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Ribociclib + Nonsteroidal Aromatase Inhibitor as Adjuvant Treatment in Patients With HR+/HER2− Early Breast Cancer: Final Invasive Disease–Free Survival Analysis From the NATALEE Trial

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KEY FINDINGS & CONCLUSIONS

- In this protocol-specified final iDFS analysis of NATALEE, ribociclib plus NSAI continued to demonstrate a statistically significant improvement in iDFS over NSAI alone, with 78.3% of patients no longer on ribociclib treatment at data cutoff[13]
- The iDFS benefit was consistent across key prespecified subgroups, including patients with stage II, III, node-negative, and node-positive disease[16]
- Results for distant disease–free survival favored ribociclib + NSAI over NSAI alone
- The incidence of the most frequently observed adverse events was stable with additional follow-up, with the 3-year regimen of ribociclib (400-mg starting dose) being well tolerated in the adjuvant setting[13]
- These results from NATALEE further emphasize the significant iDFS benefit of 3 years of ribociclib plus NSAI over NSAI alone in a broad population of patients with HR+/HER2− early breast cancer at risk of recurrence

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INTRODUCTION

- Although early breast cancer (EBC) is treated with curative intent, a considerable risk of disease recurrence remains (27% to 37% for stage II and 46% to 57% for stage III hormone receptor–positive, human epidermal growth factor receptor 2–negative [HR+/HER2− EBC)[1-3]
- Ribociclib, a cyclin-dependent kinase 4/6 inhibitor, has become the standard of care for treating patients with HR+/HER2− advanced breast cancer[4-12]
- Ribociclib plus a nonsteroidal aromatase inhibitor (NSAI) showed a significant benefit in invasive disease–free survival (iDFS; primary endpoint) over NSAI alone (hazard ratio, 0.748; 95% CI, 0.618-0.906; 1-sided P=.0014) in patients with stage II/III HR+/HER2− EBC at risk of recurrence, including those with node-negative (N0) disease at the second interim efficacy analysis of the NATALEE trial[13]
- We present the final protocol-specified analysis of iDFS for the NATALEE trial

METHODS

Statistical Methods

- This protocol-specified final iDFS analysis was planned after approximately 500 iDFS events (data cutoff date: July 21, 2023)
- iDFS, as defined by Standardized Definitions for Efficacy End Points criteria (version 1.0), was evaluated by the Kaplan-Meier method
- Statistical comparison was made by a stratified log-rank test
- P values are 1-sided and nominal and were not adjusted for multiple comparisons

Figure 1. NATALEE Study Design[13-15]

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **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]

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

Ribociclib 400 mg/d 3 wk on/1 wk off for 3 y

NSAI Letrozole or anastrozole[d] for ≥5 y **+ goserelin** in men and premenopausal women

NSAI Letrozole or anastrozole[d] for ≥5 y **+ goserelin** in men and premenopausal women

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, 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.

RESULTS

Patient Disposition

Figure 2. Patient Disposition

Second Interim Efficacy Analysis
Data cutoff: January 11, 2023
iDFS events: n=426

Final iDFS Analysis
Data cutoff: July 21, 2023
iDFS events: n=509

Ribociclib + NSAI, n=2549 (second interim efficacy analysis)
- NSAI ongoing: 1984 (77.8%)
  - **RIB ongoing: 1147 (45.0%)**
- Stopped RIB: 1377 (54.0%)
  - **Completed 3 years: 515 (20.2%)**
  - **Early discontinuation: 862 (33.8%)**
    - Discontinued due to AEs: 477 (18.7%)

Ribociclib + NSAI, n=2549 (final iDFS analysis)
- NSAI ongoing: 1914 (75.1%)
  - **RIB ongoing: 528 (20.7%)**
- Stopped RIB: 1996 (78.3%)
  - **Completed 3 years: 1091 (42.8%)**
  - **Early discontinuation: 905 (35.5%)**
    - Discontinued due to AEs: 498 (19.5%)

NSAI alone, n=2552 (second interim efficacy analysis)
- NSAI ongoing: 1826 (71.6%)
- Discontinued NSAI: 617 (24.2%)

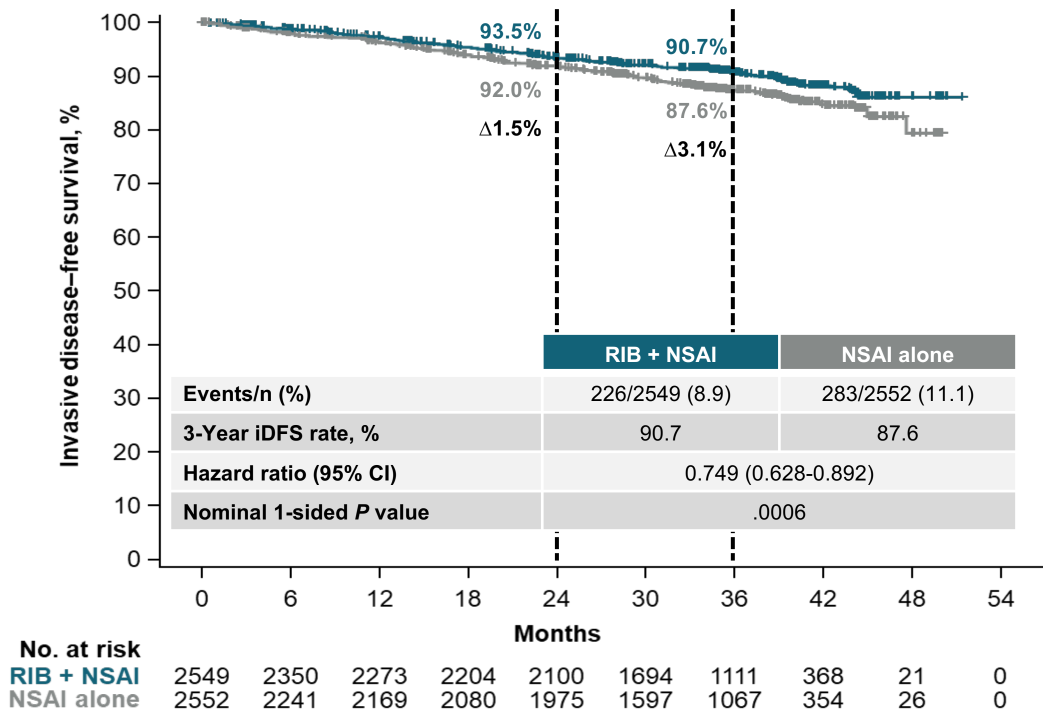
NSAI alone, n=2552 (final iDFS analysis)
- NSAI ongoing: 1748 (68.5%)
- Discontinued NSAI: 693 (27.2%)

AE, adverse event; RIB, ribociclib.

Invasive Disease–Free Survival

- The median follow-up for iDFS was 33.3 months (maximum, 51 months)—an additional 5.6 months from the second interim efficacy analysis[13]
- The absolute iDFS benefit with ribociclib plus NSAI was 3.1% at 3 years (**Figure 3**)
- The risk of invasive disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone

Figure 3. Invasive Disease–Free Survival

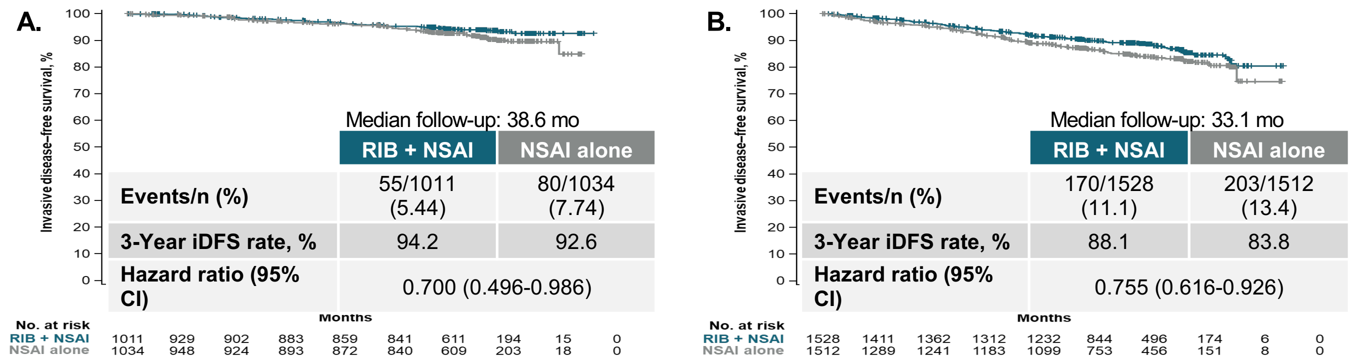


	RIB + NSAI	NSAI alone
Events/n (%)	226/2549 (8.9)	283/2552 (11.1)
3-Year iDFS rate, %	90.7	87.6
Hazard ratio (95% CI)	0.749 (0.628-0.892)	
Nominal 1-sided P value	.0006	

iDFS by Anatomical Stage

- The risk of invasive disease was reduced by 30.0% for stage II and by 24.5% for stage III disease with ribociclib plus NSAI vs NSAI alone (**Figure 4**)

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


A.
Invasive disease–free survival, %
Median follow-up: 38.6 mo
Months
No. at risk
RIB + NSAI 1011 929 902 883 859 841 611 194 15 0
NSAI alone 1034 948 924 893 872 840 609 203 18 0
B.
Invasive disease–free survival, %
Median follow-up: 33.1 mo
Months
No. at risk
RIB + NSAI 1528 1411 1362 1312 1232 844 496 174 6 0
NSAI alone 1512 1289 1241 1183 1099 753 456 151 8 0

A.

	RIB + NSAI	NSAI alone
Events/n (%)	55/1011 (5.44)	80/1034 (7.74)
3-Year iDFS rate, %	94.2	92.6
Hazard ratio (95% CI)	0.700 (0.496-0.986)	

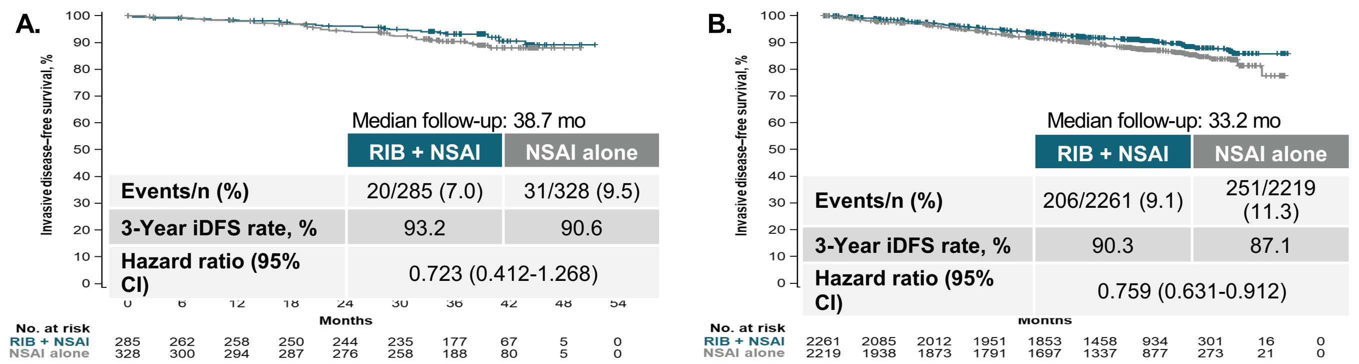
B.

	RIB + NSAI	NSAI alone
Events/n (%)	170/1528 (11.1)	203/1512 (13.4)
3-Year iDFS rate, %	88.1	83.8
Hazard ratio (95% CI)	0.755 (0.616-0.926)	

iDFS by Nodal Status

- The risk of invasive disease was reduced by 27.7% for node-negative and by 24.1% for node-positive disease with ribociclib plus NSAI vs NSAI alone (**Figure 5**)

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


A.
Invasive disease–free survival, %
Median follow-up: 38.7 mo
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
B.
Invasive disease–free survival, %
Median follow-up: 33.2 mo
Months
No. at risk
RIB + NSAI 2261 2085 2012 1951 1853 1458 934 301 16 0
NSAI alone 2219 1938 1873 1791 1697 1337 877 273 21 0

A.

	RIB + NSAI	NSAI alone
Events/n (%)	20/285 (7.0)	31/328 (9.5)
3-Year iDFS rate, %	93.2	90.6
Hazard ratio (95% CI)	0.723 (0.412-1.268)	

B.

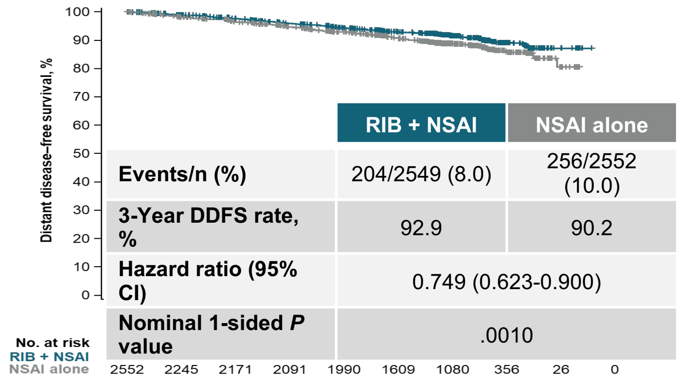
	RIB + NSAI	NSAI alone
Events/n (%)	206/2261 (9.1)	251/2219 (11.3)
3-Year iDFS rate, %	90.3	87.1
Hazard ratio (95% CI)	0.759 (0.631-0.912)	

Distant Disease–Free Survival (DDFS)

- The absolute DDFS[a] benefit with ribociclib plus NSAI was 2.7% at 3 years (**Figure 6**)
- The risk of distant disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone at the final analysis

[a] DDFS is the time from randomization to the date of the first event of distant recurrence, death by any cause, or second primary nonbreast invasive cancer (excluding basal and squamous cell carcinomas of the skin).

Figure 6. DDFS

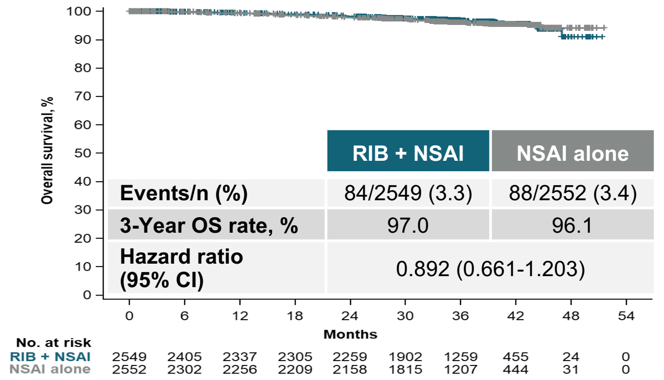


	RIB + NSAI	NSAI alone
Events/n (%)	204/2549 (8.0)	256/2552 (10.0)
3-Year DDFS rate, %	92.9	90.2
Hazard ratio (95% CI)	0.749 (0.623-0.900)	
Nominal 1-sided P value	.0010	

Overall Survival (OS)

- The median follow-up for OS was 35.9 months at the final analysis (**Figure 7**)
- The OS data require longer-term follow-up, as there were fewer than 4% of events in both treatment arms

Figure 7. OS

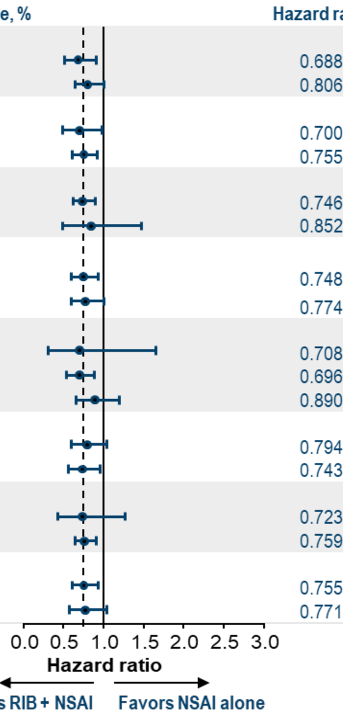


	RIB + NSAI	NSAI alone
Events/n (%)	84/2549 (3.3)	88/2552 (3.4)
3-Year OS rate, %	97.0	96.1
Hazard ratio (95% CI)	0.892 (0.661-1.203)	

iDFS Across Key Prespecified Subgroups

Table 1. iDFS Across Key Prespecified Subgroups

Subgroup	RIB + NSAI Events/n	RIB + NSAI 3-y iDFS rate, %	NSAI alone Events/n	NSAI alone 3-y iDFS rate, %	Hazard ratio	95% CI
Menopausal status						
Men and premenopausal women	83/1125	91.8	114/1132	88.2	0.688	0.519-0.913
Postmenopausal women	143/1424	89.7	169/1420	87.1	0.806	0.645-1.007
AJCC stage						
Stage II	55/1101	94.2	80/1034	92.6	0.700	0.496-0.986
Stage III	170/1528	88.1	203/1512	83.8	0.755	0.616-0.926
Prior CT						
Yes	203/2249	90.5	255/2245	87.1	0.746	0.620-0.897
No	23/300	92.0	28/307	91.2	0.852	0.491-1.479
Region						
North America/Western Europe/Oceania	131/1563	91.1	166/1565	87.5	0.748	0.595-0.941
Rest of world	95/986	90.1	117/987	87.6	0.774	0.591-1.015
Histological grade at time of surgery						
Grade 1	9/213	95.1	13/217	93.1	0.708	0.303-1.657
Grade 2	118/1460	91.5	155/1432	88.0	0.696	0.548-0.885
Grade 3	80/684	87.5	89/702	85.9	0.890	0.658-1.204
Ki-67 status[a]						
Ki-67 ≤20%	93/1199	91.8	117/1236	89.8	0.794	0.605-1.042
Ki-67 >20%	98/920	89.0	125/937	84.9	0.743	0.570-0.988
Nodal status[b,c]						
N0	20/285	93.2	31/328	90.6	0.723	0.412-1.288
N1-N3	206/2261	90.3	251/2219	87.1	0.759	0.631-0.912
Prior ET						
Yes	150/1826	91.4	186/1805	88.4	0.755	0.609-0.936
No	76/723	88.9	97/747	85.8	0.771	0.571-1.040



AJCC, American Joint Committee on Cancer; CT, chemotherapy.
[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.

Safety Profile

- No (adverse events of special interest) AESIs or clinically relevant AEs increased >1% and only a 0.8% increase in discontinuations was observed in this updated analysis[13]
- The most frequent reason for discontinuation of ribociclib was liver-related AEs (**Table2**)

Table 2. Safety Profile of Ribociclib at 400 mg

	RIB + NSAI n=2525		NSAI alone n=2442	
AESIs, %	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Neutropenia[a]	62.5	44.3	4.6	0.9
Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs[b]	26.4	8.6	11.2	1.7
QT interval prolongation[c]	5.3	1.0	1.4	0.6
ECG QT prolonged	4.3	0.3	0.7	0
Interstitial lung disease/pneumonitis[d]	1.5	0	0.9	0.1
Other clinically relevant AEs, %				
Arthralgia	37.3	1.0	43.3	1.3
Nausea	23.3	0.2	7.8	0.0
Headache	22.8	0.4	17.0	0.2
Fatigue	22.3	0.8	13.2	0.2
Diarrhea	14.5	0.6	5.5	0.1
VTE[e]	1.5	0.6	0.8	0.4

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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