Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ribociclib/LEE011

Trial Indication(s)

Hormone receptor positive (HR+)/ Human Epidermal Growth Factor Receptor 2 negative (HER2-) advanced breast cancer

Protocol Number

CLEE011A2115C

Protocol Title

A phase Ib dose escalation study of the combination of ribociclib with letrozole and dose expansion of ribociclib with hormonal therapy for the treatment of pre-(with goserelin) and postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer

Clinical Trial Phase

Phase Ib

Phase of Drug Development

Phase Ib

Study Start/End Dates

Study Start Date (First Patient First Visit): 04-Feb-2015
Primary Completion Date: 29-Sep-2022
Study Completion Date (Last Patient Last Visit): 29-Sep-2022

Reason for Termination

Not Applicable

Study Design/Methodology

This is a regional, multi-center, open-label, Phase Ib dose escalation followed by dose expansion study to report the collection of safety and efficacy data on Asian population of ribociclib and letrozole or fulvestrant or tamoxifen in pre- and postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer.

The dose escalation part of the study enrolled 26 Japanese and Asian non-Japanese postmenopausal patients with HR+/HER2-negative advanced breast cancer who had not received any prior therapy for advanced breast cancer. The expansion part of the study enrolled 62 postmenopausal women in Asian non-Japanese sites and pre- or postmenopausal patients in the Japanese sites with HR+/HER2-negative advanced breast cancer who have received no prior systemic anti-cancer therapy for advanced breast cancer or maximum one prior line of endocrine therapy (fulvestrant combination) for advanced breast cancer.

The dose escalation part of the study consisted of successive cohorts of patients receiving a standard dose of letrozole and increasing or decreasing doses of ribociclib to determine the MTD(s) and/or RP2D(s). Letrozole was dosed once daily on Days 1-28 of each 28 day cycle and ribociclib was dosed once daily on Days 1-21 of each 28 day cycle. Each cohort consisted of newly enrolled patients.

In the dose expansion part, Asian non-Japanese patients received a standard dose of letrozole and the RP2D of ribociclib established in the dose escalation part. Japanese post-menopausal women received a standard dose of either letrozole or fulvestrant with the RP2D of ribociclib established in the dose escalation part; pre-menopausal women received tamoxifen with goserelin at established doses and RP2D of ribociclib.

Centers

15 centers in 3 countries: Hong-Kong (1), Japan (13) and Singapore (1)

Objectives:

Primary Objective	Primary Endpoints
Dose escalation: To estimate the MTD and/or RP2D of the combination of letrozole and ribociclib in postmenopausal patients with HR+/HER2-negative advanced breast cancer in Japanese and Asian non-Japanese patients	Dose escalation: Frequency of DLTs at each dose level associated with administration of ribociclib and letrozole in a 28 day cycle
Dose expansion: To further evaluate the safety and tolerability of ● ribociclib in combination with letrozole in postmenopausal Asian non-Japanese patients ● ribociclib in combination with letrozole in postmenopausal Japanese patients ● ribociclib in combination with fulvestrant in postmenopausal Japanese patients ● ribociclib in combination with tamoxifen plus goserelin in premenopausal Japanese patients	Dose expansion: Adverse Events (AEs), serious AEs (SAEs), changes in hematology and chemistry values, vital signs, electrocardiograms (ECGs), dose interruptions, reductions and dose intensity

Secondary Objectives	Secondary Endpoints
Dose escalation: • To evaluate the safety and tolerability of ribociclib in combination with letrozole in Japanese and Asian non-Japanese patients • To characterize the PK of ribociclib (and relevant metabolites such as LEQ803) and letrozole when given in combination in Japanese and Asian non-Japanese patients	Dose escalation: • Adverse Events (AEs), serious AEs (SAEs), changes in hematology and chemistry values, vital signs, electrocardiograms (ECGs), dose interruptions, reductions and dose intensity. • PK parameters including but not limited to: Cmax, Tmax, and AUC0-24h, accumulation ratio and Ctrough for ribociclib (and relevant metabolites such as LEQ803) and letrozole
Dose expansion: To assess the preliminary anti-tumor activity of ● ribociclib in combination with letrozole in post menopausal Japanese and Asian non-Japanese patients ● ribociclib in combination with fulvestrant in postmenopausal Japanese patients ● ribociclib in combination with tamoxifen plus goserelin in premenopausal Japanese patients To characterize the PK of ● ribociclib (and relevant metabolites such as LEQ803) and letrozole when given in combination in Japanese and Asian non-Japanese patients ● ribociclib (and relevant metabolites such as LEQ803) when given in combination with fulvestrant in Japanese patients ● ribociclib (and relevant metabolites such as LEQ803) when given in combination with tamoxifen plus goserelin in Japanese patients	Dose expansion: Tumor response per RECIST v1.1 (by local investigator assessment): Overall Response Rate (ORR), Disease Control Rate (DCR), Clinical benefit Rate (CBR), Duration of Response (DOR) and Progression Free Survival (PFS). CBR is defined as CR, PR, or SD lasting 24 weeks or longer. PK parameters including but not limited to: Cmax, Tmax, and AUC0-24h, accumulation ratio and Ctrough for ribociclib (and relevant metabolites such as LEQ803), letrozole, fulvestrant and tamoxifen.

Test Product (s), Dose(s), and Mode(s) of Administration

Ribociclib was supplied by Novartis or its designee in the form of 50 mg and 200 mg hard gelatin capsules as individual patient supply packaged bottles. Letrozole, fulvestrant, tamoxifen and goserelin were procured locally. Storage conditions were described in the medication label.

Statistical Methods

All data were analyzed by Novartis and/or a designated CRO. The dose escalation part was supported by the analysis of the incidence of DLTs in the first cycle using a Bayesian Logistic Regression Model (BLRM) and was analyzed by Novartis.

The analysis sets are defined as follows:

- **Full analysis set (FAS):** The FAS comprised all treated patients in the dose escalation part and the dose expansion part. Unless otherwise specified, the FAS was the default analysis set used for all analyses and listing of raw data for both the dose escalation part and dose expansion part.
- **Safety set:** Consisted of all enrolled patients in the dose escalation part and the dose expansion part who received at least one dose of the study medication and had at least one valid post-baseline safety assessment.
- **Dose-determining set (DDS):** Included all patients from the safety set of the dose escalation part of the study who either completed a minimum exposure requirement and had sufficient safety evaluations or had experienced a DLT during cycle 1.
- **Pharmacokinetic analysis set (PAS):** consisted of all patients who received at least one dose of study treatment defined as ribociclib, letrozole, fulvestrant, tamoxifen and/or goserelin and had evaluable PK concentration data.

The primary objective of the dose escalation part was to estimate the MTD(s) and/or RP2D(s) of the combination of ribociclib and letrozole 2.5 mg QD in postmenopausal women with HR+, HER2-negative, advanced BC in Japanese and Asian non-Japanese populations. The MTD(s) and/or RP2D(s) were evaluated independently for each population.

The primary variable is the incidence of DLTs in Cycle 1. Estimation of the MTD of the combination treatment was based upon the estimation of the probability of DLT in Cycle 1 for patients in the DDS.

An adaptive BLRM guided by the EWOC principle guided the dose escalation of the combination treatment to its MTD/RP2D. A 5-parameter BLRM for combination treatment was fitted separately for each population (Japanese population and Asian non-

Japanese population) using the respective Cycle 1 DLT data (i.e., absence or presence of DLT) accumulated throughout the dose escalation to model the dose-toxicity relationship of ribociclib and letrozole given in combination.

The 5-parameter BLRM was formulated in the following way: Let $\pi_1(d_1)$ be the probability of DLT if ribociclib is given as a single agent at QD dose d1, $\pi_2(d_2)$ the probability of DLT if letrozole is given as a single agent at QD dose of d_2.

Dose recommendation was based on summaries of the posterior distribution of model parameters and the posterior distribution of DLT rates, including the mean, median, standard deviation, 95%-credibility interval, and the probability that the true DLT rate for each dose combination lies in one of the following categories:

- [0, 16%] under-dosing
- [16%, 35%] targeted toxicity
- [35%, 100%] excessive toxicity

Following the principle of EWOC, after each cohort of patients, the recommended next dose was the one with the highest posterior probability of DLT in the targeted toxicity interval among the doses fulfilling the overdose criterion that there is less than 25% chance of excessive toxicity.

The final recommended MTD/RP2D for the combination treatment was based on considerations of the recommendation from the BLRM, and on an overall assessment of safety taking into consideration tolerability data from subsequent cycles at dose combinations tested for this combination treatment.

The primary objectives in the dose expansion part were:

- to further evaluate the safety and tolerability of ribociclib in combination with letrozole in postmenopausal Asian non-Japanese patients
- to evaluate the safety and tolerability of ribociclib in combination with letrozole in postmenopausal Japanese patients
- to evaluate the safety and tolerability of ribociclib in combination with fulvestrant in postmenopausal Japanese patients
- to evaluate the safety and tolerability of ribociclib in combination with tamoxifen + goserelin in premenopausal Japanese patients

The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., ECG and vital signs) could have been considered as appropriate.

The following secondary efficacy endpoints were analyzed:

- Progression free survival (PFS): PFS is defined as the time from the start date of study treatment to the date of the first documented disease progression or death due to any cause. The survival distribution of PFS (as per local investigator's assessment) was estimated using the Kaplan-Meier curves by treatment group. The median, 25th and 75th percentiles for PFS for each treatment group were provided with associated 95% confidence intervals.
- Overall response rate (ORR): ORR is defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1. ORR was calculated based on the FAS. For patients with only non-measurable disease at baseline, they were included in the numerator only if a complete response was observed. Proportions of patients with ORR were presented by treatment group along with 95% exact confidence intervals.
- Disease control rate (DCR): DCR is defined as the proportion of patients with best overall response of CR or PR or SD according to RECIST 1.1. DCR was calculated based on the FAS. For patients with only non-measurable disease at baseline, they were included in the numerator only if a complete response was observed. Proportions of patients with DCR were presented by treatment group along with 95% exact confidence intervals.
- Clinical benefit rate (CBR): CBR is defined as the proportion of patients with a best overall response of confirmed CR or PR or SD lasting 24 weeks or longer, according to RECIST 1.1 criteria. CBR was calculated using the FAS based on the Investigator's tumor assessment. CBR was summarized by treatment group using descriptive statistics.
- Duration of response (DoR): DoR applied only to patients whose best overall response was CR or PR. The start date is the date of first documented response (CR or PR, which must be confirmed subsequently) and the end date is the date of event defined as the first documented progression or death due to underlying cancer. In other words, the start date was determined using the time the response was first determined and not using the time the response was confirmed. If a patient had not had an event, duration is censored at the date of last adequate tumor assessment using the same censoring rule described for PFS analysis. DoR was summarized by treatment group.
- Overall survival: Overall survival (OS) is defined as the time from the date of the start of study treatment to the date of death due to any cause. If a patient was not known to have died, then OS was censored at the date of last known date patient alive. OS was summarized by treatment group using descriptive statistics for FAS. While not in the endpoints, OS analysis was included in the CSR in alignment with the SAP. The reason is that the collection of OS data is clinically relevant given the indication and the target population.

PK parameters were determined for all PK-evaluable patients using noncompartmental method(s).

- The PK parameters for ribociclib included:

- primary: Cmax, Tmax, AUC0-24h.
- secondary: CL/F, Racc, T1/2, acc, Cavg (Day 21 only).
- other parameters (listed only): Clast, Tlast.

- The PK parameters for letrozole were the same as ribociclib, whereas the PK parameters for LEQ803 were the same as ribociclib except the secondary which includes MR.
- The PK parameters for tamoxifen on Cycle 3 Day 15 included: Cmax, Tmax and AUC0-24h.

The descriptive statistics (n, mean, CV%, standard deviation (SD), median, geometric mean, geometric CV%, minimum and maximum) were presented, if needed, by treatment group for all defined PK parameters except Tmax, where only n, median, minimum, and maximum was presented.

Study Population: Key Inclusion/Exclusion Criteria

The patient population for the study consists of:

- Postmenopausal Asian non-Japanese women with HR+, HER2-, advanced (locoregionally recurrent or metastatic) breast cancer, who have not received any prior therapy for advanced breast cancer. They were enrolled in both the Asian non-Japanese dose escalation and expansion parts of the study.
- Pre- or postmenopausal Japanese women with HR+, HER2-, advanced (locoregionally recurrent or metastatic) breast cancer, who have received no or only one line of prior therapy for advanced breast cancer. Only postmenopausal women who received no prior therapy for advanced breast cancer were enrolled in the Japanese escalation part.

Participant Flow Table

Patient disposition by dose level, Escalation part (FAS)

	Ribociclib 400 mg + Letrozole 2.5 mg (non-Japan) N=6 n (%)	Ribociclib 400 mg + Letrozole 2.5 mg (Japan) N=6 n (%)	Ribociclib 600 mg + Letrozole 2.5 mg (non-Japan) N=7 n (%)	Ribociclib 300 mg + Letrozole 2.5 mg (Japan) N=7 n (%)	All Patients N=26 n (%)
Treatment phase					
Patients treated	6 (100)	6 (100)	7 (100)	7 (100)	26 (100)
Treatment phase discontinued	6 (100)	6 (100)	7 (100)	7 (100)	26 (100)
Entered post-treatment efficacy follow-up	0	0	0	1 (14.3)	1 (3.8)
Entered survival follow-up after treatment phase	6 (100)	5 (83.3)	5 (71.4)	5 (71.4)	21 (80.8)
Primary reason for discontinuation from treatment phase	6 (100)	6 (100)	7 (100)	7 (100)	26 (100)
Adverse events	0	0	0	1 (14.3)	1 (3.8)
Progressive disease	6 (100)	5 (83.3)	4 (57.1)	5 (71.4)	20 (76.9)
Physician decision	0	0	1 (14.3)	0	1 (3.8)
Patient/Guardian decision	0	0	1 (14.3)	1 (14.3)	2 (7.7)
Study Terminated by Sponsor	0	1 (16.7)	1 (14.3)	0	2 (7.7)
Post-treatment follow-up phase					
Post-treatment follow-up discontinued	0	0	0	1 (14.3)	1 (3.8)
Primary reason for discontinuation of post-treatment follow-up phase	0	0	0	1 (14.3)	1 (3.8)
Death	0	0	0	1 (14.3)	1 (3.8)

Percentage is based on N.
Reasons for discontinuation are from the End of Treatment Disposition and End of Post-Treatment Follow-up Phase Disposition CRF pages.
"Study terminated by Sponsor" category includes patients who transitioned to another clinical study that continued provision of ribociclib.

Patient disposition, Expansion part (FAS)

	Ribociclib 600 mg + Letrozole 2.5 mg (non-Japan) N=16 n (%)	Ribociclib 300 mg + Letrozole 2.5 mg (Japan) N=15 n (%)	Ribociclib 300 mg + Fulvestrant 500 mg (Japan) N=16 n (%)	Ribociclib 300 mg + Tamoxifen 20 mg (Japan) N=15 n (%)	All Patients N=62 n (%)
Treatment phase					
Patients treated	16 (100)	15 (100)	16 (100)	15 (100)	62 (100)
Treatment phase discontinued	16 (100)	15 (100)	16 (100)	15 (100)	62 (100)
Entered post-treatment efficacy follow-up	0	2 (13.3)	1 (6.3)	2 (13.3)	5 (8.1)
Entered survival follow-up after treatment phase	14 (87.5)	11 (73.3)	16 (100)	15 (100)	56 (90.3)
Primary reason for discontinuation from treatment phase	16 (100)	15 (100)	16 (100)	15 (100)	62 (100)
Adverse events	1 (6.3)	2 (13.3)	0	0	3 (4.8)
Progressive disease	13 (81.3)	8 (53.3)	16 (100)	14 (93.3)	51 (82.3)
Physician decision	0	2 (13.3)	0	1 (6.7)	3 (4.8)
Study Terminated by Sponsor	2 (12.5)	3 (20.0)	0	0	5 (8.1)
Post-treatment follow-up phase					
Post-treatment follow-up discontinued	0	2 (13.3)	1 (6.3)	2 (13.3)	5 (8.1)
Primary reason for discontinuation of post-treatment follow-up phase	0	2 (13.3)	1 (6.3)	2 (13.3)	5 (8.1)
Progressive disease	0	1 (6.7)	1 (6.3)	1 (6.7)	3 (4.8)
Physician decision	0	1 (6.7)	0	1 (6.7)	2 (3.2)

Percentage is based on N.
Reasons for discontinuation are from the End of Treatment Disposition and End of Post-Treatment Follow-up Phase Disposition CRF pages.
"Study terminated by Sponsor" category includes patients who transitioned to another clinical study that continued provision of ribociclib.

Baseline Characteristics

Demographics by dose level, Escalation part (FAS)

Demographic Variable	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N=6	Ribociclib 400mg + letrozole 2.5mg (Japan) N=6	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=7	Ribociclib 300mg + letrozole 2.5mg (Japan) N=7	All patients N=26
Age (years)					
Mean	52.3	63.8	62.0	64.3	60.8
Standard deviation	8.24	7.99	5.92	8.75	8.74
Median	54.5	63.0	61.0	67.0	61.0
Minimum	41.0	55.0	54.0	49.0	41.0
Maximum	61.0	77.0	72.0	76.0	77.0
Age category (years) -n (%)					
<65 Years	6 (100)	4 (66.7)	5 (71.4)	2 (28.6)	17 (65.4)
≥65 Years	0	2 (33.3)	2 (28.6)	5 (71.4)	9 (34.6)
Race -n (%)					
Asian	6 (100)	6 (100)	7 (100)	7 (100)	26 (100)
Ethnicity -n (%)					
Chinese	3 (50.0)	0	6 (85.7)	0	9 (34.6)
East Asian	1 (16.7)	0	0	0	1 (3.8)
Indonesian	1 (16.7)	0	0	0	1 (3.8)
Japanese	0	6 (100)	0	7 (100)	13 (50.0)
Malay	1 (16.7)	0	1 (14.3)	0	2 (7.7)
Weight (kg)					
Mean	56.4	52.4	59.5	53.9	55.6
Standard Deviation	6.00	7.47	14.12	6.92	9.24
Median	56.5	49.1	60.5	55.8	55.6
Minimum	49.1	45.6	39.7	44.5	39.7
Maximum	64.4	63.5	78.5	64.2	78.5

Demographic Variable	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N=6	Ribociclib 400mg + letrozole 2.5mg (Japan) N=6	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=7	Ribociclib 300mg + letrozole 2.5mg (Japan) N=7	All patients N=26
Height (cm)					
Mean	158.3	152.7	154.6	156.7	155.6
Standard Deviation	3.40	3.87	7.48	6.85	5.87
Median	159.0	152.6	154.0	157.5	156.1
Minimum	154.0	147.1	144.0	142.5	142.5
Maximum	161.8	158.2	164.0	163.0	164.0
Body mass index (kg/m2)					
Mean	22.5	22.5	25.3	21.9	23.1
Standard Deviation	2.57	3.01	7.68	2.30	4.53
Median	22.3	22.1	25.4	22.5	22.5
Minimum	18.8	18.9	15.9	17.8	15.9
Maximum	25.8	26.9	37.9	24.8	37.9
ECOG performance status -n (%)					
0	3 (50.0)	6 (100)	7 (100)	5 (71.4)	21 (80.8)
1	3 (50.0)	0	0	2 (28.6)	5 (19.2)

Demographics by dose level, Expansion part (FAS)

Demographic Variable	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=16	Ribociclib 300mg + letrozole 2.5mg (Japan) N=15	Ribociclib 300mg + fulvestrant 500mg (Japan) N=16	Ribociclib 300mg + tamoxifen 20mg (Japan) N=15	All patients N=62
Age (years)					
Mean	55.4	68.5	61.6	44.3	57.5
Standard Deviation	7.87	10.21	10.83	5.51	12.39
Median	53.0	69.0	63.0	44.0	54.0
Minimum	43.0	49.0	43.0	34.0	34.0
Maximum	72.0	83.0	78.0	53.0	83.0
Age category (years) -n (%)					
<65 Years	13 (81.3)	4 (26.7)	8 (50.0)	15(100)	40 (64.5)
≥65 Years	3 (18.8)	11 (73.3)	8 (50.0)	0	22 (35.5)
Race -n (%)					
Asian	16(100)	15(100)	16(100)	15(100)	62(100)
Ethnicity -n (%)					
Chinese	11 (68.8)	0	0	0	11 (17.7)
Indonesian	2 (12.5)	0	0	0	2 (3.2)
Japanese	0	15 (100)	16 (100)	15 (100)	46 (74.2)
Malay	3 (18.8)	0	0	0	3 (4.8)
Weight (kg)					
Mean	59.4	56.2	56.5	56.5	57.2
Standard Deviation	11.02	10.38	11.08	10.03	10.47
Median	59.1	53.5	56.4	55.3	56.7
Minimum	40.7	39.5	37.5	39.5	37.5
Maximum	80.9	76.0	81.3	71.8	81.3
Height (cm)					
Mean	155.0	154.7	155.1	160.4	156.2

Demographic Variable	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=16	Ribociclib 300mg + letrozole 2.5mg (Japan) N=15	Ribociclib 300mg + fulvestrant 500mg (Japan) N=16	Ribociclib 300mg + tamoxifen 20mg (Japan) N=15	All patients N=62
Standard Deviation	3.97	7.32	7.52	5.14	6.46
Median	155.0	156.4	157.5	159.5	157.0
Minimum	148.0	136.0	142.1	151.9	136.0
Maximum	161.0	162.5	165.6	169.1	169.1
Body mass index (kg/m2)					
Mean	24.7	23.5	23.4	21.9	23.4
Standard Deviation	4.40	4.25	3.76	3.43	4.01
Median	24.6	22.3	23.7	21.9	23.0
Minimum	17.6	18.3	16.6	16.0	16.0
Maximum	34.1	31.4	31.5	26.8	34.1
ECOG performance status -n (%)					
0	11 (68.8)	12 (80.0)	14 (87.5)	14 (93.3)	51 (82.3)
1	5 (31.3)	3 (20.0)	2 (12.5)	1(6.7)	11 (17.7)

Primary Outcome Result(s)

Dose limiting toxicities by primary system organ class, preferred term and dose level, Escalation part (Dose-determining set)

Primary system organ class Preferred term	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N=6 n (%)	Ribociclib 400mg + letrozole 2.5mg (Japan) N=6 n (%)	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=7 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N=7 n (%)
-Any primary system organ class				
-Total	1 (16.7)	3 (50.0)	1 (14.3)	1 (14.3)
Blood and lymphatic system disorders				
-Total	0	0	0	1 (14.3)
Neutropenia	0	0	0	1 (14.3)
Hepatobiliary disorders				
-Total	0	1 (16.7)	0	0
Hepatic function abnormal	0	1 (16.7)	0	0
Investigations				
-Total	1 (16.7)	3 (50.0)	1 (14.3)	0
Alanine aminotransferase increased	0	2 (33.3)	1 (14.3)	0
Aspartate aminotransferase increased	1 (16.7)	2 (33.3)	0	0
Blood creatinine increased	0	1 (16.7)	0	0
Neutrophil count decreased	1 (16.7)	0	0	0

System organ classes are presented in alphabetical order; preferred terms are sorted within primary system organ class in descending frequency in the 600 mg column.
A patient with multiple occurrences of DLTs under one dose level is counted only once in the AE category for that dose level.
A patient with multiple DLTs within a primary system organ class is counted only once in the total row.
Functional DLTs are also included. Functional DLTs are DLTs that do not fit the protocol definition of DLTs but were deemed relevant by Principal Investigators and were used to guide dose escalation.
MedDRA Version 25.0 has been used for the reporting of adverse events.

Secondary Outcome Result(s)

Best overall response as per local investigator's assessment, Expansion part (FAS)

	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 16		Ribociclib 300mg + letrozole 2.5mg (Japan) N = 15		Ribociclib 300mg + fulvestrant 500mg (Japan) N = 16		Ribociclib 300mg + tamoxifen 20mg (Japan) N = 15	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Patients with measurable disease at baseline	15 (93.8)		13 (86.7)		13 (81.3)		15 (100)	
Patients with non-measurable disease only at baseline	1 (6.3)		2 (13.3)		3 (18.8)		0	
Best Overall Response								
Non-CR/Non-PD	1 (6.3)		2 (13.3)		3 (18.8)		0	
Partial Response (PR)	8 (50.0)		10 (66.7)		3 (18.8)		10 (66.7)	
Progressive Disease (PD)	3 (18.8)		0		2 (12.5)		0	
Stable Disease (SD)	4 (25.0)		3 (20.0)		8 (50.0)		5 (33.3)	
Overall Response Rate (ORR)	8 (50.0)	[25.5,74.5]	10 (66.7)	[42.8,90.5]	3 (18.8)	[0.0,37.9]	10 (66.7)	[42.8,90.5]
Disease control rate (DCR: CR+PR+SD)	12 (75.0)	[53.8,96.2]	13 (86.7)	[69.5,100.0]	11 (68.8)	[46.0,91.5]	15 (100)	[100.0,100.0]
Clinical Benefit Rate (CBR: CR+PR+(SD+Non-CR/Non-PD>24 weeks))	13 (81.3)	[62.1,100.0]	14 (93.3)	[80.7,100.0]	12 (75.0)	[53.8,96.2]	15 (100)	[100.0,100.0]

N: The total number of patients in the treatment group. It is the denominator for percentage (%) calculation.
n: Number of patients who are at the corresponding category.
The 95% CI for the frequency distribution of each variable were computed based on normal approximation.

Overall summary of duration of response as per local investigator's assessment, Expansion part (FAS)

	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 16	Ribociclib 300mg + letrozole 2.5mg (Japan) N = 15	Ribociclib 300mg + fulvestrant 500mg (Japan) N = 16	Ribociclib 300mg + tamoxifen 20mg (Japan) N = 15
n/N (%)	5/8 (62.5)	6/10 (60.0)	3/3 (100)	9/10 (90.0)
Percentiles (95% CI)				
25th	9.2 (3.7, 35.0)	11.0 (5.6, 35.9)	9.2 (9.2, NE)	9.7 (4.6, 16.4)
50th	12.9 (3.7, NE)	35.9 (5.6, NE)	15.7 (9.2, NE)	14.7 (4.6, 34.1)
75th	NE (12.9, NE)	NE (35.9, NE)	20.3 (9.2, NE)	34.1 (12.9, NE)
% Event-free probability estimates (95% CI)				
Month 3	100.0 (100, 100)	100.0 (100, 100)	100.0 (100, 100)	100.0 (100, 100)
Month 4.5	87.5 (38.7, 98.1)	100.0 (100, 100)	100.0 (100, 100)	100.0 (100, 100)
Month 6	75.0 (31.5, 93.1)	90.0 (47.3, 98.5)	100.0 (100, 100)	80.0 (40.9, 94.6)
Month 9	75.0 (31.5, 93.1)	90.0 (47.3, 98.5)	100.0 (100, 100)	80.0 (40.9, 94.6)

	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 16	Ribociclib 300mg + letrozole 2.5mg (Japan) N = 15	Ribociclib 300mg + fulvestrant 500mg (Japan) N = 16	Ribociclib 300mg + tamoxifen 20mg (Japan) N = 15
Month 12	75.0 (31.5, 93.1)	70.0 (32.9, 89.2)	66.7 (5.4, 94.5)	70.0 (32.9, 89.2)

Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point.
Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups;
Greenwood formula is used for CIs of Kaplan Meier estimates.
n : Total number of events included in the analysis.
N : Total number of patients included in the analysis.

Overall summary of Progression Free Survival (months) as per local investigator's assessment, Expansion part (FAS)

	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 16	Ribociclib 300mg + letrozole 2.5mg (Japan) N = 15	Ribociclib 300mg + fulvestrant 500mg (Japan) N = 16	Ribociclib 300mg + tamoxifen 20mg (Japan) N = 15
n/N (%)	13/16 (81.3)	9/15 (60.0)	16/16 (100)	13/15 (86.7)
Median	12.7	41.2	10.9	27.4
Percentiles (95% CI)				
25th	6.3 (1.7, 12.7)	22.1 (7.4, 41.2)	5.9 (1.1, 9.1)	14.6 (6.4, 25.8)
50th	12.7 (5.4, 27.4)	41.2 (12.7, NE)	10.9 (5.4, 19.4)	27.4 (11.3, 35.7)
75th	27.4 (12.7, NE)	NE (41.2, NE)	20.4 (9.1, 24.7)	35.7 (25.8, NE)
% Event-free probability estimates (95% CI)				
Month 9	56.3 (29.5, 76.2)	92.9 (59.1, 99.0)	56.3 (29.5, 76.2)	86.7 (56.4, 96.5)
Month 15	42.2 (18.1, 64.6)	78.6 (47.2, 92.5)	43.8 (19.8, 65.6)	72.2 (41.7, 88.6)
Month 21	35.2 (13.3, 58.2)	78.6 (47.2, 92.5)	25.0 (7.8, 47.2)	72.2 (41.7, 88.6)
Month 27	28.1 (8.9, 51.4)	64.3 (34.3, 83.3)	6.3 (0.4, 24.7)	50.6 (23.3, 72.7)

Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point.
Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups;
Greenwood formula is used for CIs of Kaplan Meier estimates.
n : Total number of events included in the analysis.
N : Total number of patients included in the analysis.

Overall summary of overall survival (months), Expansion part (FAS)

	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 16	Ribociclib 300mg + letrozole 2.5mg (Japan) N = 15	Ribociclib 300mg + fulvestrant 500mg (Japan) N = 16	Ribociclib 300mg + tamoxifen 20mg (Japan) N = 15
n/N (%)	12/16 (75.0)	6/15 (40.0)	10/16 (62.5)	4/15 (26.7)
Percentiles (95% CI)				

	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 16	Ribociclib 300mg + letrozole 2.5mg (Japan) N = 15	Ribociclib 300mg + fulvestrant 500mg (Japan) N = 16	Ribociclib 300mg + tamoxifen 20mg (Japan) N = 15
25th	18.3 (13.5, 28.6)	31.2 (15.2, NE)	23.5 (4.5, 27.0)	57.3 (16.4, NE)
50th	29.6 (17.3, 54.2)	NE (25.0, NE)	27.3 (23.1, NE)	NE (18.7, NE)
75th	NE (28.6, NE)	NE (NE, NE)	NE (27.0, NE)	NE (NE, NE)
% Event-free probability estimates (95% CI)				
Month 12	100.0 (100, 100)	100.0 (100, 100)	93.8 (63.2, 99.1)	100.0 (100, 100)
Month 18	75.0 (46.3, 89.8)	93.3 (61.3, 99.0)	81.3 (52.5, 93.5)	93.3 (61.3, 99.0)
Month 24	56.3 (29.5, 76.2)	86.7 (56.4, 96.5)	68.8 (40.5, 85.6)	80.0 (50.0, 93.1)
Month 30	50.0 (24.5, 71.0)	80.0 (50.0, 93.1)	43.8 (19.8, 65.6)	80.0 (50.0, 93.1)
Month 36	37.5 (15.4, 59.8)	66.7 (37.5, 84.6)	43.8 (19.8, 65.6)	80.0 (50.0, 93.1)
Month 42	31.3 (11.4, 53.6)	66.7 (37.5, 84.6)	43.8 (19.8, 65.6)	80.0 (50.0, 93.1)

Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups; Greenwood formula is used for CIs of Kaplan Meier estimates.
n: Total number of events included in the analysis.
N: Total number of patients included in the analysis.

Summary of PK parameters for Ribociclib by visit and treatment group on C1D21 (Japanese - PK set)

Dose level	Statistics	Cmax (ng/mL)	Tmax (hr)	AUC0-24h (hr*ng/mL)	CL/F (L/hr)	Racc	T1/2, acc (hr)	Cavg (ng/mL)
Ribociclib 400 mg + Letrozole 2.5 mg (Escalation - Japan) (N=6)	n	3	3	3	2	3	3	2
	Mean (Standard Deviation)	1150 (77.7)	N/A	14900 (3840)	31.2 (3.55)	3.07 (0.588)	42.1 (9.93)	538 (61.2)
	CV% mean	6.7	N/A	25.8	11.4	19.2	23.6	11.4
	Geo-mean	1150	N/A	14600	31.1	3.0	41.3	536.0
	CV% geo-mean	6.7	N/A	25.3	11.5	20.3	25.5	11.5
	Median	1130	2.03	13700	31.2	3.21	44.6	538
	[Min; Max]	[1090; 1240]	[2.02; 6]	[11800; 19200]	[28.7; 33.7]	[2.42; 3.57]	[31.2; 50.6]	[494; 581]
Ribociclib 300 mg + Letrozole 2.5 mg (Escalation and Expansion - Japan) (N=22)	n	11	11	11	11	11	11	11
	Mean (Standard Deviation)	868 (381)	N/A	11300 (4400)	29.7 (10.2)	2.61 (1.17)	34.2 (19.9)	476 (187)
	CV% mean	44.0	N/A	39.0	34.3	44.7	58.2	39.2
	Geo-mean	804.0	N/A	10600	28.0	2.4	29.3	446.0
	CV% geo-mean	42.0	N/A	37.8	37.9	44.4	65.6	37.9

Dose level	Statistics	Cmax (ng/mL)	Tmax (hr)	AUC0-24h (hr*ng/mL)	CL/F (L/hr)	Racc	T1/2, acc (hr)	Cavg (ng/mL)
	Median	800	3.92	10400	28.8	2.45	31.7	433
	[Min; Max]	[451; 1800]	[1.97; 5.92]	[6400; 21200]	[13.9; 46.5]	[1.27; 5.29]	[10.8; 79.4]	[269; 901]
Ribociclib 300 mg + Tamoxifen 20 mg (Expansion - Japan) (N=15)	n	7	7	7	7	7	7	7
	Mean (Standard Deviation)	468 (220)	N/A	5890 (2670)	58.4 (20.9)	1.87 (0.291)	21.7 (5.06)	247 (110)
	CV% mean	47.0	N/A	45.3	35.9	15.6	23.3	44.8
	Geo-mean	428.0	N/A	5450	54.7	1.9	21.2	229.0
	CV% geo-mean	48.2	N/A	42.9	42.6	14.7	21.8	42.6
	Median	380	3.98	5040	59.1	1.8	20.6	211
	[Min; Max]	[221; 856]	[1.88; 4.1]	[3420; 10600]	[28.4; 87.3]	[1.54; 2.46]	[15.8; 31.9]	[143; 440]
Ribociclib 300 mg + Fulvestrant 500 mg (Expansion - Japan) (N=16)	n	10	10	10	10	10	10	10
	Mean (Standard Deviation)	867 (697)	N/A	10600 (7360)	36.4 (16.2)	2.54 (0.631)	33.1 (10.7)	447 (306)
	CV% mean	80.4	N/A	69.6	44.4	24.9	32.3	68.5
	Geo-mean	708.0	N/A	9060	32.6	2.5	31.6	384.0
	CV% geo-mean	67.7	N/A	58.9	58.4	24.7	32.8	58.4
	Median	620	2.99	8810	33.6	2.35	30	372
	[Min; Max]	[340; 2610]	[0.983; 4.13]	[4570; 29200]	[10.3; 65.2]	[1.77; 3.45]	[19.9; 48.5]	[192; 1220]

n: number of patients with non-missing values.
CV% = coefficient of variation (%) = Standard Deviation /mean*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1) *100.
AUC0-24h: refers to AUClast (AUC from time zero to the last quantifiable concentration).

Summary of PK parameters for ribociclib by visit and treatment group on C1D21 (non-Japanese - PK set)

Dose level	Statistics	Cmax (ng/mL)	Tmax (hr)	AUC0-24h (hr*ng/mL)	CL/F (L/hr)	Racc	T1/2, acc (hr)	Cavg (ng/mL)
Ribociclib 400mg + letrozole 2.5mg (Escalation – non-Japan) (N=6)	n	2	2	2	2	2	2	2
	Mean (Standard Deviation)	1400 (7.07)	N/A	15800 (4720)	26.3 (7.75)	2.07 (0.154)	25.2 (2.66)	663 (196)
	CV% mean	0.5	N/A	29.9	29.5	7.4	10.6	29.5
	Geo-mean	1390	N/A	15400	25.7	2.1	25.1	649.0
	CV% geo-mean	0.5	N/A	31.1	30.6	7.5	10.6	30.6

Dose level	Statistics	Cmax (ng/mL)	Tmax (hr)	AUC0-24h (hr*ng/mL)	CL/F (L/hr)	Racc	T1/2, acc (hr)	Cavg (ng/mL)
Ribociclib 600mg + letrozole 2.5mg (Escalation and Expansion – non-Japan) (N=23)	Median	1400	1.5	15800	26.3	2.07	25.2	663
	[Min; Max]	[1390;1400]	[1; 2]	[12400; 19100]	[20.8.; 31.8]	[1.96; 2.18]	[23.3; 27]	[525; 802]
	n	6	6	6	6	6	6	6
	Mean (Standard Deviation)	1620 (283)	N/A	21800 (4740)	28.4 (5.78)	2 (0.453)	23.8 (7.87)	913 (193)
	CV% mean	17.5	N/A	21.7	20.4	22.7	33.0	21.1
	Geo-mean	1600	N/A	21400	27.9	2.0	22.7	897.0
	CV% geo-mean	16.7	N/A	21.8	21.0	22.9	34.6	21.0
	Median	1560	3.12	20600	29.5	1.89	22	847
	[Min; Max]	[1330; 2120]	[2; 4.03]	[16000; 28200]	[21.3; 36.8]	[1.45; 2.58]	[14.2; 34]	[679; 1170]

n: number of patients with non-missing values.
CV% = coefficient of variation (%) = Standard Deviation /mean*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1) *100.
AUC0-24h: refers to AUClast (AUC from time zero to the last quantifiable concentration).

Safety Results

Summary of adverse events, Escalation part (Safety Set)

	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N = 6			Ribociclib 400mg + letrozole 2.5mg (Japan) N = 6			Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 7			Ribociclib 300mg + letrozole 2.5mg (Japan) N = 7		
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
All deaths [1]	5 (83.3)			4 (66.7)			1 (14.3)			4 (57.1)		
On-treatment deaths [2]	0			0			0			0		
Adverse events	6 (100)	5 (83.3)	1 (16.7)	6 (100)	6 (100)	2 (33.3)	7 (100)	7 (100)	1 (14.3)	7 (100)	5 (71.4)	3 (42.9)
Suspected to be drug-related	6 (100)	5 (83.3)	0	6 (100)	6 (100)	2 (33.3)	7 (100)	7 (100)	1 (14.3)	7 (100)	5 (71.4)	3 (42.9)
Serious adverse events	1 (16.7)	1 (16.7)	0	3 (50.0)	2 (33.3)	2 (33.3)	3 (42.9)	1 (14.3)	0	2 (28.6)	1 (14.3)	1 (14.3)
Suspected to be drug-related	0	0	0	2 (33.3)	1 (16.7)	2 (33.3)	1 (14.3)	1 (14.3)	0	1 (14.3)	0	1 (14.3)
AEs leading to discontinuation	0	0	0	2 (33.3)	0	2 (33.3)	3 (42.9)	1 (14.3)	0	2 (28.6)	1 (14.3)	1 (14.3)
Suspected to be drug-related	0	0	0	2 (33.3)	0	2 (33.3)	2 (28.6)	1 (14.3)	0	2 (28.6)	1 (14.3)	1 (14.3)
AEs requiring dose interruption and/or adjustment	5 (83.3)	5 (83.3)	0	6 (100)	6 (100)	0	7 (100)	7 (100)	1 (14.3)	6 (85.7)	4 (57.1)	2 (28.6)
Suspected to be drug-related	4 (66.7)	4 (66.7)	0	6 (100)	6 (100)	0	7 (100)	7 (100)	1 (14.3)	6 (85.7)	4 (57.1)	2 (28.6)

Preferred term	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N = 6			Ribociclib 400mg + letrozole 2.5mg (Japan) N = 6			Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 7			Ribociclib 300mg + letrozole 2.5mg (Japan) N = 7		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
AEs requiring additional therapy	5 (83.3)	3 (50.0)	1 (16.7)	6 (100)	4 (66.7)	2 (33.3)	7 (100)	5 (71.4)	1 (14.3)	5 (71.4)	2 (28.6)	1 (14.3)
Suspected to be drug-related	4 (66.7)	2 (33.3)	0	6 (100)	3 (50.0)	2 (33.3)	7 (100)	4 (57.1)	1 (14.3)	5 (71.4)	1 (14.3)	1 (14.3)
Clinically notable AEs	5 (83.3)	5 (83.3)	0	6 (100)	6 (100)	2 (33.3)	7 (100)	7 (100)	1 (14.3)	7 (100)	4 (57.1)	2 (28.6)
Suspected to be drug-related	5 (83.3)	5 (83.3)	0	6 (100)	6 (100)	2 (33.3)	7 (100)	7 (100)	1 (14.3)	7 (100)	4 (57.1)	2 (28.6)

Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category.
Patients with events in more than 1 category are counted once in each of those categories.
Suspected to be drug related refers to any component of study treatment
[1] All deaths including those >30 days after end of treatment.
[2] Deaths occurring >30 days after end of treatment are not included.
Additional therapy includes all non-drug therapy and concomitant medications.

Summary of adverse events, Expansion part (Safety Set)

Preferred term	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 16			Ribociclib 300mg + letrozole 2.5mg (Japan) N = 15			Ribociclib 300mg + fulvestrant 500mg (Japan) N = 16			Ribociclib 300mg + tamoxifen 20mg (Japan) N = 15		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
All deaths [1]	12 (75.0)			6 (40.0)			10 (62.5)			4 (26.7)		
On-treatment deaths [2]	0			0			0			0		
Adverse events	16 (100)	14 (87.5)	6 (37.5)	15 (100)	13 (86.7)	5 (33.3)	16 (100)	13 (81.3)	4 (25.0)	15 (100)	13 (86.7)	2 (13.3)
Suspected to be drug-related	16 (100)	14 (87.5)	3 (18.8)	15 (100)	12 (80.0)	4 (26.7)	16 (100)	13 (81.3)	2 (12.5)	15 (100)	13 (86.7)	1 (6.7)
Serious adverse events	6 (37.5)	4 (25.0)	2 (12.5)	4 (26.7)	3 (20.0)	1 (6.7)	3 (18.8)	3 (18.8)	0	2 (13.3)	2 (13.3)	0
Suspected to be drug-related	1 (6.3)	1 (6.3)	0	1 (6.7)	1 (6.7)	1 (6.7)	0	0	0	2 (13.3)	2 (13.3)	0
AEs leading to discontinuation	3 (18.8)	0	1 (6.3)	4 (26.7)	2 (13.3)	1 (6.7)	1 (6.3)	1 (6.3)	0	4 (26.7)	3 (20.0)	0
Suspected to be drug-related	2 (12.5)	0	0	3 (20.0)	2 (13.3)	1 (6.7)	1 (6.3)	1 (6.3)	0	4 (26.7)	3 (20.0)	0
AEs requiring dose interruption and/or adjustment	14 (87.5)	14 (87.5)	4 (25.0)	14 (93.3)	13 (86.7)	4 (26.7)	13 (81.3)	12 (75.0)	2 (12.5)	13 (86.7)	11 (73.3)	2 (13.3)
Suspected to be drug-related	14 (87.5)	14 (87.5)	3 (18.8)	13 (86.7)	12 (80.0)	3 (20.0)	13 (81.3)	12 (75.0)	2 (12.5)	13 (86.7)	11 (73.3)	1 (6.7)
AEs requiring additional therapy	15 (93.8)	7 (43.8)	3 (18.8)	15 (100)	6 (40.0)	3 (20.0)	15 (93.8)	9 (56.3)	0	15 (100)	7 (46.7)	1 (6.7)
Suspected to be drug-related	12 (75.0)	5 (31.3)	1 (6.3)	11 (73.3)	5 (33.3)	2 (13.3)	9 (56.3)	6 (37.5)	0	11 (73.3)	7 (46.7)	0
Clinically notable AEs	15 (93.8)	14 (87.5)	5 (31.3)	15 (100)	12 (80.0)	3 (20.0)	16 (100)	12 (75.0)	2 (12.5)	15 (100)	13 (86.7)	1 (6.7)

Preferred term	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 16			Ribociclib 300mg + letrozole 2.5mg (Japan) N = 15			Ribociclib 300mg + fulvestrant 500mg (Japan) N = 16			Ribociclib 300mg + tamoxifen 20mg (Japan) N = 15		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Suspected to be drug-related	15 (93.8)	14 (87.5)	3 (18.8)	15 (100)	11 (73.3)	3 (20.0)	16 (100)	12 (75.0)	1 (6.3)	15 (100)	12 (80.0)	1 (6.7)

- Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category.
Patients with events in more than 1 category are counted once in each of those categories.
- Suspected to be drug related refers to any component of study treatment
[1] All deaths including those >30 days after end of treatment.
[2] Deaths occurring >30 days after end of treatment are not included.
Additional therapy includes all non-drug therapy and concomitant medications.

Adverse events, regardless of study treatment relationship, by preferred term, maximum grade and dose level, Escalation part (≥20.0% all grades, any treatment arm) (Safety set)

Preferred term	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N=6			Ribociclib 400mg + letrozole 2.5mg (Japan) N=6			Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=7			Ribociclib 300mg + letrozole 2.5mg (Japan) N=7		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
-Total	6 (100)	4 (66.7)	1 (16.7)	6 (100)	4 (66.7)	2 (33.3)	7 (100)	6 (85.7)	1 (14.3)	7 (100)	3 (42.9)	3 (42.9)
Arthralgia	1 (16.7)	0	0	3 (50.0)	0	0	5 (71.4)	0	0	2 (28.6)	0	0
Cough	2 (33.3)	0	0	1 (16.7)	0	0	4 (57.1)	0	0	0	0	0
Upper respiratory tract infection	2 (33.3)	0	0	1 (16.7)	0	0	4 (57.1)	0	0	1 (14.3)	0	0
Alanine aminotransferase increased	1 (16.7)	1 (16.7)	0	3 (50.0)	1 (16.7)	1 (16.7)	3 (42.9)	2 (28.6)	0	4 (57.1)	1 (14.3)	0
Back pain	0	0	0	1 (16.7)	0	0	3 (42.9)	0	0	1 (14.3)	0	0
Diarrhoea	1 (16.7)	0	0	2 (33.3)	0	0	3 (42.9)	0	0	0	0	0
Dry skin	1 (16.7)	0	0	0	0	0	3 (42.9)	0	0	0	0	0
Dyspepsia	2 (33.3)	0	0	0	0	0	3 (42.9)	0	0	0	0	0
Headache	0	0	0	1 (16.7)	0	0	3 (42.9)	0	0	1 (14.3)	0	0
Hypoaesthesia	0	0	0	0	0	0	3 (42.9)	0	0	0	0	0
Nausea	1 (16.7)	0	0	0	0	0	3 (42.9)	0	0	1 (14.3)	0	0
Neutropenia	2 (33.3)	2 (33.3)	0	1 (16.7)	1 (16.7)	0	3 (42.9)	3 (42.9)	0	1 (14.3)	0	1 (14.3)
Neutrophil count decreased	3 (50.0)	3 (50.0)	0	4 (66.7)	4 (66.7)	0	3 (42.9)	2 (28.6)	1 (14.3)	6 (85.7)	3 (42.9)	0
Pruritus	0	0	0	2 (33.3)	0	0	3 (42.9)	0	0	1 (14.3)	0	0
Alopecia	3 (50.0)	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Anaemia	0	0	0	1 (16.7)	0	0	2 (28.6)	1 (14.3)	0	1 (14.3)	0	0

	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N=6			Ribociclib 400mg + letrozole 2.5mg (Japan) N=6			Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=7			Ribociclib 300mg + letrozole 2.5mg (Japan) N=7		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Aspartate aminotransferase increased	1 (16.7)	0	0	2 (33.3)	0	1 (16.7)	2 (28.6)	2 (28.6)	0	4 (57.1)	1 (14.3)	0
Cataract	0	0	0	0	0	0	2 (28.6)	1 (14.3)	0	0	0	0
Constipation	1 (16.7)	0	0	2 (33.3)	0	0	2 (28.6)	0	0	1 (14.3)	0	0
Decreased appetite	0	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Dizziness	0	0	0	1 (16.7)	0	0	2 (28.6)	0	0	0	0	0
Dry eye	0	0	0	0	0	0	2 (28.6)	0	0	1 (14.3)	0	0
Dyspnoea	0	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Epigastric discomfort	0	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Fatigue	1 (16.7)	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Hypokalaemia	2 (33.3)	0	0	1 (16.7)	0	0	2 (28.6)	0	0	0	0	0
Influenza like illness	1 (16.7)	0	0	1 (16.7)	0	0	2 (28.6)	0	0	0	0	0
Malaise	2 (33.3)	0	0	1 (16.7)	0	0	2 (28.6)	0	0	0	0	0
Muscle spasms	0	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Myalgia	0	0	0	1 (16.7)	0	0	2 (28.6)	0	0	0	0	0
Oropharyngeal pain	0	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Osteoporosis	1 (16.7)	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Palpitations	0	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Photopsia	0	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Platelet count decreased	0	0	0	0	0	0	2 (28.6)	0	0	1 (14.3)	0	0
Rash	2 (33.3)	0	0	3 (50.0)	0	0	2 (28.6)	0	0	2 (28.6)	0	0
Rash pruritic	2 (33.3)	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Rhinorrhoea	1 (16.7)	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Tendonitis	0	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0	0	2 (28.6)	0	0	0	0	0
Vomiting	2 (33.3)	0	0	1 (16.7)	0	0	2 (28.6)	0	0	1 (14.3)	0	0
Weight decreased	0	0	0	0	0	0	2 (28.6)	0	0	1 (14.3)	0	0
Weight increased	0	0	0	1 (16.7)	0	0	2 (28.6)	0	0	0	0	0
Blood creatinine increased	0	0	0	3 (50.0)	0	0	1 (14.3)	0	0	3 (42.9)	0	0
Pyrexia	1 (16.7)	0	0	2 (33.3)	0	0	1 (14.3)	0	0	0	0	0
Stomatitis	1 (16.7)	0	0	3 (50.0)	0	0	1 (14.3)	0	0	1 (14.3)	0	0
Cystitis	0	0	0	2 (33.3)	0	0	0	0	0	1 (14.3)	0	0

	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N=6			Ribociclib 400mg + letrozole 2.5mg (Japan) N=6			Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=7			Ribociclib 300mg + letrozole 2.5mg (Japan) N=7		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Nasopharyngitis	0	0	0	2 (33.3)	0	0	0	0	0	1 (14.3)	0	0
White blood cell count decreased	0	0	0	3 (50.0)	2 (33.3)	0	0	0	0	4 (57.1)	0	0

Preferred terms are sorted in descending frequency of all grades column, as reported in the 600 mg column.
A patient with multiple occurrences of an AE under one dose level is counted only once in the AE category for that dose level under the maximum grade.
A patient with multiple AEs is counted only once in the total row under the maximum grade.
MedDRA Version 25.0 has been used.

Adverse events, regardless of study treatment relationship, by preferred term, maximum grade and dose level (≥15.0% all grades, any treatment arm), Expansion part (Safety Set)

	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=16			Ribociclib 300mg + letrozole 2.5mg (Japan) N=15			Ribociclib 300mg + fulvestrant 500mg (Japan) N=16			Ribociclib 300mg + tamoxifen 20mg (Japan) N=15		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
-Total	16 (100)	8 (50.0)	6 (37.5)	15 (100)	8 (53.3)	5 (33.3)	16 (100)	9 (56.3)	4 (25.0)	15 (100)	11 (73.3)	2 (13.3)
Neutropenia	9 (56.3)	5 (31.3)	2 (12.5)	0	0	0	0	0	0	0	0	0
Electrocardiogram QT prolonged	7 (43.8)	0	0	3 (20.0)	0	0	2 (12.5)	0	0	6 (40.0)	0	0
Back pain	6 (37.5)	2 (12.5)	0	3 (20.0)	0	0	1 (6.3)	1 (6.3)	0	3 (20.0)	0	0
Diarrhoea	6 (37.5)	0	0	4 (26.7)	1 (6.7)	0	2 (12.5)	0	0	3 (20.0)	1 (6.7)	0
Upper respiratory tract infection	6 (37.5)	0	0	2 (13.3)	0	0	1 (6.3)	0	0	1 (6.7)	0	0
Vomiting	6 (37.5)	0	0	5 (33.3)	0	0	2 (12.5)	0	0	4 (26.7)	0	0
Alanine aminotransferase increased	5 (31.3)	2 (12.5)	0	6 (40.0)	3 (20.0)	0	8 (50.0)	3 (18.8)	0	9 (60.0)	4 (26.7)	0
Cough	5 (31.3)	0	0	3 (20.0)	0	0	1 (6.3)	0	0	1 (6.7)	0	0
Neutrophil count decreased	5 (31.3)	4 (25.0)	1 (6.3)	14 (93.3)	8 (53.3)	2 (13.3)	12 (75.0)	8 (50.0)	1 (6.3)	10 (66.7)	5 (33.3)	1 (6.7)
Pruritus	5 (31.3)	0	0	0	0	0	0	0	0	0	0	0
Anaemia	4 (25.0)	0	0	6 (40.0)	2 (13.3)	0	4 (25.0)	1 (6.3)	0	2 (13.3)	1 (6.7)	0
Aspartate aminotransferase increased	4 (25.0)	3 (18.8)	0	6 (40.0)	0	0	8 (50.0)	0	0	9 (60.0)	1 (6.7)	0
Dyspepsia	4 (25.0)	0	0	0	0	0	0	0	0	0	0	0
Fatigue	4 (25.0)	0	0	0	0	0	2 (12.5)	0	0	2 (13.3)	0	0
Headache	4 (25.0)	0	0	2 (13.3)	0	0	2 (12.5)	0	0	5 (33.3)	0	0

	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=16			Ribociclib 300mg + letrozole 2.5mg (Japan) N=15			Ribociclib 300mg + fulvestrant 500mg (Japan) N=16			Ribociclib 300mg + tamoxifen 20mg (Japan) N=15		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hypocalcaemia	4 (25.0)	0	0	1 (6.7)	0	0	0	0	0	3 (20.0)	0	1 (6.7)
Hypokalaemia	4 (25.0)	0	0	2 (13.3)	0	2 (13.3)	2 (12.5)	0	1 (6.3)	0	0	0
Influenza like illness	4 (25.0)	0	0	1 (6.7)	0	0	0	0	0	0	0	0
Malaise	4 (25.0)	0	0	4 (26.7)	0	0	1 (6.3)	0	0	3 (20.0)	0	0
Nausea	4 (25.0)	0	0	5 (33.3)	0	0	4 (25.0)	0	0	3 (20.0)	0	0
Rash	4 (25.0)	0	0	3 (20.0)	0	0	4 (25.0)	0	0	2 (13.3)	0	0
Aphthous ulcer	3 (18.8)	0	0	0	0	0	0	0	0	0	0	0
Blood creatinine increased	3 (18.8)	0	0	3 (20.0)	0	0	3 (18.8)	0	1 (6.3)	3 (20.0)	0	0
Constipation	3 (18.8)	0	0	1 (6.7)	0	0	2 (12.5)	0	0	2 (13.3)	0	0
Dysgeusia	3 (18.8)	0	0	2 (13.3)	0	0	0	0	0	0	0	0
Hypercalcaemia	3 (18.8)	0	0	0	0	0	0	0	0	0	0	0
Hypophosphataemia	3 (18.8)	0	0	0	0	0	0	0	0	0	0	0
Pyrexia	3 (18.8)	0	0	2 (13.3)	0	0	3 (18.8)	0	0	3 (20.0)	0	0
Rhinorrhoea	3 (18.8)	0	0	0	0	0	0	0	0	0	0	0
Arthralgia	2 (12.5)	0	0	6 (40.0)	0	0	3 (18.8)	0	0	4 (26.7)	0	0
Decreased appetite	2 (12.5)	0	0	3 (20.0)	0	0	1 (6.3)	0	0	3 (20.0)	0	0
Stomatitis	2 (12.5)	0	0	5 (33.3)	0	0	4 (25.0)	0	0	5 (33.3)	0	0
Hot flush	1 (6.3)	0	0	3 (20.0)	0	0	1 (6.3)	0	0	5 (33.3)	0	0
Insomnia	1 (6.3)	0	0	0	0	0	1 (6.3)	0	0	4 (26.7)	0	0
Lipase increased	1 (6.3)	0	1 (6.3)	4 (26.7)	2 (13.3)	0	1 (6.3)	0	1 (6.3)	2 (13.3)	1 (6.7)	0
Pneumonia	1 (6.3)	1 (6.3)	0	4 (26.7)	0	0	0	0	0	0	0	0
Rash maculo-papular	1 (6.3)	0	0	3 (20.0)	0	0	1 (6.3)	0	0	0	0	0
Weight increased	1 (6.3)	0	0	2 (13.3)	1 (6.7)	0	0	0	0	4 (26.7)	1 (6.7)	0
White blood cell count decreased	1 (6.3)	1 (6.3)	0	11 (73.3)	2 (13.3)	0	10 (62.5)	2 (12.5)	0	9 (60.0)	3 (20.0)	0
Amylase increased	0	0	0	2 (13.3)	0	0	1 (6.3)	1 (6.3)	0	3 (20.0)	0	0
Cystitis	0	0	0	3 (20.0)	0	0	1 (6.3)	0	0	1 (6.7)	0	0
Lymphocyte count decreased	0	0	0	1 (6.7)	0	0	3 (18.8)	2 (12.5)	0	1 (6.7)	0	0
Nasopharyngitis	0	0	0	7 (46.7)	0	0	6 (37.5)	0	0	7 (46.7)	0	0
Pharyngitis	0	0	0	3 (20.0)	0	0	1 (6.3)	0	0	3 (20.0)	0	0

	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=16			Ribociclib 300mg + letrozole 2.5mg (Japan) N=15			Ribociclib 300mg + fulvestrant 500mg (Japan) N=16			Ribociclib 300mg + tamoxifen 20mg (Japan) N=15		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Preferred terms are sorted in descending frequency of all grades column, as reported in the 600 mg column.
A patient with multiple occurrences of an AE under one dose level is counted only once in the AE category for that dose level under the maximum grade.
A patient with multiple AEs is counted only once in the total row under the maximum grade.
MedDRA Version 25.0 has been used.

Adverse events, suspected to be study treatment related, by preferred term and dose level (≥20.0% all grades, all treatment arms), Escalation part (Safety set)

Preferred term	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N=6 n (%)	Ribociclib 400mg + letrozole 2.5mg (Japan) N=6 n (%)	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=7 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N=7 n (%)
-Total	6 (100)	6 (100)	7 (100)	7 (100)
Alanine aminotransferase increased	1 (16.7)	3 (50.0)	3 (42.9)	4 (57.1)
Nausea	0	0	3 (42.9)	0
Neutropenia	2 (33.3)	1 (16.7)	3 (42.9)	1 (14.3)
Neutrophil count decreased	3 (50.0)	4 (66.7)	3 (42.9)	6 (85.7)
Alopecia	3 (50.0)	0	2 (28.6)	0
Arthralgia	0	1 (16.7)	2 (28.6)	2 (28.6)
Aspartate aminotransferase increased	1 (16.7)	2 (33.3)	2 (28.6)	4 (57.1)
Diarrhoea	0	0	2 (28.6)	0
Dyspepsia	0	0	2 (28.6)	0
Osteoporosis	1 (16.7)	0	2 (28.6)	0
Thrombocytopenia	0	0	2 (28.6)	0
Malaise	2 (33.3)	1 (16.7)	1 (14.3)	0
Pruritus	0	2 (33.3)	1 (14.3)	1 (14.3)
Rash	2 (33.3)	3 (50.0)	1 (14.3)	2 (28.6)
Stomatitis	1 (16.7)	3 (50.0)	1 (14.3)	1 (14.3)
Blood creatinine increased	0	3 (50.0)	0	3 (42.9)
Constipation	1 (16.7)	2 (33.3)	0	1 (14.3)
Cystitis	0	2 (33.3)	0	1 (14.3)
White blood cell count decreased	0	3 (50.0)	0	4 (57.1)

Preferred term	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N=6 n (%)	Ribociclib 400mg + letrozole 2.5mg (Japan) N=6 n (%)	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=7 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N=7 n (%)

Preferred terms are sorted in descending frequency as reported in the 600 mg column.
A patient with multiple occurrences of an AE under one dose level is counted only once in the AE category for that dose level.
A patient with multiple adverse events is counted only once in the total row.
Suspected to be drug related refers to any component of study treatment.
MedDRA Version 25.0 has been used.

Adverse events, suspected to be study treatment related, by preferred term (≥15.0% all grades, all treatment arms), Expansion part (Safety set)

Preferred term	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=16 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N=15 n (%)	Ribociclib 300mg + fulvestrant 500mg (Japan) N=16 n (%)	Ribociclib 300mg + tamoxifen 20mg (Japan) N=15 n (%)
-Total	16 (100)	15 (100)	16 (100)	15 (100)
Neutropenia	8 (50.0)	0	0	0
Electrocardiogram QT prolonged	7 (43.8)	3 (20.0)	2 (12.5)	6 (40.0)
Neutrophil count decreased	5 (31.3)	14 (93.3)	12 (75.0)	10 (66.7)
Alanine aminotransferase increased	4 (25.0)	6 (40.0)	7 (43.8)	9 (60.0)
Aspartate aminotransferase increased	4 (25.0)	6 (40.0)	7 (43.8)	9 (60.0)
Nausea	4 (25.0)	4 (26.7)	2 (12.5)	2 (13.3)
Blood creatinine increased	2 (12.5)	2 (13.3)	3 (18.8)	2 (13.3)
Malaise	1 (6.3)	3 (20.0)	1 (6.3)	1 (6.7)
Rash	1 (6.3)	3 (20.0)	2 (12.5)	2 (13.3)
Stomatitis	1 (6.3)	4 (26.7)	2 (12.5)	3 (20.0)
White blood cell count decreased	1 (6.3)	11 (73.3)	10 (62.5)	9 (60.0)
Anaemia	0	6 (40.0)	3 (18.8)	2 (13.3)
Arthralgia	0	1 (6.7)	3 (18.8)	2 (13.3)
Hot flush	0	3 (20.0)	1 (6.3)	5 (33.3)
Lipase increased	0	3 (20.0)	1 (6.3)	1 (6.7)
Lymphocyte count decreased	0	1 (6.7)	3 (18.8)	1 (6.7)
Weight increased	0	0	0	3 (20.0)

Preferred terms are sorted in descending frequency as reported in the 600 mg column.
A patient with multiple occurrences of an AE under one dose level is counted only once in the AE category for that dose level.
A patient with multiple adverse events is counted only once in the total row.
Suspected to be drug related refers to any component of study treatment.
MedDRA Version 25.0 has been used.

Deaths by primary system organ class, preferred term and dose level, Escalation part (Safety Set)

Primary system organ class Principal cause of death	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N = 6 n (%)	Ribociclib 400mg + letrozole 2.5mg (Japan) N = 6 n (%)	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 7 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N = 7 n (%)
Any primary system organ class	5 (83.3)	4 (66.7)	1 (14.3)	4 (57.1)
Study indication as cause of death				
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (83.3)	4 (66.7)	1 (14.3)	2 (28.6)
Breast cancer	5 (83.3)	4 (66.7)	1 (14.3)	2 (28.6)
Other as cause of death				
Any primary system organ class	0	0	0	2 (28.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (14.3)
Acute myeloid leukaemia	0	0	0	1 (14.3)
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (14.3)
Aspiration	0	0	0	1 (14.3)

System organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency as reported in the 600 mg column
All deaths during the study are included.

Deaths by primary system organ class and preferred term, Expansion part (Safety Set)

Primary system organ class Principal cause of death	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 16 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N = 15 n (%)	Ribociclib 300mg + fulvestrant 500mg (Japan) N = 16 n (%)	Ribociclib 300mg + tamoxifen 20mg (Japan) N = 15 n (%)
Any primary system organ class	12 (75.0)	6 (40.0)	10 (62.5)	4 (26.7)
Study indication as cause of death				
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (68.8)	6 (40.0)	10 (62.5)	4 (26.7)
Breast cancer	11 (68.8)	6 (40.0)	10 (62.5)	4 (26.7)
Other as cause of death				
Any primary system organ class	1 (6.3)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (6.3)	0	0	0
Acute lymphocytic leukaemia	1 (6.3)	0	0	0

System organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency as reported in the 600 mg column
All deaths during the study are included.

Adverse events leading to discontinuation, by preferred term, and dose level (at least 20% incidence), Escalation part (Safety set)

Preferred term	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N=6 n (%)	Ribociclib 400mg + letrozole 2.5mg (Japan) N=6 n (%)	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=7 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N=7 n (%)
-Total	0	2 (33.3)	3 (42.9)	2 (28.6)
Alanine aminotransferase increased	0	1 (16.7)	2 (28.6)	1 (14.3)
Aspartate aminotransferase increased	0	1 (16.7)	2 (28.6)	0

AEs leading to discontinuation of any component of study treatment are included
Preferred terms are sorted in descending frequency as reported in the 600 mg column.
A patient with multiple occurrences of an AE is counted only once in the AE category
A patient with multiple AEs is counted only once in the total row
MedDRA Version 25.0 has been used.

Adverse events leading to discontinuation, by preferred term (at least 15% incidence), Expansion part (Safety set)

Preferred term	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 16 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N = 15 n (%)	Ribociclib 300mg + fulvestrant 500mg (Japan) N = 16 n (%)	Ribociclib 300mg + tamoxifen 20mg (Japan) N = 15 n (%)
-Total	3 (18.8)	4 (26.7)	1 (6.3)	4 (26.7)
Alanine aminotransferase increased	2 (12.5)	1 (6.7)	1 (6.3)	3 (20.0)

AEs leading to discontinuation of any component of study treatment are included
Preferred terms are sorted in descending frequency as reported in the 600 mg column.
A patient with multiple occurrences of an AE is counted only once in the AE category
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MedDRA Version 25.0 has been used.

Adverse events requiring dose adjustment or interruption, by preferred term and dose level (at least 20% incidence), Escalation part (Safety set)

Preferred term	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N=6 n (%)	Ribociclib 400mg + letrozole 2.5mg (Japan) N=6 n (%)	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=7 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N=7 n (%)
-Total	5 (83.3)	6 (100)	7 (100)	6 (85.7)
Alanine aminotransferase increased	1 (16.7)	2 (33.3)	3 (42.9)	2 (28.6)
Neutrophil count decreased	2 (33.3)	4 (66.7)	3 (42.9)	3 (42.9)
Aspartate aminotransferase increased	1 (16.7)	2 (33.3)	2 (28.6)	1 (14.3)
Neutropenia	2 (33.3)	1 (16.7)	2 (28.6)	1 (14.3)
Blood creatinine increased	0	2 (33.3)	1 (14.3)	0

Preferred term	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N=6 n (%)	Ribociclib 400mg + letrozole 2.5mg (Japan) N=6 n (%)	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=7 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N=7 n (%)

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MedDRA Version 25.0 has been used.

Adverse events requiring dose adjustment or interruption by preferred term and dose level (at least 15% incidence), Expansion part (Safety set)

Preferred term	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 16 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N = 15 n (%)	Ribociclib 300mg + fulvestrant 500mg (Japan) N = 16 n (%)	Ribociclib 300mg + tamoxifen 20mg (Japan) N = 15 n (%)
-Total	14 (87.5)	14 (93.3)	13 (81.3)	13 (86.7)
Neutropenia	7 (43.8)	0	0	0
Neutrophil count decreased	5 (31.3)	10 (66.7)	7 (43.8)	6 (40.0)
Alanine aminotransferase increased	3 (18.8)	3 (20.0)	4 (25.0)	6 (40.0)
Aspartate aminotransferase increased	3 (18.8)	4 (26.7)	3 (18.8)	5 (33.3)
Electrocardiogram QT prolonged	3 (18.8)	2 (13.3)	0	5 (33.3)

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A patient with multiple AEs is counted only once in the total
MedDRA Version 25.0 has been used.

Adverse events requiring additional therapy, by preferred term and dose level (at least 20% incidence), Escalation part (Safety set)

Preferred term	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N=6 n (%)	Ribociclib 400mg + letrozole 2.5mg (Japan) N=6 n (%)	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=7 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N=7 n (%)
-Total	5 (83.3)	6 (100)	7 (100)	5 (71.4)
Cough	2 (33.3)	1 (16.7)	4 (57.1)	0
Upper respiratory tract infection	2 (33.3)	1 (16.7)	4 (57.1)	0
Neutrophil count decreased	1 (16.7)	0	3 (42.9)	0
Pruritus	0	2 (33.3)	3 (42.9)	1 (14.3)
Arthralgia	1 (16.7)	3 (50.0)	2 (28.6)	2 (28.6)
Cataract	0	0	2 (28.6)	0
Dry eye	0	0	2 (28.6)	1 (14.3)

Preferred term	Ribociclib 400mg + letrozole 2.5mg (non-Japan) N=6 n (%)	Ribociclib 400mg + letrozole 2.5mg (Japan) N=6 n (%)	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N=7 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N=7 n (%)
Dyspepsia	2 (33.3)	0	2 (28.6)	0
Headache	0	0	2 (28.6)	1 (14.3)
Hypokalaemia	2 (33.3)	1 (16.7)	2 (28.6)	0
Influenza like illness	1 (16.7)	1 (16.7)	2 (28.6)	0
Oropharyngeal pain	0	0	2 (28.6)	0
Osteoporosis	0	0	2 (28.6)	0
Rash	1 (16.7)	3 (50.0)	2 (28.6)	2 (28.6)
Rash pruritic	2 (33.3)	0	2 (28.6)	0
Rhinorrhoea	0	0	2 (28.6)	0
Tendonitis	0	0	2 (28.6)	0
Alanine aminotransferase increased	1 (16.7)	2 (33.3)	1 (14.3)	3 (42.9)
Constipation	1 (16.7)	2 (33.3)	1 (14.3)	1 (14.3)
Diarrhoea	0	2 (33.3)	1 (14.3)	0
Pyrexia	1 (16.7)	2 (33.3)	1 (14.3)	0
Stomatitis	1 (16.7)	2 (33.3)	1 (14.3)	1 (14.3)
Aspartate aminotransferase increased	1 (16.7)	2 (33.3)	0	1 (14.3)
Cystitis	0	2 (33.3)	0	1 (14.3)
Nasopharyngitis	0	2 (33.3)	0	1 (14.3)

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MedDRA Version 25.0 has been used.

Adverse events requiring additional therapy by preferred term (at least 15% incidence), Expansion part (Safety set)

Preferred term	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 16 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N = 15 n (%)	Ribociclib 300mg + fulvestrant 500mg (Japan) N = 16 n (%)	Ribociclib 300mg + tamoxifen 20mg (Japan) N = 15 n (%)
-Total	15 (93.8)	15 (100)	15 (93.8)	15 (100)
Upper respiratory tract infection	6 (37.5)	2 (13.3)	0	1 (6.7)
Back pain	5 (31.3)	2 (13.3)	1 (6.3)	3 (20.0)
Cough	4 (25.0)	3 (20.0)	1 (6.3)	0
Rash	4 (25.0)	3 (20.0)	2 (12.5)	1 (6.7)
Stomatitis	2 (12.5)	4 (26.7)	3 (18.8)	4 (26.7)

Preferred term	Ribociclib 600mg + letrozole 2.5mg (non-Japan) N = 16 n (%)	Ribociclib 300mg + letrozole 2.5mg (Japan) N = 15 n (%)	Ribociclib 300mg + fulvestrant 500mg (Japan) N = 16 n (%)	Ribociclib 300mg + tamoxifen 20mg (Japan) N = 15 n (%)
Arthralgia	1 (6.3)	4 (26.7)	2 (12.5)	2 (13.3)
Insomnia	1 (6.3)	0	1 (6.3)	4 (26.7)
Alanine aminotransferase increased	0	3 (20.0)	4 (25.0)	5 (33.3)
Aspartate aminotransferase increased	0	2 (13.3)	4 (25.0)	4 (26.7)
Cystitis	0	3 (20.0)	1 (6.3)	1 (6.7)
Nasopharyngitis	0	5 (33.3)	4 (25.0)	6 (40.0)
Pharyngitis	0	3 (20.0)	1 (6.3)	2 (13.3)
Rhinorrhoea	3 (18.8)	0	0	0
Pruritus	4 (25.0)	0	0	0
Hypocalcaemia	4 (25.0)	1 (6.7)	0	1 (6.7)
Hypokalaemia	4 (25.0)	2 (13.3)	0	0
Neutrophil count decreased	4 (25.0)	0	2 (12.5)	1 (6.7)
Influenza like illness	4 (25.0)	0	0	0
Pyrexia	3 (18.8)	1 (6.7)	2 (12.5)	2 (13.3)
Vomiting	3 (18.8)	1 (6.7)	0	1 (6.7)
Anaemia	3 (18.8)	2 (13.3)	1 (6.3)	0

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MedDRA Version 25.0 has been used.

Other Relevant Findings:

None

Conclusion:

The study met its primary endpoint. It was possible to establish MTD/RP2D dose in the Escalation part for both Asian Japanese and Asian Non-Japanese patients. Also, ribociclib in combination with endocrine partners and/or goserelin was associated with a manageable and predictable safety profile in the intended target population in the Expansion part for both Japanese and Asian Non-Japanese patients.

No new safety signals or unexpected safety findings were observed in the subjects treated with ribociclib. The overall safety and tolerability profile of ribociclib at MTD/RP2D dose in combination with endocrine partners and/or goserelin observed in this study was as expected and consistent between treatment arms and with the known safety profile, in line with the current prescribing information of ribociclib.

Date of Clinical Study Report:

10-Mar-2023