Original Study

Efficacy and Safety of Ribociclib With Letrozole in US Patients Enrolled in the MONALEESA-2 Study

Denise A. Yardley,[1,2] Lowell Hart,[1,3] Anne Favret,[4,5] Sibel Blau,[6] Sami Diab,[4,7] Donald Richards,[4,8] Joseph Sparano,[9] J. Thad Beck,[10] Paul Richards,[4,11] Patrick Ward,[4,12] Bhuvaneswari Ramaswamy,[13] Michaela Tsai,[14] Kimberly Blackwell,[15] Timothy Pluard,[16] Sara M. Tolaney,[17] Francisco J. Esteva,[18] Cristina I. Truica,[19] Carlos Alemany,[20] Gena Volas-Redd,[21] Mikhail Shtivelband,[22] Das Purkayastha,[23] Anand A. Dalal,[23] Michelle Miller,[23] Gabriel N. Hortobagyi[24]

Abstract

Endocrine therapy is standard care for postmenopausal women with hormone receptor-positive (HR^+)/$HER2^-$ advanced breast cancer (ABC). A Mammary Oncology Assessment of LEE011's (Ribociclib's) Efficacy and Safety (MONALEESA-2) study subset of postmenopausal women with HR^+/$HER2^-$ ABC without previous treatment for advanced disease were randomized to ribociclib/letrozole or placebo/letrozole. Improved progression-free survival was observed in patients treated with first-line ribociclib/letrozole versus placebo/letrozole, consistent with the global population. These results suggest ribociclib/letrozole is safe and effective in this patient population.

Background: In the Mammary Oncology Assessment of LEE011's (Ribociclib's) Efficacy and Safety (MONALEESA-2) study, combination treatment with the selective inhibitor of cyclin-dependent kinases 4/6 ribociclib with letrozole significantly improved progression-free survival (PFS) versus letrozole alone in postmenopausal women with hormone receptor-positive HR^+/$HER2^-$ advanced breast cancer (ABC). Herein we present results from the subset of US patients enrolled in MONALEESA-2. **Patients and Methods:** Postmenopausal women with HR^+/$HER2^-$ ABC without previous treatment for advanced disease were randomized (1:1) to ribociclib 600 mg/d (3 weeks on/1 week off) with letrozole 2.5 mg/d (continuous) or placebo with letrozole. The primary end point was locally assessed PFS. **Results:** Overall, 213 US patients were enrolled in MONALEESA-2 (ribociclib, n = 100; placebo, n = 113). Baseline characteristics were similar between treatment groups and consistent with the global population. With a median follow-up of 27 months, 38 (38%) and 29 (26%) patients in the ribociclib and placebo groups, respectively, had continued to receive treatment. Median PFS was 27.6 months with ribociclib and 15.0 months with placebo (hazard ratio, 0.53). The most common

These results were presented, in part, as a poster at the 40th Annual San Antonio Breast Cancer Symposium, December 5-9, 2017 (P5-21-27).

This work was supported by Novartis Pharmaceutical Corporation. The funder of the study had a role in the study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to the data and are responsible for the accuracy and completeness of this report. The corresponding author had final responsibility for the decision to submit for publication.

[1]Sarah Cannon Research Institute, Nashville, TN
[2]Tennessee Oncology, Nashville, TN
[3]Florida Cancer Specialists, Fort Myers, FL
[4]US Oncology Network, McKesson Specialty Health, The Woodlands, TX
[5]Virginia Cancer Specialists, PC, Fairfax, VA
[6]Division of Hematology-Oncology, Northwest Medical Specialties, PLLC, Puyallup, WA
[7]Rocky Mountain Cancer Centers, LLP, Aurora, CO
[8]Texas Oncology, PA, Tyler, TX
[9]Department of Oncology, Montefiore Medical Center, Bronx, NY
[10]Highlands Oncology Group, Fayetteville, AR
[11]Oncology and Hematology Associates of Southwest Virginia, Inc, DBA Blue Ridge Cancer Care, Salem, VA
[12]Oncology Hematology Care, Cincinnati, OH
[13]Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center/Wexner Medical Center, Columbus, OH
[14]Virginia Piper Cancer Institute, Allina Health, Minneapolis, MN
[15]Department of Medicine, Duke University Medical Center, Durham, NC
[16]Saint Luke's Cancer Institute, Saint Luke's Health Systems, Kansas City, MO
[17]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA
[18]Department of Medicine, Perlmutter Cancer Center at NYU Langone Health, New York, NY
[19]Department of Medicine, Pennsylvania State Cancer Institute, Hershey, PA
[20]Florida Hospital Cancer Institute, Orlando, FL
[21]Georgia Cancer Specialists affiliated with Northside Hospital Cancer Institute, Atlanta, GA
[22]Ironwood Cancer and Research Center, Chandler, AZ
[23]Novartis Pharmaceuticals Corporation, East Hanover, NJ
[24]Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Submitted: Nov 14, 2018; Revised: Jan 29, 2019; Accepted: Feb 15, 2019; Epub: Feb 28, 2019

Address for correspondence: Denise A. Yardley, MD, 250 25th Avenue North, Suite 100, Nashville, TN 37203
Fax: 615-986-0029; E-mail contact: dyardley@tnonc.com

1526-8209/$ - see frontmatter
https://doi.org/10.1016/j.clbc.2019.02.007

all-cause adverse events were neutropenia (ribociclib, 72.0% [n = 72]; placebo, 4.6% [n = 5]), nausea (ribociclib, 69.0% [n = 69]; placebo, 44.0% [n = 48]), and fatigue (ribociclib, 60.0% [n = 60]; placebo, 50.5% [n = 55]). Two patients (ribociclib, 2.0%; placebo, 0%) experienced febrile neutropenia. **Conclusion:** In the US subset of MONALEESA-2, ribociclib with letrozole showed superior efficacy versus letrozole alone. These findings are consistent with the global population and support first-line use of ribociclib with letrozole in patients with $HR^+/HER2^-$ ABC.

Clinical Breast Cancer, Vol. 19, No. 4, 268-77 © 2019 Published by Elsevier Inc.
Keywords: Advanced breast cancer, CDK4/6 inhibitor, First-line, $HR^+/HER2^-$, Metastatic, Postmenopausal

Introduction

Approximately 155,000 women were estimated to be living with metastatic breast cancer in the United States in 2017, including women with recurrent and de novo breast cancer.[1] This figure represents a 50% increase in prevalence from 1990, in part because of the increase in 5-year survival rates in women with de novo breast cancer over the past 2 decades.[1] Despite these improvements, breast cancer remains the second leading cause of cancer-related death in women in the United States and results in approximately 41,000 deaths in women each year.[2]

Treatment goals for advanced or metastatic breast cancer include delaying the progression of disease, extending survival, and maintaining or improving quality of life (QoL).[3,4] According to US treatment guidelines, endocrine therapy (ET) is the standard of care for postmenopausal women with advanced or metastatic hormone receptor-positive (HR^+)/$HER2^-$ breast cancer[5,6]; however, most patients will eventually experience disease progression.[7-9]

Treatment with an aromatase inhibitor as monotherapy in the first-line setting can result in a median progression-free survival (PFS) of 14.5 to 16.0 months.[10-12] Combination treatment with ET and a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) can delay disease progression in the first-line setting.[10-12] The CDK4/6 inhibitors ribociclib, palbociclib, and abemaciclib in combination with an aromatase inhibitor are approved by the US Food and Drug Administration (FDA) as first-line treatment options for women with $HR^+/HER2^-$ advanced breast cancer.[13-15] In the international, phase III Mammary Oncology Assessment of LEE011's (Ribociclib's) Efficacy and Safety (MONALEESA-2) study (clinicaltrials.gov identifier, NCT01958021), ribociclib with letrozole significantly prolonged PFS (primary end point) in postmenopausal women with $HR^+/HER2^-$ advanced breast cancer versus letrozole with placebo.[11,16] On the basis of these data, ribociclib with letrozole was approved by the FDA for the treatment of postmenopausal women with HR^+ $HER2^-$ advanced breast cancer without previous treatment for advanced disease.[13]

To confirm that the benefits of ribociclib with letrozole in US patients were consistent with the overall MONALEESA-2 study population, an exploratory analysis of efficacy and safety was conducted in patients enrolled in US study sites, who comprised approximately 30% of the overall MONALEESA-2 study population.

Patients and Methods

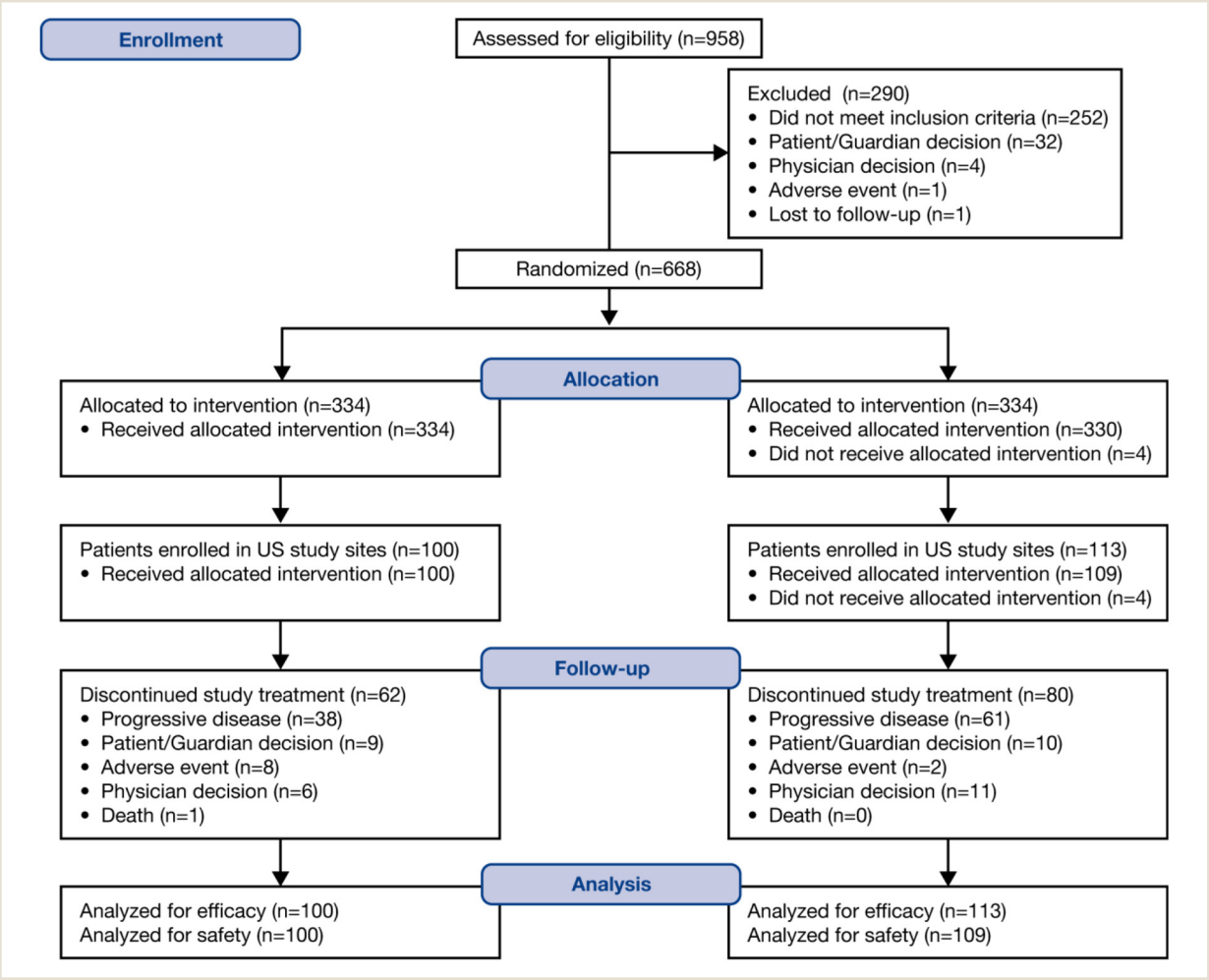
Study Design

The MONALEESA-2 (clinicaltrials.gov identifier, NCT01958021) is a randomized, double-blind, placebo-controlled, phase III trial of ribociclib with letrozole or placebo with letrozole being conducted at 223 sites in 29 countries, including 74 study sites in the United States (the study design for MONALEESA-2 has been previously described[16]). MONALEESA-2 met the primary end point of PFS at the planned interim analysis, showing a 44% reduction in the risk of progression in patients treated with ribociclib with letrozole compared with patients treated with placebo with letrozole (hazard ratio, 0.56; 95% confidence interval [CI], 0.43-0.72).[16] The trial will remain blinded until a sufficient number of events occur to make a determination of overall survival (OS) rate. Enrolled patients were randomized (1:1) to treatment with ribociclib 600 mg/d for 3 weeks followed by 1 week off, with letrozole 2.5 mg/d (continuous), or once-daily placebo for 3 weeks followed by 1 week off, with letrozole 2.5 mg/d (continuous). Dose reductions of ribociclib (from 600 to 400 mg or 400 to 200 mg) or placebo were allowed for intolerable or severe adverse events (AEs). No dose reductions were allowed for letrozole. Study treatment was continued until disease progression, death, unacceptable toxicity, or any other reason (eg, withdrawal of consent, lost to follow-up). Patients who permanently discontinued ribociclib/placebo could continue letrozole treatment during the study. Crossover to the alternate treatment group was not allowed.

Patients

Postmenopausal women ≥18 years of age with locally determined HR^+ (estrogen receptor-positive [ER^+] or progesterone receptor-positive [PR^+])/$HER2^-$ locoregionally recurrent or metastatic breast cancer who had not received previous therapy for advanced disease and whose disease was not amenable to curative therapy were eligible for study enrollment. Postmenopausal status was defined by previous bilateral oophorectomy, age ≥60 years, or age <60 years and amenorrhea for ≥12 months (in the absence of ovarian suppression or chemotherapy, tamoxifen, or toremifene use during this period) with follicle-stimulating hormone and estradiol levels in the postmenopausal range. To be considered for enrollment, patients were required to have had either measurable disease (≥1 measurable lesion defined according to Response Evaluable Criteria in Solid Tumors [RECIST] 1.1[17]) or ≥1 predominantly lytic bone lesion. Additional inclusion criteria included an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and adequate bone marrow and organ function.[18] Patients were ineligible if they had central nervous system metastases, impaired gastrointestinal function, or active cardiac disease or history of cardiac dysfunction. Patients with a corrected QT interval (QTcF; Fridericia formula) >450 ms at screening were not eligible. Concomitant treatment with medication known to prolong the QT interval or induce torsades de pointes was not permitted.

Figure 1 Consolidated Standards of Reporting Trials Diagram



Previous treatment with any CDK4/6 inhibitor, systemic hormonal therapy, or chemotherapy for advanced breast cancer was not allowed, except for letrozole or anastrozole initiated for advanced disease ≤14 days before randomization. (Neo)adjuvant therapy for breast cancer was allowed; however, if patients had received previous (neo)adjuvant letrozole or anastrozole, then a disease-free interval >12 months from the completion of treatment until randomization was required.

End Points and Assessments

The primary end point of the study was locally assessed PFS. PFS was determined on the basis of investigator-assessed tumor response per RECIST 1.1 and was defined as time from randomization to the date of first documented disease progression or death from any cause. PFS was censored at the last adequate tumor response for the following reasons: patient did not have a PFS event at the time of the analysis cutoff point or before the start of a different antineoplastic treatment other than the study treatment; a PFS event occurred after a new anticancer study treatment was given; or a PFS event occurred after ≥2 missing tumor assessments.

Overall survival was the key secondary end point. Other secondary end points included overall response rate (ORR), clinical benefit rate (CBR), health-related QoL, and safety and tolerability in patients treated with ribociclib with letrozole versus placebo with letrozole. The secondary end points ORR (proportion of patients with best overall response [BOR] of confirmed complete response [CR] or partial response [PR]) and CBR (proportion of patients with BOR of confirmed CR or PR or stable disease lasting ≥24 weeks) were determined according to investigator assessment per RECIST 1.1. Tumor assessments for overall response were performed at baseline, every 8 weeks after randomization during the first 18 months of the study, and then every 12 weeks thereafter. Confirmation of CR or PR was required using repeat assessments ≥4 weeks after the first initially reported CR or PR. Health-related QoL was determined using patient-reported outcomes of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), version 3.0, which incorporates 3 symptom scales (nausea/vomiting, pain, fatigue), a scale of global health/QoL, and 5 functional scales (social, physical, emotional, role, and cognitive).[19]

Table 1 Baseline Patient and Disease Characteristics

Characteristic	Ribociclib With Letrozole (n = 100)	Placebo With Letrozole (n = 113)
Median Age (Range), Years	60 (23-85)	61 (29-88)
Race, n (%)		
Caucasian	82 (82.0)	99 (87.6)
Black	8 (8.0)	6 (5.3)
Asian	4 (4.0)	2 (1.8)
Other/unknown	6 (6.0)	6 (5.3)
ECOG PS, n (%)		
0	60 (60.0)	60 (53.1)
1	40 (40.0)	53 (46.9)
Metastatic Site, n (%)		
Visceral	58 (58.0)	62 (54.9)
Lung	44 (44.0)	45 (39.8)
Liver	19 (19.0)	24 (21.2)
Other	8 (8.0)	8 (7.1)
Bone	78 (78.0)	81 (71.7)
Bone only	21 (21.0)	27 (23.9)
Metastatic Sites Involved, n (%)		
0	0	1 (0.9)
1	30 (30.0)	45 (39.8)
2	29 (29.0)	33 (29.2)
≥3	41 (41.0)	34 (30.1)
Disease-Free Interval, n (%)		
De novo metastatic disease	41 (41.0)	41 (36.3)
≤12 months	1 (1.0)	1 (0.9)
>12 months	58 (58.0)	71 (62.8)
Previous (Neo)Adjuvant CT, n (%)	40 (40.0)	52 (46.0)
Previous (Neo)Adjuvant ET, n (%)	47 (47.0)	51 (45.1)

Abbreviations: CT = chemotherapy; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = endocrine therapy.

The EORTC QLQ-C30 was provided during screening, every 8 weeks during the first 18 months, and every 12 weeks thereafter. Safety was assessed as AEs according to the Common Terminology Criteria for Adverse Events, version 4.03, including events occurring during treatment and those within 30 days of the last dose of the study treatment.[20] Hematologic and chemistry laboratory assessments were conducted at baseline, on day 15 of the first treatment cycle, and on day 1 of subsequent treatment cycles until the end of study treatment. Electrocardiogram assessments were conducted at baseline, on day 15 of cycle 1, and on day 1 of cycles 2 through 9. Additional assessments were conducted in any patients with QTcF >480 ms during the study.

Statistical Analysis

Efficacy end points were determined among US randomized patients, a subset of the full-analysis population. PFS was estimated using the Kaplan-Meier method and compared between treatment groups using stratified log rank tests. Hazard ratios and 95% CIs for PFS were determined from a stratified Cox proportional hazards model. Subgroup analyses of PFS were performed according to baseline patient and disease characteristic categories. BOR data were summarized according to treatment groups with standard Wald asymptotic 95% CIs. Treatment groups were compared with the Cochran–Mantel–Haenszel χ^2 test. Change from baseline in EORTC QLQ-C30 response data was determined in patients who completed the questionnaire at baseline and analyzed using a linear mixed effect model. For safety assessments, AE incidence rates were reported in the safety population, which consisted of all patients who had received ≥1 dose of study treatment and had ≥1 post-baseline safety assessment.

Ethical Approval

Written informed consent was obtained from all patients before screening. The study protocol and informed consent form were reviewed by the independent ethics committee or institutional review board for each center. This study was conducted according to the ethical principles of the Declaration of Helsinki.

Results

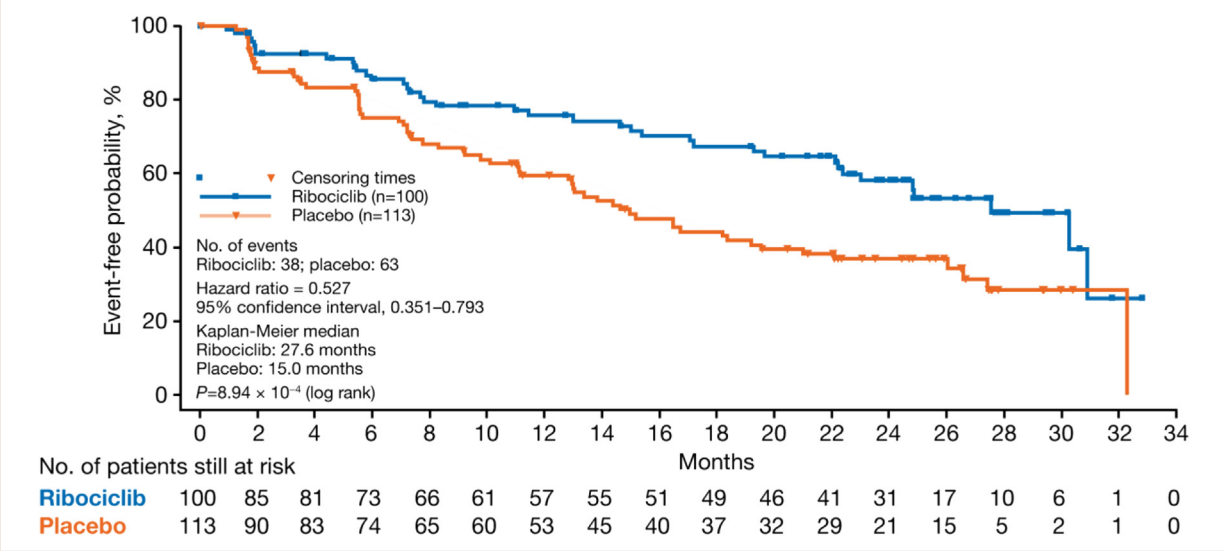
Patient Characteristics and Study Treatment

Between January 24, 2014, and March 24, 2015, a total of 668 patients were enrolled in the worldwide MONALEESA-2 study,[16] including 213 patients treated at US sites (Figure 1). The median age of patients in the US subset was 60 years in the ribociclib with letrozole group and 61 years in the placebo with letrozole group (Table 1). Baseline patient and disease characteristics were similar between study groups and consistent with the global population.[16] Most patients were Caucasian (ribociclib group, n = 82 [82.0%]; placebo group, n = 99 [87.6%]) and had an ECOG PS of 0 (ribociclib group, n = 60 [60.0%]; placebo group, n = 60 [53.1%]). Visceral metastases (ribociclib group, n = 58 [58.0%]; placebo group, n = 62 [54.9%]) were more common than bone-only metastases (ribociclib group, n = 21 [21.0%]; placebo group, n = 27 [23.9%]).

With a median follow-up duration of 27 months from the date of randomization to the data cutoff point (January 4, 2017), 100 patients (100%) and 109 patients (96.5%) in the ribociclib and placebo groups had received study treatment, respectively, and 38 patients (38.0%) and 29 patients (25.7%), respectively, continued study treatment. The most common reason for study discontinuation in either treatment group was progressive disease (ribociclib group, n = 38 [38.0%]; placebo group, n = 61 [54.0%]); 8 patients in the ribociclib group and 2 in the placebo group ended study treatment because of an AE.

The median rates of relative dose intensity were 86.7% for ribociclib, 100% for placebo, and 99.7% and 100% for letrozole in the ribociclib and placebo treatment groups, respectively. Fifty-four patients (54.0%) in the ribociclib group had dose reductions (most commonly because of neutropenia) compared with 7 patients (6.4%) in the placebo group. Reasons for dose reduction in the placebo group were AE (n = 3), dosing error (n = 2), and physician decision (n = 2). Dose reduction of letrozole was not allowed.

Figure 2 Kaplan-Meier Plot of Progression-Free Survival in US Patients Assessed by Local Investigator



Efficacy

Significant improvement in PFS was observed in patients treated with ribociclib with letrozole versus placebo with letrozole (hazard ratio, 0.53 [95% CI, 0.35-0.79]; $P = .000894$; Figure 2). Median PFS in the ribociclib group was 27.6 months (95% CI, 22.2 to not estimable) compared with 15.0 months (95% CI, 11.1-19.5) in the placebo group. PFS benefits with ribociclib were observed in subgroup analyses of multiple baseline disease characteristics, including number of metastatic disease sites involved, presence of liver/lung metastases, bone-only metastases, previous (neo)adjuvant hormonal therapy, and de novo metastatic disease (Supplemental Table 1). OS data were immature at the time of the analysis. At the data cutoff date, 15 patients (15.0%) in the ribociclib group and 20 patients (18.3%) in the placebo group had died. One patient (in the ribociclib group) died in ≤30 days of last study treatment. This patient was hospitalized on study day 504 because of sepsis and died because of hospital-associated pneumonia and acute respiratory insufficiency 25 days after the last dose of ribociclib (study day 498). White blood cell and absolute neutrophil counts were normal at hospitalization and at the time pneumonia was diagnosed.

Among all randomized patients, the ORR was 39.0% (95% CI, 29.4-48.6) in the ribociclib group and 26.5% (95% CI, 18.4-34.7) in the placebo group ($P = .029$; Table 2). CR was reported in 5 patients in the ribociclib group and 2 patients in the placebo group; 34 and 28 patients, respectively, had a BOR of PR. In patients with measurable disease at baseline (ribociclib group, n = 71; placebo group, n = 78), the ORR was 54.9% (95% CI, 43.4-66.5) in the ribociclib group and 38.5% (95% CI, 27.7-49.3) in the placebo group ($P = .023$). A reduction in tumor size was observed as early as 8 weeks in 83.1% (n = 54/65) of patients in the ribociclib arm and 72.5% (n = 50/69) in the placebo group. Most tumor responses occurred within the first 4 months of study treatment initiation. In patients with a confirmed CR or PR, the Kaplan-Meier-estimated median duration of response was 26.7 months (95% CI, 17.7 to not estimable) in the ribociclib group and 16.6 months (95% CI, 11.1 to not estimable) in the placebo group.

At baseline, the EORTC QLQ-C30 global health status/QoL questionnaire was completed by 99% (n = 99/100) and 98% (n = 111/113) of patients enrolled in the ribociclib and placebo groups, respectively. Overall QoL was generally higher during treatment compared with baseline in the ribociclib and placebo groups (Figure 3). Median time to 10% definitive deterioration of EORTC QLQ-C30 global health status/QoL scale score was similar among the treatment groups (ribociclib group, 27.6 months [95% CI, 24.9 to not estimable]; placebo group, 27.6 months [95% CI, 16.7 to not estimable]). Among patients with an EORTC QLQ-C30 pain symptom score at baseline and at 8 weeks, 63.2% (n = 43/68) in the ribociclib group and 50.0% (n = 31/62) in the placebo group had a reduction in pain at 8 weeks. The median change in pain score among all evaluable patients was −50.0% in the ribociclib group and −12.5% in the placebo group. A significantly greater decrease in mean percent change from baseline in pain score was observed at week 8 in the ribociclib group compared with the placebo group ($P = .017$). The reduction in pain from baseline in the ribociclib group was maintained throughout study treatment.

Safety

In the safety population, the most common all-cause AEs of any grade in patients treated with ribociclib with letrozole were neutropenia (72.0% [n = 72] vs. 4.6% [n = 5] in the placebo group), nausea (69.0% [n = 69] vs. 44.0% [n = 48] in the placebo group), and fatigue (60.0% [n = 60] vs. 50.5% [n = 55] in the placebo group; Table 3). Grade 3/4 AEs occurring in ≥20% of patients in either study group included neutropenia (ribociclib group, 56.0% [n = 56]; placebo group, 0% [n = 0]), decreased white blood cell count (ribociclib group, 16.0% [n = 16]; placebo group, 0% [n = 0]), and hypertension (ribociclib group, 11.0% [n = 11];

Table 2 Best Overall Response

	Ribociclib With Letrozole	Placebo With Letrozole
All Patients, n	100	113
Best overall response, n (%)		
CR	5 (5.0)	2 (1.8)
PR	34 (34.0)	28 (24.8)
SD	23 (23.0)	31 (27.4)
NCRNPD[a]	25 (25.0)	29 (25.7)
PD	7 (7.0)	13 (11.5)
Unknown	6 (6.0)	10 (8.8)
ORR, % (95% CI)[b]	39.0 (29.4-48.6)	26.5 (18.4-34.7)
P	.029	
CBR, % (95% CI)[c]	76.0 (67.6-84.4)	67.3 (58.6-75.9)
P	.074	
Patients With Measurable Disease at Baseline, n	71	78
Best overall response, n (%)		
CR	5 (7.0)	2 (2.6)
PR	34 (47.9)	28 (35.9)
SD	23 (32.4)	31 (39.7)
PD	4 (5.6)	12 (15.4)
Unknown	5 (7.0)	5 (6.4)
ORR, % (95% CI)[b]	54.9 (43.4-66.5)	38.5 (27.7-49.3)
P	.023	
CBR, % (95% CI)[d]	76.1 (66.1-86.0)	61.5 (50.7-72.3)
P	.030	

Abbreviations: CBR = clinical benefit rate; NCRNPD = neither complete response nor progressive disease; SD = stable disease.
[a]NCRNPD refers to patients with nontarget disease only who did not have disappearance of all nontarget lesions (ie, CR) and did not have unequivocal progression of existing nontarget lesions or the emergence of new lesions (ie, PD). This response categorization can be considered equivalent to SD.
[b]ORR defined as CR + PR.
[c]CBR defined as CR + PR + SD + NCRNPD ≥24 weeks.
[d]CBR defined as CR + PR + SD ≥24 weeks.

placebo group, 11.0% [n = 12]). Febrile neutropenia was reported in 2 patients (both in the ribociclib group). The Kaplan-Meier-estimated median time to first occurrence of Grade ≥2 neutropenia was 4.0 weeks (95% CI, 2.1-4.1) in patients treated with ribociclib with letrozole. Most of the neutropenic events in this study were uncomplicated and did not require additional therapy. One patient in the ribociclib group discontinued study treatment because of neutropenia and pericardial effusion in the context of multiple preexisting medical conditions after developing Grade 3 neutropenia on study day 15; ribociclib was discontinued 2 days later.

Infections were reported in 63 patients (63.0%) in the ribociclib group and 59 patients (54.1%) in the placebo group. Grade 3/4 infections occurred in 12 patients in the ribociclib group and 5 patients in the placebo group; events occurring in >2 patients included pneumonia (ribociclib group, n = 3; placebo group, n = 1) and sepsis (ribociclib group, n = 3; placebo group, n = 0). Two patients in the ribociclib group experienced Grade 4 infections (pneumonia and sepsis) compared with no patients in the placebo group. One patient had Grade 4 acute respiratory insufficiency and hospital-associated pneumonia with ribociclib 200 mg treatment. The second patient had Grade 4 sepsis and Grade 2 urinary tract infection on day 18; ribociclib was permanently discontinued because of sepsis on study day 18, but the patient continued letrozole treatment.

Liver enzyme elevations were more frequent in the ribociclib group. There were 14 patients (14.0%) with increased alanine aminotransferase (ALT; any grade) in the ribociclib group versus 3 patients (2.8%) in the placebo group; 14 patients (14.0%) in the ribociclib group and 7 patients (6.4%) in the placebo group had increased aspartate aminotransferase (AST; any grade). Grade 3/4 ALT and AST elevations in the ribociclib group were reported in 5 (5.0%) and 4 (4.0%) patients, respectively; in the placebo group, they were reported in 2 (1.8%) and 2 patients (1.8%), respectively. For most patients who experienced a Grade 3/4 ALT/AST elevation, the first episode occurred within the first 3 months of treatment. Two patients in the ribociclib group and none in the placebo group permanently discontinued study treatment because of increased ALT/AST levels. One patient in the ribociclib group met the criteria for Hy's law (elevated ALT/AST and total bilirubin without cholestasis). This patient's case was suspected to be related to ribociclib treatment, but this interpretation was confounded by use of black cohosh, a medicinal herb, of which use was prohibited during the study. The patient's liver enzyme levels returned to normal after discontinuation of study treatment.

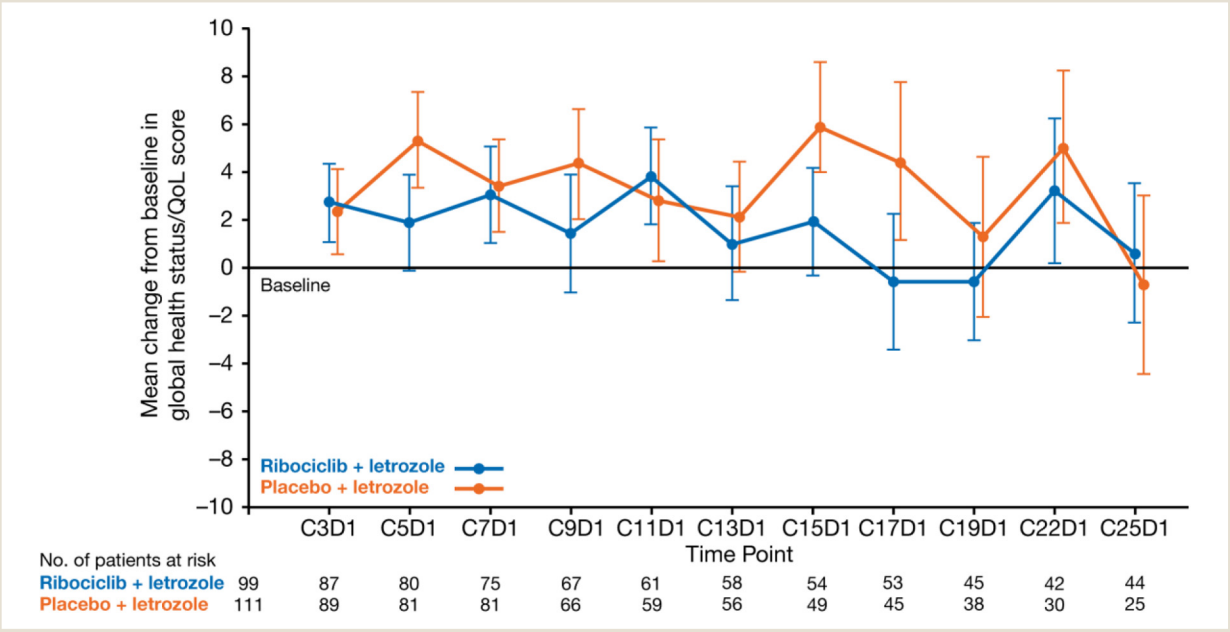
A postbaseline QTcF measurement >480 ms was observed in 2 patients (2.0%) in the ribociclib group and 2 patients (1.8%) in the placebo group. All events of QTcF >480 ms in the ribociclib group occurred during the first treatment cycle, suggesting no cumulative treatment effects on the QT interval. One patient (0.9%) in the placebo group and no patients in the ribociclib group had QTcF >500 ms, which occurred on study day 686 and led to permanent discontinuation of the study treatment.

Adverse events that led to dose interruptions occurred in 68 patients (68.0%) and 15 patients (13.8%) in the ribociclib and placebo groups, respectively. AEs leading to dose interruption in >2 patients in the ribociclib group included neutropenia (n = 31), decreased neutrophil count (n = 18), nausea (n = 9), fatigue (n = 8), decreased white blood cell count (n = 8), diarrhea (n = 6), vomiting (n = 5), increased ALT (n = 3), anemia (n = 3), increased AST (n = 3), and dehydration (n = 3); no event led to dose interruption in >2 patients in the placebo group. AEs led to dose reductions in 45 patients (45%) and 3 patients (2.8%) in the ribociclib and placebo groups, respectively. AEs that led to dose reduction in >2 patients in the ribociclib group were neutropenia (n = 21), diarrhea (n = 3), and fatigue (n = 3); no event led to dose reduction in >2 patients in the placebo group.

Discussion

In the US subset of MONALEESA-2, ribociclib with letrozole was well tolerated and provided a significant PFS benefit compared with letrozole with placebo in postmenopausal women with $HR^+/HER2^-$ advanced breast cancer without previous therapy for advanced disease. The additional use of ribociclib provided a 47.0% lower relative risk of progression than letrozole with placebo, and the median duration of PFS was extended by more than 1 year (27.6 months vs. 15.0 months). The clinical benefit of ribociclib with letrozole was also shown by improvements in

Figure 3 Mean Change From Baseline in EORTC QLQ-C30 Global Health Status/QoL Score



Error bars represent the standard error of the mean. Data included assessments with ≥25 patients in each treatment group. Patients at risk are those who completed the questionnaire at the respective time point and at baseline. Higher scores indicate more improvement in QoL.
Abbreviations: C = cycle; D = day; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; QoL = quality of life.

objective tumor response, reductions in pain score and tumor size at 8 weeks, and maintenance of overall QoL compared with letrozole alone. These results suggest that the additional use of ribociclib did not negatively affect overall QoL and that QoL improvements were maintained throughout the duration of study treatment. The observed improvement in PFS with ribociclib in the US subset is consistent with the results from the global study population of MONALEESA-2.[11] In the updated PFS analysis from MONALEESA-2 (26 months of follow-up), treatment with ribociclib with letrozole was associated with a 43% relative reduction of risk of progression compared with placebo with letrozole (hazard ratio, 0.57; 95% CI, 0.46-0.70; $P = .0000000963$). The median PFS in the global population was 25.3 months (95% CI, 23.0-30.3) with ribociclib with letrozole compared with 16.0 months (95% CI, 13.4-18.2) with placebo with letrozole.

These results are interesting, particularly in the context of previous reports of geographic differences in safety event reporting and in patient-reported QoL.[21-26] Geographic differences in AE reporting might be because of differences in investigator training, culture, or lack of consistency between US FDA regulations and International Conference on Harmonisation E2A guidelines for AE reporting.[21-24] In addition, reports of regional differences in QoL end points and symptoms in patients with breast cancer suggest that those living in different countries might differentially report the effects of treatment,[25,26] possibly leading to differences in patient care. Despite these potential differences, the results of the MONALEESA-2 US subset analysis show similar tolerability and clinical benefits of ribociclib with letrozole treatment compared with those in the overall study population of MONALEESA-2.[11] The results of this study are consistent with the results from Ongoing Trials in the Management of Breast Cancer (PALOMA-2) study, which showed that the efficacy and safety data of the CDK4/6 inhibitor palbociclib in the North American subset were similar to that in the overall population.[27]

In the US subset of MONALEESA-2, exploratory analyses of PFS showed a benefit of ribociclib across a range of baseline patient and disease characteristic subsets. Similarly, in the global MONALEESA-2 population, exploratory PFS analyses showed that ribociclib with letrozole improved PFS compared with letrozole alone in patients regardless of age, race/ethnicity, ECOG PS, hormone receptor positivity (ER^+/PR^-, ER^-/PR^+, or ER^+/PR^+), site of metastases, de novo versus recurrent metastatic disease, and previous adjuvant therapy.[11,16,28] In a subset analysis of MONALEESA-2 in patients with de novo advanced breast cancer, prolonged PFS was observed in patients in the ribociclib group compared with those assigned to placebo (hazard ratio, 0.45; 95% CI, 0.27-0.75); the estimated 12-month PFS rates were 82% and 66%, respectively.[29] The PFS benefits of ribociclib in patients with recurrent disease were similar (hazard ratio 0.60; 95% CI, 0.45-0.81).[16] The results from the US subset of MONALEESA-2, along with data from other MONALEESA-2 subset analyses, show the benefits of ribociclib in multiple subgroup populations of postmenopausal women with $HR^+/HER2^-$ advanced breast cancer.

No new safety signals were observed in the US patient subset.[11,16] The safety profile of ribociclib with letrozole was manageable. The rate of discontinuations because of AEs was low and consistent with the observed tolerability in the global study population.[11] Incidence rates of hematologic AEs were similar to that in

Table 3 Adverse Events Regardless of Relationship to Study Drug

AE[a]	Ribociclib With Letrozole (n = 100)[b]			Placebo With Letrozole (n = 109)[b]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Total[c]	99 (99.0)	60 (60.0)	21 (21.0)	107 (98.2)	46 (42.2)	3 (2.8)
AE Occurring in ≥20% of Study Patients in Either Group						
Neutropenia[d]	72 (72.0)	42 (42.0)	14 (14.0)	5 (4.6)	0	0
Nausea	69 (69.0)	3 (3.0)	0	48 (44.0)	1 (0.9)	1 (0.9)
Fatigue	60 (60.0)	6 (6.0)	0	55 (50.5)	1 (0.9)	0
Diarrhea	48 (48.0)	2 (2.0)	0	37 (33.9)	2 (1.8)	1 (0.9)
Vomiting	45 (45.0)	5 (5.0)	0	27 (24.8)	2 (1.8)	1 (0.9)
Arthralgia	44 (44.0)	2 (2.0)	1 (1.0)	43 (39.4)	2 (1.8)	0
Constipation	40 (40.0)	2 (2.0)	0	37 (33.9)	0	0
Alopecia	34 (34.0)	0	0	18 (16.5)	0	0
Hot flush	34 (34.0)	0	0	46 (42.2)	0	0
Headache	32 (32.0)	1 (1.0)	0	32 (29.4)	1 (0.9)	0
Back pain	29 (29.0)	6 (6.0)	0	23 (21.1)	1 (0.9)	0
Cough	29 (29.0)	0	0	22 (20.2)	0	0
Decreased WBC count	27 (27.0)	15 (15.0)	1 (1.0)	4 (3.7)	0	0
Urinary tract infection	27 (27.0)	2 (2.0)	0	21 (19.3)	0	0
Upper respiratory tract infection	26 (26.0)	0	0	22 (20.2)	0	0
Anemia	24 (24.0)	3 (3.0)	2 (2.0)	10 (9.2)	2 (1.8)	0
Decreased appetite	24 (24.0)	0	0	22 (20.2)	0	0
Hepatobiliary toxicity[e]	24 (24.0)	4 (4.0)	2 (2.0)	15 (13.8)	6 (5.5)	0
Hypertension	23 (23.0)	11 (11.0)	0	17 (15.6)	12 (11.0)	0
Insomnia	22 (22.0)	0	0	18 (16.5)	0	0
AE of Special Interest						
QTcF prolonged	4 (4.0)	0	0	3 (2.8)	1 (0.9)	0
Thrombocytopenia	6 (6.0)	0	0	0	0	0
Venous embolic/thrombotic event	2 (2.0)	1 (1.0)	0	2 (1.8)	0	0

Data are presented as n (%).
Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; QTcF = corrected QT interval (Fridericia formula); WBC = white blood cell.
[a]Patients with multiple occurrences of an AE are included once for each AE category.
[b]AE rates were determined among patients who received ≥1 dose of study treatment.
[c]Patients with multiple AEs are counted once.
[d]Includes the following terms: neutropenia, neutrophil count decreased, and febrile neutropenia; 2 patients (both in the ribociclib group) experienced febrile neutropenia.
[e]Includes the following terms: increased ALT, increased AST, increased blood alkaline phosphatase, hypoalbuminemia, increased blood bilirubin, increased international normalized ratio, hepatomegaly, and hyperbilirubinemia.

the global study population, although nonhematologic AE rates tended to be slightly higher in US patients in both treatment groups relative to the global population.[11] Most nonhematologic AEs were Grade 1/2, which do not require dose modification per the ribociclib package insert.[13] Consistent with other reports from studies of CDK4/6 inhibitors with ET in patients with advanced breast cancer,[10,12,16,30,31] neutropenia was the most frequently reported Grade 3/4 AE in the ribociclib group (56.0%). In the US subset of MONALEESA-2, neutropenia was manageable with dose modifications and did not require additional therapy in most patients; 1 patient discontinued ribociclib treatment because of neutropenia (nonfebrile). In the ribociclib group, a smaller percentage of patients with QTcF interval >480 ms was observed in the US subset (2 patients [2%]) compared with the overall population (11 patients [3.3%])[16]; however, the study was not powered to compare differences in AE rates between regional subsets and the overall population. The QTcF findings from the US subset support the manufacturer's prescribing information, which states to avoid use of ribociclib in patients with QTcF values ≥450 ms, to avoid use of concomitant medications known to prolong QTcF, and to reduce the ribociclib dose in patients with asymptomatic QT prolongation >480 ms.[13]

Conclusion

The US subset analysis of MONALEESA-2 confirmed the significant PFS benefits of ribociclib with letrozole versus placebo with letrozole for the treatment of postmenopausal women with $HR^+/HER2^-$ advanced breast cancer in the United States. Further analyses from MONALEESA-2, including OS, will be reported at a later date. Ongoing phase III studies from the MONALEESA trial program are investigating ribociclib in multiple settings and in combination with different endocrine therapies. In MONALEESA-3 (NCT02422615), ribociclib with the selective estrogen receptor degrader fulvestrant is being investigated in men and postmenopausal women with $HR^+/HER2^-$ advanced breast cancer whose disease has

progressed after treatment with ≤1 previous line of ET. In MONALEESA-7 (NCT02278120), significantly improved PFS (primary end point) was observed for pre-/perimenopausal women with HR+/HER2− advanced breast cancer treated with first-line ribociclib in combination with ET and ovarian suppression versus placebo in combination with ET and ovarian suppression.[31]

Clinical Practice Points

- Current practice guidelines recommend ET as standard care for select women with advanced or metastatic HR+/HER2− breast cancer.
- Although these guidelines describe combination treatment with ET and a targeted agent such as a CDK4/6 inhibitor as a first-line treatment option, the recommendations do not state whether endocrine monotherapy or ET in combination with a targeted agent is preferred.
- Data from multiple phase III trials of combination therapy with CDK4/6 inhibitors with ET show the benefits of combination treatment compared with monotherapy in delaying disease progression in the first-line setting.
- Despite these findings, a survey conducted in the United States conducted in 2017 showed that approximately 30% of patients with HR+/HER2− advanced breast cancer receive first-line endocrine monotherapy, suggesting that further evidence on the benefits of CDK4/6 inhibitors in combination with ET is needed.
- The present report on the US subset of the phase III MONALEESA-2 trial investigating the CDK4/6 inhibitor ribociclib with letrozole versus letrozole alone in postmenopausal women with HR+/HER2− advanced breast cancer addresses this gap by confirming the PFS benefits of combination treatment in a US patient population.
- The results from this US subset of MONALEESA-2 provide further evidence of the improvement in PFS observed in patients with HR+/HER2− advanced breast cancer treated with first-line ribociclib with letrozole versus placebo with letrozole.
- Our findings suggest ribociclib with letrozole is a safe and effective treatment in this patient population.

Acknowledgments

Ribociclib was discovered by Novartis Institutes for BioMedical Research in collaboration with Astex Pharmaceuticals. Editorial assistance was provided under the direction of the authors by Jonathan Morgan, PhD, and Sherri Damlo, MedThink SciCom (Cary, NC), with support from Novartis Pharmaceuticals Corporation.

Disclosure

D.A. Yardley, L. Hart, A. Favret, S. Diab, D. Richards, J.T. Beck, P. Richards, P. Ward, M. Tsai, and T. Pluard have received research support from Novartis Pharmaceuticals Corporation. D.A. Yardley has received grant support outside of the supported work from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Biomarin, Biothera Pharmaceuticals, Bristol-Myers Squibb, Celgene, Celldex, Clovis, Concordia, Eli Lilly, Eisai, Exelixis, G1 Therapeutics, Genzyme, GlaxoSmithKline, Imclone, Incyte, Ipsen Pharmaceuticals, Janssen, MedImmune, Medivation, Merck, Merrimack Pharmaceuticals, Novartis, Pfizer, Roche/Genentech, Sanofi, Spectrum Pharmaceuticals, and Tesaro; and has received consulting fees outside of the supported work from Abraxis, bioTheranostics, Celgene, Daiichi Sankyo, Eisai, Eli Lilly, ELM Medical Limited, Merck, Nippon-Kayaku, Novartis, Pfizer, R-Pharm US, Roche/Genentech, and Spectrum Pharmaceuticals. B. Ramaswamy has received research support from Novartis Pharmaceuticals Corporation and Pfizer and has received an honorarium for serving on an academic advisory board for Pfizer. S. Blau has received research support from Novartis Pharmaceuticals Corporation and consulting fees from Bristol-Myers Squibb. J. Sparano has received research support from Novartis Pharmaceuticals Corporation and PreCOG, LLC. K. Blackwell has received research support from Novartis Pharmaceuticals Corporation, Celgene, Genentech, and Pfizer, and fees from Novartis Pharmaceutical Corporation, Advaxis, Amgen, AstraZeneca, Bayer, Celgene, Coherus Biosciences, Eisai, Eli Lilly and Company, Genentech, Hospira, Incyte, GI Therapeutics, MacroGenics, Merck, Pfizer, Pierian Biosciences, Puma, Roche, Sandoz, Syndax, and Mylan. S.M. Tolaney has received research support from Novartis Pharmaceuticals Corporation, Pfizer, Nektar, Eli Lilly and Company, Genentech, Merck, AstraZeneca, Bristol-Meyers Squibb, Eisai, and Exelixis, and has served as an advisor to Novartis, Merck, Pfizer, Nektar, Eli Lilly, Genentech, AstraZeneca, Nanostring, and Puma. F.J. Esteva has received research support from Novartis Pharmaceuticals Corporation and consulting fees from Novartis Pharmaceuticals Corporation, Pfizer, Genentech, and Roche. C.I. Truica has received research support and consulting fees from Novartis Pharmaceuticals Corporation. C. Alemany has participated in a speakers bureau for Alexion. G. Volas-Redd has received consulting fees from Novartis Pharmaceuticals Corporation and Pfizer. D. Purkayastha, A.A. Dalal, and M. Miller are paid employees of Novartis Pharmaceuticals Corporation. G.N. Hortobagyi has received research support from Novartis Pharmaceuticals Corporation and consulting fees from Peregrine Pharmaceuticals, Eli Lilly and Company, and Roche. M. Shtivelband has stated no conflicts of interest.

Supplemental Data

The supplemental table accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2019.02.007.

References

1. Mariotto AB, Etzioni R, Hurlbert M, et al. Estimation of the number of women living with metastatic breast cancer in the United States. *Cancer Epidemiol Biomarkers Prev* 2017; 26:809-15.
2. American Cancer Society. Cancer Facts & Figures 2018. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed: August 28, 2018.
3. Chung CT, Carlson RW. Goals and objectives in the management of metastatic breast cancer. *Oncologist* 2003; 8:514-20.
4. Smith I. Goals of treatment for patients with metastatic breast cancer. *Semin Oncol* 2006; 33:2-5.
5. National Comprehensive Cancer Network Inc (NCCN). NCCN Clinical Practice Guidelines in Oncology. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf. Accessed: August 28, 2018.
6. Rugo HS, Rumble RB, Macrae E, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology guideline. *J Clin Oncol* 2016; 34:3069-103.
7. Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole vs. tamoxifen as first-line therapy of advanced breast cancer in postmenopausal

women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003; 21:2101-9.
8. Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *J Clin Oncol* 2000; 18:3758-67.
9. Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women. *J Clin Oncol* 2008; 26:4883-90.
10. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016; 375:1925-36.
11. Hortobagyi GN, Stemmer SM, Burris HA, et al. *Updated results from MONALEESA-2, a phase III trial of first-line ribociclib + letrozole in hormone receptor-positive, HER2-negative advanced breast cancer*, Presented at the American Society of Clinical Oncology Annual Meeting, Chicago, IL, June 2-6 2017.
12. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* 2017; 35:3638-46.
13. *Kisqali (ribociclib) Tablets [prescribing information]*. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018.
14. *Ibrance (palbociclib) Capsules [prescribing information]*. New York, NY: Pfizer Inc; 2018.
15. *Verzenio (abemaciclib) [prescribing information]*. Indianapolis, IN: Eli Lilly and Company; 2018.
16. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 2016; 375:1738-48.
17. Eisenhauer E, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228-47.
18. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5:649-56.
19. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85:365-76.
20. National Cancer Institute Cancer Therapy Evaluation Program. Common terminology criteria for adverse events (CTCAE), version 4.0. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed: August 28, 2018.
21. Levit LA, Perez RP, Smith DC, et al. Streamlining adverse events reporting in oncology: an American Society of Clinical Oncology research statement. *J Clin Oncol* 2018; 36:617-23.
22. Yusuf S, Wittes J. Interpreting geographic variations in results of randomized, controlled trials. *N Engl J Med* 2016; 375:2263-71.
23. Ribeiro-Vaz I, Silva A-M, Santos CC, et al. How to promote adverse drug reaction reports using information systems—a systematic review and meta-analysis. *BMC Med Inform Decis Mak* 2016; 16:27.
24. Guimarães PO, Lopes RD, Stevens SR, et al. Reporting clinical end points and safety events in an acute coronary syndrome trial: results with integrated collection. *J Am Heart Assoc* 2017; 6:e005490.
25. Hahn EA, Holzner B, Kemmler G, et al. Cross-cultural evaluation of health status using item response theory: FACT-B comparisons between Austrian and US patients with breast cancer. *Eval Health Prof* 2005; 28:233-59.
26. Shim EJ, Mehnert A, Koyama A, et al. Health-related quality of life in breast cancer: a cross-cultural survey of German, Japanese, and South Korean patients. *Breast Cancer Res Treat* 2006; 99:341-50.
27. Gelmon KA, Castrellon A, Joy AA, et al. *Efficacy and safety of palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: findings by geographic region from PALOMA-2*, Presented at the 40th Annual San Antonio Breast Cancer Symposium; San Antonio, TX; Dec 5-9 2017.
28. Sonke GS, Hart LL, Campone M, et al. 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 Res Treat* 2018; 167:659-69.
29. O'Shaughnessy J, Petrakova K, Sonke GS, et al. Ribociclib plus letrozole vs. letrozole alone in patients with de novo HR^+, $HER2^-$ advanced breast cancer in the randomized MONALEESA-2 trial. *Breast Cancer Res Treat* 2018; 168:127-34.
30. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib vs. fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol* 2016; 17:425-39.
31. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR^+/$HER2^-$ advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol* 2017; 35:2875-84.

Supplemental Table 1 Subgroup Analyses of PFS

Subgroup	Ribociclib With Letrozole (n = 100)			Placebo With Letrozole (n = 113)			Ribociclib Versus Placebo
	Patients, n	Events, n	Median PFS, Months	Patients, n	Events, n	Median PFS, Months	Hazard Ratio (95% CI)
(Neo)Adjuvant Chemotherapy							
No	60	18	30.3	61	29	18.2	0.477 (0.260-0.875)
Yes	40	20	23.0	52	34	14.4	0.545 (0.309-0.961)
(Neo)Adjuvant Hormonal Therapy							
AI	30	15	23.0	25	19	13.8	0.461 (0.228-0.932)
Tamoxifen and others	17	7	NE	26	14	13.0	0.652 (0.263-1.620)
None	53	16	30.3	62	30	18.2	0.497 (0.267-0.926)
De Novo Metastasis							
No	59	24	23.0	72	44	13.8	0.514 (0.309-0.853)
Yes	41	14	30.3	41	19	26.6	0.643 (0.319-1.295)
Number of Metastatic Sites							
<3	59	18	30.3	79	41	18.2	0.502 (0.287-0.879)
≥3	41	20	19.6	34	22	9.8	0.452 (0.242-0.843)
Liver/Lung Involvement							
No	48	16	30.3	51	24	22.1	0.647 (0.341-1.227)
Yes	52	22	24.8	62	39	11.1	0.501 (0.296-0.850)
Bone-Only Metastasis							
No	79	32	27.6	86	49	12.8	0.470 (0.298-0.744)
Yes	21	6	NE	27	14	26.0	0.830 (0.302-2.280)

Abbreviations: AI = aromatase inhibitor; NE = not estimable; PFS = progression-free survival.