


ORIGINAL ARTICLE

Ribociclib, a CDK 4/6 inhibitor, plus endocrine therapy in Asian women with advanced breast cancer

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Abstract

The ongoing, Phase Ib MONALEESASIA study is evaluating the efficacy and safety of ribociclib plus endocrine therapy in Asian patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer. Eligible patients from Japan, Hong Kong, and Singapore were enrolled in this 2-phase study consisting of a dose-escalation phase to determine the maximum-tolerated dose and the recommended Phase II dose of ribociclib plus letrozole, and a dose-expansion phase to evaluate safety and tolerability of ribociclib plus letrozole, fulvestrant, or tamoxifen. An exploratory biomarker analysis evaluating expression of target genes was also conducted. In the dose-escalation phase, the maximum-tolerated/recommended Phase II doses of ribociclib were lower in Japanese patients (300 mg) than

Abbreviations: ABC, advanced breast cancer; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC_{0-24h}, area under the curve from 0-24 h; BL, baseline; BMI, body mass index; C1D15, cycle 1 day 15; CBR, clinical benefit rate; CC, cell cycle; CDK4/6, cyclin-dependent kinases 4 and 6; CI, confidence interval; CL/F, apparent oral clearance; C_{max}, maximum (peak) drug concentration; CV, coefficient of variation; CYP, cytochrome P450; DEM, dose-escalation meeting; DLT, dose-limiting toxicity; ECG, electrocardiogram; ECOG PS, ECOG performance status; ET, endocrine therapy; EWOC, escalation with overdose control; FUL, fulvestrant; Geo-mean, geometric mean; GOS, goserelin; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; LET, letrozole; LFT, liver function test; log, logarithmic; MTD, maximum-tolerated dose; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; QD, once daily; QTcF, QT interval corrected using Fridericia's formula; RDE, recommended dose for expansion; RIB, ribociclib; RP2D, recommended Phase II dose; SAE, serious adverse event; SD, stable disease; sqrt, square root; T_{1/2 acc}, effective half-life determined based on drug accumulation ratio at steady state; TAM, tamoxifen; T_{max}, time to reach maximum (peak) drug concentration.

Ioannis Gounaris was an employee of Novartis Pharmaceuticals Corporation when the reported analyses were conducted and is now an employee of Merck Serono Ltd UK.

Mihaela Gazdoiu was an employee of Novartis Pharmaceuticals Corporation when the reported analyses were conducted.

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in Asian non-Japanese patients (600 mg). Ribociclib plus endocrine therapy at the recommended Phase II dose had a manageable safety profile, with neutropenia and elevated liver transaminases being the most common adverse events leading to dose modifications or discontinuations, and it demonstrated evidence of clinical activity in both Japanese and Asian non-Japanese patients. Preliminary efficacy in Asian

populations is similar to that observed in White populations studied in previous ribociclib (MONALEESA) trials. Biomarker analysis demonstrated suppression of pharmacodynamic biomarker gene expression, indicating inhibition of target genes by ribociclib combined with endocrine therapy. Results from the ongoing study support the use of ribociclib in combination with letrozole in Asian non-Japanese patients at the same dose (600 mg) as White patients. In Japanese patients, a lower dose of ribociclib (300 mg) should be considered. Clinicaltrials.gov: NCT02333370.

KEYWORDS

Asian, biomarker, breast cancer, CDK4/6i, ribociclib

1 | INTRODUCTION

Endocrine therapy (ET) is the current standard of care in initial lines of therapy for women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) ABC.¹ However, resistance to ET remains an area of significant concern for patients with ABC, prompting the need for treatment options that prolong or restore sensitivity to ET.

Data from preclinical and clinical studies suggest that inhibition of cyclin-dependent kinases 4 and 6 (CDK4/6) may delay the development of endocrine resistance,²⁻⁴ thus offering a potential route for treatments to enhance sensitivity to ET. Ribociclib, an oral, selective inhibitor of CDK4/6,^{5,6} has demonstrated clinical benefit in HR+, HER2- ABC when used in combination with ET.⁷⁻⁹

Ribociclib is currently approved for use in the United States and European Union as a 600 mg/d, 3 wk on/1 wk off regimen.^{5,6} In the United States, ribociclib is indicated in combination with an aromatase inhibitor for the treatment of premenopausal, perimenopausal, or postmenopausal women with HR+, HER2- ABC as initial ET, or in combination with fulvestrant for postmenopausal women with HR+, HER2- ABC as initial ET or following disease progression on ET.⁵ In the European Union, ribociclib is indicated in combination with an aromatase inhibitor or fulvestrant for the treatment of women with HR+, HER2- ABC as initial ET or in women who have received prior ET.⁶

Three global Phase III studies have been conducted to assess the efficacy and safety of ribociclib in combination with ET for the treatment of women with HR+, HER2- ABC: MONALEESA-2

(ribociclib plus letrozole for the treatment of postmenopausal patients), MONALEESA-3 (ribociclib plus fulvestrant for the treatment of postmenopausal patients), and MONALEESA-7 (ribociclib plus goserelin, combined with either a nonsteroidal aromatase inhibitor [letrozole or anastrozole] or tamoxifen for the treatment of premenopausal patients).⁷⁻⁹

The MONALEESA-2 trial met its primary endpoint of significantly improved PFS at the interim analysis, demonstrating a clinically meaningful and statistically significant treatment benefit vs letrozole monotherapy.⁸ In the MONALEESA-3 trial, patients receiving ribociclib plus fulvestrant experienced a statistically significant and clinically meaningful improvement in PFS with a manageable safety profile,⁹ as well as a statistically significant longer overall survival, compared with patients receiving placebo plus fulvestrant.¹⁰ The MONALEESA-7 trial met its primary endpoint of significantly improved PFS at the first analysis,⁷ and significantly longer overall survival for ribociclib vs placebo was demonstrated.¹¹ However, the MONALEESA studies enrolled patients predominantly from non-Asian countries, with Asian patients accounting for 8.4%, 9.3%, and 30.0% of the study populations in MONALEESA-2, MONALEESA-3, and MONALEESA-7, respectively.⁷⁻⁹

To address the limited data in the Asian patient population, the MONALEESASIA (NCT02333370) study was designed to evaluate the safety, pharmacokinetics (PK), and efficacy of ribociclib plus ET in patients from Asian countries with HR+, HER2- ABC; the study ran in parallel with the MONALEESA trials. Here, the results of the dose-escalation (ribociclib plus letrozole) and dose-expansion (ribociclib plus letrozole, fulvestrant, or tamoxifen) phases of the study are reported. Results of an exploratory biomarker analysis, including gene expression profiling and pharmacodynamic changes of targeted genes, are also included.

2 | MATERIALS AND METHODS

2.1 | Patients

The MONALEESASIA study enrolled 88 Asian patients with HR+, HER2- advanced (locoregionally recurrent or metastatic) breast cancer up to the data cut-off date of March 2, 2018; Japanese patients were enrolled in Japan, and Asian non-Japanese patients were enrolled in Hong Kong and Singapore. No prior therapy for ABC was permitted except in Japanese patients who were enrolled into the ribociclib plus fulvestrant group in the dose-expansion phase, for whom

one prior ET was permitted. Patients were required to have histologically and/or cytologically confirmed diagnosis of estrogen receptor-positive and/or progesterone receptor-positive, HER2- breast cancer, as well as adequate bone marrow and organ function. Patients were postmenopausal, except for Japanese patients treated with tamoxifen in the dose-expansion phase who were required to be premenopausal or perimenopausal. These patients also received goserelin as part of their treatment.

Key exclusion criteria for this study included: any prior CDK4/6 inhibitor or prior systemic anticancer therapy (including hormonal therapy and chemotherapy) for ABC (except for the ribociclib plus fulvestrant group in the dose-expansion phase); major surgery ≤ 14 d prior to starting study drug which resulted in major side-effects from which the patient had not recovered; radiotherapy ≤ 4 wk or limited palliative radiotherapy ≤ 2 wk prior to starting the study drug which resulted in major side-effects from which the patient had not recovered; and cardiac disease or a history of cardiac dysfunction, including QTcF of ≥ 450 ms at the time of screening. Other exclusion criteria included patients on concomitant medication with a known risk of QT interval prolongation and/or known to cause Torsades de Pointes that could not be discontinued or replaced, and patients receiving substances known to be strong inducers or inhibitors of cytochrome P450 (CYP) 3A4 and CYP3A5.

Written informed consent was obtained from all patients. The trial was designed, implemented, and reported in accordance with Good Clinical Practice, all applicable regulatory requirements, and the guiding principles of the Declaration of Helsinki. The study protocol and amendments were reviewed and approved by the local independent ethics committees.

At least 12 patients were planned to be treated for each population in the dose-escalation phase to determine the MTD/recommended Phase II dose (RP2D). Approximately 15 patients were planned to be treated in each dose-expansion arm to gain further information on safety and tolerability and to provide additional PK and pharmacodynamic data to guide the selection of dosing for future studies.

2.2 | Dose and regimen selections

The MONALEESASIA study was conducted in 2 phases (a dose-escalation phase followed by a dose-expansion phase) for both Japanese and Asian non-Japanese patient populations.

2.2.1 | Dose-escalation phase

The dose-escalation phase was conducted to establish the MTD and RP2D of ribociclib in combination with letrozole. The incidence of DLTs was evaluated in the first cycle of treatment in the Japanese and Asian non-Japanese patient populations. Dose escalation was performed using an adaptive Bayesian Logistic Regression Model (BLRM) guided by the EWOC principle.

At least 6 evaluable patients had to be treated at each dose level to determine the MTD and/or RP2D for each population. Evaluable patients were those who have had at least 75% of the planned doses for both ribociclib and letrozole, and at least 50% of the planned doses administered on the same day and/or experience a DLT during the first 28-d cycle. Patients had to be treated for a minimum of 1 cycle (28 d) with ribociclib plus letrozole and have completed the scheduled safety assessment. To better understand the safety, tolerability, and PK of the combination, additional cohorts of patients may be enrolled at the same dose, preceding dose, or to intermediate dose level before or while proceeding with further dose escalation.

The MTD was defined as the highest drug dose not expected to cause DLTs in $>35\%$ of the treated patients in the first cycle of ribociclib plus letrozole treatment. The final recommended MTD/RP2D for the combination of ribociclib and letrozole was based on the recommendation from the BLRM and an overall assessment of safety, taking into consideration tolerability data from subsequent cycles at the tested doses.

Patients in the dose-escalation phase received letrozole at a dose of 2.5 mg once daily (QD) on days 1-28 of each 28-d cycle, plus ribociclib starting at 400 mg QD (3 wk on/1 wk off) in the initial cohort of patients and escalating up to 600 mg QD (3 wk on/1 wk off) in a subsequent cohort. The ribociclib doses were determined based on a review of the safety, tolerability, and PK observed at different dose levels tested in the single-agent first-in-human study (CLEE011X2101),¹² the Japanese Phase I study (CLEE011X1101),¹³ and the Phase I combination study with letrozole (CLEE011X2107).¹⁴

2.2.2 | Dose-expansion phase

All Asian non-Japanese patients in the dose-expansion phase received letrozole (2.5 mg QD) plus ribociclib at the RP2D established in the dose-escalation phase of the study.

Japanese patients received intervention according to menopausal status. Japanese postmenopausal patients in the dose-expansion phase received ribociclib at the RP2D on days 1-21 of each 28-d cycle plus either letrozole at 2.5 mg QD on days 1-28 of each 28-d cycle, or fulvestrant 500 mg, dosed every 28 days (cycle n day 1) with one additional dose on day 15 of cycle 1. Japanese premenopausal patients in the dose-expansion phase received tamoxifen 20 mg QD on days 1-28 of each 28-d cycle, goserelin 3.6 mg implanted subcutaneously on day 1 of every 28-d cycle, and ribociclib at the RP2D on days 1-21 of each 28-day cycle.

2.3 | Study assessments

2.3.1 | Safety

In the dose-escalation phase, the primary objective was to calculate the MTD and RP2D of the ribociclib plus letrozole combination and

report the incidence of DLTs in cycle 1. The safety of the combination of ribociclib and letrozole was evaluated through reported AEs, serious AEs (SAEs), changes in hematology, and chemistry values, vital signs, electrocardiograms, dose interruptions, dose reductions, and dose intensity.

A DLT was defined as an AE or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications other than study drugs that meets any of the pre-specified criteria (defined in Table S1), during the first 28-d cycle. A functional DLT was defined as a DLT that happened during cycle 2 or receipt of <75% of the planned dose of ribociclib in the first 28-d cycle due to toxicities (except grade 3 neutropenia) attributable to ribociclib.

In the dose-expansion phase, the primary objective was to evaluate the safety and tolerability of all treatment combinations using the safety assessments listed above.

2.3.2 | Pharmacokinetics

To characterize the PK of ribociclib as a single agent and in the presence of the combination partners, blood samples were obtained from all patients enrolled in the study for analysis of plasma concentrations of ribociclib, LEQ803 (a major metabolite of ribociclib), letrozole, fulvestrant, and tamoxifen. All data are on file, but only ribociclib PK parameters are presented in this manuscript.

PK parameters, including maximum (peak) drug concentration (C_{max}), time to reach maximum (peak) drug concentration (T_{max}), area under the curve from 0-24 h ($AUC_{0-24 h}$), apparent oral clearance (CL/F), and effective half-life determined based on drug accumulation ratio at steady state ($T_{1/2 acc}$), were determined by non-compartmental methods using Phoenix (v.8.0, Pharsight).

2.3.3 | Efficacy

After the baseline assessment, imaging assessments were performed every 8 wk after cycle 1 day 1 during the first 18 mo and every 12 wk thereafter. The preferred imaging methodology was computed tomography with intravenous contrast.

All patients (in the dose-escalation and dose-expansion phases) who discontinued treatment for reasons other than disease progression were followed on this schedule until occurrence of disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision (whichever was earlier). If a patient started a new anticancer therapy prior to progression, tumor evaluations continued with the same schedule until disease progression was documented.

Preliminary clinical antitumor activity was investigated by evaluation of ORR and CBR. ORR was defined as the proportion of patients with the best overall response, as per local investigator/radiologist review of complete response, plus partial response. CBR was defined as complete response, partial response, or stable

disease for 24 wk or longer based on RECIST v.1.1 (by local investigator assessment) for each treatment combination.

2.3.4 | Biomarkers

Tumor samples from baseline (at screening; $n = 68$) and on-treatment (cycle 1 day 15; $n = 5$) were collected and assessed for mRNA expression by NanoString nCounter[®] GX Human Cancer Reference panel consisting of 230 genes. Dynamic changes of gene expression were displayed by longitudinal plots.

3 | RESULTS

The MONALEESASIA study was initiated in February 2015. At the time of the first DEM, 12 patients had been enrolled and treated with ribociclib 400 mg QD (3 wk on/1 wk off) plus letrozole 2.5 mg administered continuously for 28 d (28-d cycle). After a review of all the available clinical data at the DEM, it was apparent that Japanese patients were experiencing more DLTs than Asian non-Japanese patients. Consequently, the study protocol was amended to assess the safety and efficacy of Japanese and Asian non-Japanese populations separately.

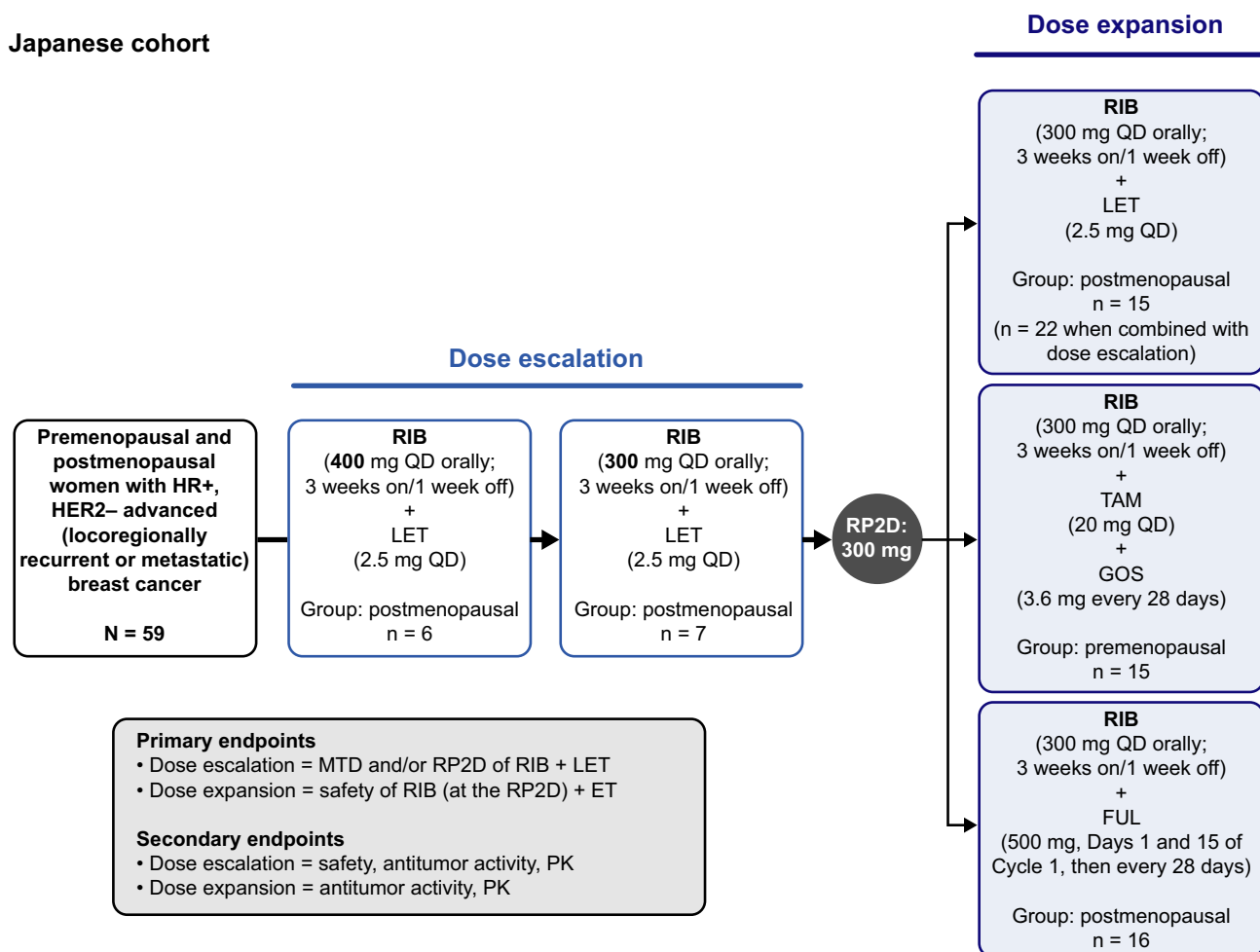
3.1 | Japanese patient population

At the time of the first DEM review, 6 Japanese patients had been enrolled and treated with ribociclib 400 mg QD (3 wk on/1 wk off) and letrozole 2.5 mg QD administered continuously for 28 d (28-d cycle) (Figure 1). All 6 patients were evaluable for DLT analysis, and 3 DLTs (including one functional DLT) occurred: cycle 2 dose delay > 7 d due to a grade 2/3 elevation in aspartate aminotransferase (AST)/alanine aminotransferase (ALT) and grade 3 neutropenia; grade 4 elevation in LFTs; grade 2 blood creatinine elevation and grade 4 elevation in LFTs in cycle 2 (functional DLT). After DEM review of the clinical safety data, the principal investigators and sponsor representatives decided to reduce the dose of ribociclib to 300 mg QD (3 wk on/1 wk off) in a second group. Seven patients were treated and no DLTs per protocol were recorded in this group, except for 1 functional DLT due to grade 4 neutropenia, leading to dose reduction. This patient was later permanently discontinued from ribociclib treatment due to grade 3 ALT increase at cycle 3.

The MTD of ribociclib was 400 mg in combination with letrozole. After reviewing efficacy and safety data the DEM declared ribociclib 300 mg plus letrozole to be the RP2D.

Following the dose-escalation phase, 46 patients were enrolled in the 3 protocol-defined dose-expansion groups where patients received ribociclib at the RP2D dose of 300 mg QD (3 wk on/1 wk off) (Figure 1). Postmenopausal patients received either ribociclib plus letrozole ($n = 15$) or ribociclib plus fulvestrant ($n = 16$). Premenopausal patients received ribociclib plus tamoxifen and goserelin ($n = 15$).

Japanese cohort



Asian non-Japanese cohort

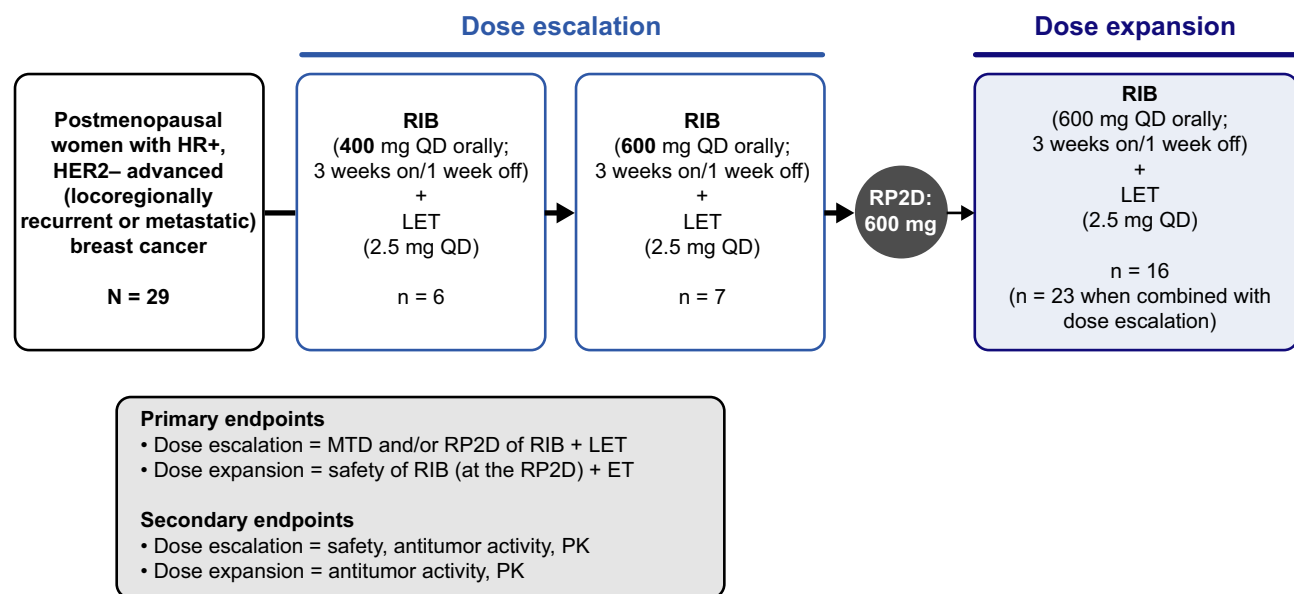


FIGURE 1 Treatment groups for Japanese and Asian non-Japanese patients. ET, endocrine therapy; FUL, fulvestrant; GOS, goserelin; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; LET, letrozole; MTD, maximum-tolerated dose; PK, pharmacokinetics; QD, once daily; RIB, ribociclib; RP2D, recommended Phase II dose; TAM, tamoxifen

TABLE 1 Characteristics and disposition in Japanese patients

	RIB 400 mg + LET 2.5 mg (n = 6)	RIB 300 mg + LET 2.5 mg (n = 22) ^a	RIB 300 mg + TAM 20 mg (n = 15)	RIB 300 mg + FUL 500 mg (n = 16)	All patients (n = 59)
Baseline characteristic					
Median age, y (range)	63 (55-77)	68 (49-83)	44 (34-53)	63 (43-78)	60 (34-83)
Age < 65 y	4 (66.7)	6 (27.3)	15 (100)	8 (50.0)	33 (55.9)
Age ≥ 65 y	2 (33.3)	16 (72.7)	0	8 (50.0)	26 (44.1)
Median BMI ^b , kg/m ² (range)	22.1 (18.9-26.9)	22.3 (17.8-31.4)	21.9 (16.0-26.8)	23.7 (16.6-31.5)	22.3 (16.0-31.5)
Baseline ECOG PS, n (%)					
0	6 (100)	17 (77.3)	14 (93.3)	14 (87.5)	51 (86.4)
1	0	5 (22.7)	1 (6.7)	2 (12.5)	8 (13.6)
Stage at time of study entry, n (%)					
III	0	1 (4.5)	1 (6.7)	0	2 (3.4)
IV	6 (100)	21 (95.5)	14 (93.3)	16 (100)	57 (96.6)
Patient disposition					
Median duration of study treatment, mo (range)	21.7 (13-34)	14.2 (0-27)	13.7 (6-19)	10.4 (1-16)	-
Treatment ongoing ^c , n (%)	1 (16.7)	14 (63.6)	10 (66.7)	7 (43.8)	32 (54.2)
End of treatment, n (%)	5 (83.3)	8 (36.4)	5 (33.3)	9 (56.3)	27 (45.8)
Reason for end of study treatment, n (%)					
AE	0	1 (4.5)	0	0	1 (1.7)
Physician decision	0	0	1 (6.7)	0	1 (1.7)
Disease progression	5 (83.3)	6 (27.3)	4 (26.7)	9 (56.3)	24 (40.7)
Patient or guardian decision	0	1 (4.5)	0	0	1 (1.7)

Abbreviations: AE, adverse event; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; FUL, fulvestrant; LET, letrozole; RIB, ribociclib; TAM, tamoxifen.

^aIncludes patients from both the dose-escalation and dose-expansion phases.

^bBMI [kg/m²] = weight [kg]/(height [m]²).

^cPatients were continuing study treatment at the time of the cut-off (March 2, 2018).

3.1.1 | Patient characteristics and disposition

Patient characteristics and disposition for the combined dose-escalation and dose-expansion cohorts are summarized in Table 1. At data cut-off (March 2, 2018), 32 of 59 (54.2%) patients were still receiving study treatment. Patients were given the study treatment for a median of 21.7 mo in the ribociclib 400 mg plus letrozole group, and for a median of 14.2, 13.7, and 10.4 mo in the ribociclib 300 mg plus letrozole, tamoxifen, and fulvestrant groups, respectively (Table 1).

3.1.2 | Safety

The most common AEs, for which grade 3/4 occurrences were observed in ≥10% of any population cohort, were neutropenia, leukopenia, and abnormal LFTs (Table 2). The most commonly reported grade 3/4 AEs were neutropenia, leukopenia, and abnormal LFTs. SAEs were recorded across the different dosing regimen groups: 2 (33.3%), 3 (13.6%), 2 (13.3%), and 2 (12.5%) patients in the ribociclib 400 mg

plus letrozole, ribociclib 300 mg plus letrozole, ribociclib 300 mg plus tamoxifen, and ribociclib 300 mg plus fulvestrant groups, respectively. Of the 9 SAEs observed, 5 were considered drug related; these included abnormal hepatic function, increased ALT, increased AST, increased blood creatinine, diarrhea, interstitial lung disease, and erythema multiforme.

Ribociclib dosing changes due to AEs are presented in Table 3. The most common AEs leading to ribociclib dose reduction in the Japanese population were neutropenia, occurring in 9 (15.3%) patients; 8 (13.6%) of whom experienced grade ≥ 3 neutropenia; and increased ALT, occurring in 7 (11.9%) patients; 3 (5.1%) of whom experienced grade ≥ 3 increased ALT (Table S2). Increased ALT and increased AST were the most common AEs leading to dose interruptions (15 patients [25.4%] and 10 patients [16.9%], respectively), and dose discontinuations (5 patients [8.5%] and 3 patients [5.1%], respectively).

New QTcF > 480 ms occurred in 0/6, 2/22, 2/15, and 0/16 patients in the ribociclib 400 mg plus letrozole, ribociclib 300 mg plus letrozole, ribociclib 300 mg plus tamoxifen, and ribociclib 300 mg plus fulvestrant groups, respectively. QTcF > 500 ms was not observed.

TABLE 2 All-cause AEs and laboratory abnormalities ($\geq 10\%$ grade 3/4 in any cohort) in Japanese patients

AE, n (%)	RIB 400 mg + LET 2.5 mg (n = 6)		RIB 300 mg + LET 2.5 mg (n = 22) ^a		RIB 300 mg + TAM 20 mg (n = 15)		RIB 300 mg + FUL 500 mg (n = 16)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Neutropenia ^b	5 (83.3)	5 (83.3)	20 (90.9)	13 (59.1)	9 (60.0)	6 (40.0)	12 (75.0)	9 (56.3)
Leukopenia ^c	3 (50.0)	2 (33.3)	15 (68.2)	3 (13.6)	9 (60.0)	2 (13.3)	10 (62.5)	1 (6.3)
Increased ALT	3 (50.0)	2 (33.3)	8 (36.4)	2 (9.1)	9 (60.0)	4 (26.7)	8 (50.0)	3 (18.8)
Increased AST	2 (33.3)	1 (16.7)	8 (36.4)	0	9 (60.0)	1 (6.7)	8 (50.0)	0
Increased lipase	1 (16.7)	1 (16.7)	4 (18.2)	2 (9.1)	2 (13.3)	1 (6.7)	1 (6.3)	1 (6.3)
Lymphopenia	1 (16.7)	0	1 (4.5)	0	1 (6.7)	0	3 (18.8)	2 (12.5)
Abnormal hepatic function	1 (16.7)	1 (16.7)	1 (4.5)	1 (4.5)	0	0	0	0

Note: A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FUL, fulvestrant; LET, letrozole; RIB, ribociclib; TAM, tamoxifen.

^aIncludes patients from both the dose-escalation and dose-expansion phases.

^bIncludes "neutropenia" and "neutrophil count decreased."

^cIncludes "leukopenia" and "white blood cell count decreased."

TABLE 3 Ribociclib dose changes due to AEs in Japanese patients

	RIB 400 mg + LET 2.5 mg (n = 6)	RIB 300 mg + LET 2.5 mg (n = 22) ^a	RIB 300 mg + TAM 20 mg (n = 15)	RIB 300 mg + FUL 500 mg (n = 16)	All patients (n = 59)
Median duration of RIB exposure, mo (range)	19.1 (0-34)	14.2 (0-27)	12.5 (0-17)	10.2 (1-16)	-
RIB dose interruption due to AE ^b , n (%)	4 (66.7)	18 (81.8)	13 (86.7)	12 (75.0)	47 (79.7)
RIB dose reduction due to AE ^b , n (%)	6 (100)	10 (45.5)	9 (60.0)	4 (25.0)	29 (49.2)
RIB dose discontinuation due to AE, n (%)	2 (33.3)	2 (9.1)	4 (26.7)	1 (6.3)	9 (15.3)

Abbreviations: AE, adverse event; FUL, fulvestrant; LET, letrozole; RIB, ribociclib; TAM, tamoxifen.

^aIncludes patients from both the dose-escalation and dose-expansion phases.

^bIncludes patients who experienced more than one dose interruption/reduction.

3.1.3 | Pharmacokinetics

At steady state, ribociclib was rapidly absorbed in all cohorts, with median T_{max} ranging from 2.0-4.0 h (Table 4). At the dose of 300 mg, the geometric mean of ribociclib exposure ($AUC_{0-24\text{ h}}$ and C_{max}) was similar when either letrozole or fulvestrant was the ET partner, but lower when given in combination with tamoxifen. The geometric mean exposure ($AUC_{0-24\text{ h}}$ and C_{max}) at steady state was higher with the ribociclib 400 mg plus letrozole combination than when ribociclib was administered at a 300 mg dose. Consistently, the geometric mean of CL/F was similar with ribociclib 400 mg and ribociclib 300 mg in combination with letrozole, as well as in combination with fulvestrant, but was higher in combination with tamoxifen. Geometric mean $T_{1/2,acc}$ values were also lower in the ribociclib plus tamoxifen group than in combination with letrozole or fulvestrant.

3.1.4 | Efficacy

Preliminary efficacy was observed in all cohorts (Figure 2); CBR was $\geq 75\%$ and ORR values were 33.3%, 59.1%, and 66.7% for ribociclib

400 mg plus letrozole, ribociclib 300 mg plus letrozole, and ribociclib 300 mg plus tamoxifen, respectively. In the ribociclib plus fulvestrant cohort, in which patients had received prior treatment in the metastatic setting, the ORR was 18.8%.

3.2 | Asian non-Japanese patient population

At the time of the DEM, 6 Asian non-Japanese patients had been enrolled and treated with ribociclib 400 mg QD (3 wk on/1 wk off) and letrozole 2.5 mg QD administered continuously for 28 d (28-d cycle) (Figure 1). All 6 patients were evaluable for DLT analysis; 1 functional DLT was observed due to grade 3 neutropenia and grade 2 LFT abnormalities leading to dose reduction/interruption.

After the DEM, the dose of ribociclib was increased to 600 mg QD in a second group of 7 patients; 1 protocol-defined DLT of grade 3 increased ALT for >4 d consecutively was observed. Based on the BLRM estimation, PK analysis, and the review of the clinical safety data, the MTD and RP2D were determined to be ribociclib 600 mg QD (3 wk on/1 wk off) plus letrozole 2.5 mg/d (continuous) for postmenopausal Asian non-Japanese patients.

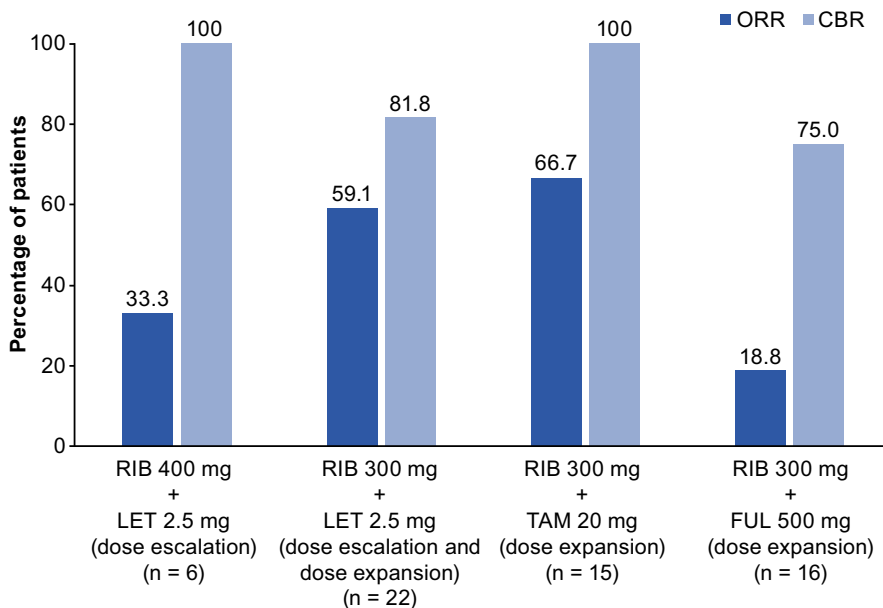
TABLE 4 Ribociclib PK parameters at steady state (cycle 1, day 21) in Japanese patients

PK parameter	RIB 400 mg + LET 2.5 mg (n = 6)	RIB 300 mg + LET 2.5 mg (n = 22) ^a	RIB 300 mg + TAM 20 mg (n = 15)	RIB 300 mg + FUL 500 mg (n = 16)
Median T_{max} (range), h [n]	2.03 (2.02-6.00) [3]	3.92 (1.97-5.92) [11]	3.98 (1.88-4.10) [7]	2.99 (0.98-4.13) [10]
Geo-mean C_{max} (CV% geo-mean), ng/mL [n]	1150.0 (6.7) [3]	804.0 (42.0) [11]	428.0 (48.2) [7]	708.0 (67.7) [10]
Geo-mean AUC_{0-24h} (CV% geo-mean), h-ng/mL [n]	14 600 (25.3) [3]	10 600 (37.8) [11]	5450 (42.9) [7]	9060 (58.9) [10]
Geo-mean CL/F (CV% geo-mean), L/h [n]	31.1 (11.5) [2]	28.0 (37.9) [11]	54.7 (42.6) [7]	32.6 (58.4) [10]
Geo-mean $T_{1/2,acc}$ (CV% geo-mean), h [n]	41.3 (25.5) [3]	29.3 (65.6) [11]	21.2 (21.8) [7]	31.6 (32.8) [10]

Note: Quantitation values below the limit of 1.00 ng/mL were set to zero; values of zero concentrations were considered as missing in geometric mean calculations; CV% = standard deviation/mean × 100, CV% geo-mean = sqrt (exp [variance for log transformed data] - 1) × 100.

Abbreviations: AUC_{0-24h} , area under the concentration-time curve from time 0 to 24 h; CL/F, apparent oral clearance; C_{max} , maximum concentration; CV, coefficient of variation; exp, exponential; FUL, fulvestrant; geo-mean, geometric mean; LET, letrozole; log, logarithmic; PK, pharmacokinetic; RIB, ribociclib; sqrt, square root; $T_{1/2,acc}$, the effective half-life determined based on drug accumulation ratio at steady state; TAM, tamoxifen; T_{max} , time to maximum concentration.

^aIncludes patients from both the dose-escalation and dose-expansion phases.

**FIGURE 2** Preliminary efficacy in Japanese patients. CBR, clinical benefit rate; FUL, fulvestrant; LET, letrozole; ORR, overall response rate; RIB, ribociclib; TAM, tamoxifen

After the dose-escalation phase, 16 patients were enrolled in the protocol-defined dose-expansion group (Figure 1), where ribociclib was given at a dose of 600 mg QD in combination with letrozole.

3.2.1 | Patient characteristics and disposition

Patient characteristics and disposition are summarized in Table 5. At data cut-off, 1 of 6 patients receiving ribociclib 400 mg in the dose-escalation phase and 10 of 23 patients receiving ribociclib 600 mg in the dose-escalation and dose-expansion phases were still receiving the study treatment. Patients were given the study treatment for a median of 16.2 and 10.9 mo in the combinations of ribociclib 400 mg plus letrozole and ribociclib 600 mg plus letrozole, respectively (Table 5).

3.2.2 | Safety

The most common AEs, for which grade 3/4 occurrences were observed in ≥10% of any population cohort, reported by patients were neutropenia, increased ALT, and increased AST (Table 6). The most common grade 3/4 AEs were neutropenia, increased ALT, and increased AST. SAEs were reported in 1 (16.7%) and 8 (34.8%) patients in the ribociclib 400 mg plus letrozole and ribociclib 600 mg plus letrozole combinations, respectively. Of the 9 SAEs observed, 2 were considered drug related; these included abnormal liver function tests (increased ALT and AST) and febrile neutropenia. AEs that led to a change in ribociclib dosing are presented in Table 7; dose interruptions due to AEs were experienced by 4 (66.7%) and 17 (73.9%) patients in the ribociclib 400 and 600 mg dosing groups, respectively, and dose reductions due to AEs were reported in 2 (33.3%) and 12 (52.2%) patients in the ribociclib 400 and 600 mg dosing groups, respectively.

TABLE 5 Characteristics and disposition in Asian non-Japanese patients

	RIB 400 mg + LET 2.5 mg (n = 6)	RIB 600 mg + LET 2.5 mg (n = 23) ^a	All patients (n = 29)
Baseline characteristic			
Median age, y (range)	54.5 (41.0-61.0)	58.0 (43.0-72.0)	57.0 (41.0-72.0)
Age < 65 y	6 (100)	18 (78.3)	24 (82.8)
Age ≥ 65 y	0	5 (21.7)	5 (17.2)
Median BMI ^b , kg/m ² (range)	22.3 (18.8-25.8)	25.1 (15.9-37.9)	24.1 (15.9-37.9)
Baseline ECOG PS, n (%)			
0	3 (50.0)	18 (78.3)	21 (72.4)
1	3 (50.0)	5 (21.7)	8 (27.6)
Stage at time of study entry, n (%)			
III	0	1 (4.3)	1 (3.4)
IV	6 (100)	22 (95.7)	28 (96.6)
Patient disposition			
Median duration of study treatment, mo (range)	16.2 (2-31)	10.9 (2-27)	-
Treatment ongoing ^c , n (%)	1 (16.7)	10 (43.5)	11 (37.9)
End of treatment, n (%)	5 (83.3)	13 (56.5)	18 (62.1)
Reason for end of study treatment, n (%)			
AE	0	1 (4.3)	1 (3.4)
Physician decision	0	0	0
Disease progression	5 (83.3)	11 (47.8)	16 (55.2)
Patient or guardian decision	0	1 (4.3)	1 (3.4)

Abbreviations: AE, adverse event; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; LET, letrozole; RIB, ribociclib.

^aIncludes patients from both the dose-escalation and dose-expansion phases.

^bBMI [kg/m²] = weight [kg]/(height [m]²).

^cPatients were continuing study treatment at the time of the cut-off (March 2, 2018).

Neutropenia was the most common AE leading to ribociclib dose reduction in the Asian non-Japanese population, it was experienced by 6 patients (20.7%) and all instances were grade ≥ 3 (Table S3). The most common AEs leading to dose interruptions were neutropenia (19 patients [65.5%], all of whom experienced grade ≥ 3) and increased ALT (7 patients [24.1%], of whom 4 [13.8%] experienced grade ≥ 3). Dose discontinuations were most commonly due to increased ALT and increased AST, following the protocol recommendations based on laboratory findings, each of which occurred in 4 patients (13.8%).

New QTcF > 480 ms occurred in 4 (17.4%) patients receiving ribociclib 600 mg plus letrozole and in no patients receiving the ribociclib 400 mg dose. QTcF > 500 ms was not observed.

3.2.3 | Pharmacokinetics

In Asian non-Japanese patients, ribociclib was rapidly absorbed in both treatment groups (Table 8). As expected, the geometric mean of ribociclib exposure (AUC_{0-24h} and C_{max}) was higher with the

600 mg dose than the 400 mg dose in combination with letrozole. Consistently, geometric mean CL/F and geometric mean T_{1/2,acc} values were comparable between the 2 dose groups.

3.2.4 | Efficacy

Preliminary efficacy results can be seen in Figure 3. In the ribociclib 400 mg dose-escalation group, ORR and CBR were 50.0% and 66.7%, respectively. In the ribociclib 600 mg dose-escalation and dose-expansion groups, these values were 56.5% and 87.0% for ORR and CBR, respectively.

3.3 | Exploratory biomarker analysis

At the cut-off date (March 2, 2018), NanoString data were available from 68 patients at baseline and pharmacodynamic changes of gene expression were assessed in the 5 pairs of pretreatment and post-treatment tumor samples available. The group of E2F-responsive

AE, n (%)	RIB 400 mg + LET 2.5 mg (n = 6)		RIB 600 mg + LET 2.5 mg (n = 23) ^a	
	All grades	Grade 3/4	All grades	Grade 3/4
Neutropenia ^b	4 (66.7)	4 (66.7)	18 (78.3)	17 (73.9)
Increased ALT	1 (16.7)	1 (16.7)	8 (34.8)	4 (17.4)
Increased AST	1 (16.7)	0	6 (26.1)	5 (21.7)
Hypophosphatemia	1 (16.7)	1 (16.7)	3 (13.0)	0
Hypercalcemia	1 (16.7)	1 (16.7)	2 (8.7)	0

Note: A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LET, letrozole; RIB, ribociclib.

^aIncludes patients from both the dose-escalation and dose-expansion phases.

^bIncludes "neutropenia" and "neutrophil count decreased."

TABLE 6 All-cause AEs and laboratory abnormalities ($\geq 10\%$ grade 3/4 in any cohort) in Asian non-Japanese patients

	RIB 400 mg + LET 2.5 mg (n = 6)	RIB 600 mg + LET 2.5 mg (n = 23) ^a	All patients (n = 29)
Median duration of RIB exposure, mo (range)	16.0 (1-31)	9.0 (0-27)	-
RIB dose interruption due to AE ^b , n (%)	4 (66.7)	17 (73.9)	21 (72.4)
RIB dose reduction due to AE ^b , n (%)	2 (33.3)	12 (52.2)	14 (48.3)
RIB dose discontinuation due to AE, n (%)	0	5 (21.7)	5 (17.2)

Abbreviations: AE, adverse event; LET, letrozole; RIB, ribociclib.

^aIncludes patients from both the dose-escalation and dose-expansion phases.

^bIncludes patients who experienced more than one dose interruption/reduction.

TABLE 7 Ribociclib dose changes due to AEs in Asian non-Japanese patients

PK parameter	RIB 400 mg + LET 2.5 mg (n = 6)	RIB 600 mg + LET 2.5 mg (n = 23) ^a
Median T_{max} (range), h [n]	1.5 (1-2) [2]	3.12 (2-4) [6]
Geo-mean C_{max} (CV% geo-mean), ng/mL [n]	1390 (0.5) [2]	1600 (16.7) [6]
Geo-mean AUC_{0-24h} (CV% geo-mean), h·ng/mL [n]	15 400 (31.1) [2]	21 400 (21.8) [6]
Geo-mean CL/F (CV% geo-mean), L/h [n]	25.7 (30.6) [2]	27.9 (21.0) [6]
Geo-mean $T_{1/2,acc}$, h [n]	25.1 (10.6) [2]	22.7 (34.6) [6]

Note: Quantitation values below the limit of 1.00 ng/mL were set to zero; values of zero concentrations were considered as missing in geometric mean calculations; CV% = standard deviation/mean $\times 100$, CV% geo-mean = $\sqrt{\exp[\text{variance for log transformed data}] - 1} \times 100$.

Abbreviations: AUC_{0-24h} , area under the concentration-time curve from time 0 to 24 h; CL/F, apparent oral clearance; C_{max} , maximum concentration; CV, coefficient of variation; exp, exponential; geo-mean, geometric mean; LET, letrozole; log, logarithmic; PK, pharmacokinetic; RIB, ribociclib; sqrt, square root; $T_{1/2,acc}$, the effective half-life determined based on drug accumulation ratio at steady state; T_{max} , time to maximum concentration.

^aIncludes patients from both the dose-escalation and dose-expansion phases.

TABLE 8 Ribociclib PK parameters at steady state (cycle 1 day 21) in Asian non-Japanese patients

genes included *RET*, *E2F1*, *FANCG*, *MYC*, *PCNA*, *CCNA2*, *CCND1*, *EGR1*, *JUNB*, *MSH2*, *TP53*, *TYMS*, and *WEE1*. Cell cycle-related genes group included *CCNA2*, *CCND1*, *CCND2*, *CCND3*, *CCNE1*, *CDK2*, *CDK4*, *CDK6*, *E2F1*, *E2F3*, *TFDP1*, *CDKN1A*, *CDKN2A*, *CDKN2B*, and *CDKN2C*. As shown in Figure 4, decreased mRNA expression was observed in post-treatment samples compared with pre-treatment

samples in biomarkers such as E2F-responsive genes, *MYC*, *TYMS*, and cell cycle-related genes, including CDK genes, indicating target inhibition.

Among the 68 patients whose baseline mRNA expression profiling data were available, there were 5 good responders and 6 poor responders. Good responders were defined as patients

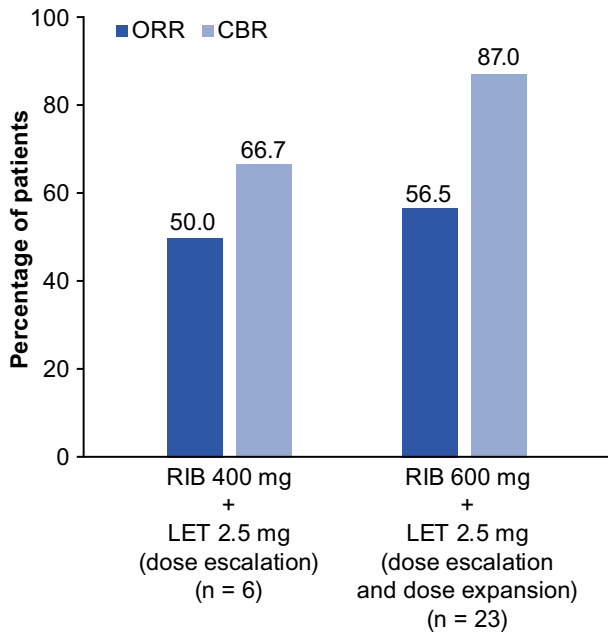


FIGURE 3 Preliminary efficacy in Asian non-Japanese patients. CBR, clinical benefit rate; LET, letrozole; ORR, overall response rate; RIB, ribociclib

without disease progression after 24 mo post-randomization, and poor responders were defined as patients whose disease progressed within 8 wk post-randomization. Baseline gene expression profiles between good and poor responders were compared, and differential gene expression patterns were observed for genes involved in the CDK pathway and cell proliferation (Figure 5). In good responders, higher expression levels of *MAP3K8* and genes regulated by *E2F* were observed compared with poor responders. Conversely, in poor responders higher expression levels of *TYMS*, *FGFR1*, and cell cycle-related genes were observed compared with good responders.

4 | DISCUSSION

In this ongoing study, a 2-phase protocol was implemented to determine the MTD and RP2D for ribociclib and assess its efficacy and safety in Asian populations with HR+, HER2- ABC. Japanese and Asian non-Japanese patient groups were separately evaluated after observing differences in the safety and tolerability profile in Japanese patients in the initial review. Following the completion

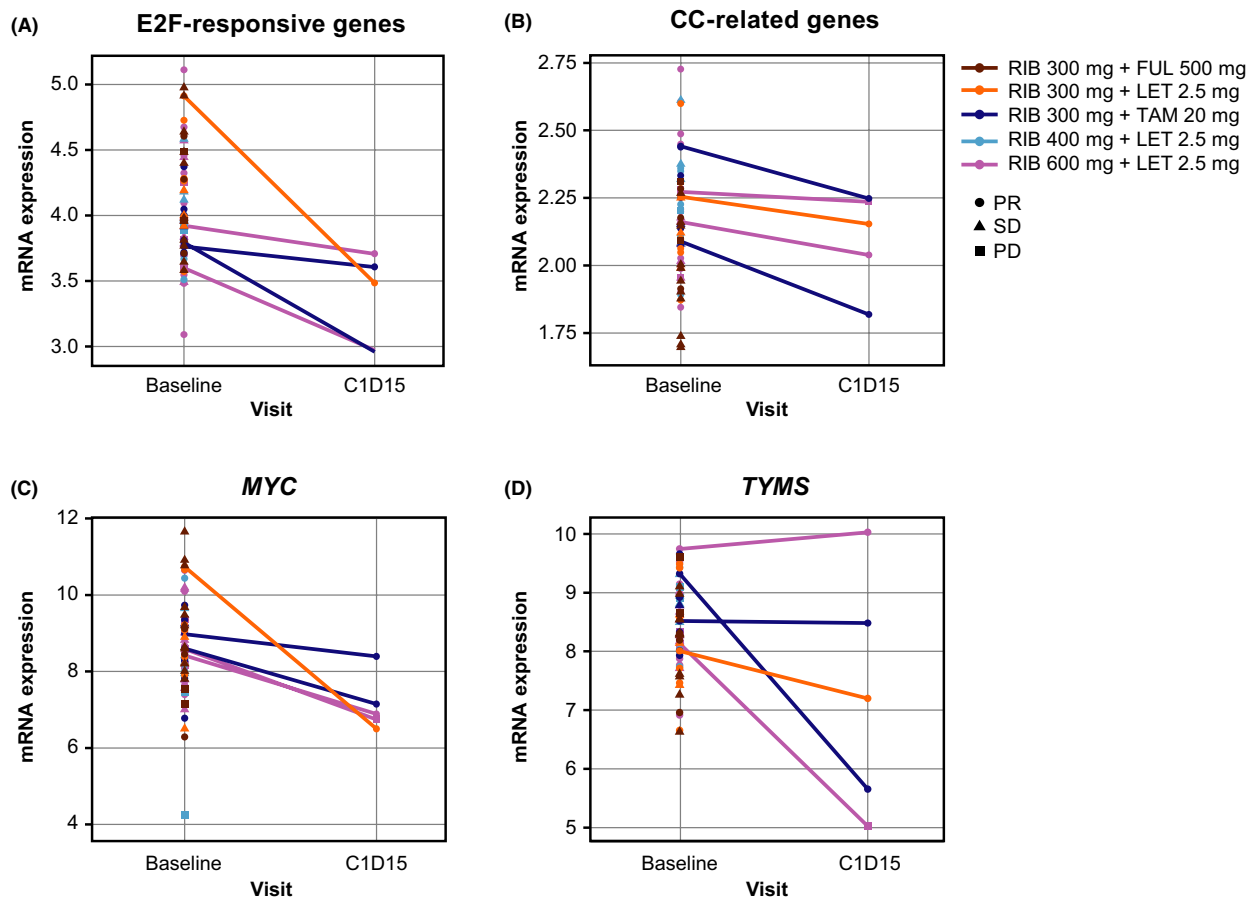


FIGURE 4 Pharmacodynamic changes of gene expression. The gene expression dynamics were assessed in patients for (A) E2F-responsive genes, (B) cell cycle-related genes, (C) *MYC*, and (D) *TYMS*. BL, baseline; CC, cell cycle; CDK, cyclin-dependent kinase; C1D15, cycle 1 day 15; FUL, fulvestrant; LET, letrozole; PD, progressive disease; PR, partial response; RIB, ribociclib; SD, stable disease; TAM, tamoxifen

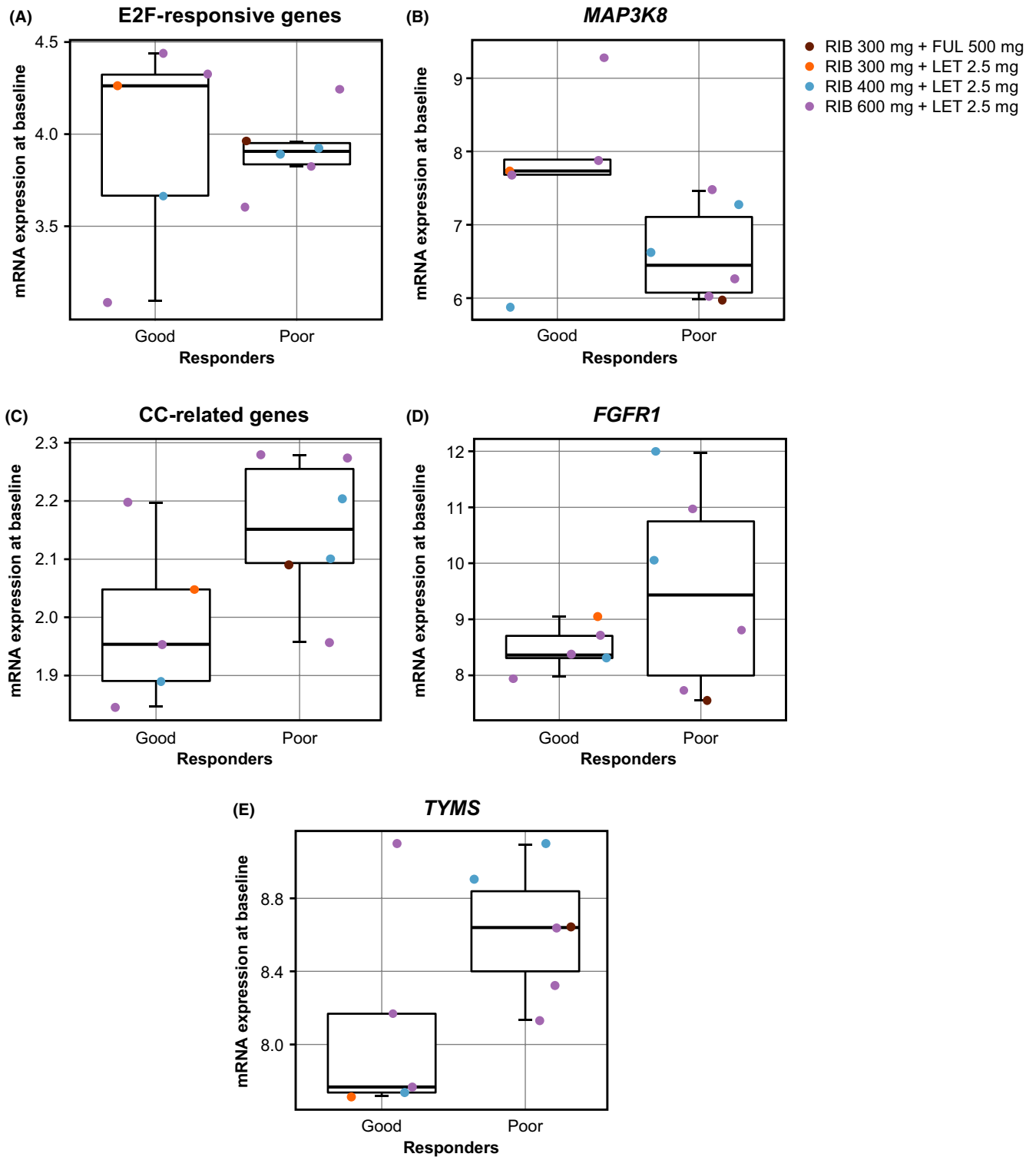


FIGURE 5 Differential mRNA expression at baseline between good and poor responders* for genes involved in cell cycle, proliferation, and breast cancer. Gene expression was assessed between good and poor responders for (A) E2F-responsive genes, (B) *MAP3K8*, (C) cell cycle-related genes, (D) *FGFR1*, and (E) *TYMS*. *At the cut-off date (March 2, 2018), patients who had not progressed after 24 mo post-randomization ($n = 5$) were considered good responders; patients who had progressed within 8 wk ($n = 6$) were considered poor responders. FUL, fulvestrant; LET, letrozole; RIB, ribociclib

of the dose-escalation phase and review of all the safety data, the RP2D of ribociclib in combination with ET partners was declared as 300 mg QD (3 wk on/1 wk off) for the Japanese population and

600 mg QD (3 wk on/1 wk off) for the Asian non-Japanese population. As such, the MTD and RP2D were lower in Japanese patients than the RDE of 600 mg in White patients.¹²

PK data for ribociclib and ET partners showed that ribociclib exposure (C_{\max} and $AUC_{0-24\text{h}}$) was similar between both Japanese and Asian non-Japanese populations at the 400 mg QD dose. Ribociclib exposure for the ribociclib 600 mg plus letrozole combination in the Asian non-Japanese population was comparable with the historical single-agent study at the 600 mg ribociclib dose, which included predominantly White patients (geometric mean C_{\max} of 1820 ng/mL and geometric mean $AUC_{0-24\text{h}}$ of 23 800 hr·ng/mL).^{12,15} These results suggest that there is no substantial difference in ribociclib exposure between Asian non-Japanese, Japanese, and White patient populations; however, due to the small sample size ($n = 6$ for both Japanese and Asian non-Japanese groups at 400 mg dose) a definitive conclusion could not be drawn.

Our data indicate that the combination with letrozole and fulvestrant did not impact the PK of ribociclib; this is consistent with previously published data demonstrating no difference of ribociclib exposure by these ET partners at the ribociclib 600 mg dose.¹⁵ Ribociclib exposure in combination with tamoxifen was lower compared with its exposure when combined with letrozole or fulvestrant in Japanese patients. This may be due to the induction potential of tamoxifen on CYP3A4,¹⁶ given that ribociclib is a CYP3A substrate.

At the initial ribociclib dose of 400 mg, results showed a higher toxicity in the Japanese group compared with the Asian non-Japanese group; however, the PK exposure of ribociclib was comparable between the 2 groups, and the higher toxicity profile observed in the Japanese population remains to be explained.

At the RP2D, ribociclib plus letrozole had a manageable and comparable safety profile, with neutropenia, increased ALT, and increased AST leading to dose modifications or treatment discontinuations in both Japanese and Asian non-Japanese populations. In a pooled analysis of the MONALEESA studies with ribociclib 600 mg QD,¹⁷ neutropenia was the most common grade 3/4 AE in Asian (47.1%) and non-Asian (45.6%) patients treated with ribociclib and discontinuation due to AEs were lower in Asian (2.2%) than in non-Asian (7.1%) patients.

Although at different RP2D doses, ribociclib demonstrated evidence of clinical activity in both populations. Overall, these results are similar to those observed in previous MONALEESA studies (ORR ranging between 32.4% and 40.9%; CBR ranging between 70.2% and 79.6%),⁷⁻⁹ which were predominantly conducted in White patients treated with ribociclib 600 mg QD, the dose approved in the United States and the European Union.^{5,6} The use of ribociclib was also shown to benefit Asian patients in the pooled analysis of the MONALEESA studies,¹⁷ where the median PFS improvement in Asian patients was 12.7 mo with placebo and not reached with ribociclib (hazard ratio = 0.49 [95% CI, 0.34-0.70]). ORR was 49.3% in Asian patients and 38.2% in non-Asian patients treated with ribociclib.

In the pharmacodynamic biomarker analysis, suppression of expression of genes such as *TYMS*, which is involved in cell proliferation,¹⁸ and E2F-responsive genes, which are regulated by the CDK4/6 pathway,¹⁹ indicated that ribociclib plus ET inhibited the intended CDK4/6 target pathway. Differences in baseline gene expression patterns for genes involved in cell proliferation and cell cycle control

were observed between patients with sustained responses (good responders) and those who progressed within 2 treatment cycles (poor responders). Higher baseline mRNA expression of *FGFR1* was observed in the poor responders group. *FGFR1* amplification/overexpression has been reported as a mechanism of resistance to ET in combination with CDK4/6 inhibitors,²⁰ which could help in interpretation of these results.

The results of this study require further validation and should be interpreted with caution due to the low patient numbers enrolled and the study's non-randomized, open-label design.

In conclusion, the results of this ongoing study indicate that ribociclib in combination with ET at the RP2D demonstrated a manageable safety profile with predictable/tolerable AEs in both Japanese and Asian non-Japanese patient populations. Preliminary efficacy in the Asian non-Japanese population was comparable with that observed in White populations investigated in previous MONALEESA trials at the same dose of ribociclib 600 mg, while a ribociclib dose of 300 mg should be considered for the treatment of Japanese patients.

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DISCLOSURE

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under the responsibility of Novartis Pharmaceuticals Corporation, and it was funded by Novartis Pharmaceuticals Corporation; ribociclib was provided by Novartis Pharmaceuticals Corporation and letrozole, fulvestrant, tamoxifen, and goserelin were provided locally; Novartis Pharmaceuticals Corporation collected and analyzed the data and contributed to the interpretation of the study. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication; medical editorial assistance was provided by Sara Henriques of Healthcare Consultancy Group, LLC, and funded by Novartis Pharmaceuticals Corporation; Joanne Chiu has no conflicts of interest; Seung Jin Kim has no conflicts of interest; Mitsue Saito has no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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