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Sara A. Hurvitz | shurvitz@fredhutch.org

# Five-Year Analysis of Distant Disease-Free Survival Across Key Subgroups From The Phase 3 NATALEE Trial of Ribociclib Plus a Nonsteroidal Aromatase Inhibitor in Patients with HR+/HER2− Early Breast Cancer

Sara Hurvitz,[1] Michal Jarzab,[2] Alistair Ring,[3] Priyanka Sharma,[4] Ionut Temciuc,[5] Huilin Hu,[6] Murat Akdere,[7] Juan Pablo Zarate,[6] Denise A. Yardley[8]

[1]University of Washington, Fred Hutchinson Cancer Center, Seattle, WA, USA; [2]Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland; [3]Royal Marsden Hospital NHS Foundation Trust, Surrey, UK; [4]University of Kansas Medical Center, Westwood, KS, USA; [5]Translational Research in Oncology, Edmonton, AB, Canada; [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [7]Novartis Pharma AG, Basel, Switzerland; [8]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA

## KEY FINDINGS & CONCLUSIONS

- This prespecified 5-year landmark analysis in NATALEE demonstrated that the combination of RIB + NSAI consistently reduced distant recurrence in patients with HR+/HER2− EBC
  - The DDFS and DRFS benefit with RIB + NSAI in the ITT population was improved with all patients off RIB treatment for a median of 2 years
  - The DDFS benefit with RIB + NSAI was improved compared with the prespecified 3-year NATALEE analysis across most key subgroups, including patients with high-risk N0 disease
- These findings support the use of adjuvant RIB + NSAI to reduce distant recurrence risk in NATALEE-eligible high-risk HR+/HER2− EBC patient population
- Additional follow-up data from NATALEE will further elucidate the potential of RIB to reduce late recurrences in the heterogeneous population of patients with high-risk HR+/HER2− EBC

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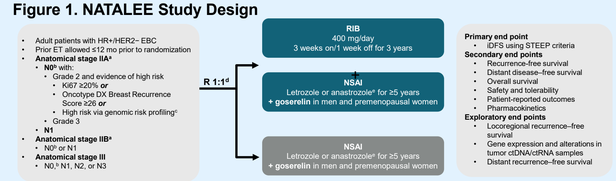
## INTRODUCTION

- For patients with hormone receptor–positive (HR+) early breast cancer (EBC), distant recurrence remains a significant concern as metastatic breast cancer is still considered incurable[1,2]
- As risk of distant recurrence depends on different disease features, assessing the impact of current adjuvant treatments on distant disease recurrence across patient subgroups, including by stage or nodal status, is relevant to treatment selection
- The phase 3 NATALEE trial reported distant disease–free survival (DDFS) benefit with ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) vs NSAI alone in patients with stage II/III HR+/human epidermal growth factor receptor 2–negative (HER2−) EBC[3]
  - The DDFS benefit with RIB + NSAI vs NSAI alone was maintained with additional follow-up (hazard ratio [HR], 0.749 [95% CI: 0.623-0.900])[4,5]
  - Distant recurrence–free survival (DRFS) benefit with RIB + NSAI was also observed in the intent-to-treat (ITT) population[5]
- We report overall DDFS and DRFS as well as DDFS across clinically relevant subgroups from the prespecified 5-year landmark analysis of the NATALEE trial

## METHODS

- In the NATALEE trial, patients underwent 1:1 randomization to receive RIB (400 mg/day; 3 weeks on/1 week off for 3 years) + NSAI (anastrozole 1 mg/day or letrozole 2.5 mg/day for 5 years) or NSAI alone (**Figure 1**)
  - In both treatment arms, men and premenopausal women also received goserelin
- Eligible patients had anatomical stage IIA (node negative [N0] with additional risk factors or N1 [1-3 axillary lymph nodes]), IIB, or III disease as defined by the American Joint Committee on Cancer guidelines, 8th ed.
- DDFS, as defined by Standardized Definitions for Efficacy End Points (STEEP) version 1.0 criteria, was assessed as a secondary endpoint in the ITT population and across subgroups of anatomical stage, nodal status, menopausal status, Ki67 score, age, and prior endocrine therapy (ET) duration[6]
- DRFS, which does not include second primary invasive non–breast cancers, as defined by STEEP 1.0 criteria, was assessed as an exploratory endpoint in the ITT population[6]

### Figure 1. NATALEE Study Design




[a] Enrollment of patients with stage II disease was capped at 40%. [b] N0 was evaluated at diagnosis and after surgery, and the worse of the two findings was used in staging. [c] Genomic high risk is defined as at least one of the following: Oncotype DX Breast Recurrence Score ≥26, Prosigna PAM50 score of high risk, or EndoPredict EPclin Risk Score of high risk. [d] Open-label design. [e] Per investigator choice.
ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; HER2, human epithelial growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease–free survival; N2, 4-9 axillary lymph nodes; N3, ≥10 axillary lymph nodes or collarbone lymph nodes; NSAI, nonsteroidal aromatase inhibitor; PAM50, Prediction Analysis of Microarray 50; R, randomized; RIB, ribociclib; STEEP, Standardized Definitions for Efficacy End Points.

## RESULTS

### Sites of Distant Recurrences

- The most common sites of distant recurrence were bone, liver, lung/pleura, and distant lymph nodes, with fewer events observed with RIB + NSAI vs NSAI alone across all sites (**Table 1**)

**Table 1. Sites of Distant Recurrence in NATALEE**

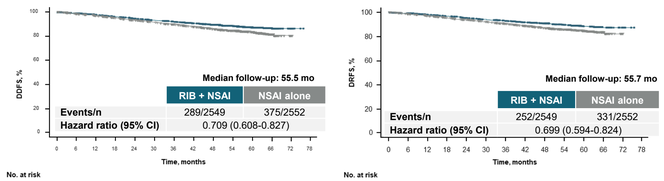
| Site of DDFS recurrence event, n (%)[a,b] | RIB + NSAI n = 2549 | NSAI alone n = 2552 | Total N = 5101 |
|---|---|---|---|
| Number of patients with distant recurrence DDFS events[a] | 212 | 304 | 516 |
| Bone | 128 (5.0) | 171 (6.7) | 299 (5.9) |
| Liver | 65 (2.6) | 92 (3.6) | 157 (3.1) |
| Lung/pleura | 45 (1.8) | 69 (2.7) | 114 (2.2) |
| Distant lymph nodes | 36 (1.4) | 46 (1.8) | 82 (1.6) |
| Central nervous system | 19 (0.7) | 20 (0.8) | 39 (0.8) |
| Other | 15 (0.6) | 18 (0.7) | 33 (0.6) |

[a] Excluding death and second primary non–breast cancer. [b] Patients may have had multiple DDFS recurrence sites counted in the table, but distant recurrence was counted only once per patient.
DDFS, distant disease–free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

### Distant Recurrences in the ITT Population

- At the updated data cutoff of May 28, 2025, with all patients off RIB treatment for a median of 2 years, RIB + NSAI demonstrated a DDFS benefit in the ITT population (median duration of follow-up for DDFS, 55.5 months) (**Figure 2**)
  - DRFS benefit with RIB + NSAI vs NSAI alone (HR, 0.699 [95% CI: 0.594-0.824]) was also observed in the ITT population

**Figure 2. DDFS and DRFS in the NATALEE ITT Population**




### DDFS by Anatomical Stage

- RIB + NSAI improved DDFS over NSAI alone across all anatomical stage groups (**Figure 3**)
- Absolute DDFS benefit with RIB + NSAI over NSAI alone showed improvements from 3 to 5 years, regardless of anatomic stage (**Table 2**)

**Figure 3. DDFS by Anatomical Stage in NATALEE**

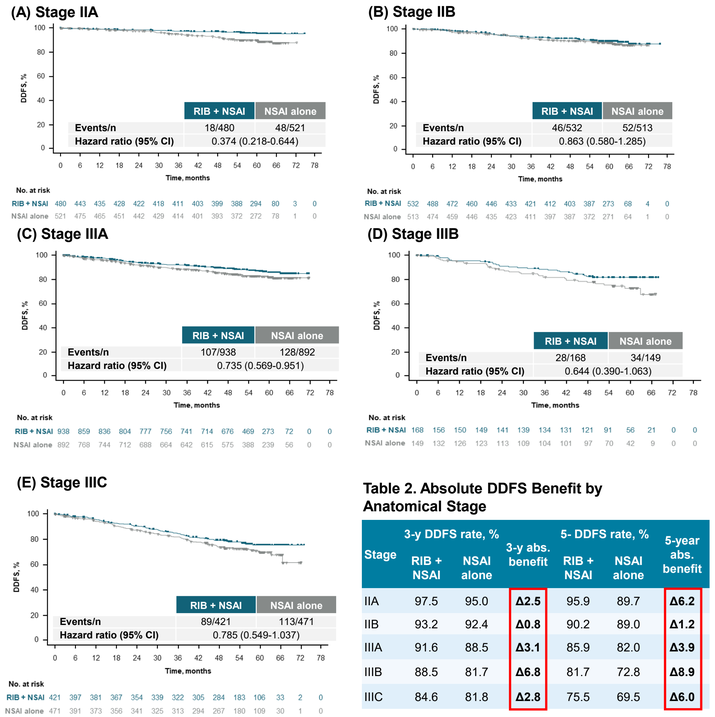



**Table 2. Absolute DDFS Benefit by Anatomical Stage**

| Stage | 3-y DDFS rate, % RIB + NSAI | 3-y DDFS rate, % NSAI alone | 3-y abs. benefit | 5- DDFS rate, % RIB + NSAI | 5- DDFS rate, % NSAI alone | 5-year abs. benefit |
|---|---|---|---|---|---|---|
| IIA | 97.5 | 95.0 | **Δ2.5** | 95.9 | 89.7 | **Δ6.2** |
| IIB | 93.2 | 92.4 | **Δ0.8** | 90.2 | 89.0 | **Δ1.2** |
| IIIA | 91.6 | 88.5 | **Δ3.1** | 85.9 | 82.0 | **Δ3.9** |
| IIIB | 88.5 | 81.7 | **Δ6.8** | 81.7 | 72.8 | **Δ8.9** |
| IIIC | 84.6 | 81.8 | **Δ2.8** | 75.5 | 69.5 | **Δ6.0** |

### DDFS by Nodal Status

- The DDFS benefit was consistent regardless of nodal status and increased from 3 to 5 years (**Figure 4, Table 3**)

**Figure 4. DDFS by Nodal Status in NATALEE**

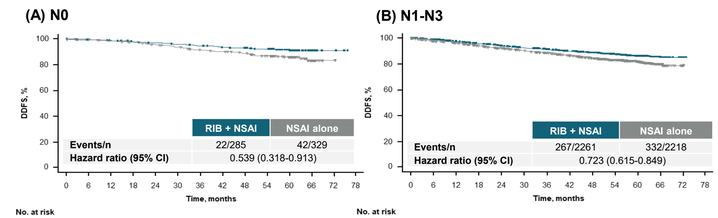



**Table 3. Absolute DDFS Benefit by Nodal Status**

| Subgroup | 3-y DDFS rate, % RIB + NSAI | 3-y DDFS rate, % NSAI alone | 3-y abs. benefit | 5-y DDFS rate, % RIB + NSAI | 5-y DDFS rate, % NSAI alone | 5-y abs. benefit |
|---|---|---|---|---|---|---|
| Nodal status | | | | | | |
| N0 | 94.6 | 91.5 | **Δ3.1** | 91.6 | 85.8 | **Δ5.8** |
| N1-N3 | 91.3 | 88.8 | **Δ2.5** | 86.1 | 82.0 | **Δ4.1** |

### DDFS by Menopausal Status, Ki67 Status, Age Group, and Prior ET Duration

- RIB + NSAI showed consistent DDFS benefits regardless of menopausal status, Ki67 status, age, and prior duration of ET, with increasing absolute benefits from 3 to 5 years across most subgroups (**Table 4**)

**Table 4. DDFS by Menopausal Status, Ki67 Status, Age Group, and Prior ET Duration in NATALEE**

| Subgroup | Events/n RIB + NSAI | Events/n NSAI alone | 3-y DDFS rate, % RIB + NSAI | 3-y DDFS rate, % NSAI alone | 3-y abs. benefit | 5-y DDFS rate, % RIB + NSAI | 5-y DDFS rate, % NSAI alone | 5-y abs. benefit | HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| Menopausal status | | | | | | | | | |
| Premenopausal[a] | 110/1126 | 147/1132 | 92.8 | 90.0 | **Δ2.8** | 88.5 | 84.4 | **Δ4.1** | 0.685 (0.535-0.877) |
| Postmenopausal | 179/1423 | 228/1420 | 90.7 | 88.4 | **Δ2.3** | 85.4 | 81.0 | **Δ4.4** | 0.725 (0.596-0.882) |
| Ki67 score | | | | | | | | | |
| ≤20 | 118/1200 | 166/1241 | 92.8 | 90.5 | **Δ2.3** | 88.5 | 84.2 | **Δ4.3** | 0.691 (0.545-0.875) |
| >20 | 126/919 | 157/932 | 89.9 | 87.3 | **Δ2.6** | 84.6 | 79.8 | **Δ4.8** | 0.725 (0.572-0.918) |
| Age | | | | | | | | | |
| <40 y | 31/250 | 44/293 | 92.3 | 86.8 | **Δ5.5** | 85.5 | 80.5 | **Δ5.0** | 0.650 (0.409-1.032) |
| ≥40 y | 258/2299 | 331/2259 | 91.6 | 89.4 | **Δ2.2** | 86.9 | 82.7 | **Δ4.2** | 0.717 (0.610-0.844) |
| <65 y | 237/2142 | 298/2186 | 91.8 | 89.7 | **Δ2.1** | 87.2 | 83.7 | **Δ3.5** | 0.743 (0.626-0.881) |
| ≥65 y | 52/407 | 77/366 | 90.8 | 85.7 | **Δ5.1** | 84.7 | 75.4 | **Δ9.3** | 0.572 (0.402-0.815) |
| Prior ET | | | | | | | | | |
| <12 weeks | 78/748 | 102/718 | 92.4 | 89.7 | **Δ2.7** | 87.7 | 83.2 | **Δ4.5** | 0.664 (0.494-0.893) |
| ≥12 but <26 weeks | 79/651 | 92/664 | 91.4 | 89.3 | **Δ2.1** | 85.4 | 83.4 | **Δ2.0** | 0.813 (0.601-1.099) |
| ≥26 weeks | 40/358 | 55/353 | 92.5 | 89.5 | **Δ3.0** | 87.5 | 80.7 | **Δ6.8** | 0.666 (0.401-1.005) |

[a] Also includes men.

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