Impact of ribociclib dose reduction on overall survival in patients with HR+/HER2− advanced breast cancer in MONALEESA -3 and -7

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Michelino De Laurentiis,[1] Luis de la Cruz Merino,[2] Lowell Hart,[3] Aditya Bardia,[4] Seock-Ah Im,[5] Joohyuk Sohn,[6] Patrick Neven,[7] Miguel Martin,[8] Yan Ji,[9] Shu Yang,[9] Huilin Hu,[9] Agnes Lteif,[9] Debu Tripathy[10]

[1]IRCCS Istituto Nazionale Tumori, "Fondazione G. Pascale," Naples, Italy; [2]Hospital Universitario Virgen Macarena, Department of Medicine, Universidad de Sevilla, Seville, Spain; [3]Florida Cancer Specialists and Research Institute, Sarah Cannon Research Institute, Fort Myers, FL, USA; [4]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA; [5]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea; [6]Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; [7]Multidisciplinary Breast Centre, Universitair Ziekenhuis Leuven, Leuven, Belgium; [8]Instituto de Investigación Sanitaria Gregorio Marañon, Centro de Investigación Biomédica en Red de Cáncer, Grupo Español de Investigación en Cáncer de Mama, Universidad Complutense Madrid, Madrid, Spain; [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [10]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Introduction

- In the Phase III MONALEESA (ML)-3 (NCT02422615) and ML-7 (NCT02278120) trials, ribociclib (RIB) plus endocrine therapy (ET) vs ET alone demonstrated a significant progression-free survival (PFS) and overall survival (OS) benefit in patients (pts) with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2−) advanced breast cancer (ABC)[1-4]
  - ML-3: Median OS was not reached (NR) for RIB + fulvestrant (FUL) and 40.0 months for PBO + FUL (HR, 0.72 [95% CI, 0.57-0.92][3]
  - ML-7: In the nonsteroidal aromatase inhibitor (NSAI) cohort, median OS was NR for RIB + NSAI and 40.7 months for PBO + NSAI (HR, 0.70 [95% CI, 0.50-0.98])[4]
- Dose reductions of RIB from 600 mg to 400 mg and 400 mg to 200 mg per day are permitted for the management of treatment-related adverse events (AEs) and to allow patients to continue RIB treatment[5]
- A previous analysis on the impact of dose reductions on PFS showed that patients continued to derive benefit from ribociclib regardless of dose[6]

Objective

To analyze the impact of RIB dose reduction and relative dose intensity on OS benefit in patients from ML-3 and the ML-7 NSAI cohort

Methods

Patients and Study Details

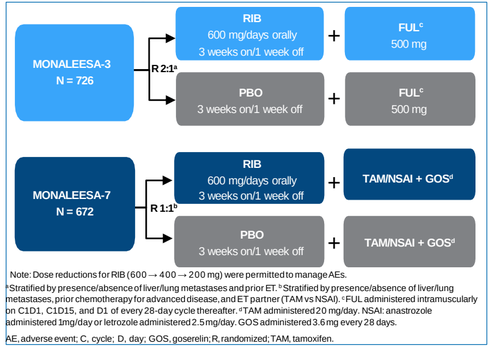
- The ML-3 and ML-7 patient populations are shown in **Table 1** and study designs in **Figure 1**

Table 1. 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]	✗

[a] 14% in each arm. [b] Patients who had relapsed on 1 ET partner < 12 mo prior to randomization were randomized to the opposite ET arm. PD, progressive disease.

Figure 1. Study Designs



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

[a]Stratified by presence/absence of liver/lung metastases and prior ET. [b]Stratified by presence/absence of liver/lung metastases, prior chemotherapy for advanced disease, and ET partner (TAM vs NSAI). [c]FUL administered intramuscularly on C1D1, C1D15, and D1 of every 28-day cycle thereafter. [d]TAM administered 20 mg/day. NSAI: anastrozole administered 1mg/day or letrozole administered 2.5 mg/day. GOS administered 3.6 mg every 28 days.

AE, adverse event; C, cycle; D, day; GOS, goserelin; R, randomized; TAM, tamoxifen.

Statistical Methods

- Patients on RIB + ET who received at least one dose of any component of study treatment were included in the analyses
- Two statistical methods were used to analyze the effect of dose on OS:
  1. Cox model with time-varying covariates and 2. landmark survival analysis
- **For the Cox model,** the 2 time-varying covariates were dose reductions (yes, no) and relative dose intensity 2 (RDI2; low, medium, high) and were considered separately as univariate analyses
  - RDI2 represents the RDI during the period from first dose reduction or interruption to last dose date
  - All patients were classified in the "high" group, then either remained or were moved to the "medium" or "low" group according to the tertile of RDI2 at the time of first dose reduction/interruption and remained in the respective group until death or censoring. With dose reduction as the time-varying covariate, it was defined in a similar manner
  - The relationship of OS and time-varying covariates was illustrated using a modified Kaplan-Meier method[7]
- **For landmark analyses**, only dose reduction (yes, no) was considered
  - 3 and 6 months were selected because these time points were nearest the median time to first dose reduction and captured an adequate number of patients
  - Patients with exposure duration of < landmark were excluded from the analysis
  - Patients were categorized (yes, no) according to whether a dose reduction occurred prior to the landmark time, regardless of subsequent dose changes
- Hazard ratios for yes vs no are presented for dose reduction, whereas HRs for medium vs high and low vs high are presented for RDI2

Results

Patient Characteristics, Dose Reduction Details, and Safety

- In ML-3, 384/483 (79.5%) patients required a dose reduction or interruption, and 197/483 (40.7%) patients required a dose reduction; in ML-7, 204/246 (82.9%) patients required a dose reduction or interruption, and 101/246 (41.1%) required a dose reduction
- Patient characteristics were well balanced between patients who had no dose reduction compared with patients who had ≥ 1 dose reduction in both trials (**Table 2**)
- Dose reductions were most commonly due to neutropenia and decreased neutrophil count
  - ML-3 and ML-7 neutropenia: (all grade) 38.1%, 44.6%, and (grade 3/4) 26.4%, 36.6%
  - ML-3 and ML-7 decreased neutrophil count: (all grade) 7.6%, 16.8%, and (grade 3/4) 6.6%, 15.8%
- AEs in patients with and without dose reductions were consistent with those in the overall population (data not shown)
- Median time to first dose reduction was 3.5 months in ML-3 and 2.8 months in ML-7 (NSAI)

Table 2. Baseline Characteristics

	ML-3		ML-7 NSAI Cohort	
	RIB 600 mg	RIB ≥ 1 Dose Reduction	RIB 600 mg	RIB ≥ 1 Dose Reduction
No. of patients	287	197	147	101
Age, median, years	64.0	63.0	43.0	43.0
ECOG PS, %				
0	63.4	65.5	77.6	68.3
1	36.2	34.5	21.8	30.7
Line of ET, %				
First line	47.7	50.8	100[a]	100[a]
Early relapse/second line	51.2	45.7	--	--
Prior chemotherapy for ABC, %	--	--	17.0	7.9

[a] Of these, 34.7% and 42.2% of patients with and without ≥ 1 dose reduction had early relapse, respectively.

Overall Survival by Dose Reduction

- In both ML-3 and ML-7, the OS benefit was maintained regardless of dose reduction and was consistent with that of the overall population based on the HRs from the time-dependent Cox models (**Figure 2**)
- A landmark analysis of OS revealed consistent results at 3 and 6 months (**Table 3**)

Figure 2. Time-Varying Cox Regression Analysis of OS by Dose Reduction for ML-3 (A) and the ML-7 NSAI cohort (B)

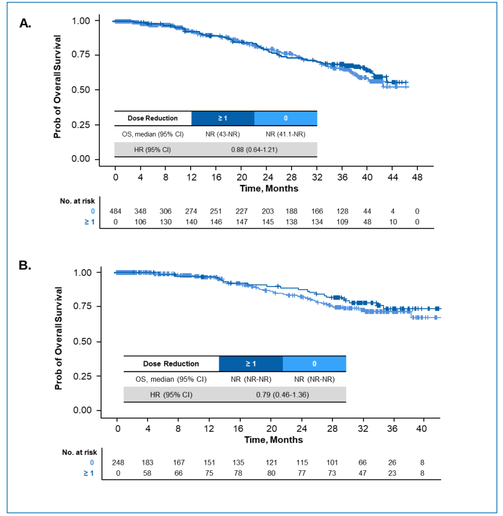


Figure 3. Time-Varying Cox Regression Analysis of OS by RDI for ML-3 (A) and the ML-7 NSAI cohort (B)

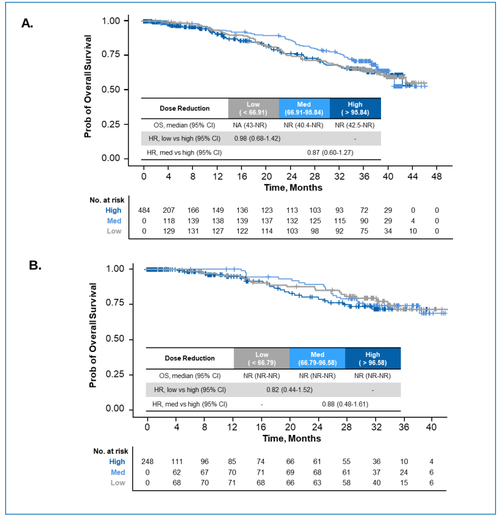


Table 3. Landmark Analysis of OS Based on Dose Reductions

Study/ Landmark	Patients on Tx > Landmark, n (%)	Dose Reduction Before Landmark	n (%)	Events, n	2-Year Post-Landmark OS (95% CI)	HR (95% CI)
ML-3						
3 months	384 (79.3)	No	301 (78.4)	88	0.82 (0.78-0.87)	1.11 (0.72-1.73)
		Yes	83 (21.6)	26	0.76 (0.67-0.86)	
6 months	340 (70.2)	No	243 (71.5)	60	0.84 (0.79-0.88)	1.13 (0.71-1.78)
		Yes	97 (28.5)	26	0.80 (0.72-0.88)	
ML-7 NSAI Cohort						
3 months	220 (88.7)	No	173 (78.6)	37	0.83 (0.77-0.89)	0.95 (0.46-1.97)
		Yes	47 (21.4)	9	0.86 (0.76-0.97)	
6 months	201 (81.0)	No	145 (72.1)	26	0.84 (0.78-0.90)	1.04 (0.50-2.16)
		Yes	56 (27.9)	10	0.85 (0.76-0.95)	

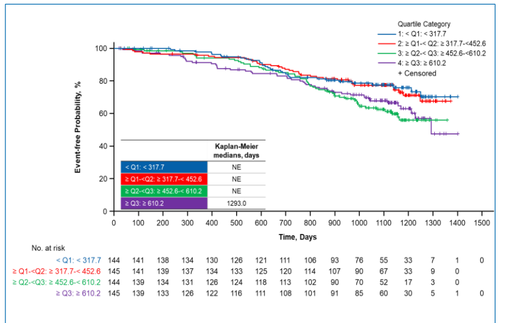
Overall Survival by Relative Dose Intensity

- RDI based on time from first reduction/interruption (RDI2) was divided into tertiles (low, medium, and high); these tertiles were well balanced between groups in both trials
- Consistent with the overall and dose reduction populations, RIB demonstrated OS benefit, regardless of RDI (**Figure 3**)

Overall Survival by Pharmacokinetic Exposure

- No apparent relationship was observed between pharmacokinetic exposure (geometric mean of model-predicted C_{trough} ([ng/mL] on non-zeroing dosing days) and OS, suggesting no clear impact of RIB exposure and related dose reductions on OS (**Figure 4**)

Figure 4. OS by Pharmacokinetic Exposure in ML-3 and -7 NSAI Cohort[a]



[a] Patients in the PK-Safety set were categorized into one of four quartiles based on the values of geometric mean population PK model predicted ribociclib C_{trough} (ng/mL) on non-zero dosing days.

Conclusions

- Dose reductions of ribociclib do not compromise OS benefit
- No relationship is observed between OS and ribociclib dose reduction, RDI, or drug exposure
- These findings suggests that patients starting on ribociclib at 600 mg who require a dose modification for AE management or other reasons do not lessen the survival benefit

References

1. Slamon DJ, et al. *N Engl J Med.* 2020;382(6):514-524.
2. Im S-A, et al. *N Engl J Med.* 2019;381:307-316.
3. Slamon DJ, et al. *J Clin Oncol.* 2018;36:2465-2472.
4. Tripathy D, et al. *Lancet Oncol.* 2018;19:904-915.
5. Kisqali [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2020.
6. Beck JT, et al. SABCS 2018 [poster P6-18-06].
7. Snappin SM, et al. *Am Statistician.* 2005;59:301-307.

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