Poster# **PD5-10**

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Pooled Analysis of Patients Treated With 1st-Line Ribociclib + Endocrine Therapy in the MONALEESA Studies: Long-Term Progression-Free Survival

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KEY FINDINGS & CONCLUSIONS

- In the MONALEESA phase 3 studies, approximately 1 in 4 patients treated with 1st-line RIB + ET derived long-term response (PFS>4 years), and approximately 1 in 5 postmenopausal patients derived very-long-term response (PFS>5 years)
- Long-term/very-long-term response was more evident in patients with better prognostic factors
  - These patients were less likely to have ≥3 metastatic sites, had a lower mean ctDNA fraction, were less likely to have *TP53* alterations detected by ctDNA at baseline, and exhibited lower gene expression of *CCNE1* and a higher proportion of luminal A disease vs patients without long-term/very-long-term response
  - Some patients with unfavorable prognostic factors (liver involvement, ≥3 metastatic sites) still achieved long-term/very-long-term response
- This exploratory analysis suggests long-term response with 1st-line RIB + ET treatment is achieved by 23% of patients with HR+/HER2− ABC, including some with unfavorable prognostic factors

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INTRODUCTION

- Ribociclib (RIB), in combination with endocrine therapy (ET), is approved as 1st-line treatment of patients with HR+/HER2− advanced breast cancer (ABC), and its use demonstrates statistically significant improvements in progression-free survival (PFS) and overall survival (OS) in every phase 3 trial of patients with ABC (MONALEESA [ML], ML-2, ML-3, and ML-7)[1-7]
- This analysis is intended to aid in understanding the clinical characteristics and biomarkers of patients with HR+/HER2− ABC who might derive long-term treatment benefit from RIB + ET
- We present an exploratory analysis of pooled patients with ABC who received 1st-line RIB treatment in the ML trials, which assessed the clinical characteristics and biomarkers of patients who derived long-term (PFS>4 years) and very-long-term (PFS>5 years) benefit

METHODS

- In the ML trials, pre- (ML-7) and postmenopausal (ML-2, ML-3) patients with HR+/HER2− ABC received RIB + ET or placebo + ET as 1st- or 2nd-line treatment
- This pooled analysis of ML-2 (median follow-up: 6.7 years), ML-3 (median follow-up: 5.9 years), and ML-7 (median follow-up: 4.5 years) included only patients who received 1st-line RIB treatment
  - Patients were excluded if they experienced early relapse (treatment-free interval [TFI] ≤12 months on [neo]adjuvant ET) or if they were treated with tamoxifen in ML-7. All 1st-line patients have ET-specific TFI >12 months but may have other antineoplastic treatments, resulting in overall TFI ≤12 months
- Long-term response (LTR) was defined as PFS >4 years (non-LTR: ≤4 years), and very-long-term response (VLTR) was defined as PFS >5 years (non-VLTR: ≤5 years)
  - Given that the median PFS of patients treated with CDK4/6 inhibitors for 1st-line ABC treatment is approximately 2 years, the definition of LTR in this study was selected to be a doubling of the median outcome
- LTR and VLTR analyses are conducted for 2 different populations
  - LTR analysis included ML-2, ML-3, and ML-7, and VLTR analysis included only ML-2 and ML-3 (studies in postmenopausal patients only) as the median follow-up for ML-7 was <5 years (less than the definition for VLTR)
  - Patients who experienced VLTR also experienced LTR
- Patients who were censored with no PFS event prior to the LTR (4 years) or VLTR (5 years) cutoff time were classified as having "unknown" LTR/VLTR status
  - Censoring reasons included lost to follow-up, ongoing without event, adequate assessment no longer available, event after ≥2 missing assessments, withdrew consent, and new cancer therapy added
- Biomarker analyses were performed using baseline circulating tumor DNA (ctDNA) data from a targeted next-generation sequencing panel (558 genes) or gene expression data of tumor samples from a customized NanoString (Bruker Spatial Biology), panel (800 genes)
- Nominal *P* values (unadjusted) are exploratory and were calculated to compare characteristics of responders vs nonresponders, with *t* tests for numerical variables and Chi-squared test for categorical variables
- This analysis is descriptive and hypothesis generating. No steps were taken to adjust for potential confounders

RESULTS

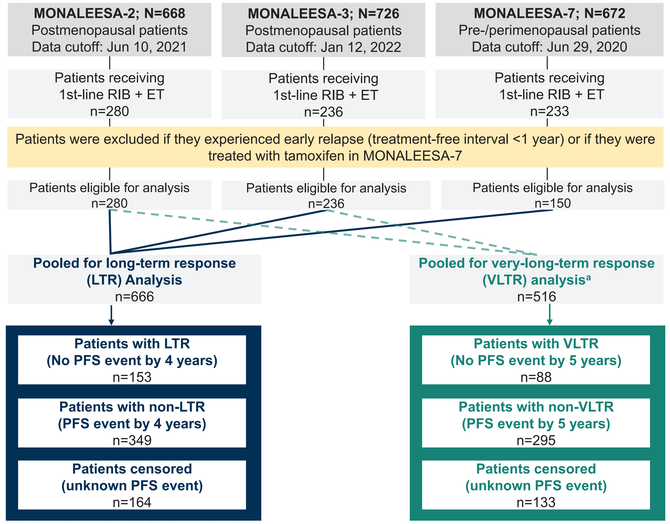
Long-Term Responders

- This analysis comprised 666 patients with HR+/HER2− ABC taking 1st-line RIB + ET from 3 pooled ML trials (pooled median follow-up: 6.1 years); 109 (16%) patients were still on treatment at data cutoff (**Figure 1**)
- A total of 153 patients (23%) exhibited LTR, and 164 (25%) patients were censored before LTR cutoff
  - Similar proportions of patients had LTR across the ML trials (ML-2 [n=63, 23%]; ML-3 [n=56, 24%]; ML-7 [n=34, 23%])
- Patients with LTR had a median PFS of 6.8 years (95%CI: 6.4, not estimable [NE]) and a median OS not yet reached NE (7, NE)

Very-Long-Term Responders

- This analysis comprised 516 patients with HR+/HER2− ABC taking 1st-line RIB + ET who were pooled from the ML-2 and ML-3 trials (postmenopausal patients only; pooled median follow-up: 6.4 years); 67 (13%) were still on treatment at data cutoff (**Figure 1**)
- A total of 88 (17%) patients exhibited VLTR [(ML-2 [n=44, 16%]; ML-3 [n=44, 19%]) and 133 (26%) patients were censored before VLTR cutoff
- Patients with VLTR had a median PFS of 6.8 years (95%CI: 6.8, NE); median OS was not yet reached

Figure 1. Patient Selection for Pooled Analyses



[a]All patients who experienced VLTR also experienced LTR.
ET, endocrine therapy; PFS, progression-free survival; RIB, ribociclib.

Baseline characteristics

Patients with LTR

- Patient characteristics, (age, body mass index, menopausal status, and Eastern Cooperative Oncology Group performance status) were balanced between those with LTR and those with non-LTR (**Table 1**)
- A similar proportion of premenopausal (n=34/150; 22.7%) and postmenopausal patients (n=119/516; 23.1%) exhibited LTR
- Compared with patients with non-LTR, patients with LTR were less likely to have liver metastasis (25.5% vs 16.3%, respectively) and ≥3 metastatic sites (43.0% vs 30.1%, respectively)
- Similar proportions of patients with LTR vs non-LTR had lung involvement (37.9% vs 40.1%, respectively), bone-only disease (24.2% vs 19.5%), and rates of de novo (43.1% vs 39.5%) and recurrent disease (51.0% vs 52.2%)

Patients with VLTR

- Patient characteristics were generally balanced between those with VLTR and those with non-VLTR (**Table 1**)
  - Similar proportions of patients with VLTR and non-VLTR had liver involvement, lung involvement, visceral disease, and bone-only disease
- Compared with patients with non-VLTR, patients with VLTR were less likely to have ≥3 metastatic sites (43.1% vs 26.1%, respectively)

Table 1. Baseline Characteristics of Patients With LTR and VLTR

Parameter	Patients with LTR n=153	Patients with non-LTR[a] n=349	*P* value[b]	Patients with VLTR n=88	Patients with non-VLTR[a] n=295	*P* value[b]
Patient characteristics						
Age, mean (SD), year	59.3 (11.9)	58.0 (12.4)	0.282	63.6 (9.4)	62.5 (9.9)	0.318
BMI, mean (SD), kg/m^2	27.5 (5.6)	26.6 (5.5)	0.132	28.3 (5.6)	27.0 (5.4)	0.058
Menopausal status, n (%)						
Postmenopausal	119 (77.8)	273 (78.2)	1	88 (100)	295 (100)	—
Premenopausal	34 (22.2)	76 (21.8)		—	—	
ECOG PS at baseline, n (%)						
0	106 (69.3)	210 (60.2)	0.13	60 (68.2)	169 (57.3)	0.088
1	47 (30.7)	138 (39.5)		28 (31.8)	126 (42.7)	
Combination partner (+ goserelin), n (%)						
Anastrozole	4 (2.6)	9 (2.6)	1	—	—	—
Fulvestrant	56 (36.6)	128 (36.7)		44 (50.0)	138 (46.8)	0.682
Letrozole	93 (60.8)	212 (60.7)		44 (50.0)	157 (53.2)	
Disease characteristics, n (%)						
De novo	66 (43.1)	138 (39.5)	0.215	40 (45.5)	111 (37.6)	0.468
Recurrent						
TFI≤12 months	4 (2.6)	23 (6.6)		4 (4.5)	9 (3.1)	
TFI >12 months	74 (48.4)	159 (45.6)		39 (44.3)	156 (52.9)	
Liver involvement	25 (16.3)	89 (25.5)	0.032	14 (15.9)	61 (20.7)	0.403
Lung involvement	58 (37.9)	140 (40.1)	0.714	31 (35.2)	125 (42.4)	0.283
Visceral disease	86 (56.2)	217 (62.2)	0.246	50 (56.8)	181 (61.4)	0.523
Bone-only disease	37 (24.2)	68 (19.5)	0.284	24 (27.3)	56 (19.0)	0.126
No. of metastatic sites						
0[d]	0	2 (0.6)	0.034	0 (0.0)	2 (0.7)	0.029
1	52 (34.0)	93 (26.6)		31 (35.2)	78 (26.4)	
2	55 (35.9)	104 (29.8)		34 (38.6)	88 (29.8)	
3+	46 (30.1)	150 (43.0)		23 (26.1)	127 (43.1)	

[a]Patients who were censored before LTR/VLTR cutoff are not included in this table. [b]*P* value testing denotes the difference in means (numerical variable; *t* test) or independence (categorical variable; Chi-squared test) between the given baseline variable and patients with LTR vs non-LTR. [c]Time from the end of (neo)adjuvant treatment to disease recurrence. All 1st-line patients have ET-specific TFI >12 months but may have other antineoplastic treatments, resulting in overall TFI ≤12 months. [d]ML trials included patients with locally advanced disease.
BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; LTR, long-term response; ML, MONALEESA; TFI, treatment-free interval; VLTR, very-long-term response.

Biomarker analyses

Patients with LTR

- Compared with patients with non-LTR, patients with LTR had a lower mean ctDNA fraction (5% vs 13%) and were less likely to have *CCND1* or *TP53* alterations detected by ctDNA at baseline (**Table 2**)
- Patients with LTR also had lower gene expression of *CCNE1* (−0.24 vs 0.13, respectively)
- Intrinsic subtype analysis (PAM50 based) revealed that patients with LTR had a higher proportion of luminal A disease vs those with non-LTR [37.9% vs 25.8%, respectively], along with lower proportions with basal and HER2E subtypes
- Of note, LTR was seen in 2 patients with basal subtype, a phenotype considered resistant to CDK4/6 inhibitor treatment, and in 6 patients with HER2E, representing 11.1% (n=6/54) of all patients with HER2E in the cohort

Patients with VLTR

- Patients with VLTR were less likely to have *TP53* alterations detected by ctDNA at baseline and exhibited a lower mean ctDNA fraction vs those with non-VLTR (4% vs 12%, respectively) (**Table 2**)
- Patients with VLTR also had lower gene expression of *CCNE1* vs those with non-VLTR (−0.34 vs 0.03, respectively) and a higher proportion of luminal A disease (37.5% vs 29.8%, respectively)

Table 2. Biomarker Analyses of Patients With LTR and VLTR

Biomarkers	Patients with LTR n=153	Patients with non-LTR[a] n=349	*P* value[b]	Patients with VLTR n=88	Patients with non-VLTR[a] n=295	*P* value[b]
ctDNA						
ctDNA fraction, mean (SD)	0.05 (0.09)	0.13 (0.15)	<0.001	0.04 (0.08)	0.12 (0.15)	<0.001
CCND1 alteration, n (%)						
Positive	3 (2.0)	33 (9.5)	0.009	2 (2.3)	26 (8.8)	0.118
Negative	120 (78.4)	245 (70.2)		66 (75.0)	207 (70.2)	
Missing	30 (19.6)	71 (20.3)		20 (22.7)	62 (21.0)	
TP53 alteration, n (%)						
Positive	4 (2.6)	52 (14.9)	<0.001	1 (1.1)	39 (13.2)	0.019
Negative	119 (77.8)	226 (64.8)		67 (76.1)	194 (65.8)	
Missing	30 (19.6)	71 (20.3)		20 (22.7)	62 (21.0)	
Tumor mRNA expression						
CCNE1, mean (SD)	−0.24 (0.85)	0.13 (0.97)	0.002	−0.34 (0.83)	0.03 (0.91)	0.01
Intrinsic subtype, n (%)						
Basal	2 (1.3)	18 (5.2)	0.008	0 (0.0)	14 (4.7)	0.092
HER2E	6 (3.9)	37 (10.6)		4 (4.5)	31 (10.5)	
Luminal A	58 (37.9)	90 (25.8)		33 (37.5)	88 (29.8)	
Luminal B	19 (12.4)	54 (15.5)		10 (11.4)	44 (14.9)	
Not analyzed	54 (35.3)	118 (33.8)		32 (36.4)	90 (30.5)	
Normal	14 (9.2)	32 (9.2)		9 (10.2)	28 (9.5)	

[a]Patients who were censored before LTR/VLTR cutoff are not included in this table. [b]*P* value testing denotes the difference in means (numerical variable; *t* test) or independence (categorical variable; Chi-squared test) between the given baseline variable and patients with LTR vs non-LTR.
ctDNA, circulating tumor DNA; LTR, long-term response; SD, standard deviation; VLTR, very-long-term response.

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