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Baseline characteristics and efficacy endpoints for patients with node-negative HR+/HER2− early breast cancer in NATALEE

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KEY FINDINGS & CONCLUSIONS

- Ribociclib plus NSAI improved iDFS over NSAI alone, with a consistent benefit seen in DDFS and DRFS, in the node-negative subgroup of patients in NATALEE
- The 3-year control arm iDFS, DDFS, and DRFS rates underscore the risk of recurrence and unmet need of NATALEE patients with node-negative disease who are treated with current standard of care
- Safety results in the node-negative subgroup were consistent with the ITT population
- These findings demonstrate the efficacy and tolerability of adding ribociclib to NSAI in select patients with node-negative HR+/HER2− EBC who are at high risk of recurrence despite current standard of care

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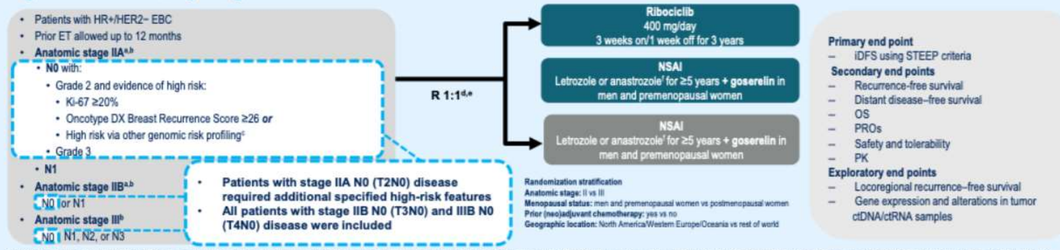
INTRODUCTION

- After adjuvant endocrine therapy (ET), the risk of recurrence persists among patients with stage II/III hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) early breast cancer (EBC), regardless of nodal involvement[1]
- Approximately 40% of patients with ER+ BC have node-negative disease, and 22% of these patients will experience disease recurrence within 20 years of diagnosis[1]
- NATALEE assessed ribociclib + nonsteroidal aromatase inhibitor (NSAI) vs NSAI alone in patients with stage II/III HR+/HER2− EBC at risk of recurrence, including select patients with node-negative disease
- NATALEE (N = 5101) met its primary end point (iDFS) and continued to show benefit with additional follow-up, with a significant iDFS improvement with ribociclib + NSAI (n = 2549) vs NSAI alone (n = 2552) in the ITT population (hazard ratio, 0.749; 95% CI, 0.628-0.892; nominal 1-sided P=.0006)[2,3]
- Here, we report baseline characteristics, efficacy, and safety for the node-negative subgroup (n = 613) in the NATALEE trial
- These findings demonstrate the efficacy and tolerability of adding ribociclib to NSAI in select patients with node-negative HR+/HER2− EBC who are at high risk of recurrence despite current standard of care

METHODS

Figure 1. NATALEE Study Design[4,5]


Patients with HR+/HER2− EBC
Prior ET allowed up to 12 months
Anatomic stage IIA[a,b]
N0 with:
Grade 2 and evidence of high risk:
Ki-67 ≥20%
Oncotype DX Breast Recurrence Score ≥26 or
High risk via other genomic risk profiling[c]
Grade 3
N1
Anatomic stage IIB[a,b]
N0 or N1
Anatomic stage III[b]
N0, N1, N2, or N3
Patients with stage IIA N0 (T2N0) disease required additional specified high-risk features
All patients with stage IIB N0 (T3N0) and IIIB N0 (T4N0) disease were included
R 1:1[d,e]
Ribociclib
400 mg/day
3 weeks on/1 week off for 3 years
NSAI
Letrozole or anastrozole[f] for ≥5 years + goserelin in men and premenopausal women
NSAI
Letrozole or anastrozole[f] for ≥5 years + goserelin in men and premenopausal women
Randomization stratification
Anatomic stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
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

ctDNA/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; ITT, intention to treat; 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; PROs, patient reported outcomes; R, randomized; 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] N0 was determined either clinically and confirmed surgically as needed. [c] Genomic high risk is defined as at least one of the following: Oncotype Dx Breast Recurrence Score ≥26, PAM50 score of "High Risk," MammaPrint score of "High Risk," EndoPredict EPclin Risk score of "High Risk".
[d] 5101 patients were randomized from January 10, 2019, to April 20, 2021. [e] Open-label design. [f] Per investigator choice.

RESULTS

- In the intention-to-treat (ITT) population, 78% of pts completed 3 years of ribociclib treatment or discontinued early; 21% were still on treatment at the time of this analysis (data cutoff: July 21, 2023; median follow-up, 33 months)

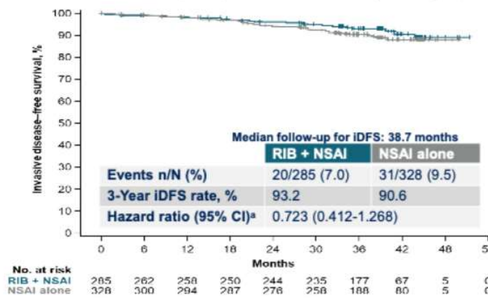
Table 1. Baseline Characteristics in the NATALEE Node-Negative Subgroup

Parameter	RIB + NSAI n = 285	NSAI alone n = 328	All patients N = 613
Age, median (min-max), years	55 (29-81)	55 (24-89)	55 (24-89)
Anatomic stage, n (%)[a]			
Stage IIA[b]			
G2[c]	212 (74)	241 (73)	453 (74)
Ki-67 ≥20%[c]	104 (49)	128 (53)	232 (51)
Ki-67 <20% with high	70 (33)	91 (38)	161 (36)
genomic risk[c,d]	6 (3)	11 (5)	17 (4)
Ki-67 <20% with unknown	28 (13)	26 (11)	54 (12)
genomic risk[c,d,e]	104 (49)	109 (45)	213 (47)
G3[c]	48 (17)	44 (13)	92 (15)
Stage IIB	25 (9)	40 (12)	65 (11)
Stage IIIB			
T status, n (%)[a]			
T1	0 (0)	3 (1)	3 (<1)
T2	212 (74)	241 (73)	453 (74)
T3	48 (17)	44 (13)	92 (15)
T4	25 (9)	40 (12)	65 (11)
Grade, n (%)[a,f]			
G1	5 (2)	8 (2)	13 (2)
G2	149 (52)	178 (54)	327 (53)
G3	127 (45)	138 (42)	265 (43)
Prior Therapy			
Prior (neo)adjuvant CT, n (%)			
Yes	205 (72)	232 (71)	437 (71)
Neoadjuvant	90 (32)	99 (30)	189 (31)
Adjuvant	121 (42)	136 (41)	257 (42)
Prior ET, n (%)[g]			
Yes	169 (59)	204 (62)	373 (61)

CT, chemotherapy; ET, endocrine therapy; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] Derived using TNM from surgery for patients having not received (neo)adjuvant treatment, or as worst stage derived using TNM at diagnosis and TNM from surgery for patients having received (neo)adjuvant treatment. [b] Among the N0 subgroup with stage IIA disease, 2 patients in each treatment arm had G1 disease, and grade was not determined or missing in another 2 patients in each treatment arm. [c] Stage IIA used as denominator for calculating percentages. [d] Among the N0 subgroup with stage IIA disease, 6 patients in each treatment arm had missing Ki-67 measurements. [e] These patients were enrolled prior to the first protocol amendment incorporating Ki-67 and genomic profiling requirements into the eligibility criteria for patients in the N0 subgroup with stage IIA and G2 disease. [f] Grade was not determined or missing for 4 patients in each treatment arm. [g] Patient may have already received any standard (neo)adjuvant ET, but randomization should have occurred ≤12 months from the initial start date of ET.

Figure 2. iDFS in the NATALEE Node-Negative Subgroup

- Ribociclib improved iDFS, distant disease-free survival (DDFS), and distant recurrence-free survival (DRFS) in the NATALEE node-negative subgroup


Invasive disease–free survival, %
100
90
80
70
60
50
40
30
20
10
0
Median follow-up for iDFS: 38.7 months
RIB + NSAI
NSAI alone
Events n/N (%) 20/285 (7.0) 31/328 (9.5)
3-Year iDFS rate, % 93.2 90.6
Hazard ratio (95% CI)[a] 0.723 (0.412-1.268)
0 6 12 18 24 30 36 42 48 54
Months
No. at risk
RIB + NSAI 285 262 258 250 244 235 177 67 5 0
NSAI alone 328 300 294 287 276 258 188 80 5 0

iDFS, invasive disease–free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] This was not a preplanned analysis and no formal P value was spent or tested.

Table 2. DDFS and DRFS in the NATALEE Node-Negative Subgroup

Efficacy outcome	RIB + NSAI n = 285	NSAI alone n = 328
DDFS		
Events, n	17	27
3-y rate (95% CI), %	94.3 (90.6-96.6)	91.5 (87.6-94.2)
Hazard ratio (95% CI)	0.703 (0.383-1.290)	
DRFS		
Events, n	12	23
3-y rate (95% CI), %	96.3 (93.0-98.1)	92.5% (88.8-95.1)
Hazard ratio (95% CI)	0.580 (0.289-1.170)	

DDFS, distant disease–free survival; DRFS, distant recurrence–free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

Figure 3. Safety in NATALEE node-negative subgroup

- The rate of discontinuation due to all grade adverse events (AEs) was 24% with RIB + NSAI

	RIB + NSAI n = 283		NSAI alone n = 318	
AESIs, %	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia[a]	168 (59)	111 (39)	19 (6)	5 (2)
Febrile neutropenia	0	0	0	0
Liver-related AEs[b]	86 (30)	29 (10)	32 (10)	5 (2)
ALT elevations	69 (24)	28 (10)	13 (4)	2 (<1)
AST elevations	61 (22)	16 (6)	14 (4)	3 (<1)
QT interval prolongation[c]	15 (5)	3 (1)	4 (1)	3 (<1)
ECG QT prolonged	11 (4)	1 (<1)	1 (<1)	0
ILD pneumonitis[d]	6 (2)	0	2 (<1)	0
Other clinically relevant AEs,%				
Arthralgia	105 (37)	4 (1)	146 (46)	5 (2)
Nausea	58 (20)	1 (<1)	21 (7)	0
Headache	58 (20)	1 (<1)	40 (13)	0
Fatigue	61 (22)	3 (1)	47 (15)	1 (<1)
Diarrhea	47 (17)	4 (1)	22 (7)	0
VTE[e]	4 (1)	1 (<1)	0	0

AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; ILD, interstitial lung disease; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib; VTE, venous thromboembolic event.
[a] This is a grouped term that combines neutropenia and neutrophil count decreased. [b] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [c] This is a grouped term. [d] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung disease. [e] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for venous thromboembolism.

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Disclosures

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