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# Impact of ribociclib dose reduction on efficacy in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative early breast cancer in NATALEE

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## KEY FINDINGS & CONCLUSIONS

- This post hoc exploratory analysis of the NATALEE trial suggests that the clinical benefit of ribociclib is maintained despite dose reduction in patients with HR+/HER2− EBC
  - Ribociclib dose reduction occurred early in treatment and most commonly due to an AE
  - Analysis of iDFS by RDI demonstrated that the RDI of ribociclib did not impact iDFS benefit
    - Consistent results were observed after adjusting for patients who discontinued ribociclib earlier than 36 months
      - The adjusted analysis was focused on RDI and does not address the impact of ribociclib duration on efficacy
    - Additional analysis (RDI2) to address immortal time bias supported these results
  - Landmark analysis of dose reduction (yes, no) further supported similar iDFS regardless of ribociclib dose reduction
- The majority of patients who discontinued ribociclib did so without prior dose reduction, suggesting that there may be opportunities for dose reduction in these patients to keep them on treatment
- The results of this analysis suggest that it may be possible to implement a dose reduction of ribociclib to 200 mg/day when needed to manage AEs without compromising treatment efficacy for patients with HR+/HER2− EBC

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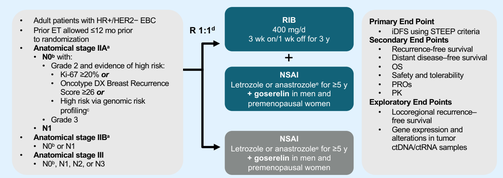
## INTRODUCTION

- The phase III NATALEE trial showed a statistically significant and clinically meaningful invasive disease-free survival (iDFS) benefit with ribociclib + a nonsteroidal aromatase inhibitor (NSAI) vs NSAI alone in patients with stage II/III HR+/HER2− EBC that deepened even after all patients stopped ribociclib (HR, 0.715; 95% CI, 0.609-0.840; median follow-up, 44.2 months)[1,2]
  - Patients in NATALEE were treated with 400 mg/day starting dose of ribociclib; however, dose modification to manage AEs was allowed, including reduction of ribociclib from 400 mg/day to 200 mg/day[1]
  - Ribociclib has received FDA approval for adjuvant treatment of patients with stage II/III HR+/HER2− EBC at risk for recurrence[3]
- Using a prior data cut, (data cutoff: 21 July 2023; median follow-up, 33.3 months) analysis of iDFS for NATALEE participants with or without dose reduction, according to time to dose reduction, showed that ribociclib dose reduction due to adverse events (AEs) did not impact efficacy[4]
- In this exploratory NATALEE analysis using the most recent data cut, we analyzed patients with or without ribociclib dose reduction and the impact of relative dose intensity on efficacy

## METHODS

- Patients were randomized 1:1 to RIB 400 mg/d (3 weeks on/1 week off for 3 years) + NSAI (≥5 years) or NSAI alone in the NATALEE trial; men and premenopausal women also received goserelin (**Figure 1**)

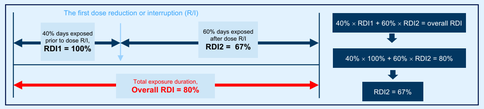
### Figure 1. NATALEE Study Design




[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," MammaPrint score of "High Risk," EndoPredict EPclin Risk score of "High Risk". [d] Open-label design. [e] Per investigator choice.
cfDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease–free survival; N0, no nodal involvement/node-negative; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, ≥10 axillary lymph nodes or collarbone lymph nodes; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in adjuvant breast cancer trials.

- For the management of AEs, one dose reduction of ribociclib from 400 mg/day to 200 mg/day was allowed; dose re-escalation to 400 mg/day was not permitted
- The data cutoff date for this exploratory analysis was 29 April 2024
- Relative dose intensity (RDI), defined as the actual cumulative dose per duration of exposure (adjusted for the 3-weeks-on/1-week-off schedule) divided by the planned dose intensity of 400 mg/day, was analyzed by grouping patients into low, medium, or high RDI tertiles
  - An unstratified Cox proportional hazards model was used to compare iDFS rates with ribociclib + ET across these tertiles
- Adjusted RDI (taking into account patients with early ribociclib discontinuation) was also determined and analyzed by low, medium, or high tertiles
  - Patients who discontinued ribociclib before 36 months due to an iDFS event had their RDI calculated using their actual exposure time
  - Those who discontinued before 36 months for any other reason had their RDI calculated using time to iDFS event (if iDFS event <36 months and after dose reduction) or using 36 months (if the iDFS event >36 months or if there was no iDFS event)
  - This adjusted analysis focused on RDI and does not address the impact of ribociclib duration on efficacy
- Analysis using two Cox proportional hazards models with time-varying covariates (dose reductions [yes, no] and relative dose intensity 2 [RDI2; low, medium, high]) were performed (**Figure 2**)
  - RDI2 is the RDI during the period from first dose reduction or interruption to last dose
  - While RDI considers the entire treatment period, it does not contain a time element; RDI2 is a time-dependent RDI that accounts for immortal time bias
- Landmark (LM) analyses were also performed to assess the association between dose reductions and iDFS
  - Patients were categorized (yes, no) by whether a dose reduction occurred prior to the LM time; those with exposure less than the LM were excluded
  - LM analyses address the potential for immortal-time bias by separating patients into two groups (e.g., dose reductions: yes vs no) at LM time points and following these different groups forward in time

### Figure 2. RDI2 Methodology




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

## RESULTS

### Baseline characteristics in patients with and without a dose reduction

- Among the 2526 patients treated in the ribociclib + NSAI arm, 687 (27.2%) had a ribociclib dose reduction, and 1839 (72.8%) did not
- Baseline characteristics were balanced between patients with and without dose reduction (**Table 1**)
- The median iDFS follow-up time was 44.2 months, for both the overall population and the RIB + ET arm

**Table 1. Baseline characteristics between patients with and without dose reductions**

| Parameter | With dose reduction n = 687 | Without dose reduction n = 1839 |
|---|---|---|
| **Age, median (min-max), years** | 52.0 (25-90) | 52.0 (24-84) |
| **Menopausal status, n (%)** | | |
| Men and premenopausal women | 295 (50.3) | 822 (44.7) |
| Postmenopausal women | 392 (57.1) | 1017 (55.3) |
| **Anatomical stage, n (%)[a]** | | |
| Stage I | 3 (0.4) | 6 (0.3) |
| Stage II | 257 (37.4) | 741 (40.3) |
| Stage III | 426 (62.0) | 1092 (59.4) |
| **Nodal status at diagnosis, n (%)[b]** | | |
| NX | 88 (12.8) | 183 (10.0) |
| N0 | 166 (24.2) | 522 (28.4) |
| N1 | 284 (41.3) | 756 (41.1) |
| N2/N3 | 135 (19.7) | 344 (18.7) |
| **Prior ET, n (%)** | | |
| Yes | 512 (74.5) | 1302 (70.8) |
| **Prior (neo)adjuvant CT, n (%)** | | |
| Yes | 618 (90.0) | 1613 (87.7) |
| **ECOG PS, n (%)[c]** | | |
| 0 | 560 (81.5) | 1527 (83.0) |
| 1 | 126 (18.3) | 311 (16.9) |

[a] Missing anatomical stage for 1 (0.1%) patient with dose reduction. [b] Missing nodal status for 14 (2.0%) patients with dose reduction and 34 (1.8) patients without dose reduction. [c] Missing ECOG PS for 1 (0.1) patient with dose reduction and 1 (0.1) patient without dose reduction.
CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ET, endocrine therapy; N, node.

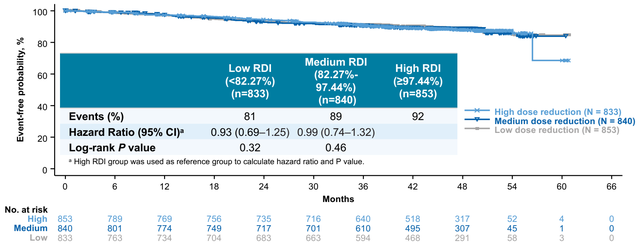
### Ribociclib dose reduction details

- Among 687 patients with a ribociclib dose reduction, the median time to ribociclib dose reduction was 3.3 months, and the most common reason for a dose reduction was an AE (84.7% [582/687])
  - Additional reasons for ribociclib dose reduction included dosing error (13.7% [94/687]) and physician decision (2.2% [15/687])
- The most common AEs leading to dose reduction were neutropenia (14.1% [355/2526]), ALT increase (1.9% [48/2526]), leukopenia (1.7% [44/2526]), and fatigue (1.1% [27/2526]; **Table 2**)
- The median duration of ribociclib exposure was similar among patients with and without a dose reduction (median, 35.7 months in both groups)
- Among those who discontinued ribociclib due to an AE (n=509), 358 (70.3%) had no prior dose reduction

### iDFS by RDI of ribociclib

- iDFS was similar irrespective of the RDI of ribociclib; low (0 to <82.27%), medium (82.27% to <97.44%), and high (≥97.44%) RDI corresponded to similar iDFS (low vs high HR, 0.931; medium vs high HR, 0.985) (**Figure 3**)

### Figure 3. KM plot of iDFS by RDI




| | Low RDI (<82.27%) (n=833) | Medium RDI (82.27%-97.44%) (n=840) | High RDI (≥97.44%) (n=853) |
|---|---|---|---|
| **Events (%)** | 81 | 89 | 92 |
| **Hazard Ratio (95% CI)[a]** | 0.93 (0.69–1.25) | 0.99 (0.74–1.32) | |
| **Log-rank *P* value** | 0.32 | 0.46 | |

[a] High RDI group was used as reference group to calculate hazard ratio and *P* value.

| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| High | 853 | 789 | 769 | 756 | 735 | 716 | 640 | 518 | 317 | 52 | 4 | 0 |
| Medium | 840 | 801 | 774 | 749 | 717 | 701 | 610 | 495 | 307 | 45 | 1 | 0 |
| Low | 833 | 763 | 734 | 704 | 683 | 663 | 594 | 468 | 291 | 58 | 3 | 0 |

RDI, relative dose intensity.

**Table 2. AEs leading to ribociclib dose reduction**

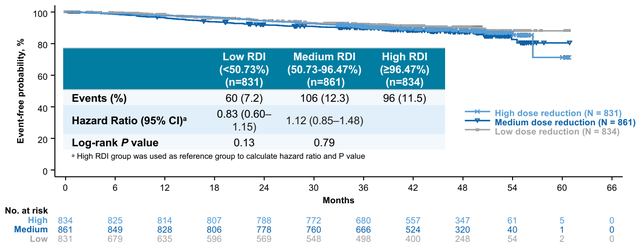
| | Ribociclib + NSAI arm: Patients with a dose reduction (n = 2526) | |
|---|---|---|
| **AEs requiring dose reduction in ≥0.5% of patients, n (%)** | **All grade** | **Grade ≥3** |
| **Neutropenia[a]** | 355 (14.1) | 308 (12.2) |
| **ALT increased** | 48 (1.9) | 22 (0.9) |
| **Leukopenia[b]** | 44 (1.7) | 15 (0.6) |
| **Fatigue** | 27 (1.1) | 4 (0.2) |
| **AST increased** | 17 (0.7) | 3 (0.1) |

[a] Combined preferred terms 'neutropenia' (All grade: 212 [8.4%] ; grade≥3: 181 [7.2%]) and 'neutrophil count decreased' (all grade: 143 [5.7%]; grade≥3: 127 [5.0%]). [b] Combined preferred terms 'leukopenia' (all grade: 18 [0.7%] ; grade≥3: 8 [0.3%]) and 'white blood cell count decreased' (All grade: 26 [1.0%] ; grade≥3: 7 [0.3%]).
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; GGT, gamma-glutamyltransferase, NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

### iDFS by adjusted relative dose intensity of ribociclib

- When adjusted RDI was used to account for patients who discontinued ribociclib earlier than 36 months, iDFS remained similar in all patients regardless of adjusted RDI (low vs high HR, 0.83; medium vs high HR, 1.12; **Figure 4**)

### Figure 4. iDFS by adjusted RDI




| | Low RDI (<50.73%) (n=831) | Medium RDI (50.73-96.47%) (n=861) | High RDI (≥96.47%) (n=834) |
|---|---|---|---|
| **Events (%)** | 60 (7.2) | 106 (12.3) | 96 (11.5) |
| **Hazard Ratio (95% CI)[a]** | 0.83 (0.60–1.15) | 1.12 (0.85–1.48) | |
| **Log-rank *P* value** | 0.13 | 0.79 | |

[a] High RDI group was used as reference group to calculate hazard ratio and *P* value

| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| High | 834 | 825 | 814 | 807 | 788 | 772 | 680 | 557 | 347 | 61 | 5 | 0 |
| Medium | 861 | 849 | 828 | 806 | 778 | 760 | 666 | 524 | 320 | 40 | 1 | 0 |
| Low | 831 | 813 | 679 | 635 | 596 | 569 | 548 | 498 | 400 | 248 | 54 | 2 | 0 |

RDI, relative dose intensity.

### RDI2 and Landmark Analysis

- iDFS remained similar in all patients regardless of RDI2 (low vs high HR [95% CI], 1.07 [0.78-1.48]; medium vs high HR [95% CI], 1.32 [0.99-1.74])
- LM analyses demonstrated that patients with ribociclib dose reduction had similar post-LM time iDFS compared to those who did not (**Table 3**)

**Table 3. LM analysis of iDFS rates by dose reductions**

| LM Time, months[a] | Pts on treatment longer than LM Time, n (%) | Dose reduction prior to LM Time | Subgroup, n (%) | 3-Year post-LM time, iDFS rate (95% CI)[b] | Post-LM time, hazard ratio (95% CI)[c] |
|---|---|---|---|---|---|
| 3 | 2204 (87.3) | Yes | 252 (11.4) | 93.1 (89.0-95.7) | **0.84 (0.54-1.30)** |
| | | No | 1952 (88.6) | 90.4 (89.0-91.7) | |
| 6 | 2041 (80.8) | Yes | 360 (17.6) | 91.9 (88.4-94.4) | **0.80 (0.54-1.19)** |
| | | No | 1681 (82.4) | 90.6 (89.0-92.0) | |
| 12 | 1906 (75.5) | Yes | 405 (21.2) | 92.2 (88.9-94.5) | **0.81 (0.54-1.21)** |
| | | No | 1501 (78.8) | 91.0 (89.2-92.4) | |

[a] Each LM time represents a distinct patient population treated on and after the LM. [b] iDFS rate by 3 years after given LM time. [c] Dose reduction, yes vs no.

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