Ribociclib in patients with HR+/HER2− advanced breast cancer and resistance to prior endocrine therapy in the MONALEESA-3 and -7 trials

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Introduction

- Endocrine therapy (ET) resistance is a major clinical challenge in patients with ER+ advanced breast cancer (ABC)[1]
- In the Phase III MONALEESA (ML)-3 (NCT02422615) and ML-7 (NCT02278120) trials, ribociclib (RIB) + ET demonstrated significant improvements in progression-free survival (PFS) as well as an overall survival (OS) benefit over placebo (PBO) + ET in patients with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) ABC (**Table 1**)[2-5]
- A proportion of patients enrolled in each trial had prior ET exposure, and some were considered to be ET resistant; thus, outcomes in this patient subset are important for informing clinical practice

Table 1. Survival Outcomes in the Intent-to-Treat Populations of ML-3 and ML-7

Outcome	ML-3[2,4]	ML-7[3,5]
	RIB + ET vs PBO + ET	RIB + ET vs PBO + ET
PFS, median, months	20.5 vs 12.8	23.8 vs 13.0
HR (95% CI)	0.59 (0.48-0.73), *P* < 0.001	0.55 (0.44-0.69), *P* < 0.0001
OS, median, months	NR vs 40.0	NR vs 40.9
HR (95% CI)	0.72 (0.57-0.92), *P* = 0.00455	0.71 (0.54-0.95), *P* = 0.00973

Objective

To assess outcomes associated with RIB + ET in patients with ET-resistant disease enrolled in the ML-3 trial and the nonsteroidal aromatase inhibitor (NSAI) cohort of the ML-7 trial

Methods

Patients and Study Designs

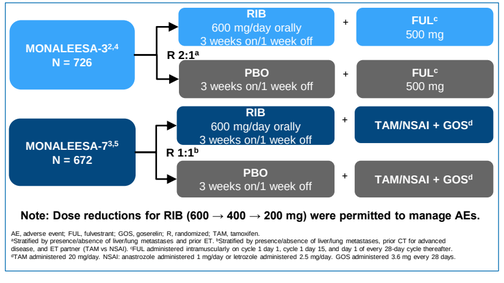
- The ML-3 and ML-7 patient populations are shown in **Table 2,** and study designs in **Figure 1**

Table 2. Patient Populations in ML-3 and ML-7

Study	Menopausal Status	Prior CT for ABC	De Novo ABC	Relapse > 12 mo From End of (Neo)adj ET	Relapse on or ≤ 12 mo after End of (Neo)adj ET	PD on 1L ET
ML-3	Post	✗	✓	✓	✓	✓
ML-7	Pre/peri	✓[a]	✓	✓	✓[b]	✗

1L, first line; CT, chemotherapy; PD, progressive disease.
[a]14% in each arm. [b]Patients that relapsed on 1 ET partner < 12 months prior to randomization were randomized to the opposite ET arm.

Figure 1. Study Designs



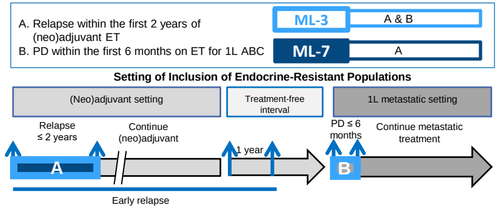
Note: Dose reductions for RIB (600 → 400 → 200 mg) were permitted to manage AEs.

AE, adverse event; FUL, fulvestrant; GOS, goserelin; R, randomized; TAM, tamoxifen.
[a]Stratified by presence/absence of liver/lung metastases and prior ET. [b]Stratified by presence/absence of liver/lung metastases, prior CT for advanced disease, and ET partner (TAM vs NSAI). [c]FUL administered intramuscularly on cycle 1 day 1, cycle 1 day 15, and day 1 of every 28-day cycle thereafter. [d]TAM administered 20 mg/day. NSAI: anastrozole administered 1 mg/day or letrozole administered 2.5 mg/day. GOS administered 3.6 mg every 28 days.

Methods

- Patients with resistance to prior ET in the ML-3 and -7 (NSAI cohort) trials were analyzed
- Important ad hoc definitions used in this analysis are listed in **Figure 2**
- PFS and OS were assessed using Cox regression and Kaplan-Meier methods
- PFS rate at 6 months while on study was assessed since the 2L proportion (including early relapse [relapse on (neo)adjuvant ET or within 12 months of ending (neo)adjuvant ET; **Figure 2**]) of this ET-resistant population had PD in < 6 months on prior ET in the 1L setting

Figure 2. Ad Hoc Definitions of ET Resistance



Results

- Of the 726 and 495 patients enrolled in ML-3 and -7 (NSAI cohort), 78 and 85, respectively, were considered ET resistant (**Table 3**)

Table 3. Endocrine-Resistant Population Baseline Characteristics

	MONALEESA-3		MONALEESA-7	
	RIB + FUL (n = 53)	PBO + FUL (n = 25)	RIB + NSAI (n = 44)	PBO + NSAI (n = 41)
Age, median, years	60	61	41	45
Race, %				
White	77	92	57	54
Asian	15	4	36	29
Other/unknown	8	4	7	17
ECOG PS, %				
0	62	76	75	83
1	38	24	23	17
Missing	0	0	2	0
Site of metastasis, %				
Visceral	53	64	61	63
Bone only	25	20	25	32
Prior chemotherapy for ABC, %	–	–	9	12
A (defined above), %[a]	72	84	100	100
B (defined above), %[a]	26	16	–	–

[a]For ML-3, there was missing data for 1 patient in the endocrine-resistant subgroup of the RIB + FUL arm; therefore, only 52 of 53 patients are accounted for here.

PFS in Patients with Endocrine Resistance

- The 6-month PFS rate was longer for the RIB vs PBO arms in the ML-3 (67% vs 46%) and ML-7 (74% vs 46%) trials (**Figure 3**)
  - Median PFS was 13.4 vs 5.7 mo (HR, 0.62), respectively, in ML-3 (**Figure 4A**)
  - Median PFS was 14.5 vs 5.6 mo (HR, 0.56), respectively, in ML-7 (**Figure 4B**)

Figure 3. 6-Month PFS Rate in Patients With Endocrine Resistance

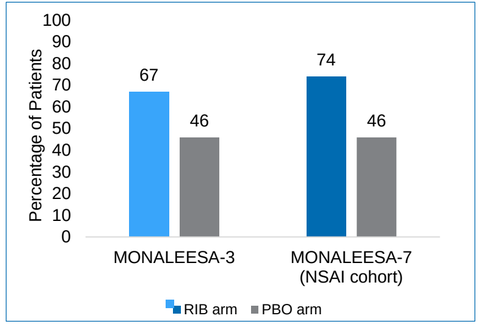
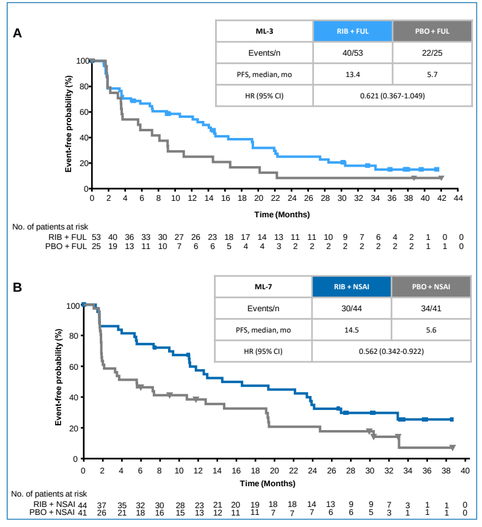


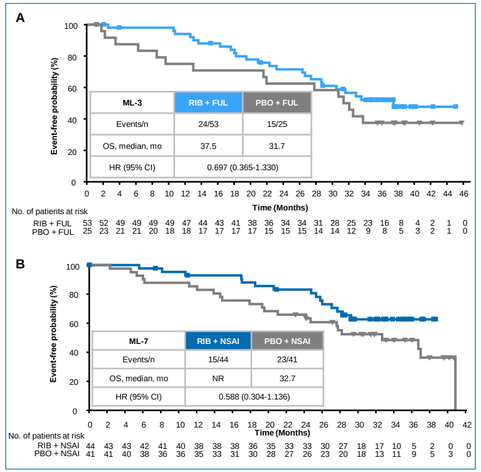
Figure 4. Kaplan-Meier Curves for PFS for ML-3 (A) and ML-7 (B)



OS in Patients With Endocrine Resistance

- Median OS was 37.5 vs 31.7 mo (HR, 0.70) in ML-3 (**Figure 5A**), consistent with the overall patient population in ML-3
- Consistent with the NSAI cohort in ML-7, median OS was not reached vs 32.7 mo (HR, 0.59) in ML-7 (**Figure 5B**)

Figure 5. Kaplan-Meier Curves OS for ML-3 (A) and ML-7 (B)



Response in Patients With Endocrine Resistance

- Overall response rates for RIB vs PBO were 17% vs 16% (95% CI, −16.6 to 18.6) in ML-3 and 40.9% vs 9.8% (95% CI, 14.0 to 48.3) in ML-7; clinical benefit rates for RIB vs PBO were 60.4% vs 44.0% (95% CI, −7.1 to 39.9) in ML-3 and 70.5% vs 46.3% (95% CI, 3.7 to 44.5) in ML-7

Selected Safety in Patients With Endocrine Resistance

- AEs in both trials were consistent with the overall safety populations (**Table 4**)

Table 4. All-Grade AEs in > 25% of Patients With Endocrine Resistance

	MONALEESA-3		MONALEESA-7	
All-grade AEs, %	RIB + FUL (n = 53)	PBO + FUL (n = 25)	RIB + NSAI (n = 44)	PBO + NSAI (n = 41)
Neutropenia	49.1	8.0	63.6	4.9
Arthralgia	18.9	24.0	40.9	22.0
Nausea	39.6	48.0	34.1	26.8
Fatigue	26.4	20.0	15.9	24.4
Diarrhea[a]	35.7	25.0	29.5	22.0
Back pain	20.8	24.0	27.3	17.1
Headache	9.4	20.0	27.3	24.4

[a]For ML-3, diarrhea was only reported for the 2L subgroup (RIB, n = 14; PBO, n = 4).

Conclusions

- Among patients with ET resistance in MONALEESA-3 and MONALEESA-7 (NSAI cohort), PFS > 6 months was observed in a larger proportion of patients in the RIB vs PBO arms
- The median PFS in patients with ET resistance treated with RIB was more than double that in patients treated with PBO in both studies
- In ML-3 and ML-7, RIB treatment led to a reduction in the risk of death of 30% and 41% in patients with ET resistance, and the survival benefits were consistent with the overall study populations
- Adverse events were consistent with the known safety profiles of the overall study populations in both trials
- These results confirm the consistency of RIB efficacy even in a clinically challenging ET-resistant population

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