RIBECCA - A Phase 3b, Multi-center, Open-label Study for Women With Estrogen Receptor–Positive, Locally Advanced or Metastatic Breast Cancer Treated With Ribociclib (LEE011) in Combination With Letrozole: Final Results

PS10-31

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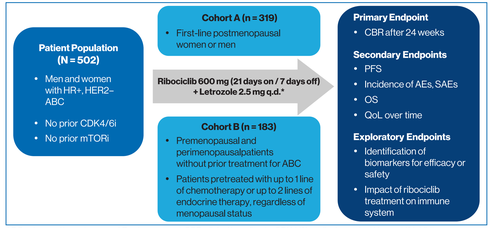
Introduction

- Ribociclib is an orally bioavailable, selective cyclin dependent kinase 4/6 (CDK4/6) inhibitor that has demonstrated significant clinical activity with longer overall survival (OS) in women (any menopausal status) with hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced or metastatic breast cancer (BC).[1]
- RIBECCA (RIBociclib for the trEatment of advanCed breast CAncer), a phase 3b, multicenter, open-label study, was conducted in Germany among patients (men and women) with HR+, HER2– locally advanced or metastatic BC who received ribociclib (RIB) in combination with letrozole.
- This study assessed the efficacy and safety of RIB in combination with letrozole along with its impact on quality of life (QoL) in a patient population broader than in MONALEESA-2 study, i.e. in patients pretreated with one line of chemotherapy and/or a maximum of two lines of endocrine therapy as well as premenopausal patients, without limitations regarding the disease-free interval after adjuvant therapy (see **Figure 1**). The primary endpoint of this study was clinical benefit rate (CBR) after 24 weeks. Here, we present the results from final analysis.

Figure 1: RIBECCA Study Design



ABC, advanced breast cancer; AE, adverse event; CBR, clinical benefit rate; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; HER2–, human epidermal growth factor receptor-2–negative; HR+, hormone receptor–positive; mTORi, mammalian target of rapamycin inhibitor; OS, overall survival; PFS, progression-free survival; Q.D., every day; QoL, quality of life; SAE, serious adverse event.

*Premenopausal women were also treated with goserelin.

Methods

- The inclusion criteria allowed to enroll women with locally advanced or metastatic BC not amenable to curative treatment by surgery or radiotherapy and with cytological or histological confirmation of estrogen receptor–positive (ER+), HER2– BC regardless of their menopausal status.
- The primary objective was to assess the CBR based on confirmed best overall response (BOR) after 24 week; secondary objectives included progression-free survival (PFS), OS, safety, and changes in QoL.
- Here we describe the baseline characteristics, CBR at 24 weeks, PFS, OS, safety, and QoL. Patients were recruited in 2 cohorts:
  - Cohort A: Postmenopausal women and men who received no prior treatment for advanced disease (first line).
  - Cohort B:
    - Premenopausal and perimenopausal women who received no prior treatment for advanced disease (first line).
    - Premenopausal, perimenopausal and postmenopausal women and men who received no more than 1 prior chemotherapy or 2 prior lines of endocrine therapy for advanced disease (later lines).
- Median PFS was estimated using the Kaplan-Meier method (bivariate analysis).
- The study end was planned for 84 weeks after the first intake of RIB of the last patient or progression of disease, whichever occurred first.

Results

Baseline Characteristics

- Between October 2016 and February 2020, a total of 487 patients were included in full analysis set, of which 482 were female and 5 male. The median observation time in this analysis (the interval from the day of screening to the date of last visit) was 10.56 months (mo) for the total population. The key baseline and tumor characteristics are summarized in **Table 1**.
- In Cohort B, 26 patients were treatment naive in the first-line setting and 154 patients were pretreated.
- The median (min - max) time since initial diagnosis of BC was 5.2 year (0 - 40) overall, with a median of 5.6 year (0 - 35) for Cohort A and 4.3 year (0 - 40) for Cohort B. Median (min - max) time from first recurrence/progression was 1.6 mo (Cohort A: 1.2 mo [0.2 - 227.5] and Cohort B: 9.1 mo [0.2 - 429.1]).

Table 1: Baseline and Tumor Characteristics

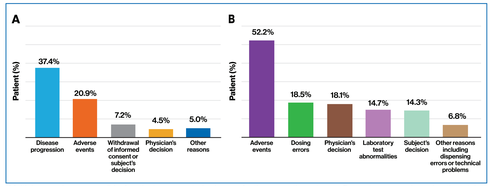
	Total (N = 487)	Cohort A (n = 307)	Cohort B (n = 180)
Median age (range)	64 (29 - 90)	66 (37 - 90)	60 (29 - 85)
Sex, n (%)			
Female	482 (99.0)	303 (98.7)	179 (99.4)
Male	5 (1.0)	4 (1.3)	1 (0.6)
Menopausal status, n (%)			
Postmenopausal	436 (90.5)	303 (100.0)	133 (74.3)
Premenopausal or perimenopausal	46 (9.5)	0 (0)	46 (5.7)
Menopausal status missing	5	4	1
ECOG-PS, n (%)			
0	329 (66.9)	212 (67.7)	117 (65.4)
1	147 (29.9)	91 (29.1)	56 (31.3)
2	16 (3.3)	10 (3.2)	6 (3.4)
Missing	10	6	4
Hormone receptor status, n (%)			
ER+	482 (99.0)	305 (99.3)	177 (98.3)
PR+	391 (80.3)	247 (80.5)	144 (80.0)
HER2+	0	0	0
Metastatic sites, n (%)			
1	237 (48.7)	167 (54.4)	70 (38.9)
2	171 (35.1)	93 (30.3)	78 (43.3)
≥ 3	66 (13.5)	35 (11.4)	31 (17.3)
Sites of metastases, n (%)			
Bone	349 (71.7)	201 (65.5)	148 (82.2)
Brain	6 (1.2)	4 (1.3)	2 (1.1)
Liver	149 (30.6)	80 (26.1)	69 (38.3)
Lung	134 (27.5)	88 (28.7)	46 (25.6)
Other	147 (30.2)	90 (29.3)	57 (31.7)
Last antineoplastic therapy prior to study start, n (%)			
No prior antineoplastic therapy	103 (21.1)	93 (30.3)	10 (5.6)
Adjuvant	296 (60.8)	199 (64.8)	97 (53.9)
Neoadjuvant	73 (15.0)	43 (14.0)	30 (16.7)
Palliative	154 (31.6)	-	154 (85.6)
Other	2 (0.4)	2 (0.7)	-

ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor–positive; HER2+, human epidermal growth factor receptor-2–positive; PR+, progesterone receptor–positive.

Patient Disposition and Dosing

- As of data cutoff April 3, 2020, a total of 487 patients were included in the full analysis set and 502 patients were included in safety analysis set.
- About 119 patients (24.4%) were still ongoing treatment at the end of the entire study.
- Median daily dose intensity for RIB was 524.27 mg (range: 158.7 mg - 666.7 mg).
- In total, 366 (75.2%; Cohort A, 211 [68.7%] and Cohort B, 155 [86.1%]) had discontinued the study drug before study completion. The reasons were disease progression (182 [37.4%]), adverse events (AEs; 102 [20.9%]), withdrawal of informed consent/subject's decision (35 [7.2%]), physician's decision (22 [4.5%]), and other reasons (25 [5.0%]) (see **Figure 2A**).
- About 345 patients (68.7%) had at least 1 dose interruption. The most frequent reasons for dose interruptions were AEs (262 [52.2%]), followed by dosing errors (93 [18.5%]), physician's decision, (91 [18.1%]), laboratory test abnormalities (74 [14.7%]), and subject's decision (72 [14.3%]). Other reasons (34 [6.8%]) include dispensing errors or technical problems (see **Figure 2B**).
- Most dose interruptions (33.5%) occurred during the first 3 months of study treatment. The median duration of a single dose interruption was 5 days (range: 1 - 34 days) and median duration of all dose interruptions per patient was 18 days (range: 1 - 236 days).
- Reductions in RIB dose for any reasons were documented in 31 patients (6.2%); 14 patients (2.8%) reduced the dose because of AEs, 6 patients (1.2%) per subject decision, 6 patients (1.2%) per physician's decision, and 3 patients (0.6%) per protocol. The other reasons for RIB dose reductions were dosing error (2 [0.4%]) or laboratory test abnormality (1 [0.2%]).

Figure 2: Reasons for Discontinuation (A) or Interruption* of Study Treatment (B)



*Multiple records were possible. A patient was counted only once for the respective category. Percentages were based on the total number of patients in the analysis population.

Efficacy Data

- The confirmed CBR was 60.8% (95% confidence interval [CI]: 56.3 - 65.1) for the total population and 63.2% (95% CI, 57.5 - 68.6) and 56.7% (95% CI: 49.1 - 64.0) for Cohorts A and B, respectively (see **Table 2**).
- The overall CBR by week 24 based on non-confirmed BOR (N = 487) was 69.2% (95% CI: 64.9 - 73.3).
- Median PFS was 21.8 mo in Cohort A and 11.0 mo in Cohort B (see **Figure 3**).
  - The number of patients with an event of progression or death was 146 (47.6%) in Cohort A, and 119 (66.1%) in Cohort B.
- Death due to any cause was documented in 21.8% and 38.3% of patients, respectively, in Cohort A and Cohort B. Median OS time was not reached in this study. 25%-percentiles were 28.2 mo (95% CI: 22.9; not estimable) in Cohort A and 21.3 mo (95% CI: 17.1; 26.1) in Cohort B.

Table 2: Efficacy Data by Week 24: Full Analysis Set

	Total (N = 487) n (%) [95% CI]	Cohort A (n = 307) n (%) [95% CI]	Cohort B (n = 180) n (%) [95% CI]
Best overall response (BOR) by week 24 – confirmed			
Complete response (CR)	3 (0.6) [0.1 - 1.8]	3 (1.0) [0.2 - 2.8]	0 (0.0) [0.0 - 2.0]
Partial response (PR)	91 (18.7) [15.3 - 22.4]	67 (21.8) [17.3 - 26.9]	24 (13.3) [8.7 - 19.2]
Stable disease (SD)	163 (33.5) [29.3 - 37.9]	101 (32.9) [27.7 - 38.5]	62 (34.4) [27.5 - 41.9]
Progressive disease (PD)	59 (12.1) [9.4 - 15.3]	33 (10.7) [7.5 - 14.8]	26 (14.4) [9.7 - 20.4]
Non-complete response, non-progressive disease (NCRNPD)	39 (8.0) [5.8 - 10.8]	23 (7.5) [4.8 - 11.0]	16 (8.9) [5.2 - 14.0]
Unknown	132 (27.1) [23.2 - 31.3]	80 (26.1) [21.2 - 31.3]	52 (28.9) [22.4 - 36.1]
Overall response rate (ORR, i.e. BOR of CR or P by week 24)	94 (19.3) [15.9 - 23.1]	70 (22.8) [18.2 - 27.9]	24 (13.3) [8.7 - 19.2]
Clinical benefit rate (CBR, i.e. BOR of CR or PR or SD or NCRNPD) by week 24	**296 (60.8) [56.3 - 65.1]**	**194 (63.2) [57.5 - 68.6]**	**102 (56.7) [49.1 - 64.0]**

Safety Data

- Among 502 patients in the safety set, 500 patients (99.6%) experienced at least one treatment-emergent AE, of which 470 patients (93.8%) had AE with a suspected drug relation to RIB.
- Serious AEs were documented in 147 patients (29.3%; Cohort A, 30.4%; Cohort B, 27.3). Twelve patients had an AE with a fatal outcome; 3 fatal treatment-emergent AEs in 2 patients were considered as possibly related to RIB (dyspnea and pneumonia, and febrile neutropenia).
- The most frequent treatment-emergent AEs (≥ 20%) were neutropenia or neutrophil count decreased (60.6%), nausea (42.0%), fatigue (39.2%), alopecia (35.1%), leukopenia or decreased white blood cells (30.7%), nasopharyngitis (28.5%), diarrhea (25.3%), increased alanine aminotransferase (ALT, 22.9%), and increased aspartate aminotransferase (20.7%) (see **Table 3**).
- Grade 3 and 4 treatment-emergent AEs were found in 60.8% and 15.3% of the patients, respectively; the most common grade 3 treatment-emergent AEs were neutropenia (36.9%) and leukopenia (11.6%), and grade 4 treatment-emergent AEs were increased ALT (4.2%) and neutropenia (3.8%).

Table 3: Frequency of Treatment-emergent AEs by Preferred Terms Occurring in ≥ 10% of Patients: Safety Analysis Set

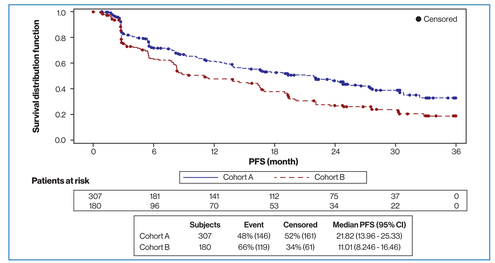
MedDRA Primary System Organ Class, n (%)	Total (N = 502)	Cohort A (n = 319)	Cohort B (n = 183)
Neutropenia and/or neutrophil count decreased	304 (60.6)	195 (61.1)	109 (59.6)
Nausea	211 (42.0)	132 (41.4)	79 (43.2)
Fatigue	197 (39.2)	123 (38.6)	74 (40.4)
Alopecia	176 (35.1)	119 (37.3)	57 (31.2)
Leukopenia and/or white blood cell count decreased	154 (30.7)	98 (30.7)	56 (30.6)
Nasopharyngitis	143 (28.5)	94 (29.5)	49 (26.8)
Diarrhoea	127 (25.3)	86 (27.0)	41 (22.4)
Increased ALT	115 (22.9)	79 (24.8)	36 (19.7)
Increased AST	104 (20.7)	68 (21.3)	36 (19.7)
Vomiting	98 (19.5)	67 (21.0)	31 (16.9)
Arthralgia	96 (19.1)	57 (17.9)	39 (21.3)
Constipation	95 (18.9)	63 (19.7)	32 (17.5)
Headache	92 (18.3)	56 (17.6)	36 (19.7)
Anaemia	84 (16.7)	46 (14.4)	38 (20.8)
Dyspnoea	79 (15.7)	53 (16.6)	26 (14.2)
Cough	75 (14.9)	53 (16.6)	22 (12.0)
Pain in extremity	75 (14.9)	52 (16.3)	23 (12.6)
Hot flush	74 (14.7)	44 (13.8)	30 (16.4)
Rash	66 (13.2)	47 (14.7)	19 (10.4)
Pruritus	63 (12.6)	45 (14.1)	18 (9.8)
Back pain	62 (12.4)	38 (11.9)	24 (13.1)
Decreased appetite	62 (12.4)	43 (13.5)	19 (10.4)
Stomatitis	60 (12.0)	33 (10.3)	27 (14.8)
Oedema peripheral	58 (11.6)	36 (11.3)	22 (12.0)
Insomnia	57 (11.4)	31 (9.7)	26 (14.2)
Thrombocytopenia and/or platelet count decreased	53 (10.6)	32 (10.0)	21 (11.5)
Bone pain	52 (10.4)	36 (11.3)	16 (8.7)
Gamma-glutamyltransferase increased	51 (10.2)	33 (10.3)	18 (9.8)
Vertigo	50 (10.0)	33 (10.3)	17 (9.3)
Electrocardiogram QT prolonged	37 (7.4)	23 (7.2)	14 (7.6)

MedDRA 19.1, 20.0, 20.1, 21.0, 22.0, and 22.1.
Treatment-emergent AEs are those that started during on-treatment period plus 30 days.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities.

Quality of Life

- Health-related quality of life (HRQoL) was assessed at week 24 using the EORTC QLQ-C30 and BR23 questionnaires.
- Analyses of functional scales and symptom scales/items of EORTC QLQ-C30 and BR23 questionnaire showed no clinically meaningful changes from the baseline for the majority of subscales. Only the subscales 'future perspective' and 'pain' showed a moderate deterioration in both cohorts, whereas the item 'upset by hair loss' showed an improvement.

Figure 3: Kaplan-Meier Estimate of Progression-Free Survival



CI, confidence interval; PFS, progression-free survival.

Conclusions

- The results of the final analysis confirmed clinical benefit in this broader patient population. The confirmed CBR (60.8%) observed in this study is in line with results from the pivotal phase 3 trials.[1,2,3]
- The median PFS was longer in the first-line setting in Cohort A (21.8 months) than in Cohort B (11.0 months) including patients receiving later-lines of treatment. This corresponds well to the results from the MONALEESA trial program.
- The combination of RIB and letrozole was associated with a manageable safety profile that is consistent with previous experience.
- The QoL results based on EORTC-QLQ-C30 and BR23 support that treatment with RIB generally maintains patients' HRQoL.

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