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Adjuvant Ribociclib Plus Nonsteroidal Aromatase Inhibitor in Patients With HR+/HER2− Early Breast Cancer: 4-Year Outcomes From the NATALEE Trial

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KEY FINDINGS & CONCLUSIONS

- In this 4-year landmark analysis, ribociclib + NSAI continued to demonstrate an iDFS and DDFS benefit over NSAI alone by reducing the risk of disease recurrence by 28.5% (Hazard ratio, 0.715)
  - The absolute iDFS benefit continued to increase from 2.7% at 3 years to 4.9% at 4 years showing benefit after the end of three years of ribociclib treatment
  - The increasing efficacy benefit with RIB + NSAI was consistent across subgroups and secondary endpoints
  - OS follow-up is ongoing, with a positive trend seen in favor of RIB + NSAI
  - The safety profile remained stable with additional follow-up
- NATALEE results continue to support the benefit of adding 3 years of ribociclib to adjuvant NSAI in a broad population of patients with HR+/HER2− EBC at risk of recurrence

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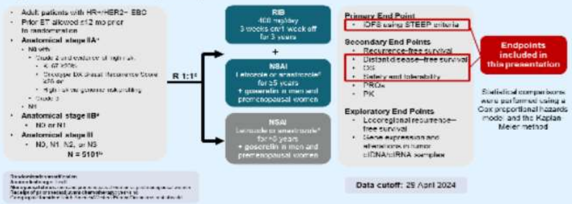
INTRODUCTION

- In the NATALEE trial, the addition of ribociclib to standard-of-care nonsteroidal aromatase inhibitor (NSAI) demonstrated a significant improvement in invasive disease-free survival (iDFS) over NSAI alone in patients with stage II or III hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) early breast cancer (EBC) at risk of recurrence[1,2]
- Second interim efficacy analysis (median iDFS follow-up, 27.7 mo): 20.2% of patients had completed the planned 3 years of ribociclib treatment; Hazard ratio, 0.748 (95% CI, 0.618-0.906); 1-sided P=0.0014 [1,2]
- Protocol-specified final iDFS analysis (median iDFS follow-up, 33.3 mo): 42.8% of patients had completed 3 years of ribociclib; Hazard ratio, 0.749 (95% CI, 0.628-0.892); nominal 1-sided P=0.0006 [3]
- We report results from an exploratory 4-year landmark analysis of NATALEE, with an additional 10.9 months of follow-up since the final iDFS analysis, assessing efficacy and safety beyond the planned 3-year treatment duration **with all patients off ribociclib**

METHODS

Figure 1. NATALEE Study Design[3-6]



ct, circulating tumor; ET, endocrine therapy; N, node; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; 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]5101 patients were randomized from January 10, 2019 to April 20, 2021. [c]Open-label design. [d]Per investigator choice.

Table 1. NATALEE iDFS Analyses Over Time

Analysis time points	Second interim efficacy analysis[1]	Protocol-specified final iDFS analysis[3]	4-year landmark analysis
Data cutoff	11 January 2023	21 July 2023	29 April 2024
Median follow-up for iDFS, months	27.7	33.3	44.2
iDFS events, n	426	509	603
Off RIB treatment, %	54.0	78.3	100
Completed 3 years of RIB treatment, %	20.2	42.8	62.8

iDFS, invasive disease–free survival; RIB, ribociclib.

RESULTS

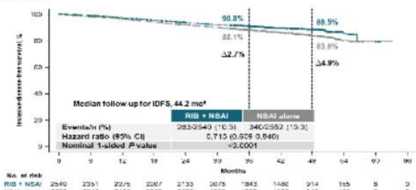
- At the data cutoff, median duration of exposure to study treatment was 45.1 months in the ribociclib (RIB) + NSAI arm vs 45.0 months in the NSAI alone arm
- All patients are off RIB, and 62.8% completed the 3-year duration (**Table 2**)

Table 2. Patient Disposition

n (%)	RIB + NSAI n=2549		NSAI alone n=2552
Randomized	2549 (100)		2552 (100)
Treated	2526 (99.1)		2441 (95.7)
NSAI treatment ongoing	1794 (70.4)		1625 (63.8)
Completed 3 y RIB treatment	1601 (62.5)		–
Completed 5y study treatment	10 (0.4)		9 (0.4)
	RIB	NSAI	NSAI
Early discontinuation	923 (36.2)	722 (28.3)	804 (31.5)
Primary reason for early discontinuation			
AE	509 (20.0)	136 (5.3)	124 (4.9)
Disease relapse	127 (5.0)	196 (7.7)	267 (10.5)
Patient/physician decision	160 (6.3)	206 (8.1)	189 (7.4)
Lost to follow-up	8 (0.3)	15 (0.6)	21 (0.8)
Death	6 (0.2)	9 (0.4)	5 (0.2)
Other[a]	114 (4.5)	160 (6.2)	197 (7.7)

AE, adverse event; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] Other includes withdrawal by patient, protocol deviation, among other reasons.

Figure 2. Significant iDFS benefit was observed with RIB + NSAI after the planned 3-year treatment



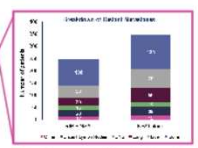
iDFS, invasive disease–free survival; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] An additional 10.9 months of follow-up compared with the protocol-specified final iDFS analysis.

Table 3. The majority of iDFS events were distant recurrences, which were more common in the NSAI only arm

Type and site of first iDFS event, n (%)	RIB + NSAI n=2549	NSAI Alone n=2552
Distant recurrence	175 (6.9)	246 (9.6)
Local/regional invasive recurrence	25 (1.0)	49 (1.9)
Second primary nonbreast cancer	39 (1.5)	46 (1.8)
Death	17 (0.7)	11 (0.4)
Invasive contralateral breast tumor	11 (0.4)	10 (0.4)
Invasive ipsilateral breast tumor	8 (0.3)	9 (0.4)

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

Figure 3. Breakdown of Distant Metastases in ITT Population



CNS, central nervous system; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

iDFS Across Key Prespecified Subgroups

- Consistent iDFS benefit was observed across subgroups (**Table 4**)
  - RIB + NSAI demonstrated an increasing magnitude of iDFS benefit over time for stage II/III disease (**Figure 4**)
  - RIB + NSAI showed an increasing magnitude of iDFS benefit over time for patients with N0 or N1-3 disease (**Figure 5**)

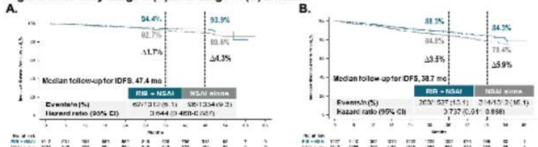
Table 4. iDFS Across Key Prespecified Subgroups

Subgroup	RIB + NSAI Events/n	RIB + NSAI 4-y iDFS rate, %	NSAI alone Events/n	NSAI alone 4-y iDFS rate, %	Hazard ratio	95% CI
Menopausal status						
Men and premenopausal women	99/1125	90.7	137/1132	85.3	0.677	0.523-0.877
Postmenopausal women	164/1424	86.8	203/1420	82.2	0.760	0.619-0.933
AJCC stage						
Stage II	62/1012	93.9	96/1034	89.6	0.644	0.468-0.887
Stage III	200/1527	84.3	244/1512	78.4	0.737	0.611-0.888
Prior CT						
Yes	238/2249	88.2	309/2245	83.0	0.715	0.604-0.846
No	25/300	90.7	31/307	87.5	0.827	0.488-1.401
Region						
North America/Western Europe/Oceania	151/1563	88.9	195/1565	84.2	0.726	0.587-0.898
Rest of world	112/986	88.0	145/987	82.6	0.722	0.564-0.925
Ki-67 status[a]						
Ki-67 ≤20%	106/1199	89.9	142/1236	85.9	0.737	0.573-0.948
Ki-67 >20%	113/920	86.3	149/937	80.4	0.709	0.555-0.905
Nodal status[b,c]						
N0	23/285	92.1	38/328	87.0	0.666	0.397-1.118
N1-N3	240/2261	88.0	301/2219	83.0	0.731	0.617-0.866
Prior ET						
Yes	176/1830	89.2	227/1807	84.5	0.718	0.589-0.874
No	87/719	86.7	113/745	81.4	0.752	0.568-0.994

Hazard ratio (0.0–3.0): Favors RIB + NSAI ← → Favors NSAI alone

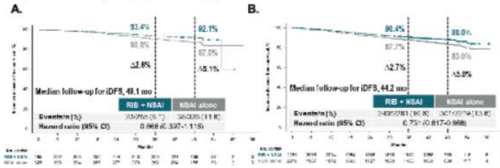
AJCC, American Joint Committee on Cancer; CT, chemotherapy; ET, endocrine therapy; iDFS, invasive disease–free survival; ITT, intent to treat; N, node; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] From archival tumor tissue. [b] Nodal status classification according to AJCC staging. [c] Nodal status is from the worst stage derived per surgical specimen or at diagnosis.

Figure 4. iDFS by Stage II (A) and Stage III (B) Disease



iDFS, invasive disease–free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

Figure 5. iDFS by N0 (A) and N1-3 (B) Disease

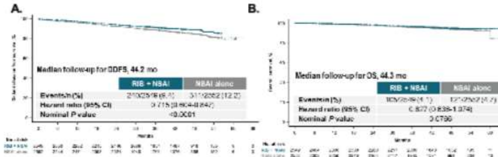


iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

Key Secondary Efficacy Endpoints

- RIB + NSAI continued to improve distant disease-free survival (DDFS) and showed a positive trend for overall survival (OS) (**Figure 6**)

Figure 6. Key Secondary Efficacy Endpoints: DDFS (A) and OS (B)



DDFS, distant disease–free survival; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.

Safety

- Incidence of adverse events (AEs) remained stable from prior analyses[1,3] (**Table 4**)
- Rates of discontinuation due to AEs (20.0%) remained stable through all of the data cuts, with a <1.0% increase from the previous cutoff[1,3]
- Liver-related AEs were predominately alanine aminotransferase/ aspartate aminotransferase (ALT/AST) elevations without concomitant bilirubin increase

Table 4. NATALEE Safety

	RIB + NSAI n=2526		NSAI alone n=2441	
AESIs, %	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia[a]	62.8	44.4	4.5	0.9
Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs[b]	26.7	8.8	11.4	1.7
QT interval prolongation[c]	5.4	1.0	1.6	0.7
ECG QT prolonged	4.4	0.2	0.6	<0.1
Interstitial lung disease/pneumonitis[d]	1.6	0	0.9	0.1
Clinically relevant AEs, %				
Arthralgia	38.8	1.0	44.4	1.3
Nausea	23.5	0.2	7.8	<0.1
Headache	22.9	0.4	17.2	0.2
Fatigue	22.6	0.8	13.5	0.2
Diarrhea	14.6	0.6	6.5	0.1
VTE[e]	1.1	0.6	0.5	0.3

AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; MedDRA, Medical Dictionary for Regulatory Activities; VTE, venous thromboembolism.
[a] Grouped term that combines neutropenia and neutrophil count decreased. [b] Grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [c] Grouped term. [d] Grouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung disease. [e] Grouped term that includes all preferred terms identified by standardized MedDRA queries for venous thromboembolism.

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Disclosures

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