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Impact of Ribociclib Dose Modifications on Overall Survival in Patients With HR+/HER2− Advanced Breast Cancer in MONALEESA-2

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KEY FINDINGS & CONCLUSIONS

- This analysis of the ML-2 trial demonstrated that the OS benefit of first-line RIB + LET was maintained in postmenopausal patients with HR+/HER2− ABC who required modification from the recommended starting dose of RIB (600 mg/day 3 weeks on/1 week off)
- Dose reduction or RDI2 did not impact OS benefit, regardless of when the dose reduction occurred or how long a patient had been treated
  - Landmark analyses were used to address the potential for guarantee-time bias
- The results of this analysis were consistent with a prior analysis of the ML-3 and ML-7 trials
- Taken together, these data from ML-2, -3, and -7 suggest that patients treated with RIB + ET requiring dose modifications from the recommended starting dose of RIB, due to AEs or other reasons, can do so without compromising OS benefit

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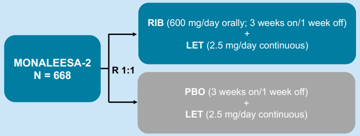
INTRODUCTION

- Each of the Phase III MONALEESA (ML)-2, -3, and -7 trials have reported a statistically significant progression-free survival and overall survival (OS) benefit with ribociclib (RIB; starting dose 600 mg/day 3 weeks on/1 week off) plus endocrine therapy (ET) compared with placebo (PBO) plus ET in patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC)[1-6]
  - In the final protocol-specified OS analysis of ML-2, the median OS was 63.9 months with RIB plus letrozole (LET) vs 51.4 months with PBO plus LET (hazard ratio, 0.76 [95% CI, 0.63-0.93]; *P* = .008)[2]
- A prior analysis of the ML-3 and -7 trials demonstrated that RIB dose modifications (reductions and/or interruptions based on protocol guidance), when needed, did not impact OS benefit with RIB plus ET[7]
- We report data on the impact of RIB dose modifications on OS benefit in patients from the ML-2 trial

METHODS

- ML-2 included postmenopausal patients with HR+/HER2− ABC who had not received prior systemic therapy for advanced disease
- The ML-2 study design is shown below (**Figure 1**)

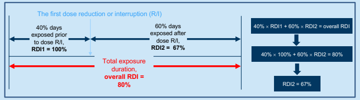
Figure 1. ML-2 Study Design



R, randomized.

- Landmark (LM) analyses were performed to assess the association between dose reductions (yes, no) and OS
  - LM analyses address the potential for guarantee-time bias by separating patients into two groups (eg, dose reductions yes vs no) at LM time points and following these different groups forward in time
    - Patients with exposure duration of < LM were excluded from the analysis
    - Patients were categorized (yes, no) by whether a dose reduction occurred prior to the LM time, regardless of subsequent dose changes

Figure 2. RDI2 Methodology



I, dose interruption; R, dose reduction; RDI, relative dose intensity.

- As an alternative, analyses using a Cox proportional hazards model with two time-varying covariates (dose reductions [yes, no] and relative dose intensity 2 [RDI2; low, medium, high]) were performed
  - RDI1 represents the period prior to dose modification. RDI2 is the RDI during the period from first dose reduction or interruption to last dose date (**Figure 2**). While RDI considers the entire treatment period, it does not contain a time element. RDI2 is a time-dependent RDI that considers immortal time bias
    - For example, **Figure 2** presents a patient who had an overall RDI of 80%, and the first dose modification occurred after 40% of the entire treatment duration; this results in an RDI2 of 67%
  - All patients were categorized in the "high" group and then either remained or were moved to the "medium" or "low" groups based on the tertile of RDI2 at the time of first dose reduction/interruption and stayed in the respective group until death or censoring. With dose reduction as the time-varying covariate, it was defined in a similar manner
  - Median OS was determined using a modified Kaplan-Meier method
- Hazard ratios for yes vs no are presented for dose reductions, whereas hazard ratios for medium vs high and low vs high are presented for RDI2

RESULTS

Patient Characteristics and Dose Reduction Details

- At the data cutoff (June 10, 2021) the median duration of follow-up from randomization to data cutoff was 79.7 months
  - Median follow-up for date of randomization to date of death or last contact was 49.35 months (min, 0; max, 86.7 months)
- In ML-2, 209/334 pts (62.6%) required a RIB dose reduction (**Table 1**)
  - Dose reductions were most commonly due to adverse events (AEs) (58.1%)
  - Median duration of RIB exposure was 19.1 vs 10.8 months for patients with ≥ 1 vs 0 RIB dose modifications
- Median time to first dose reduction was 3 months
- Baseline characteristics were balanced between patients with ≥ 1 or 0 RIB dose reductions (**Table 2**)
- RIB dose interruptions were required in 275/334 pts (82.3%)
  - AEs were the most common cause of dose interruptions (73.7%)

Table 1. RIB Dose Reductions

	RIB N=334
No. of reductions, n (%)	
0	125 (37.4)
1	124 (37.1)
2	76 (22.9)
≥ 3	9 (2.7)
No. of patients with ≥ 1 reduction by reason, n (%)	
AE	194 (58.1)
Dosing error	11 (3.3)
Lack of efficacy	1 (0.3)
Physician decision	10 (3.0)
Patient/guardian decision	11 (3.3)
Missing	3 (0.9)

Table 2. Baseline Characteristics for Patients With or Without RIB Dose Reduction

	≥ 1 Dose Reduction	0 Dose Reductions
No. of pts	209	125
Age, median, years	62.0	62.0
ECOG PS, %		
0	63.6	56.8
1	36.4	43.2
De novo, %	35.4	32.0
Non de novo, %	64.6	68.0

ECOG PS, Eastern Cooperative Oncology Group performance status.

Overall Survival by Dose Reduction

- LM analyses demonstrated similar OS for patients with and without dose reduction at multiple LM times
  - For all LM times analyzed, patients with and without dose reduction had similar post-LM 2-year OS rates (**Table 3**)
  - Post-LM hazard ratios (dose reduction yes vs no) demonstrated that OS was similar for patients with and without dose reduction, regardless of when the dose reduction occurred (**Table 3**)
    - Kaplan-Meier curves of OS were similar at the 3-month landmark analysis for pts with and without dose reduction (hazard ratio, 0.96 [95% CI, 0.68-1.36]) (**Figure 3**)
- Hazard ratios generated from the time-dependent Cox models demonstrated that the OS benefit of RIB was maintained in patients with 0 or ≥ 1 dose reductions and was consistent with the OS benefit observed in the overall population (**Figure 4**)

Table 3. LM Analysis of OS by Dose Reductions

LM Time, months[a]	Patients on Treatment Longer Than LM Time, n (%)	Dose Reduction Prior to LM Time	Subgroup, n (%)	No. of Events	2-Year Post-LM Time OS Rate (95% CI)[b]	Post-LM Time Hazard Ratio (95% CI): Dose Reduction Yes vs No
3	294 (88.0)	Yes	93 (31.6)	47	0.89 (0.83-0.96)	0.96 (0.68-1.36)
		No	201 (68.4)	106	0.85 (0.80-0.90)	
6	261 (78.1)	Yes	120 (46.0)	63	0.86 (0.80-0.93)	1.19 (0.85-1.68)
		No	141 (54.0)	68	0.88 (0.83-0.94)	
9	240 (71.9)	Yes	130 (54.2)	63	0.87 (0.81-0.93)	1.17 (0.80-1.70)
		No	110 (45.8)	50	0.88 (0.82-0.94)	
12	211 (63.2)	Yes	117 (55.5)	53	0.89 (0.83-0.95)	1.20 (0.79-1.82)
		No	94 (44.5)	38	0.89 (0.83-0.96)	
15	194 (58.1)	Yes	110 (56.7)	47	0.87 (0.81-0.94)	1.17 (0.75-1.84)
		No	84 (43.3)	32	0.90 (0.84-0.97)	
18	176 (52.7)	Yes	101 (57.4)	37	0.90 (0.84-0.96)	0.94 (0.57-1.53)
		No	75 (42.6)	29	0.88 (0.80-0.96)	

[a] Each LM time represents a distinct patient population treated on and after the LM. [b] OS rate by 2 years after given LM time.

Figure 3. LM Analysis of OS by Dose Reductions: 3 Months

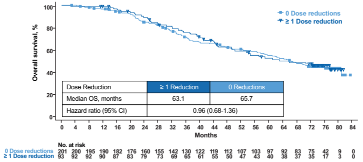
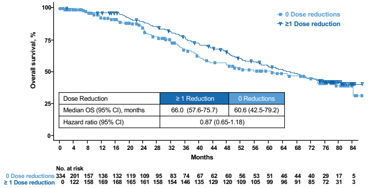


Figure 4. Time-Varying Cox Regression Analysis of OS by Dose Reduction



Adverse Events and Dose Reduction

- Among patients with and without a dose reduction, neutropenia (all grades and grade 3/4) was the most common AE (**Table 4**)
  - Neutropenia was the most common AE that led to a dose reduction (42.1%)

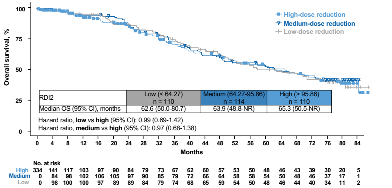
Overall Survival by Relative Dose Intensity 2

- RDI2 was calculated according to tertile: low (< 64.27%), medium (64.27%-95.86%), and high (> 95.86%)
- Regardless of RDI2, RIB demonstrated an OS benefit consistent with that observed with the overall and dose reduction populations (**Figure 5**)
  - In patients with low RDI2, median OS was 62.6 (95% CI, 50.0-80.7) months
  - In patients with medium RDI2, median OS was 63.9 (95% CI, 48.8-not reached [NR]) months
  - In patients with high RDI2, median OS was 65.3 (95% CI, 50.5-NR) months

Table 4. Adverse Events in Patients With or Without RIB Dose Reductions

AEs ≥ 20% in Any Arm, n (%)	≥ 1 Dose Reduction		0 Dose Reductions	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Neutropenia	150 (71.8)	129 (61.7)	68 (54.4)	45 (36.0)
Nausea	124 (59.3)	6 (2.9)	60 (48.0)	3 (2.4)
Diarrhea	89 (42.6)	4 (1.9)	47 (37.6)	4 (3.2)
Fatigue	97 (46.4)	7 (3.3)	47 (37.6)	4 (3.2)
Arthralgia	90 (43.1)	3 (1.4)	46 (36.8)	2 (1.6)
Vomiting	77 (36.8)	7 (3.3)	40 (32.0)	6 (4.8)
Alopecia	79 (37.8)	0	39 (31.2)	0
Constipation	66 (31.6)	1 (0.5)	34 (27.2)	3 (2.4)
Headache	64 (30.6)	1 (0.5)	34 (27.2)	1 (0.8)
Back pain	56 (26.8)	5 (2.4)	33 (26.4)	6 (4.8)
Hot flush	54 (25.8)	0	29 (23.2)	1 (0.8)
Rash	41 (19.6)	3 (1.4)	27 (21.6)	0
Cough	62 (29.7)	0	26 (20.8)	0
Hypertension	45 (21.5)	36 (17.2)	26 (20.8)	16 (12.8)
Anemia	56 (26.8)	10 (4.8)	24 (19.2)	2 (1.6)
Decreased appetite	50 (23.9)	3 (1.4)	24 (19.2)	2 (1.6)
Neutrophil count decreased	58 (27.8)	48 (23.0)	20 (16.0)	13 (10.4)
White blood cell count decreased	51 (24.4)	39 (18.7)	19 (15.2)	7 (5.6)
Pruritus	47 (22.5)	2 (1.0)	14 (11.2)	0

Figure 5. Time-Varying Cox Regression Analysis of OS by RDI2



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