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Efficacy and safety of first-line ribociclib + letrozole in patients with de novo metastatic disease and late recurrence from (neo)adjuvant therapy in MONALEESA-2

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KEY FINDINGS & CONCLUSIONS

- This exploratory analysis focuses on a subgroup of patients in ML-2 with de novo metastatic disease or late recurrence (TFI > 12 mo from end of any [neo]adjuvant therapy), excluding patients with a TFI ≤ 12 mo who represented ≈18% of the ML-2 patient population and whose prognosis is more similar to patients with pretreated ABC[6]
- The OS HR (0.75; 95% CI, 0.60-0.93) for patients with de novo metastatic disease or late recurrence was consistent with that observed in the overall population of ML-2
- The mOS for patients with de novo metastatic disease or late recurrence (RIB, 69.2 mo vs PBO, 54.3 mo) surpassed that of the overall population for both arms, reaching almost 6 years in the RIB arm
  - An ≈15-mo improvement with 1L RIB over PBO was demonstrated

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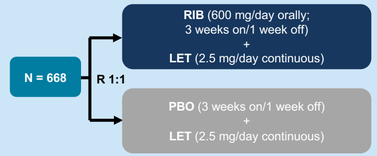
INTRODUCTION

- The final protocol-specified overall survival (OS) analysis of MONALEESA (ML)-2 reported a median (m)OS of 63.9 months with ribociclib (RIB) + letrozole (LET) vs 51.4 months with placebo (PBO) + LET (hazard ratio [HR], 0.76; 95% CI, 0.63-0.93; *P*=.008) in postmenopausal patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (ABC)[1]
- Patients in ML-2 were first line (1L) with no prior endocrine therapy (ET) for ABC[2]
  - Prior (neo)adjuvant therapy was allowed; however, for patients who had received prior (neo)adjuvant nonsteroidal aromatase inhibitor in particular, a treatment-free interval (TFI; time from end of (neo)adjuvant ET to disease recurrence) >12 mo was required
- PALOMA-2 used similar criteria for 1L patient selection but did not achieve OS benefit with palbociclib + LET (mOS, 53.9 mo) over PBO + LET (mOS, 51.2 mo) (HR, 0.956; 95% CI, 0.777-1.177; *P* = .3378)[3,4]
- In contrast, the 1L population of MONARCH 3 required a TFI >12 mo from the end of any prior (neo)adjuvant ET[5]
  - Abemaciclib + NSAI (mOS, 67.1 mo) did not meet the prespecified criteria for significance vs PBO + NSAI (mOS, 54.5 mo) in the second interim OS analysis (HR, 0.754; 95% CI, 0.584-0.974; *P* = .0301[6]); the final MONARCH 3 OS analysis is pending
- We present an exploratory ML-2 subgroup analysis that included patients with de novo metastatic disease or late recurrence (TFI > 12 mo from the end of any [neo]adjuvant therapy); i.e. excluded patients with early recurrence
  - Although treated as 1L, patients with a TFI ≤ 12 mo (early recurrence) are known to have poorer outcomes that are more similar to patients treated in the second line[7]

METHODS

- This analysis included patients in ML-2 (study design shown in **Figure 1**) with de novo metastatic disease as well as those with late recurrence
  - Patients with de novo metastatic disease had received no prior therapy for breast cancer and were identified within the patient data as those with no first recurrence/progression or first recurrence/progression within 90 days of diagnosis with no prior antineoplastic medication
  - Late recurrence was defined as a TFI > 12 months from completion of any (neo)adjuvant treatment, with no treatment for advanced or metastatic disease
- OS, progression-free survival (PFS), time to chemotherapy or death, and chemotherapy-free survival were estimated using the Kaplan-Meier method, and HRs were estimated using a stratified Cox proportional hazards model

Figure 1. ML-2 Study Design[2]



R, randomized

RESULTS

Treatment-free Interval and Disease-free Interval

- ML-2 randomized a total of 668 patients, of which 18.4% had a TFI ≤ 12 mo (59 [8.8%] for RIB and 64 [9.6%] for PBO) and were excluded from the analysis
- Of the remaining 545 patients included in this analysis, 114/275 (41.5%) in the RIB arm and 113/270 (41.9%) in the PBO arm had de novo metastatic disease; 161/275 (58.5%) in the RIB arm and 157/270 (58.1%) in the PBO arm had late recurrence (TFI > 12 mo) (**Table 1**)
- Among patients with late recurrence, the median TFI was 52.8 mo
- Additionally, 271/318 (85.2%) had a disease-free interval (DFI; time from initial diagnosis to disease recurrence) > 5 y and 148/318 (46.5%) had a DFI > 10 y
- The median follow-up time for this analysis was 79.8 mo

Table 1. Treatment-free Interval and Disease-free Interval in Patients With De Novo Metastatic Disease or Late Recurrence

	RIB + LET (n = 275)	PBO + LET (n = 270)
Total patients in analysis		
De novo metastatic disease, n (%)	114 (41.5)	113 (41.9)
Late recurrence (TFI > 12 mo), n (%)	161 (58.5)	157 (58.1)
TFI (time from end of [neo]adjuvant therapy to disease recurrence)		
N	161	157
Median, mo	52.6	54.4
≥ 36 mo, n (%)	91 (56.5)	80 (51.0)
DFI (time from initial diagnosis to disease recurrence)		
N	161	157
> 5 y, n (%)[a]	134 (83.2)	137 (87.3)
> 10 y, n (%)[a]	78 (48.4)	70 (44.6)

Patient Characteristics

- Baseline characteristics among patients with de novo metastatic disease or late recurrence were generally well balanced between the treatment arms (**Table 2**)

Table 2. Baseline Characteristics in Patients With De Novo Metastatic Disease or Late Recurrence

	RIB + LET (n = 275)	PBO + LET (n = 270)
Age, median, y	64.0	64.0
< 65 y	140 (50.9)	139 (51.5)
≥ 65 y	135 (49.1)	131 (48.5)
Race, n (%)		
Asian	26 (9.5)	17 (6.3)
Black	9 (3.3)	7 (2.6)
Caucasian	218 (79.3)	227 (84.1)
Pacific Islander	1 (0.4)	0
Other	11 (4.0)	6 (2.2)
Unknown	10(3.6)	13 (4.8)
ECOG performance status, n (%)		
0	169 (61.5)	159 (58.9)
1	106 (38.5)	111 (41.1)
Prior neoadjuvant ET[a]	0	2 (0.7)
Prior adjuvant ET[a]	120 (43.6)	108 (40.0)

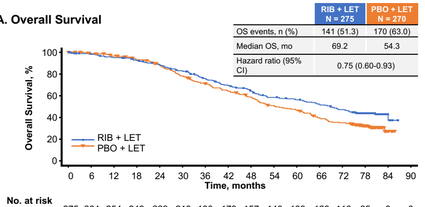
[a]A patient may have had multiple settings.

Overall Survival and Progression-free Survival

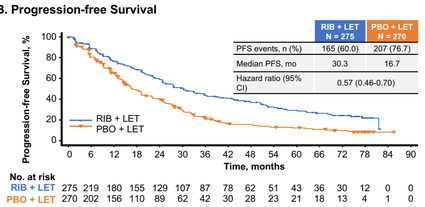
- A significantly longer OS benefit was observed with RIB + LET (mOS, 69.2 mo) vs PBO + LET (mOS, 54.3 mo) in patients with de novo metastatic disease or late recurrence (HR, 0.75; 95% CI, 0.60-0.93; *P* = .005) (**Figure 2A**)
  - A 25% relative reduction in risk of death was observed with RIB vs PBO
- RIB + LET also demonstrated a significant PFS benefit compared with PBO + LET (mPFS, 30.3 mo vs 16.7 mo) in patients with de novo metastatic disease or late recurrence (HR, 0.57; 95% CI, 0.46-0.70; *P* < .001) (**Figure 2B**)

Figure 2: Overall Survival in Patients with De Novo Metastatic Disease or Late Recurrence

A. Overall Survival



B. Progression-free Survival



Subsequent Therapy

- A similar proportion of patients in both treatment arms discontinued study treatment, and 86.2% vs 90.6% received subsequent antineoplastic therapy in the RIB vs PBO arms, respectively (**Table 3**)
- In patients with de novo metastatic disease or late recurrence, RIB + LET prolonged chemotherapy-free survival (CFS; time from randomization to first chemotherapy or death from any cause) and time to chemotherapy (TTC; time from randomization to the beginning of the first chemotherapy after discontinuation of the trial regimen) compared with placebo + letrozole (**Figure 3**) consistent with TTC and CFS reported for the ITT population of ML-2[1]
  - In patients treated with RIB + LET, mTTC was 54.1 mo vs 40.9 mo in patients treated with PBO + LET (HR, 0.74; 95% CI, 0.59-0.93; *P* = .004)
  - In the RIB arm, mCFS was 42.5 mo vs 36.1 mo in the PBO arm (HR, 0.75; 95% CI, 0.61-0.92; *P* = .002)

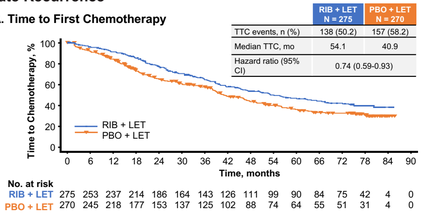
Table 3. Discontinuations and Subsequent Therapies in Patients with De Novo Metastatic Disease or Late Recurrence

	RIB + LET (n = 275)	PBO + LET (n = 270)
Patients who discontinued study treatment, n (%)	247 (89.8)	253 (93.7)
First subsequent therapy[a]	213 (86.2)	232 (90.6)
Any medication	36 (14.6)	43 (16.8)
Chemotherapy alone	26 (10.5)	24 (9.4)
Chemotherapy + hormonal therapy/other[b]	84 (34.0)	81 (31.6)
Hormonal therapy alone	61 (24.7)	79 (30.9)
Hormonal therapy + other[c]	4 (1.6)	2 (0.8)
Targeted therapy alone	1 (0.4)	0
Targeted therapy + other[d]	1 (0.4)	1 (0.4)
Immunotherapy alone	0	2 (0.8)
Other		
Subsequent CDK4/6 inhibitor		
Palbociclib	40 (16.2)	88 (34.4)
Ribociclib	13 (5.3)	5 (2.0)
Abemaciclib	6 (2.4)	10 (3.9)

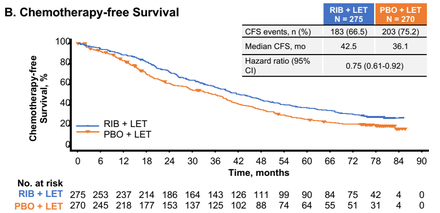
[a] Categories are mutually exclusive. [b] Includes patients who received chemotherapy in combination with any non-chemotherapy. [c] Includes patients who received hormonal therapy + other without chemotherapy. [d] Includes patients who received targeted therapy + other without chemotherapy.

Figure 3: Time to First Chemotherapy and Chemotherapy-free Survival in Patients with De Novo Metastatic Disease or Late Recurrence

A. Time to First Chemotherapy



B. Chemotherapy-free Survival



Safety

- Adverse events were consistent with those reported for the ML-2 ITT population (**Table 4**)[1,2]
  - Neutropenia was the most common adverse event (all grade and grade 3/4) in patients treated with RIB + LET
  - No new safety signals were observed

Table 4. Adverse Events in Patients With De Novo Metastatic Disease or Late Recurrence

Adverse Events by Preferred Term, ≥ 20% in Any Arm, n (%)	RIB + LET (n = 275)		PBO + LET (n = 267)	
	All Grade n (%)	Grade 3/4 n (%)	All Grade n (%)	Grade 3/4 n (%)
Neutropenia	182 (66.2)	147 (53.5)	15 (5.6)	2 (0.7)
Nausea	155 (56.4)	8 (2.9)	90 (33.7)	3 (1.1)
Fatigue	123 (44.7)	9 (3.3)	101 (37.8)	3 (1.1)
Diarrhea	118 (42.9)	7 (2.5)	78 (29.2)	3 (1.1)
Arthralgia	117 (42.5)	4 (1.5)	118 (44.2)	5 (1.9)
Alopecia	102 (37.1)	0	49 (18.4)	0
Vomiting	97 (35.3)	12 (4.4)	54 (20.2)	3 (1.1)
Constipation	84 (30.5)	3 (1.1)	62 (23.2)	0
Headache	82 (29.8)	2 (0.7)	66 (24.7)	2 (0.7)
Back pain	75 (27.3)	11 (4.0)	64 (24.0)	4 (1.5)
Cough	75 (27.3)	0	72 (27.0)	0
Anemia	70 (25.5)	12 (4.4)	22 (8.2)	6 (2.2)
Hot flush	67 (24.4)	1 (0.4)	72 (27.0)	0
Neutrophil count decreased	67 (24.4)	53 (19.3)	5 (1.9)	1 (0.4)
Decreased appetite	62 (22.5)	4 (1.5)	52 (19.5)	1 (0.4)
Hypertension	61 (22.2)	44 (16.0)	63 (23.6)	46 (17.2)
Aspartate aminotransferase increased	59 (21.5)	18 (6.5)	18 (6.7)	2 (0.7)
Alanine aminotransferase increased	58 (21.1)	32 (11.6)	18 (6.7)	3 (1.1)
Rash	57 (20.7)	3 (1.1)	26 (9.7)	1 (0.4)
White blood cell count decreased	57 (20.7)	37 (13.5)	5 (1.9)	0
Pain in extremity	54 (19.6)	0	55 (20.6)	1 (0.4)

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