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# Impact of Body Mass Index on the Safety and Efficacy of Ribociclib in Patients With HR+/HER2− Advanced Breast Cancer: Pooled Analysis of the MONALEESA-2, -3, and -7 Trials

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## KEY FINDINGS & CONCLUSIONS

- This pooled analysis demonstrated that RIB + ET vs PBO + ET improved progression-free survival and overall survival in patients with HR+/HER2− advanced breast cancer, regardless of BMI
- Patients with a BMI of ≥25 kg/m$^2$ experienced a lower incidence and severity of neutropenia, had fewer RIB dose reductions and interruptions, and had longer time to first dose reduction and drug discontinuation vs those with a BMI of <25 kg/m$^2$
- This study provides additional evidence for the benefit of RIB + ET in patients with HR+/HER2− advanced breast cancer across BMI categories

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Previously presented at San Antonio Breast Cancer Symposium, Final Publication Number: P2-09-20, Yoon Sim Yap, et al. - Reused with permission.

Poster presented at: 2025 NCODA International Spring Forum; April 23-25; Aurora, Colorado.
This study is sponsored by Novartis Pharma AG.

## INTRODUCTION

- Studies evaluating the relationship between body mass index (BMI) and outcomes in breast cancer have had conflicting results[1]
- While some studies have found a higher BMI to be associated with lower treatment efficacy in early breast cancer, the same relationship may not exist in advanced breast cancer (ABC)[1]
- To date, few studies have examined the effect of BMI on outcomes in patients receiving cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) + endocrine therapy (ET), which is the recommended standard of care in first-line treatment of HR+/HER2− ABC[2-4]
- The individual MONALEESA (ML)-2, ML-3, and ML-7 clinical trials of ribociclib (RIB) have shown consistent benefit with RIB + ET vs ET alone in patients with HR+/HER2− ABC[5-10]
- The purpose of this pooled analysis is to examine the effect of BMI on the efficacy and safety of first-line RIB + ET in patients with HR+/HER2− ABC in the ML trials

## METHODS

- ML-2, ML-3, and ML-7 are phase 3, randomized, placebo (PBO)-controlled studies evaluating the efficacy of RIB 600 mg + ET (letrozole, fulvestrant, or anastrozole) in patients with HR+/HER2− ABC (**Figure 1**)
- Patients treated with tamoxifen in ML-7 or those with early relapse (≤12 months after [neo]adjuvant ET) in any of the ML studies were excluded from this analysis
- Due to similar efficacy across BMI groups (25 to <30 and ≥30 kg/m$^2$) and the small number of underweight patients, this analysis categorized patients into 2 BMI groups: <25 (underweight + normal weight) and ≥25 (overweight + obese)
- For this pooled analysis, progression-free survival (PFS) and overall survival (OS) were evaluated between treatment arms, stratified by study and liver/lung metastases, using Kaplan-Meier methods
- The first subsequent therapy after disease progression was evaluated in each BMI group in the RIB treatment arm
- Safety and tolerability outcomes, including the frequency of adverse events (AEs) and RIB dose reductions, dose interruptions, and discontinuations, were also assessed

**Figure 1. Study Designs of the ML-2, ML-3, and ML-7 Trials**


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

## RESULTS

### Baseline Characteristics

- Of the 1190 patients (RIB, n = 655; PBO, n = 535), 484 (41%) had a BMI of <25 kg/m$^2$ (underweight, 6%; normal weight, 94%), and 706 (59%) had a BMI of ≥25 kg/m$^2$ (overweight, 55%; obese, 45%) (**Table 1**)
- Median follow-up was 79.8, 70.8, and 54.4 months in ML-2, -3, and -7, respectively
- Baseline characteristics were generally well balanced between treatment arms within each BMI subgroup
- Numerical differences between BMI groups were noted for race, age, region, and metastatic sites, with the BMI <25 group having more Asian patients and liver metastases and fewer White patients

**Table 1. Demographics and Baseline Characteristics**

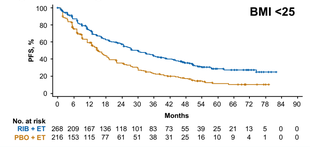
| | BMI <25 | | BMI ≥25 | |
|---|---|---|---|---|
| | RIB (n = 268) | PBO (n = 216) | RIB (n = 387) | PBO (n = 319) |
| **Median age (range), y** | 56.0 (23-91) | 56.0 (29-88) | 62.0 (28-85) | 61.0 (29-87) |
| **Menopausal status, n (%)[a]** | | | | |
| Premenopausal | 79 (29.5) | 71 (32.9) | 61 (15.8) | 57 (17.9) |
| Postmenopausal | 173 (64.6) | 129 (59.7) | 311 (80.4) | 244 (76.5) |
| **Race, n (%)** | | | | |
| Asian | 63 (23.5) | 59 (27.3) | 41 (10.6) | 25 (7.8) |
| Black | 2 (0.7) | 3 (1.4) | 12 (3.1) | 11 (3.4) |
| White | 182 (67.9) | 141 (65.3) | 300 (77.5) | 262 (82.1) |
| Other/unknown | 21 (7.8) | 13 (6.0) | 34 (8.8) | 21 (7.9) |
| **Region, n (%)** | | | | |
| Asia | 60 (22.4) | 52 (24.1) | 36 (9.3) | 21 (6.6) |
| Europe and Australia | 138 (51.5) | 105 (48.6) | 186 (48.1) | 157 (49.2) |
| Latin America | 8 (3.0) | 6 (2.8) | 12 (3.1) | 13 (4.1) |
| North America | 46 (17.2) | 43 (19.9) | 116 (30.0) | 89 (27.9) |
| Other | 16 (6.0) | 10 (4.6) | 37 (10.6) | 39 (12.2) |
| **Advanced disease status, n (%)** | | | | |
| De novo | 102 (38.1) | 89 (41.2) | 169 (43.7) | 131 (41.1) |
| Non de novo | 166 (61.9) | 127 (58.8) | 218 (56.3) | 188 (58.9) |
| **Metastatic sites, n (%)** | | | | |
| Lung | 107 (39.9) | 78 (36.1) | 152 (39.3) | 122 (38.2) |
| Liver | 71 (26.5) | 58 (26.9) | 65 (16.8) | 54 (16.9) |
| Lung or liver | 150 (56.0) | 115 (53.2) | 186 (48.1) | 158 (49.5) |
| Central nervous system | 1 (0.4) | 1 (0.5) | 3 (0.8) | 0 |
| Other | 38 (14.2) | 31 (14.4) | 52 (13.4) | 34 (10.7) |
| Bone only | 50 (18.7) | 41 (19.0) | 85 (22.0) | 76 (23.8) |

[a] Totals may not equal 100% as some patients were sterile and of childbearing age, but menopausal status was not known

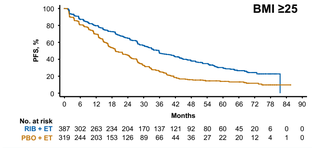
### Efficacy: Progression-Free Survival

- A consistent PFS benefit with RIB + ET vs PBO + ET was observed across both BMI groups (**Figure 2**)
  - RIB + ET prolonged median PFS by 15.1 months in patients with a BMI of <25 and 16.3 months in patients with a BMI of ≥25 compared with PBO + ET
  - There was a 44% relative reduction in risk of progression with RIB + ET vs ET alone in both BMI groups

**Figure 2. Progression-Free Survival Between Treatment Arms**




| | RIB + ET | PBO + ET |
|---|---|---|
| Events/n | 152/268 | 164/216 |
| PFS, median, months | 30.1 | 15.0 |
| **Hazard ratio (95% CI)** | **0.56 (0.44-0.70)** | |

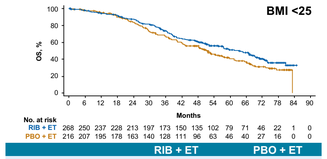



| | RIB + ET | PBO + ET |
|---|---|---|
| Events/n | 226/387 | 248/319 |
| PFS, median, months | 35.7 | 19.4 |
| **Hazard ratio (95% CI)** | **0.56 (0.47-0.68)** | |

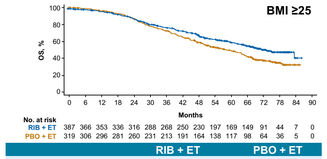
### Efficacy: Overall Survival

- An OS benefit with RIB + ET vs PBO + ET was observed across both BMI groups (**Figure 3**)
  - RIB + ET prolonged median OS by 12.0 months in patients with BMI <25 and 16.3 months in patients with BMI ≥25 compared with PBO + ET
  - There was a 23% and 30% reduction in mortality risk with RIB + ET vs PBO + ET in the BMI <25 and BMI ≥25 groups, respectively

**Figure 3.Overall survival Between Treatment Arms**




| | RIB + ET | PBO + ET |
|---|---|---|
| Events/n | 134/268 | 123/216 |
| OS, median, months | 63.4 | 51.4 |
| **Hazard ratio (95% CI)** | **0.77 (0.60-0.98)** | |




| | RIB + ET | PBO + ET |
|---|---|---|
| Events/n | 164/387 | 182/319 |
| OS, median, months | 73.9 | 57.6 |
| **Hazard ratio (95% CI)** | **0.70 (0.57-0.87)** | |

### Subsequent Therapy

- In the RIB + ET arm, the most common first subsequent treatment was ET alone in both groups (**Table 2**)
  - More patients in the BMI <25 group received subsequent chemotherapy
  - More patients in the BMI ≥25 group received targeted therapy ± ET and CDK4/6 inhibitors ± ET

**Table 2. First Subsequent Treatment in the Ribociclib Arm**

| Subsequent treatment, n (%)[a] | BMI <25 (n = 268) | BMI ≥25 (n = 387) |
|---|---|---|
| Received subsequent therapy | 181 (67.5) | 268 (69.3) |
| Chemotherapy | 59 (32.6) | 70 (26.1) |
| Endocrine therapy alone | 69 (38.1) | 107 (39.9) |
| Targeted therapy ± endocrine therapy | 46 (25.4) | 81 (30.2) |
| CDK4/6i ± endocrine therapy | 21 (11.6) | 44 (16.4) |
| Ribociclib ± endocrine therapy | 5 (2.8) | 15 (5.6) |
| Everolimus ± endocrine therapy | 20 (11.0) | 28 (10.4) |
| Others | 7 (3.9) | 10 (3.7) |

[a] Percentages in subsequent therapy groups are calculated based on the number of patients who received a first subsequent therapy.

### Safety in the Ribociclib Treatment Arm

- Lower rates of all-grade (G) and G3/4 neutropenia were observed in patients with BMI ≥25 vs <25 (**Table 3**)
- The rates of liver-related AEs and QT interval prolongation were similar between BMI groups (**Table 4**)
  - Rates of infections were higher in the BMI ≥25 group vs the BMI <25 group (66.1% vs. 53.0%, respectively), while neutropenia was lower in the BMI ≥25 group (71.1% vs. 84.7%, respectively)
- Dose reductions and interruptions due to AEs were less frequent in the BMI ≥25 vs BMI <25 group (**Table 5**)
- Longer median time to first dose reduction (23.3 vs 9.5 months) and time to drug discontinuation (26.0 vs 19.9 months) were observed in patients in the BMI ≥25 vs BMI <25 group with RIB (**Figure 4**)
  - The AEs leading to discontinuation were primarily ALT and AST elevation in both BMI groups (**Table 6**)
- Median relative ribociclib dose intensity was 91.9% and 81.8% in the BMI ≥25 and <25 groups, respectively

**Table 3. Adverse Events in the Ribociclib Arm (≥30% in Either BMI Group)**

| Safety set, n (%) Preferred terms[a] | BMI <25 (n = 268) | | BMI ≥25 (n = 387) | |
|---|---|---|---|---|
| | All grade | Grade 3/4 | All grade | Grade 3/4 |
| Total | 265 (98.9) | 241 (89.9) | 381 (98.4) | 321 (82.9) |
| Neutropenia | 183 (68.3) | 162 (60.4) | 216 (55.8) | 170 (43.9) |
| Nausea | 124 (46.3) | 7 (2.6) | 197 (50.9) | 3 (0.8) |
| Arthralgia | 96 (35.8) | 2 (0.7) | 168 (43.4) | 5 (1.3) |
| Diarrhea | 94 (35.1) | 5 (1.9) | 149 (38.5) | 12 (3.1) |
| Fatigue | 84 (31.3) | 3 (1.1) | 162 (41.9) | 10 (2.6) |
| Vomiting | 83 (31.0) | 10 (3.7) | 119 (30.7) | 8 (2.1) |

[a] Terms from Medical Dictionary for Regulatory Activities (MedDRA) 24.1.

**Table 4. Adverse Events of Special Interest in the Ribociclib Arm**

| Safety set, n (%) Grouped terms[a,b] | BMI <25 (n=268) | | BMI ≥25 (n=387) | |
|---|---|---|---|---|
| | All grade | Grade 3/4 | All grade | Grade 3/4 |
| **Hematologic AESI** | | | | |
| Neutropenia | 227 (84.7) | 203 (75.7) | 275 (71.1) | 224 (57.9) |
| Leukopenia | 93 (34.7) | 58 (21.6) | 125 (32.3) | 68 (17.6) |
| Anemia | 48 (17.9) | 10 (3.7) | 78 (20.2) | 12 (3.1) |
| Thrombocytopenia | 23 (8.6) | 1 (0.4) | 35 (9.0) | 2 (0.5) |
| **Nonhematologic AESI** | | | | |
| Infections | 142 (53.0) | 13 (4.9) | 256 (66.1) | 39 (10.1) |
| Liver-related AEs | 78 (29.1) | 33 (12.3) | 117 (30.2) | 57 (14.7) |
| Renal toxicity | 18 (6.7) | 2 (0.7) | 59 (15.2) | 5 (1.3) |
| QT interval prolongation | 29 (10.8) | 10 (3.7) | 38 (9.8) | 17 (4.4) |
| Interstitial lung disease | 4 (1.5) | 2 (0.7) | 9 (2.3) | 2 (0.5) |
| Reproductive toxicity | 2 (0.7) | 0 | 3 (0.8) | 1 (0.3) |

AESI, adverse events of special interest.
[a] Terms from MEDRA 24.1.
[b] AESI terms in this table are grouped terms. The full list of the preferred term for each AESI can be found in the supplemental table via the QR code.

**Table 5. Ribociclib Dose Modifications Due to AEs**

| Safety set, n (%) | BMI <25 (n = 268) | BMI ≥25 (n = 387) |
|---|---|---|
| Patients with ≥1 RIB interruption due to AEs | 215 (80.2) | 276 (71.3) |
| Patients with ≥1 RIB reduction due to AEs | 148 (55.2) | 157 (40.6) |

**Figure 4.Time to Ribociclib Discontinuation**

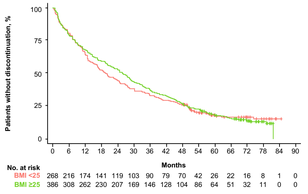



**Table 6. AEs Leading to Ribociclib Discontinuation**

| Safety set, n (%) | BMI <25 (n = 268) | BMI ≥25 (n = 387) |
|---|---|---|
| All AEs[a] | 48 (17.9) | 73 (18.9) |
| ALT[b] increased | 12 (4.5) | 22 (5.7) |
| AST[c] increased | 8 (3.0) | 10 (2.6) |
| Vomiting | 4 (1.5) | 6 (1.6) |
| Neutropenia | 3 (1.1) | 2 (0.5) |

[a] Reported values are for all-grade AEs
[b] Alanine Aminotransferase (ALT)
[c] Aspartate Aminotransferase (AST)

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### Acknowledgments

The authors thank the patients enrolled in these studies and their families, as well as the study investigators. Medical editorial assistance was provided by Nucleus Global and was funded by Novartis Pharmaceuticals Corporation. The authors had final responsibility for the poster.

### Disclosures

Y.-S. Yap reports personal fees and travel support from Lilly/DKSH, AstraZeneca, MSD, Daiichi Sankyo; personal fees from Novartis, Pfizer, Eisai, MSD, Roche; grants from MSD. A. LeVee has nothing to disclose. M. Campone reports grants to institute from Pfizer, AstraZeneca, Sanofi, Gilead, Novartis, Lilly, AbbVie, Servier, Sandoz, Accord. S. Kummel reports personal fees from Roche, Celgene, Novartis, AstraZeneca, Pfizer, Lilly, Amgen, Somatex, Daiichi Sankyo, PFM Medical, MSD Oncology, SonoScape, Gilead Sciences, Agendia; travel support from Roche, Daiichi Sankyo; uncompensated relationship with WSG. Y.H. Park reports grants and personal fees from MSD, Pfizer, Roche, AstraZeneca; grants from Gencurix, Genome Insight; personal fees from Novartis, Daiichi Sankyo, Gilead, Lilly; nonfinancial support from Pfizer, Roche. Y.-S. Lu reports grants and personal fees from Novartis, Merck Sharp & Dohme, Pfizer, AstraZeneca; personal fees from Novartis, Roche, Merck Sharp & Dohme, Pfizer, AstraZeneca, Eisai, Eli Lilly, Daiichi Sankyo. V. Stearns has nothing to disclose. F. Cardoso reports personal fees from Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, GE Oncology, Genentech, GSK, MacroGenics, Medscape, Merck-Sharp, Merus, Mylan, Mundipharma, Novartis, Pfizer, Pierre Fabre, Prime Oncology, Roche, Sanofi, Samsung Bioepis, Teva, Seagen, Debiopharm, Gilead, IQVIA, touchIME. E. Winer has nothing to disclose. M. Gao, G. Sopher, and Y. Chattar report employment and stock ownership from Novartis. J. Mortimer has nothing to disclose.