nodes	133 (39.8)	123 (36.8)
Others	20 (6.0)	10 (3.0)
None	2 (0.6)	1 (0.3)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]A patient may have received treatment in more than one setting.

arm was 14.7 months (95% CI, 13.0–16.5). The ORR in patients with measurable disease was supportive, with an ORR of 52.7% (135/256; 95% CI, 46.6–58.9) in the ribociclib-plus-letrozole arm and 37.1% (91/245; 95% CI, 31.1–43.2) in the placebo-plus-letrozole arm. The blinded independent central radiologic review PFS assessment was consistent with investigator assessment. OS data were immature, with 6.5% of patients having died.

In an update to the FDA during the review, the applicant provided additional efficacy data on PFS and OS. In this unplanned analysis, investigator-assessed PFS demonstrated an HR of 0.559 (95% CI, 0.443–0.706) in favor of ribociclib plus letrozole. Median PFS in the ribociclib-plus-letrozole arm was reached at 22.4 months (95% CI, 20.8–not estimable), and median PFS in the placebo-plus-letrozole arm was 15.3 months (95% CI, 13.4–16.7). OS results remained immature.

Safety Results

The most common adverse reactions (AR) that occurred in at least 20% of patients in MONALEESA-2 were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache, and back pain. Dose reductions due to ARs occurred in 45% of patients receiving ribociclib plus letrozole and in 3% of patients receiving placebo plus letrozole. Permanent discontinuations due to ARs were reported in 7% of patients receiving ribociclib plus letrozole, most commonly from ALT increase (4%), AST increase (3%), and vomiting (2%). On-treatment deaths were reported in three cases due to an unknown cause, a sudden death (in the setting of grade 2 QT prolongation and grade 3 hypokalemia), and progressive disease. Ribociclib prolongs the QT interval in a concentration-dependent manner. In MONALEESA-2, one patient had a >500-msec postbaseline QTcF value and nine patients out of 329 (2.7%) had a >60-msec increase from baseline in QTcF interval, all which occurred within the first 4 weeks of therapy and were reversible with dose interruption. Nine patients (2.7%) in the ribociclib-plus-letrozole arm versus three patients (0.9%) in the placebo-plus-letrozole arm experienced syncope, and no patients experienced torsades de pointes. Although 75% of patients experienced neutropenia, 1.5% developed febrile neutropenia, and 0.9% required dose discontinuation, demonstrating appropriate management by dose interruptions and reductions. Four (1%) patients showed concurrent elevations in ALT or AST greater than three times the upper limit of normal (ULN) and total bilirubin greater than two times the ULN, with normal alkaline phosphatase, in the absence of cholestasis; all patients recovered after ribociclib discontinuation.

Regulatory Insights

Despite the fact that ribociclib was studied with letrozole in MONALEESA-2, the approved indication was expanded to include all aromatase inhibitors. During the review, the applicant submitted supportive safety and pharmacokinetic data for ribociclib plus exemestane from a phase Ib dose-finding study and for ribociclib plus anastrozole from MONALEESA-7, as described above. No new safety signals or clinically relevant drug–drug interactions between ribociclib and the other aromatase inhibitors were identified. This additional aromatase inhibitor data in combination with ribociclib as well as a strong scientific and clinical rationale supported a broadened indication of ribociclib plus aromatase inhibitors, as opposed to use with letrozole alone.

On May 4, 2017, the FDA also approved the ribociclib letrozole co-pack, a co-packaged product. Information previously submitted with the original ribociclib new drug application [(NDA) cross-referenced for the co-pack NDA] demonstrated that in the phase I multicenter, open-label, dose-escalation study of oral ribociclib in patients with advanced solid tumors or lymphomas, an ORR of 5.0% ($n = 4$) in 76 patients (21 with advanced/

Table 2. FDA benefit–risk assessment for ribociclib

Dimension	Evidence and uncertainties	Conclusions and reasons
Analysis of condition	• In 2017, ~252,710 women will be diagnosed with breast cancer in the United States, and 40,610 women will die of the disease. HR-positive cancers comprise the majority of cases.	Advanced and metastatic breast cancer is serious, life-threatening, and incurable and represents an unmet medical need.
Current treatment options	• Available therapies, which include aromatase inhibitors or tamoxifen, provide a median PFS or time to progression of ~9–12 months. • Aromatase inhibitors are commonly substituted in clinical practice. • At the time of ribociclib approval, palbociclib in combination with letrozole had received accelerated approval based on a 10-month improvement in median PFS compared with letrozole alone.	Endocrine-based therapies are used in the intended population as initial therapy if possible. Letrozole is considered an active comparator arm. Subsequent lines of therapy may result in substantial toxicities (some cumulative) for this population.
Benefit	• MONALEESA-2 demonstrated improved investigator-assessed PFS (primary endpoint) in the ribociclib + letrozole arm compared with placebo + letrozole arm (HR = 0.556; 95% CI, 0.429–0.720; one-sided $P < 0.0001$), with a median PFS not reached (95% CI, 19.3–not reached) for the ribociclib + letrozole arm and 14.7 months (95% CI, 13.0–16.5) for the placebo + letrozole arm. • ORR was 52.7% (95% CI, 46.6–58.9) in the ribociclib + letrozole arm and 37.1% (95% CI, 31.1–43.2) in the placebo + letrozole arm. • At the time of the PFS analysis, only 6.5% of patients had died, and overall survival data were immature.	Evidence of effectiveness was supported by a statistically significant and clinically meaningful PFS improvement. The study was large, double-blind, placebo controlled, and randomized. Supportive ORR, BICR, and subgroup analyses further substantiate the evidence of ribociclib benefit. Despite immature OS in this population, the substantial improvement in PFS represents a clinically meaningful benefit due to delay of progression and postponement of subsequent toxic therapies.
Risk	• Common ARs in ≥20% of patients in MONALEESA-2 were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache, and back pain. • Three on-treatment deaths occurred due to unknown cause, sudden death (in the setting of grade 2 QT prolongation and grade 3 hypokalemia), and progressive disease. • QT interval was prolonged in a concentration-dependent manner in patients treated with ribociclib. No torsades de pointes cases occurred. Syncope occurred in nine patients (2.7%) in the ribociclib + letrozole arm. • 75% of patients on ribociclib + letrozole experienced neutropenia.	The safety profile of ribociclib is acceptable for the intended population. Neutropenia appeared appropriately managed, as evidenced by a low frequency of discontinuations. Hepatobiliary toxicity was manageable with appropriate dose modifications, clearly delineated in labeling. Additional aromatase inhibitor data support a broadened indication combining ribociclib with the class of aromatase inhibitors.
Risk management	• Labeling for QT interval prolongation, hepatobiliary toxicity, and neutropenia are included in warnings and precautions. • Laboratory monitoring (including electrolytes) and ECG monitoring are recommended before and during treatment. • Patients at risk of QTc prolongation should avoid ribociclib use.	No risk evaluation and mitigation strategies (REMS) are indicated. The applicant agreed to study whether an alternative dosing regimen would mitigate the QT interval prolongation risk without compromising efficacy.

metastatic breast cancer) who were treated with a monotherapy dose of 600 mg of ribociclib on a 3-week-on, 1-week-off schedule was observed. In addition, there is a strong biologic rationale for combining endocrine-based therapies with CDK4 and 6 inhibitors (6–9). The ORR and this scientific rationale further support the contribution of combination therapy of letrozole to the overall therapeutic effect of ribociclib observed in MONALEESA-2 and therefore supports the co-pack approval.

Discussion

The approval of ribociclib was based primarily on a significant and clinically meaningful improvement in investigator-assessed PFS between ribociclib plus letrozole versus placebo plus letrozole in postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer. The safety profile of ribociclib was acceptable for the indicated patient population. The most clinically important ARs in MONALEESA-2 were QT interval prolongation, hepatobiliary toxicity, and neutropenia. Because of concerns regarding QT prolongation, deemed a serious risk related to the use of the drug, the applicant agreed to study an alternative dosing regimen, after evaluation of ECG, pharmacokinetic, and efficacy data from the ongoing phase III MONALEESA-3 (CLEE011F2301) and MONALEESA-7 (CLEE011E2301) studies in advanced/metastatic breast cancer, and submit the data to the FDA as a postmarketing requirement. In addition, QT prolongation, hepatobiliary toxicity, and neutropenia were included in the warnings and precautions section of labeling. The favorable benefit–risk profile supporting approval of ribociclib is summarized in Table 2.

Multiple CDK4 and 6 inhibitors are in development, and palbociclib also has regular approval in combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer. Although inferences regarding cross-trial comparisons should not be made, a consistent improvement with ribociclib plus letrozole and palbociclib plus letrozole is seen (Fig. 1).

Estrogen receptor–positive breast cancer is a heterogeneous disease, and many patients ultimately develop resistance to

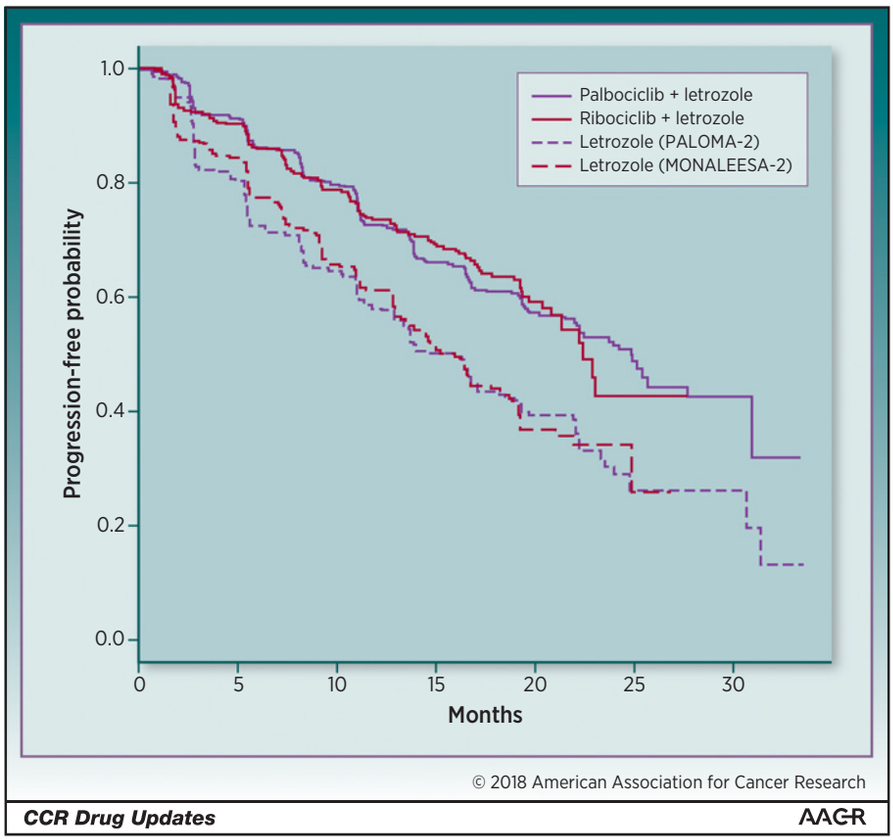

Figure 1.
Primary PFS results (local investigator using RECIST v1.1) of MONALEESA-2 (ribociclib + letrozole) and PALOMA-2 (palbociclib + letrozole). Improvement in PFS is seen across the CDK4/6 class of drugs. Cross-study inferences should not be made.

endocrine therapy alone. This underscores the importance of developing alternative therapeutic options, including combination strategies with endocrine-based and targeted therapies. In a span of approximately two years, the FDA has approved two CDK4/6 inhibitors for the first-line treatment of postmenopausal patients with advanced or metastatic breast cancer with HR-positive, HER2-negative disease. Selection of which particular CDK4 and 6 inhibitor to use is a practice-of-medicine issue outside the FDA's regulatory purview. In addition, based on results of the FALCON trial (10), fulvestrant was also approved for this population, further underscoring the development of therapeutic options in this space.

In summary, ribociclib in combination with letrozole demonstrated a statistically significant improvement in PFS in the large, randomized, double-blind study. Despite immature OS data, in patients with a life-threatening and incurable malignancy, this PFS improvement represents a clinically meaningful benefit due to the substantial delay of progression and postponement of subsequent toxic therapies. The safety profile is acceptable in the intended population. A serious risk of QT prolongation will be further evaluated with alternative dosing in a PMR and is included in the warnings and precautions section of labeling. The indication was broadened to include the class of aromatase inhibitors as these agents are used interchangeably in clinical practice and did not demonstrate any new safety signal or drug interaction when used with ribociclib. Therefore, the benefit–risk profile was favorable to support approval of ribociclib in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The Editor handling the peer review and decision-making process for this article has no relevant employment associations to disclose.

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Received August 14, 2017; revised October 27, 2017; accepted February 1, 2018; published first February 7, 2018.

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