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CLINICAL TRIAL

First-line ribociclib plus letrozole in postmenopausal women with HR+ , HER2− advanced breast cancer: Tumor response and pain reduction in the phase 3 MONALEESA-2 trial

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Abstract

Purpose The phase 3 MONALEESA-2 study demonstrated that addition of ribociclib (RIB) to letrozole (LET) significantly improved progression-free survival (PFS) in patients (pts) with hormone receptor-positive (HR+), HER2-negative (HER2−) advanced breast cancer (ABC). Here, we evaluated duration of response (DoR), tumor shrinkage, PFS by treatment-free interval (TFI), and health-related quality of life (HRQoL).

Methods Postmenopausal women ($N = 668$) with HR+ , HER2− ABC and no prior systemic therapy for ABC were randomized to RIB (600 mg/day; 3 weeks on/1 week off) plus LET (2.5 mg/day; continuous) or placebo (PBO) plus LET. Primary end point was PFS; HRQoL was the secondary end point; DoR was exploratory end point and PFS by TFI was post hoc analysis.

Results Of 501 pts with measurable disease and confirmed complete or partial response, median DoR was 26.7 months (95% CI, 24.0–NR) in the RIB arm versus 18.6 months (95% CI, 14.8–23.1) in the PBO arm. At 8 weeks, more pts in the RIB arm (32%) versus the PBO arm (17%) experienced best percentage change ≥ 60%. The average pain reduction was greater in the RIB arm (26%) versus the PBO arm (15%). PFS benefit was seen with RIB vs PBO, irrespective of TFI.

Conclusion RIB plus LET versus PBO plus LET is associated with earlier and more durable tumor response, greater degree of tumor shrinkage and pain reduction, and PFS benefit irrespective of TFI. These data further support RIB plus LET as a first-line treatment option for postmenopausal women with HR+ , HER2− ABC.

Keywords Ribociclib · Advanced breast cancer · MONALEESA-2 · CDK4/6

Introduction

Hormone receptor-positive (HR+) tumors are the most common subtype of breast cancer, constituting 75% of all breast cancers [1, 2]. Endocrine therapy (ET)-based regimens are the cornerstone of treatment in patients with HR+ , human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC) [3]. However, de novo or acquired endocrine resistance leads to tumor recurrence and approximately 50% of patients with advanced disease do not respond to first-line treatment with endocrine therapy [4–6]. Several mechanisms are implicated in ET resistance in HR+ breast cancer [7, 8]. The cyclin D–cyclin-dependent kinases 4 and 6 (CDK4/6)–inhibitor of CDK4 (INK4)–retinoblastoma tumor suppressor protein (Rb) pathway induction has been identified as one of the most common mechanisms of ET resistance and poor clinical outcome in HR+ ABC [9]. The inhibition of cyclin D–CDK4/6–INK4–Rb pathway has improved outcomes for HR+ , HER2− ABC, in both first-line and in patients whose disease had progressed after ET [10–13].

Ribociclib (LEE011) is an orally bioavailable, selective small-molecule inhibitor of CDK4 and CDK6 that blocks the

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phosphorylation of retinoblastoma protein, thereby preventing cell-cycle progression and inducing G1 phase arrest [14]. Ribociclib has demonstrated promising antitumor activity in xenograft models of estrogen receptor-positive (ER+) breast cancer as a single agent and in combination with letrozole and phosphatidylinositol 3-kinase (PI3K) inhibitors [15]. In a phase 1b study of postmenopausal women with ER+ , HER2− ABC, ribociclib had an acceptable safety profile and showed signs of clinical activity in combination with letrozole, particularly in patients who had received no previous systemic treatment for advanced disease, with an overall response rate of 46% and a clinical benefit rate of 79% among patients with measurable disease [16].

A planned interim analysis of the phase 3 Mammary Oncology Assessment of LEE011′s (ribociclib's) Efficacy and Safety (MONALEESA-2) study (NCT01958021; data cutoff January 29, 2016) demonstrated that addition of ribociclib to letrozole significantly improved progression-free survival (PFS) in postmenopausal women with HR+ , HER2− ABC [hazard ratio, 0.56; 95% confidence interval (CI), 0.43–0.72; $P = 3.29 \times 10^{-6}$] [17]. At an updated analysis, after 26.4 months of follow-up, treatment benefit with ribociclib was maintained [18]. The overall response rate was 43 versus 29% for all patients treated with ribociclib plus letrozole versus placebo + letrozole and 55 versus 39% for those with measurable disease, respectively [18].

Change in tumor burden is considered as a likely predictor of long-term outcome in patients with advanced cancer, and tumor shrinkage may be associated with improved quality of life [19]. Delayed deterioration in global QoL and pain symptoms correspond with a delay in disease progression [13]. Additionally, the treatment-free interval (TFI) has been reported as a prognostic factor and predictive marker of benefit of next treatment line across various tumors [20]. Recently reported results from a TFI analysis of abemaciclib suggest that TFI could be a potential clinical factor to determine patient subgroups who may derive benefit in patients with HR+ , HER2− ABC [21].

Here, we present the health-related quality of life (HRQoL) outcomes in patients from the MONALEESA-2 trial as well as results from preplanned exploratory analyses which evaluated tumor response and post hoc analysis of impact of TFI on PFS.

Patients and methods

Study design and participants

MONALEESA-2 (NCT01958021) is a phase 3, randomized, double-blind, international trial that enrolled postmenopausal women with HR+ , HER2− ABC who had received no prior systemic therapy for advanced disease from 223 centers in 29 countries worldwide [17]. Details of the study and participants have been reported previously [17]. Patients were required to have measurable disease with at least 1 measurable lesion as per response evaluation criteria in solid tumors (RECIST) version 1.1 [22] or at least 1 predominantly lytic bone lesion. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were excluded if they had inflammatory breast cancer, central nervous system metastases, cardiac disease or Fridericia's corrected QT interval (QTcF) > 450 ms, or impairment of gastrointestinal function that would have altered study drug absorption. Patients must not have received prior systemic therapy for advanced disease, except for ≤ 14 days of letrozole or anastrozole. The use of concomitant medications with known risk of prolonging the QT interval or inducing Torsades de Pointes was prohibited.

This study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. An independent ethics committee and institutional review boards approved the study protocol and any subsequent amendments at each participating center. A study steering committee monitored study conduct in line with the protocol. Written informed consent was obtained from all the patients.

Randomization

Patients were randomized 1:1 to receive either oral ribociclib plus letrozole (ribociclib arm) or placebo plus letrozole (placebo arm). Randomization was stratified according to the presence of liver and/or lung metastases. Screening and treatment allocation were performed using an interactive voice and web response system. Patients and investigators were blinded to the assigned treatment; both ribociclib and placebo were identical in label, packaging, appearance, and administration schedule. Treatment crossover from placebo to ribociclib was not permitted.

Treatment and procedures

Details of study treatment and procedures have been reported previously [17]. Briefly, patients received either oral ribociclib (600 mg per day on a 3-weeks-on, 1-week-off schedule in 28-day treatment cycles) plus letrozole (2.5 mg per day on a continuous schedule) or placebo plus letrozole until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. Ribociclib dose adjustments including dose interruption, reduction, and permanent discontinuation were permitted for the management of adverse events. Dose modifications of letrozole were not permitted.

Outcomes

The primary end point of the study was locally assessed PFS, according to RECIST, version 1.1, and has been reported previously [17]. The evaluation of patient-reported outcomes (PROs) for HRQoL was a secondary end point. The exploratory end points were time to response, duration of response. Time to response [complete response (CR) or partial response (PR)] was defined as the time interval between the date of randomization and the first documented response (CR or PR, which had to be confirmed subsequently). The duration of response was defined as the time from documentation of tumor response to disease progression. Post hoc analysis of PFS by subgroup according to TFI was also performed. TFI was defined as the time from last hormonal therapy to randomization and was calculated only for patients with prior hormonal therapy.

Assessments

Tumor response was assessed locally according to RECIST version 1.1 [22]. Computed tomography/magnetic resonance imaging assessments were conducted at screening, then every 8 weeks for the first 18 months, and every 12 weeks thereafter. For tumor shrinkage analyses, the patients were divided into the following 4 equal groups according to their best percentage change in target lesion size in the total population, irrespective of treatment arm: Group 1 (greatest decrease in tumor size): best percentage change in the target lesion size of at least − 60%; Group 2: best percentage change in target lesion size of between − 35 and − 60%; Group 3: best percentage change in target lesion size of between − 14 and − 35%; Group 4 (smallest decrease in tumor size): best percentage change in target lesion size of less than − 14% or tumor growth. Patients were excluded from the quartile analysis if the best percentage change was unavailable or if their best overall response was unknown.

TFI was analyzed at the following time points in both treatment groups: ≤ 24, > 24, ≤ 36, > 36, ≤ 48, > 48 months.

The EORTC QLQ-C30 was completed by patients at the beginning of each visit at screening, every 8 weeks following randomization for the first 18 months, every 12 weeks thereafter until disease progression, and at the end of treatment. Changes from baseline were analyzed using a linear effect model that incorporated treatment, stratification factors, and baseline scores. The cutoff for clinically meaningful change in EORTC QLQ-C30 scores was defined as > 5 points [23].

Results

Patient characteristics

A total of 668 patients were enrolled (334 into each treatment arm) between January 2014 and March 2015 (Fig. 1). Overall, 501 patients (256 in the ribociclib plus letrozole arm and 245 in the placebo plus letrozole arm) had measurable disease at baseline. Patient characteristics were generally well balanced between treatment arms, with the exception of a higher proportion of patients with visceral metastases in the placebo arm vs the ribociclib arm in Group 1 (83.8% vs. 63.5%) (Table 1).

Tumor response

Ribociclib plus letrozole was associated with a trend in favor of shorter time to response when compared with placebo plus letrozole. At 6 months, 37.2% of patients in the ribociclib arm achieved early response versus 23.2% of patients in the placebo arm (Fig. 2).

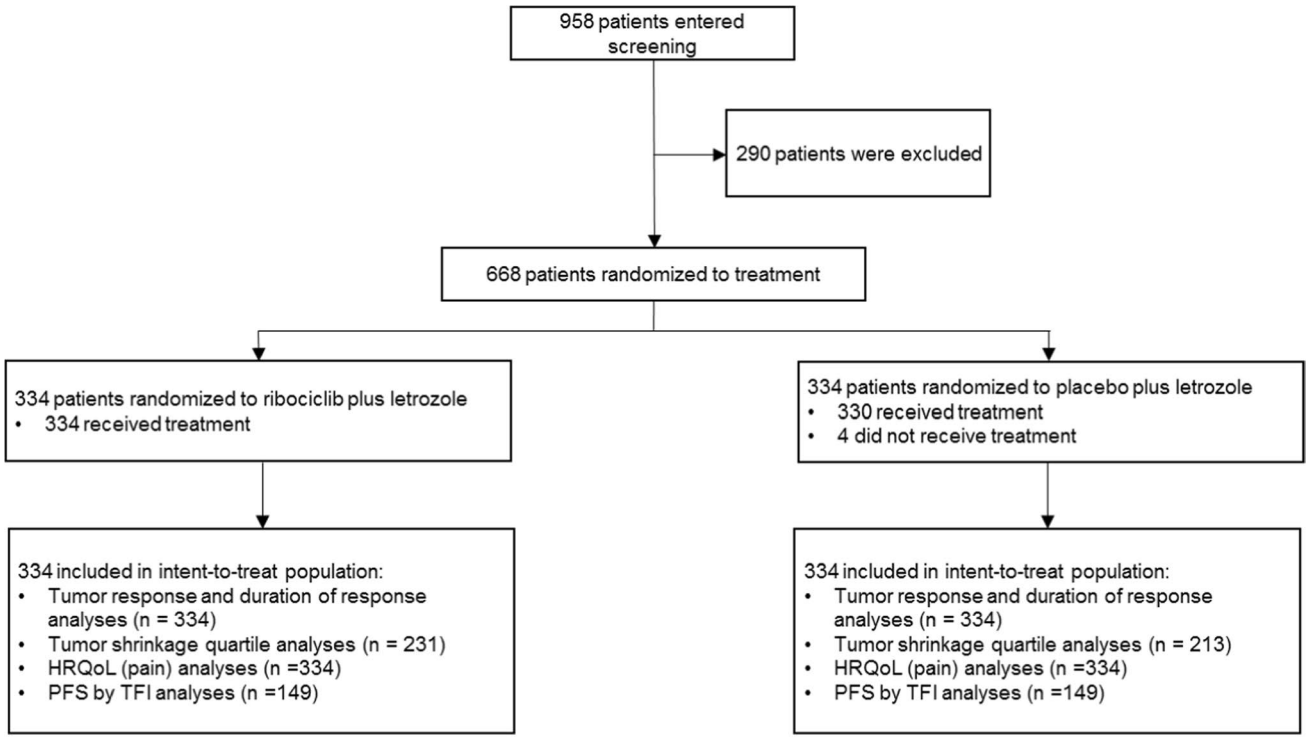
At the first tumor evaluation at 8 weeks decreased tumor size was observed in a higher proportion of patients in the ribociclib arm (76%; 180 of 238) versus the letrozole arm (67%; 152 of 227; Fig. 3). Patients with measurable disease at baseline in the ribociclib arm experienced a faster and more sustained decrease in tumor size compared with those in the placebo arm (Fig. 4). A consistent decrease in tumor size was also observed in patients with lung and/or liver metastases.

Duration of response

Ribociclib plus letrozole was associated with a trend in favor of longer duration of response. In patients with measurable disease and a confirmed complete response or partial response, the median duration of response was 26.7 months (95% CI, 24.0–not reached) for the ribociclib plus letrozole arm vs 18.6 months (95% CI, 14.8–23.1) for the placebo plus letrozole arm (Fig. 5). The probability of remaining progression-free at 24 months was 60% for patients receiving ribociclib plus letrozole versus 35% for those receiving placebo plus letrozole.

Tumor shrinkage

Overall, 444 patients were evaluable for tumor shrinkage quartile analyses. A higher proportion of patients treated with ribociclib plus letrozole (32%) versus placebo plus letrozole (17%) had the greatest decrease in tumor size (Group 1, 60%) (Fig. 6). The proportion of patients with the



CONSORT, Consolidated Standards of Reporting Trials; HRQoL, health-related quality of life; PFS, progression-free survival; TFI, treatment-free interval.

Fig. 1 Trial profile (CONSORT diagram)

least decrease in tumor size or having tumor growth (Group 4, 14%) was lower in the ribociclib plus letrozole ($n = 43$) versus placebo plus letrozole arm ($n = 68$). This was representative of an overall shift in tumor response, such that patients receiving ribociclib plus letrozole were more likely to experience greater tumor shrinkage, and patients receiving placebo plus letrozole were more likely to experience less tumor shrinkage, or even tumor growth.

Pain reduction

As reported previously, overall HRQoL (global health status/quality of life score) was maintained from baseline and was similar in both treatment arms (27.7 months to 10% of deterioration in the ribociclib plus letrozole arm vs 26.7 months in the placebo plus letrozole arm; hazard ratio, 0.944 (95% CI, 0.720–1.237) [24]. At 8 weeks, among all patients with available percentage change from baseline, the average pain reduction was greater in the ribociclib arm versus the placebo arm (26% vs. 15%, respectively). The median percentage change from baseline in EORTC QLQ-C30 pain symptom score in patients receiving ribociclib plus letrozole was − 40 vs. − 29% in those receiving placebo plus letrozole. A clinically meaningful mean reduction in pain (> 5 points) was observed in patients receiving ribociclib plus letrozole (− 6.3 points) but not in patients receiving placebo plus letrozole (− 2.7 points). For patients with clinical benefit, the mean change in pain score from baseline was − 7.0 points in the ribociclib plus letrozole arm and − 1.3 in the placebo plus letrozole arm (Table 2).

Treatment-free interval

In a post hoc analysis, PFS benefit with ribociclib was maintained irrespective of the TFI in patients who received prior (neo) adjuvant endocrine therapy. The hazard ratios for PFS were consistent across all TFI subgroups (> 24 vs. ≤ 24 months; > 36 vs. ≤ 36 months; > 48 vs. ≤ 48 months) (Fig. 7). The hazard ratios for PFS in these subgroups were consistent with that reported for the overall population [17].

Discussion

In this exploratory analysis of the MONALEESA-2 trial, ribociclib plus letrozole demonstrated rapid and durable tumor response as early as 8 weeks and maintained PFS benefit irrespective of TFI in postmenopausal women with HR+ , HER2− ABC who had received no prior systemic

Table 1 Patient baseline characteristics

	≤ Q1 (*N* = 111)		Q1–Q2 (*N* = 112)		Q2–Q3 (*N* = 110)		> Q3 (*N* = 111)	
	Ribociclib + letrozole (*n* = 74)	Placebo + letrozole (*n* = 37)	Ribociclib + letrozole (*n* = 63)	Placebo + letrozole (*n* = 49)	Ribociclib + letrozole (*n* = 51)	Placebo + letrozole (*n* = 59)	Ribociclib + letrozole (*n* = 43)	Placebo + letrozole (*n* = 68)
Age, median (range), y	59.5 (23.0–82.0)	64.0 (29.0–80.0)	62.0 (35.0–85.0)	61.0 (37.0–78.0)	64.0 (43.0–82.0)	65.0 (31.0–88.0)	65.0 (40.0–91.0)	63.0 (30.0–80.0)
Race, *n* (%)								
Caucasian	60 (81.1)	33 (89.2)	44 (69.8)	37 (75.5)	43 (84.3)	49 (83.1)	36 (83.7)	58 (85.3)
Asian	6 (8.1)	1 (2.7)	9 (14.3)	7 (14.3)	3 (5.9)	6 (10.2)	3 (7.0)	6 (8.8)
Black	2 (2.7)	1 (2.7)	2 (3.2)	1 (2.0)	3 (5.9)	1 (1.7)	2 (4.7)	0
Other/unknown	6 (8.2)	2 (5.4)	8 (12.7)	4 (8.2)	2 (4.0)	3 (5.1)	2 (4.7)	4 (5.9)
ECOG performance status, *n* (%)								
0	54 (73.0)	25 (67.6)	34 (54.0)	30 (61.2)	32 (62.7)	37 (62.7)	26 (60.5)	43 (63.2)
1	20 (27.0)	12 (32.4)	29 (46.0)	19 (38.8)	19 (37.3)	22 (37.3)	17 (39.5)	25 (36.8)
Disease stage at study entry, *n* (%)								
III	0	0	0	0	1 (2.0)	2 (3.4)	0	0
IV	74 (100)	37 (100)	63 (100)	49 (100)	50 (98.0)	57 (96.6)	43 (100)	68 (100)
Hormone receptor status, *n* (%)								
ER-positive	73 (98.6)	37 (100)	62 (98.4)	49 (100)	51 (100)	59 (100)	43 (100)	68 (100)
PgR-positive	63 (85.1)	33 (89.2)	56 (88.9)	44 (89.8)	36 (70.6)	51 (86.4)	30 (69.8)	56 (82.4)
Disease-free interval, *n* (%)								
De novo	28 (37.8)	13 (35.1)	24 (38.1)	20 (40.8)	25 (49.0)	20 (33.9)	10 (23.3)	17 (25.0)
Non-de novo	46 (62.2)	24 (64.9)	39 (61.9)	29 (59.2)	26 (51.0)	39 (66.1)	33 (76.7)	51 (75.0)
≤ 12 months	1 (1.4)	0	1 (1.6)	2 (4.1)	0	2 (3.4)	1 (2.3)	2 (2.9)
> 12 to ≤ 24 months	3 (4.1)	1 (2.7)	2 (3.2)	1 (2.0)	2 (3.9)	0	3 (7.0)	7 (10.3)
> 24 months	42 (56.8)	23 (62.2)	36 (57.1)	26 (53.1)	24 (47.1)	37 (62.7)	29 (67.4)	41 (60.3)
Number of metastatic sites, *n* (%)								
0	1 (1.4)	0	0	0	1 (2.0)	1 (1.7)	0	0
1	11 (4.9)	12 (32.4)	16 (25.4)	13 (26.5)	9 (17.6)	10 (16.9)	12 (27.9)	21 (30.9)
2	32 (43.2)	6 (16.2)	19 (30.2)	15 (30.6)	18 (35.3)	26 (44.1)	17 (39.5)	25 (36.8)
≥ 3	30 (40.5)	19 (51.4)	28 (44.4)	21 (42.9)	23 (45.1)	22 (37.3)	14 (32.6)	22 (32.3)
Site of metastases, *n* (%)								
Breast	5 (6.8)	1 (2.7)	2 (3.2)	3 (6.1)	0	4 (6.8)	1 (2.3)	2 (2.9)
Bone	43 (58.1)	16 (43.2)	41 (65.1)	34 (69.4)	36 (70.6)	39 (66.1)	33 (76.7)	44 (64.7)
Bone only	3 (4.1)	0	4 (6.3)	2 (4.1)	5 (9.8)	8 (13.6)	7 (16.3)	10 (14.7)
Visceral[a]	47 (63.5)	31 (83.8)	44 (69.8)	34 (69.4)	35 (68.6)	44 (74.6)	31 (72.1)	45 (66.2)
Lymph nodes	40 (54.1)	20 (54.1)	35 (55.6)	19 (38.8)	24 (47.1)	22 (37.3)	14 (32.6)	28 (41.2)
Other[b]	14 (18.9)	2 (5.4)	8 (12.7)	4 (8.1)	5 (9.8)	6 (10.2)	2 (4.7)	3 (4.4)

Q1 and Q3 are the 1st and 3rd quartiles of the best percent change from baseline in sum of longest diameters per local investigator review

ECOG Eastern Cooperative Oncology Group, *ER* estrogen receptor, *PgR* progesterone receptor

[a]Includes liver, lung, and other visceral sites

[b]Includes skin and bone marrow

therapy for advanced disease. HRQoL analysis showed that ribociclib plus letrozole led to greater pain reduction, as early as 8 weeks.

In MONALEESA-2, the ORR in the ribociclib arm versus placebo arm was 40.7% versus 27.5% [17]. ORR with palbociclib plus letrozole versus placebo plus letrozole in PALOMA-2 was 42.1% versus 34.7% [25] while in MONARCH-3, the ORR with abemaciclib plus nonsteroidal aromatase inhibitor (NSAI) was 59.0% versus 44.0% with placebo plus NSAI [21]. Although CDK4/6 inhibitors in combination with ET improved ORR compared to ET alone, the data presented here show that ribociclib led to faster tumor response as early as 8 weeks in postmenopausal women with HR+ , HER2− ABC and measurable disease at baseline who had received no prior systemic therapy for advanced disease.

Emerging data suggest that tumor shrinkage can predict long-term survival in patients with breast cancer. A recently published modeling analysis suggests that change in tumor size at 8 weeks may predict overall survival in the first-line

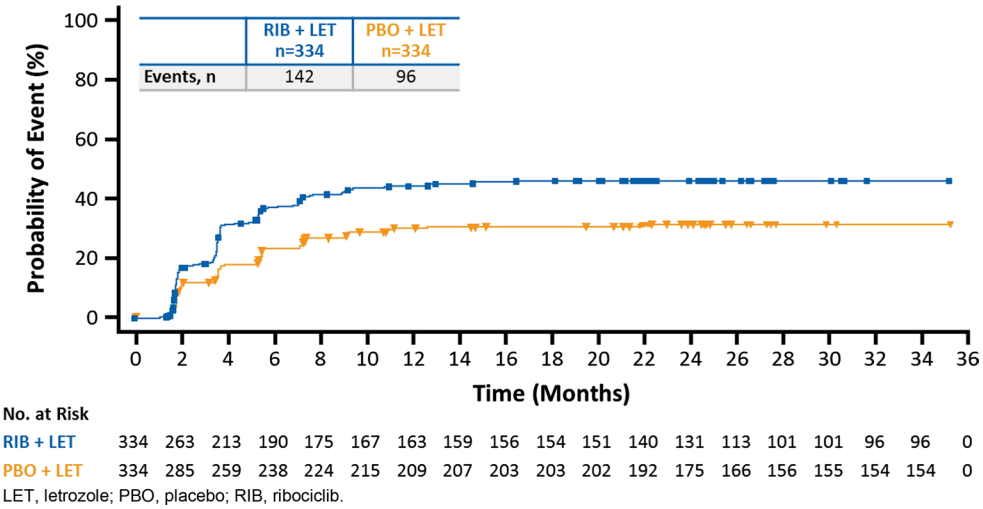


Fig. 2 Kaplan–Meier plot of time to response for patients receiving ribociclib plus letrozole versus placebo plus letrozole

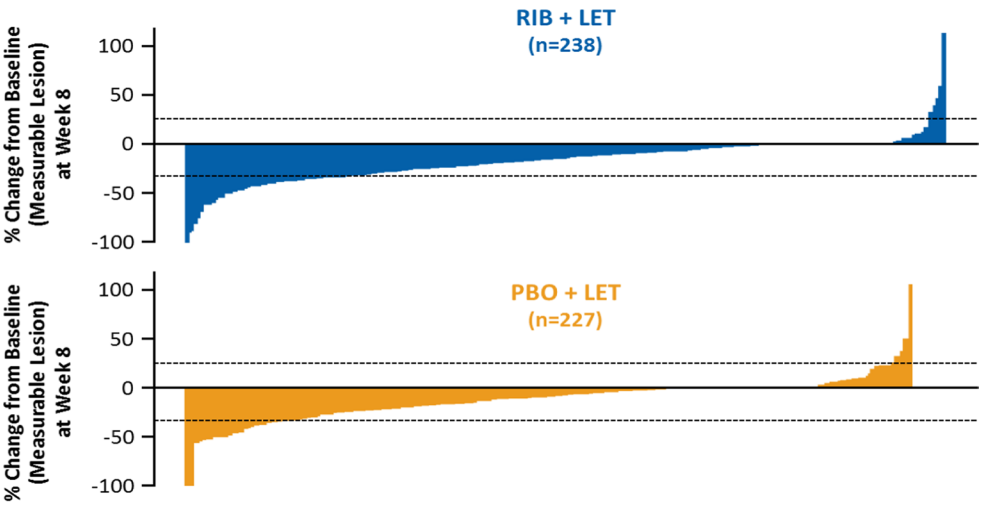
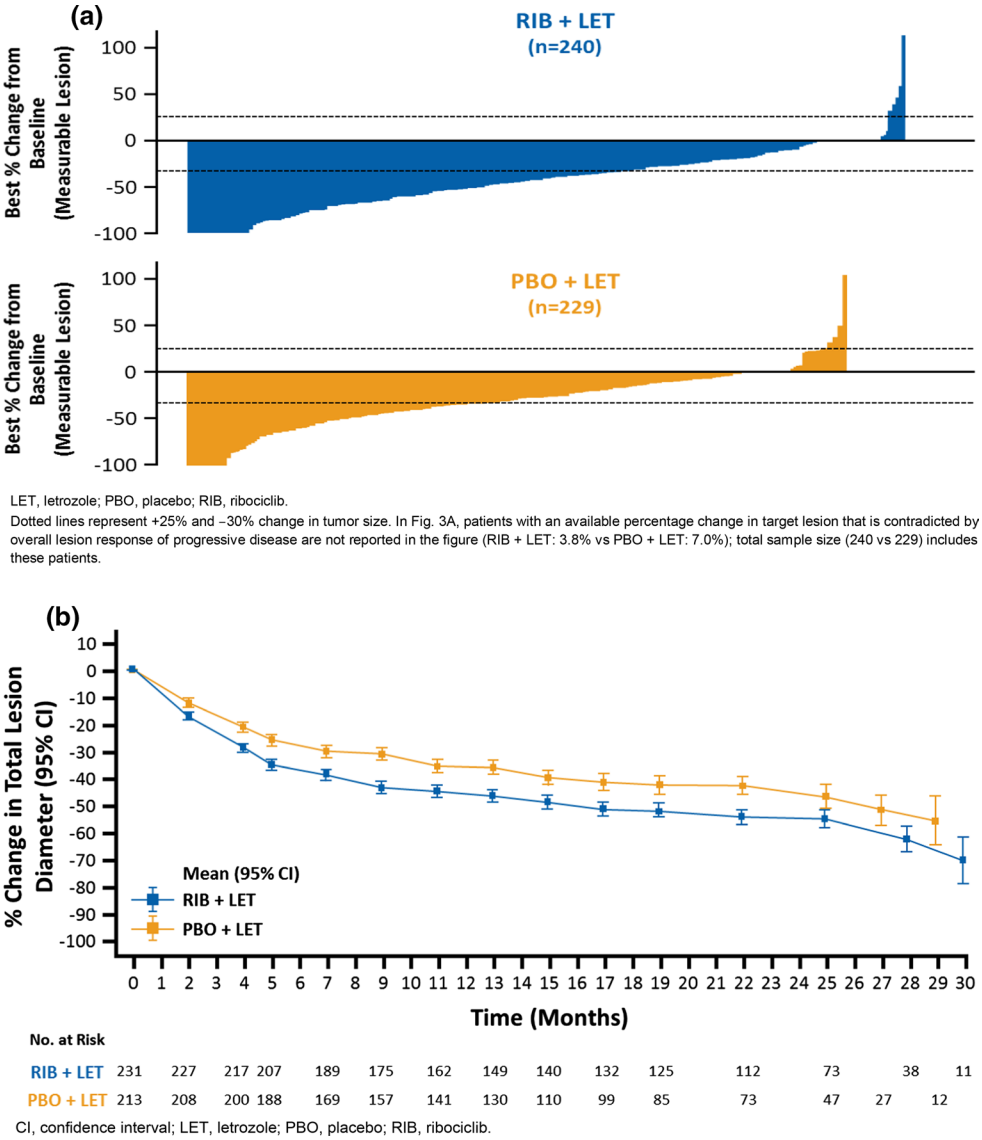


Fig. 3 Waterfall plot of percentage change in tumor size from baseline in all patients with measurable disease at the first post-baseline evaluation (week 8)

ABC therapy [26]. In MONALEESA-2, a higher proportion of patients with measurable disease at baseline in the ribociclib arm (76%) versus the placebo arm (67%) showed a decrease in tumor size at 8 weeks. Similarly, at 8 weeks, the proportion of patients who had the greatest decrease in tumor size (Group 1) was higher in the ribociclib arm (32%) versus placebo arm (17%). To our knowledge, ribociclib in combination with letrozole is the only CDK4/6 inhibitor showing tumor shrinkage as early as 8 weeks in patients with HR+ , HER2− ABC who had not received prior therapy for advanced disease.

A longer duration of response with ribociclib plus letrozole (26.7 months) versus placebo plus letrozole (18.6 months) was observed in MONALEESA-2. In PALOMA-2, the duration of response was longer with palbociclib plus letrozole (22.5 months) versus placebo plus letrozole (16.8 months) [25]. In MONARCH-3, the median duration of response was not reached with abemaciclib plus NSAI versus 14.1 months with placebo plus NSAI in patients with HR+ , HER2− ABC who had not received prior systemic therapy in the advanced setting [21]. Overall, these results suggest that the treatment with ribociclib resulted in more durable responses in patients with HR+ , HER2− ABC who had not received prior therapy for advanced disease.

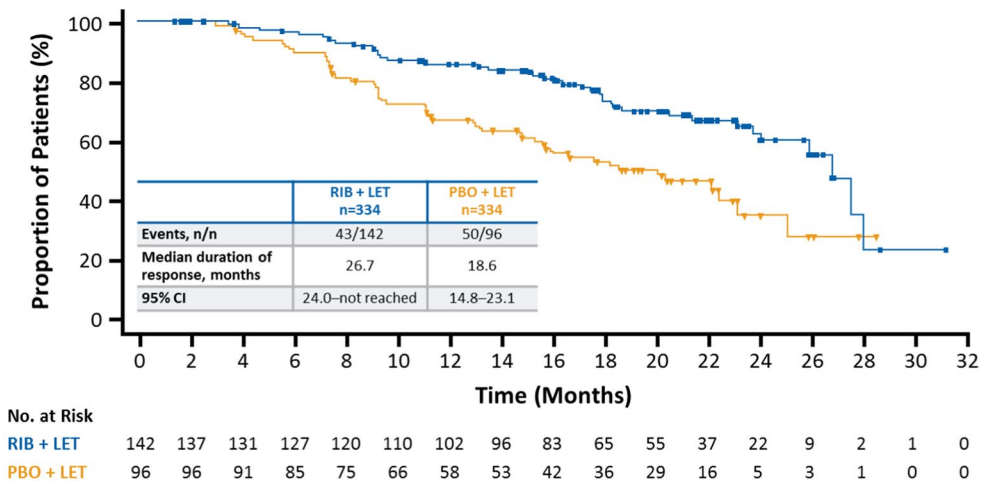
The potential of TFI as a prognostic and predictive marker of benefit of next treatment has been demonstrated across several tumor types [20]. In this subgroup analysis based on TFI of MONALEESA-2, PFS benefit with ribociclib was maintained with consistent hazard ratios across all patient subgroups irrespective of TFI. In contrast, an exploratory analysis of MONARCH-3 demonstrated that only patients with a TFI of < 36 months derived PFS benefit with abemaciclib plus NSAI compared with patients with longer



LET, letrozole; PBO, placebo; RIB, ribociclib.
Dotted lines represent +25% and −30% change in tumor size. In Fig. 3A, patients with an available percentage change in target lesion that is contradicted by overall lesion response of progressive disease are not reported in the figure (RIB + LET: 3.8% vs PBO + LET: 7.0%); total sample size (240 vs 229) includes these patients.

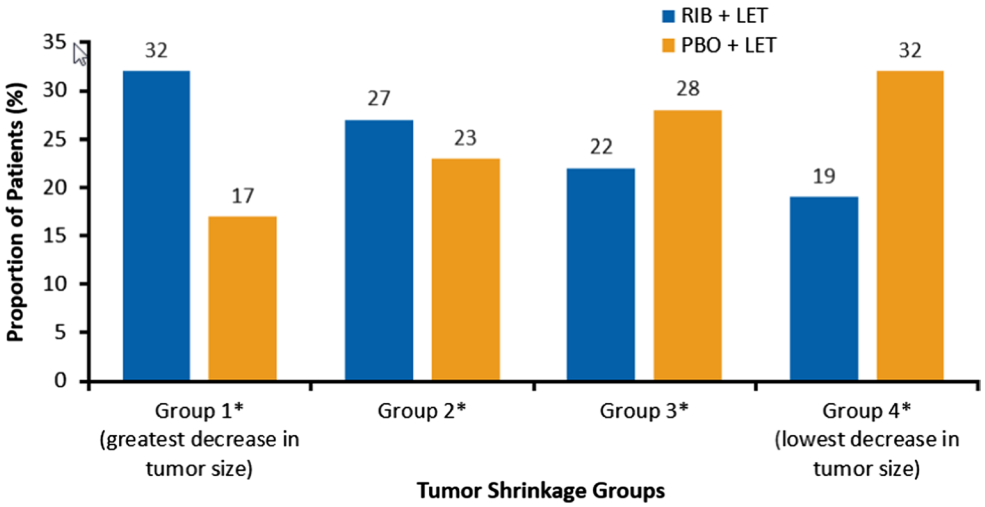
Fig. 4 **a** Tumor response. Waterfall plot of best percentage change in tumor size for all evaluable patients with measurable disease. **b** Tumor response. Percentage change in target lesion diameter over time in all evaluable patients with measurable disease

CI, confidence interval; LET, letrozole; PBO, placebo; RIB, ribociclib.



CI, confidence interval; LET, letrozole; PBO, placebo; RIB, ribociclib.

Fig. 5 Kaplan–Meier plot of duration of response per local assessment by treatment arm in patients with a complete response or partial response



LET, letrozole; PBO, placebo; RIB, ribociclib.

*Refer to "Assessments" section for best percentage change in target lesion for each group.

Fig. 6 Proportion of patients in each tumor shrinkage group by treatment arm

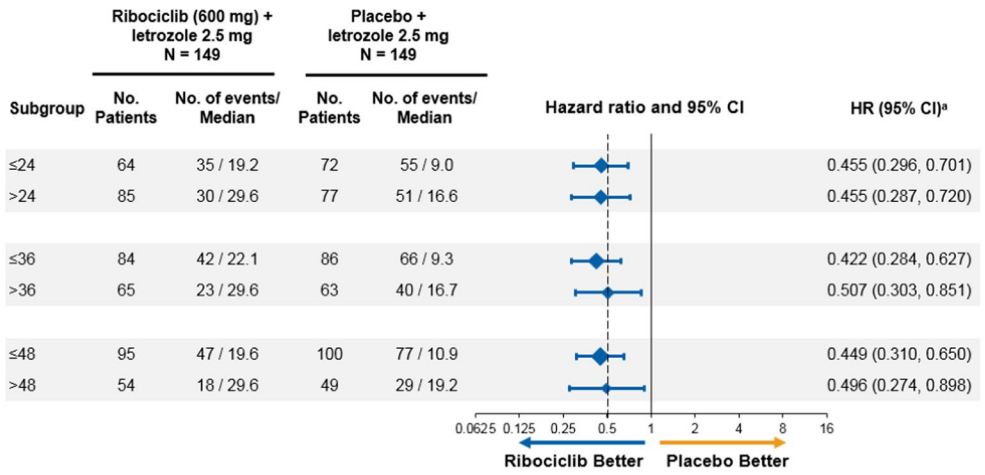
Table 2 Pain score with ribociclib plus letrozole at week 8

Week 8 HRQoL	Ribociclib + Letrozole	Placebo + Letrozole
Median percentage change from baseline in EORTC QLQ-C30 pain score	− 40%	− 29%
Mean change from baseline in EORTC QLQ-C30 pain score	− 6.3[a]	− 2.7
Mean change from baseline in EORTC QLQ-C30 pain score in patients with measurable disease at baseline who achieved clinical benefit	− 7.0[a]	− 1.3

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer's quality of life questionnaire for cancer patients

HRQoL, health-related quality of life

[a]A reduction of > 5 points from baseline was considered clinically meaningful



CI, confidence interval; ET, endocrine therapy; No., number.

[a] Hazard ratio (95% CI) is based on Cox PH model.

Size of diamonds is proportional to number of patients in each subgroup.

Fig. 7 Exploratory subgroup analyses of progression-free survival by treatment-free interval (months)

TFI > 36 months. The TFI data from MONALEESA-2 suggest that the PFS benefit with ribociclib was independent of TFI in patients with HR+ , HER2− ABC.

Ribociclib in combination with letrozole also resulted in a clinically meaningful reduction in EORTC QLQ-C30 pain score at week 8. As reported previously, in MONALEESA-2 the overall HRQoL (global health status/quality of life score) was maintained from baseline and was similar in both treatment arms [24]. In the PALOMA-3 study, the estimated overall global QoL scores ($p = 0.0313$) and improvement from baseline in pain score ($p = 0.0011$) significantly favored palbociclib plus fulvestrant group [27]. Palbociclib plus ET combination also resulted in a 36% of reduction in the risk of QoL deterioration [13]. Similarly, abemaciclib monotherapy also showed improvement from baseline in pain score ($p = 0.003$) [28]. The data presented here are the first with a CDK4/6 inhibitor to show a clinically meaningful decrease in pain as early as 8 weeks.

In conclusion, the results from these exploratory analyses suggest that ribociclib in combination with letrozole is associated with earlier and more durable tumor response, as well as greater tumor shrinkage at 8 weeks. The PFS benefit irrespective of TFI and improvement in pain symptoms with ribociclib plus letrozole further support the clinical benefit of ribociclib. These additional analyses from MONALEESA-2 demonstrate that ribociclib plus letrozole provides a valuable first-line treatment option for postmenopausal women with HR+ , HER2− ABC.

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Compliance with ethical standards

Conflict of interest Dr. Janni reports grants and personal fees from Novartis during the conduct of the study and outside the submitted work. Dr. Alba reports advisory board fees from Roche, Pfizer, and Novartis outside the submitted work. Dr. Bachelot reports personal fees from AstraZeneca, Roche, Novartis, and Pfizer; research grants from Roche, Novartis, and Pfizer outside the submitted work. Dr. Esteva reports consulting fee and research funding to his institution. Dr. Pluard reports advisory board fees from Novartis. Mr. Sutradhar is an employee of Novartis Pharmaceutical Corporation. Dr. Miller is employee of Novartis Pharmaceutical Corporation and hold Novartis stock options. Prof. Campone reports fees for advisory boards from Novartis, during the conduct of the study; and fees for advisory boards from Lilly, Sanofi, Pfizer, and AstraZeneca outside the submitted work. Dr. Diab, Dr. Gil, Dr. Beck, Ryvo, Dr. Tsai, Dr. Aunon, Dr. Kral, Dr. Ward, and Dr. Richards have nothing to disclose.

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