Hope Rugo
hope.rugo@ucsf.edu

Quality of Life With Ribociclib Plus Aromatase Inhibitor vs Abemaciclib Plus Aromatase Inhibitor as First-line Treatment of HR+/HER2− Advanced Breast Cancer, Assessed via Matching-Adjusted Indirect Comparison (MAIC)

Hope S. Rugo,[1] Joyce O'Shaughnessy,[2] Komal Jhaveri,[3] Sara M. Tolaney,[4] Fatima Cardoso,[5] Aditya Bardia,[6] Purnima Pathak,[7] Sina Haftchenary,[8] Peter A. Fasching[9]

*Presenter: Susie Moroney, PharmD, MS, BCOP

[1]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, USA; [2]Texas Oncology-Baylor University Medical Center and The US Oncology Research Network, Dallas, TX, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Dana Farber Cancer Institute, Boston, MA, USA; [5]Breast Unit, Champalimaud Clinical Centre, Champalimaud Foundation, Lisbon, Portugal; [6]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA; [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [8]Novartis Pharmaceuticals Canada, Montreal, QC, Canada; [9]University Hospital Erlangen, Comprehensive Cancer Center Erlangen–European Metropolitan Region of Nuremberg, and Department of Gynecology and Obstetrics, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany.

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KEY FINDINGS & CONCLUSIONS

- In this MAIC, individual patient data from ML-2 were matched with published data from MON-3
- The results revealed that 1L RIB + AI was associated with better symptom-related QoL compared with 1L ABE + AI in postmenopausal women with HR+/HER2− ABC
  - TTSD analysis significantly favored RIB over ABE in diarrhea, fatigue, appetite loss, and arm symptoms
- It is important to view these results in the context of the findings from a prior survey in which patients treated with CDK4/6 inhibitors identified AEs such as diarrhea (75%), fatigue (74%), and loss of appetite (54%) as having a moderate to severe impact on QoL[3]
- Differences in CDK4/6 inhibitors with respect to their safety profiles, as well as impact on QoL, provide important context for clinical decision-making in HR+/HER2− ABC

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INTRODUCTION

- Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors plus endocrine therapy (ET) are standards of care in the first-line (1L) treatment of patients with hormone receptor–positive/human epidermal growth factor receptor–negative (HR+/HER2−) advanced breast cancer (ABC)
- A statistically significant overall survival (OS) benefit with 1L ribociclib (RIB) + aromatase inhibitor (AI) was recently reported for MONALEESA-2 (ML-2)[1]; final OS results for the MONARCH 3 (MON-3) trial of 1L abemaciclib (ABE) + AI are pending
- These CDK4/6 inhibitors are known to have differences in safety profile related to their differences in target inhibition[2]
- Many adverse events (AEs), even mild, can significantly impact quality of life (QoL)[3]; thus, patient-reported outcomes (PROs) can help inform treatment decisions
- In a multi-country, cross-sectional survey of oncologists, nurses, advocates, and patients, diarrhea, fatigue, and appetite loss were identified as AEs that had a moderate to severe impact on QoL for patients treated with CDK4/6 inhibitors[3]
- While PROs have been reported for many of the Phase III CDK4/6 inhibitor trials in ABC,[4-10] in the absence of head-to-head studies, comparisons of outcomes are difficult
- A matched-adjusted indirect comparison (MAIC) analysis is strongly advocated and employed for indirect comparisons in the absence of a direct head-to-head study
- Here, results of an MAIC comparing QoL with 1L RIB + AI vs ABE + AI in postmenopausal patients with HR+/HER2− ABC are presented
  - The PALOMA-2 trial (palbociclib + AI) assessed different PRO measures than ML-2 and MON-3, and thus, could not be considered for this analysis

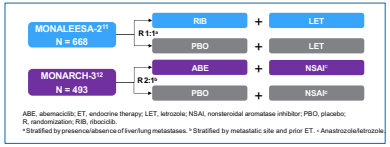
METHODS

- An anchored MAIC of QoL with RIB + AI vs ABE + AI was performed using data from European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and BR23 questionnaires: ML-2 individual patient data (data cutoff: 6/10/21) and published MON-3 data (data cutoff: 11/3/17)
- The EORTC QLQ-C30 is a PRO measure that includes functional scales (physical, social, role, cognitive, and emotional), symptom-related scales (fatigue, nausea/ vomiting, pain, dyspnea, sleep disturbances, appetite loss, constipation, and diarrhea), financial impact, and overall QoL
- The EORTC QLQ-BR23 is a breast cancer–specific module that includes questions on disease symptoms, side effects, body image, and sexual functioning
- All available QoL data were used in this analysis
- The median duration of follow-up at which QoL data were reported for MON-3 was 26.73 months, and the median follow-up for ML-2 was 79.7 months
- Patients enrolled in ML-2 were weighted to match baseline characteristics in the corresponding arms of MON-3
- Hazard ratios (HRs) were calculated using the Cox proportional hazards model, and anchored HRs were generated via the Bucher method
- Time to sustained deterioration (TTSD) was calculated as the time from randomization to a ≥ 10-point deterioration with no additional improvement above this threshold

RESULTS

- ML-2 randomized patients 1:1 to 1L RIB + letrozole (LET) or the placebo (PBO) + LET group, and MON-3 randomized patients 2:1 to 1L ABE + nonsteroidal aromatase inhibitor (NSAI) or the NSAI alone group (**Figure 1**)
- Key enrollment criteria are compared in **Table 1**

Figure 1. Study Designs



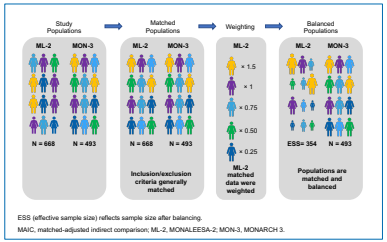
ABE, abemaciclib; ET, endocrine therapy; LET, letrozole; NSAI, nonsteroidal aromatase inhibitor; PBO, placebo; R, randomization; RIB, ribociclib.
[a] Stratified by presence/absence of liver/lung metastases. [b] Stratified by metastatic site and prior ET. [c] Anastrozole/letrozole.

Table 1. Comparison of Key Inclusion/Exclusion Criteria

Parameter	ML-2	MON-3
Inclusions	• Received no systemic treatment for ABC • Have measurable disease as defined by RECIST 1.1 or at least one predominantly lytic bone lesion • TFI > 12 months after prior (neo)adjuvant NSAI[a]	• Received no systemic treatment for ABC • Have measurable disease or nonmeasurable bone-only disease (blastic, lytic, or mixed) as defined by RECIST 1.1 • Have had adequate organ function • TFI > 12 months after any prior (neo) adjuvant ET
Exclusions	• Prior treatment with CDK4/6 inhibitors • Presence of active cardiac disease or history of cardiac dysfunction, including QTcF > 450 msec • Presence of inflammatory breast cancer	• Prior treatment with everolimus or a CDK4/6 inhibitor • Presence of visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis • Presence of inflammatory breast cancer • Evidence or history of CNS metastases

ABC, advanced breast cancer; CDK4/6; cyclin-dependent kinases 4 and 6; CNS, central nervous system; ET, endocrine therapy; NSAI, nonsteroidal aromatase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors; QTcF, corrected QT interval by Fridericia formula; TFI, treatment-free interval.
[a] ML-2 allowed a TFI ≤ 12 months if the (neo)adjuvant therapy was tamoxifen.

Figure 2. MAIC Overview and Attrition

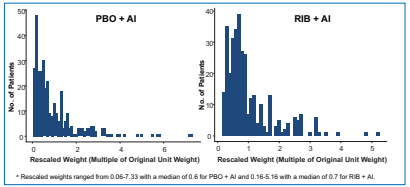


ESS (effective sample size) reflects sample size after balancing.
MAIC, matched-adjusted indirect comparison; ML-2, MONALEESA-2; MON-3, MONARCH 3.

Baseline Characteristics and Weighting

- No baseline characteristics for which data were reported were removed
- Inclusion/exclusion criteria were well balanced after matching and weighting the populations (**Figure 3** and **Table 2**)
- After weighting, the effective sample size was 205 for the RIB arm (a reduction of 39%) and 149 for the PBO arm (a reduction of 55%) (**Figure 2** and **Figure 3**)

Figure 3. Distribution of Weights for Patients in ML-2 Who Matched the Inclusion Criteria for MON-3[a]



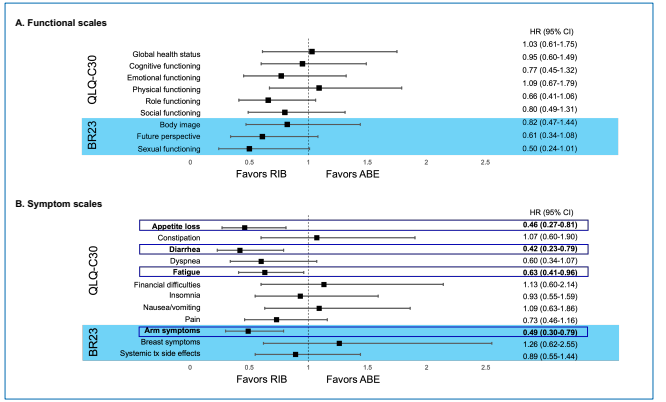
[a] Rescaled weights ranged from 0.09-7.33 with a median of 0.6 for PBO + AI and 0.16-5.16 with a median of 0.7 for RIB + AI.

Table 2. Baseline Characteristics (Unmatched and Matched)

Characteristics	Value	Unmatched				Matched			
		ML-2		MON-3		ML-2		MON-3	
		RIB+AI	PBO+AI	ABE+AI	PBO+AI	RIB+AI	PBO+AI	ABE+AI	PBO+AI
Patients	n	334	334	328	165	205	149	328	165
Age (median), years		62	63	63	63	63	63	63	63
Race, %	Caucasian	80.5	83.8	56.7	61.8	56.7	61.8	56.7	61.8
	Others	19.5	16.2	43.3	38.2	43.3	38.2	43.3	38.2
ECOG PS, %	1	38.9	39.5	41.5	37.0	41.5	37.0	41.5	37.0
	0	61.1	60.5	58.5	63.0	58.5	63.0	58.5	63.0
De novo mets disease, %	Yes	34.1	33.8	41.2	37.0	41.2	37.0	41.2	37.0
	No	65.9	66.2	58.8	63.0	58.8	63.0	58.8	63.0
PR status, %	Negative	16.5	14.7	21.3	21.8	21.3	21.8	21.3	21.8
	Positive	81.1	83.2	77.7	77.0	77.7	77.0	77.7	77.0
Metastatic site, %	Visceral	56.6	57.8	52.7	53.9	52.7	53.94	52.7	53.9
	Bone only	20.7	23.4	21.0	24.2	21.0	24.24	21.0	24.2
	Other	22.8	18.9	26.2	21.8	26.2	21.82	26.2	21.8
Prior (neo)adj chemotherapy, %	Yes	43.7	43.4	38.1	40.0	38.1	40.0	38.1	40.0
	No	56.3	56.6	61.9	60.0	61.9	60.0	61.9	60.0
ET, %	Prior AI	34.1	32.9	25.9	30.3	25.9	30.3	25.9	30.3
	Other prior ET	24.9	24.6	20.1	18.2	20.1	18.2	20.1	18.2
	No prior ET	41.0	42.5	54.0	51.5	54.0	51.5	54.0	51.5
Measurable disease, %	Yes	77.5	73.4	81.4	80.0	81.4	80.0	81.4	80.0
	No	22.5	26.6	18.6	20.0	18.6	20.0	18.6	20.0
No. of organs at baseline, %	3+	34.1	33.5	46.3	47.3	46.3	47.3	46.3	47.3
	2	35.3	31.1	23.5	24.8	23.5	24.8	23.5	24.8
	1	29.9	35.0	29.9	27.3	29.9	27.3	29.9	27.3

ABE, abemaciclib; AI, aromatase inhibitor; ECOG, PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; ML-2, MONALEESA-2; MON-3, MONARCH-3; PBO, placebo; PR, progesterone receptor; RIB, ribociclib.

Figure 4. Time to Sustained Deterioration in Functional (A) and Symptom (B) Scales



RIB + AI Was Associated With Better Symptom-Related QoL vs ABE + AI

- While no significant differences were noted in any of the EORTC QLQ-C30 or BR23 functional domains, TTSD analysis numerically favored RIB over ABE in emotional (HR, 0.77 [95% CI, 0.45-1.32]), role (HR, 0.66 [95% CI, 0.41-1.06]), and social (HR, 0.80 [95% CI, 0.49-1.31]) functioning as well as body image (HR, 0.82 [95% CI, 0.47-1.44]), future perspective (HR, 0.61 [95% CI, 0.34-1.08]), and sexual functioning (HR, 0.50 [95% CI, 0.24-1.01]) (**Figure 4A**)
- TTSD analysis significantly favored RIB over ABE in 4 symptom scales (**Figure 4B**): appetite loss (HR, 0.46 [95% CI, 0.27-0.81]), diarrhea (HR, 0.42 [95% CI, 0.23-0.79]), fatigue (HR, 0.63 [95% CI, 0.41-0.96]), and arm symptoms (includes pain in arm or shoulder, swollen arm or hand, and difficulty in raising arm) (HR, 0.49 [95% CI, 0.30-0.79])
- Notably, TTSD analysis did not significantly favor ABE over RIB in any functional or symptom scale of the QLQ-C30 or BR23

Caveats and Limitations

- While cross-trial comparisons have inherent limitations due to differences in study designs and patient populations, MAIC helps to correct for some of these differences, unlike unadjusted indirect comparison
- Only published patient characteristics for the MON-3 trial were controlled for in the MAIC analysis; thus, results may be confounded by any unreported factors
- Interpretation of these results is limited to the subset of patients in ML-2 who were matched to patients in MON-3
- Global health status (GHS) assessed in the EORTC QLQ-C30 is not an aggregate score of the different functional or symptomatic scales; thus, the GHS and specific domains are not directly linked

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