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NATALEE update: safety and treatment duration of ribociclib + nonsteroidal aromatase inhibitor in patients with HR+/HER2− early breast cancer

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KEY FINDINGS & CONCLUSIONS

- This analysis of safety in NATALEE revealed no new safety signals with ribociclib 400 mg + NSAI in HR+/HER2− EBC
- The most common AE in the ribociclib arm was neutropenia, with most grade ≥ 3 AEs being asymptomatic laboratory findings that were easily identifiable, manageable, and reversible
- AEs generally occurred early in treatment, allowing for prompt ribociclib dose adjustments
- Dose reductions did not appear to impact efficacy
- Three-year treatment with 400 mg ribociclib was well tolerated in NATALEE, and patients maintained their ribociclib treatment with timely identification and management of AEs following protocol recommendations

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INTRODUCTION

- In NATALEE, ribociclib + nonsteroidal aromatase inhibitor (NSAI) demonstrated a statistically significant invasive disease-free survival (iDFS) benefit over NSAI alone in a broad population of patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) early breast cancer (EBC)[1,2]
- The iDFS benefit was consistent across key prespecified subgroups, including patients with stage II, stage III, node-negative, and node-positive disease[1,2]
- The ribociclib 400 mg starting dose in NATALEE was chosen with the goal of improving safety and adherence while maintaining efficacy in a clinically disease-free setting[1]
- An analysis of pooled data across the MONALEESA trials suggested that dose reduction from 600 to 400 mg, when needed, does not decrease efficacy[3]
- The AMALEE trial suggested that 400 mg reduces the incidence of dose-dependent adverse events (AEs) such as neutropenia and QTcF prolongation compared with 600 mg[4]
- The 3-year ribociclib duration was chosen in an effort to prevent recurrence by prolonging cell cycle arrest and potentially causing more tumor cells to become senescent[5-7]
- Safety and tolerability data from NATALEE are needed to inform patient management during ribociclib treatment

METHODS

Figure 1. NATALEE Study Design[2,7-9]

- Adult patients with HR+/HER2− EBC
- Prior ET allowed ≤12 mo prior to randomization
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ 26 **or**
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

RIB: 400 mg/day, 3 weeks on/1 week off for 3 y
NSAI: Letrozole or anastrozole[d] for ≥ 5 y + **goserelin** in men and premenopausal women

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Trial start: Jan 2019

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; iDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; RIB, ribociclib; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.

RESULTS

- Data cutoff for final iDFS analysis was July 21, 2023
- NSAI discontinuation rate due to AEs was similar across both arms, indicating that adding ribociclib to NSAI did not impact NSAI tolerability (**Figure 2**)

Figure 2. NATALEE: Patient disposition (safety set)

RIB + NSAI
2549 patients randomized
2525 received study drug
At data cutoff:
- NSAI ongoing: 1915 (75.8%)
- Discontinued NSAI (< 5 y): 610 (24.2%)
  - Due to AEs: 131 (5.2%)
- RIB ongoing: 528 (20.9%)
- Completed ≥ 2 y RIB: 1752 (69.4%)
- Stopped RIB: 1997 (79.1%)
  - Completed 3 y RIB: 1091 (43.2%)
  - Discontinued RIB (< 3 y): 906 (35.9%)
    - Due to AEs: 498 (19.7%)

NSAI
2552 patients randomized
2442 received study drug
At data cutoff:
- NSAI ongoing: 1747 (71.5%)
- Discontinued NSAI (< 5 y): 695 (28.5%)
  - Due to AEs: 113 (4.6%)

AE, adverse event; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

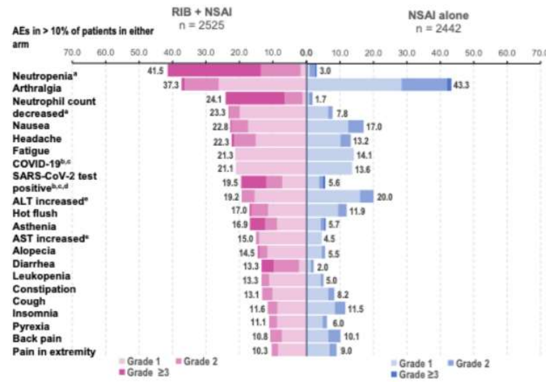
Table 1. NATALEE: Adverse Events of Special Interest

AESIs (grouped terms)	Neutropenia[a]		Liver-related AEs[c]		QT interval prolongation[d]	
	RIB + NSAI	NSAI alone	RIB + NSAI	NSAI alone	RIB + NSAI	NSAI alone
All grade	1579 (62.5)	113 (4.6)	667 (26.4)	273 (11.2)	134 (5.3)	34 (1.4)
Grade ≥3	1118 (44.3)	22 (0.9)	217 (8.6)	42 (1.7)	26 (1.0)	15 (0.6)
Time to first grade ≥2 based on laboratory values, median mo. (range)	1.0 (0.9-1.0)[b]	NE	2.8 (0.5-36.7)	9.1 (0.5-33.3)	0.5 (0.5-1.5)	1.4 (0.9-2.8)
Time to resolution of grade ≥2 to ≤1 based on laboratory values, median mo. (95% CI)	1.0 (NE)	1.0 (1.0-1.0)	0.9 (0.7-1.0)	1.4 (1.0-2.5)	0.2 (0.0-0.5)	1.1 (0.5-NE)
Dose reductions, RIB, %	14.2	0	2.6	0	0.1	0
Discontinuations, any component, %	1.1	0	8.9	0.1	0.4	0

AESI, adverse event of special interest; NE, not estimable; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] AESI grouping that includes the preferred terms neutropenia, neutrophil count decreased, febrile neutropenia, and granulocytopenia. [b] 95% CI. [c] Includes the preferred terms ALT increased, AST increased, GGT increased, blood ALP increased, and blood BILI increased. [d] AESI grouping that includes the preferred terms electrocardiogram QT prolonged, syncope, loss of consciousness, cardiac arrest, electrocardiogram repolarization abnormality, long QT syndrome, and ventricular tachycardia. All groupings were based on MedDRA searches or the combinations of such searches.

Figure 3. NATALEE: Adverse Events

- 98.0% of patients on ribociclib + NSAI experienced AEs; similarly, 87.8% of patients on NSAI alone experienced AEs (**Figure 3**)

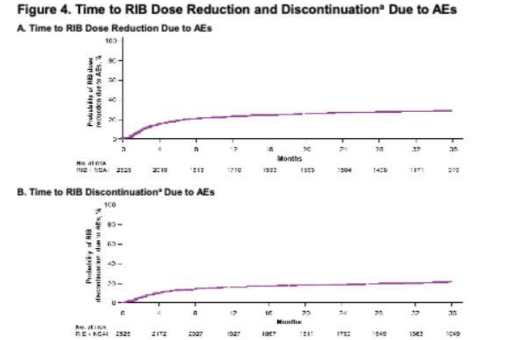


AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a] Included in the AESI grouping "neutropenia." [b] Only reported as all-grade events. [c] Included in the AESI grouping "infections." [d] Spontaneously reported (no solicited collection). [e] Included in the AESI grouping "hepatobiliary toxicity" and in the grouping "liver-related AEs" used hereafter.

NATALEE: AE-related dose reduction & discontinuation

- AE-related ribociclib dose reductions occurred in 22.8% of patients, most commonly due to neutropenia (8.5%) and neutrophil count decreased (5.6%)
  - Median time to AE-related RIB dose reduction was 3.15 months (range, 0.26-34.17 months) (**Figure 4A**)
  - Median relative dose intensity (RDI) during ribociclib treatment was 94%
- Most common AEs leading to discontinuation: ALT increased (7.1%) and AST increased (2.8%)
  - Of 19.7% of patients who discontinued due to AEs, 14.0% discontinued without prior dose reduction and 5.7% had their dose reduced before discontinuing
  - Median time to AE-related ribociclib discontinuation was 4.17 months (range, 0.10-35.75 months) (**Figure 4B**)

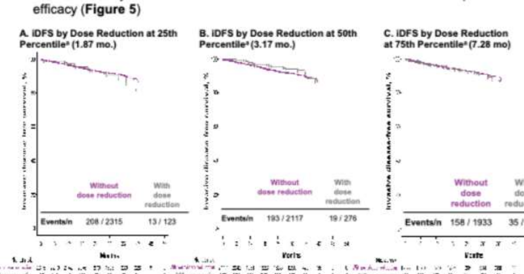
Figure 4. Time to RIB Dose Reduction and Discontinuation[a] Due to AEs



AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; RDI, relative dose intensity; RIB, ribociclib.
[a] Protocol required discontinuation for RIB dose interruption of > 28 days, or grade 4 AEs (except neutropenia and thrombocytopenia), or recurrent high-grade AEs.

Figure 5. iDFS by Dose Reduction at 25th Percentile[a] (1.87 mo), 50th Percentile[a] (3.17 mo), and 75th Percentile[a] (7.28 mo)

- Landmark analysis revealed that RIB dose reduction due to AEs did not impact efficacy (**Figure 5**)



[a] Of dose reduction time, calculated from randomization

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Disclosures

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