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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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Declaration of Interests

Dr. Peter A. Fasching reports (Last DOI update: 20 August 2024)

Advisory Board or Invited Speaker, personal: Roche, Novartis, Pfizer, Daiichi Sankyo, Eisai, MSD, AstraZeneca, Hexal, Lilly, Pierre Fabre, Seagen, Agendia, Gilead, Sanofi-Aventis, Mylan, Medac, Menarini-Stemline, Veracyte, Guardant Health

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Nonfinancial Interests: ASCO, member; Translational Research in Oncology, board member; Arbeitsgemeinschaft für Gynäkologische Onkologie e.V., member; Translational Research in Oncology, member; Deutsche Gesellschaft für Senologie e.v., member

Background

- In the NATALEE trial, the addition of ribociclib to standard-of-care NSAI demonstrated a significant improvement in iDFS over NSAI alone in patients with stage II or III HR+/HER2− 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**

EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease–free survival; NSAI, nonsteroidal aromatase inhibitor.
1. Slamon D, et al. *N Eng J Med*. 2024;390(12):1080-1091. **2.** Slamon D, et al. Oral presentation at: ASCO 2023. Oral LBA500. **3.** Hortobagyi G, et al. Oral presentation at: SABCS 2023. Oral GS03-03.

Study Design and Methods

- 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 years

+

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

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

Primary End Point
- iDFS using STEEP criteria

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

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

Endpoints included in this presentation

Statistical comparisons were performed using a Cox proportional hazards model and the Kaplan-Meier method

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

Data cutoff: 29 April 2024

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.

1. ClinicalTrials.gov. Accessed March 15, 2024. https://clinicaltrials.gov/ct2/show/NCT03701334. **2.** Slamon DJ, et al. Poster presented at: ASCO 2019. Poster TPS597. **3.** Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:1-16. **4.** Hortobagyi, G, et al. Oral presentation at: SABCS 2023. Oral GS03-03.

NATALEE iDFS Analyses Over Time

Analysis time points	Second interim efficacy analysis[1]	Protocol-specified final iDFS analysis[2]	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.

1. Slamon D, et al. *N Eng J Med*. 2024;390(12):1080-1091. **2.** Hortobagyi G, et al. Oral presentation at: SABCS 2023. Oral GS03-03.

Patient Disposition

All patients are off RIB, and 62.8% completed the 3-year duration

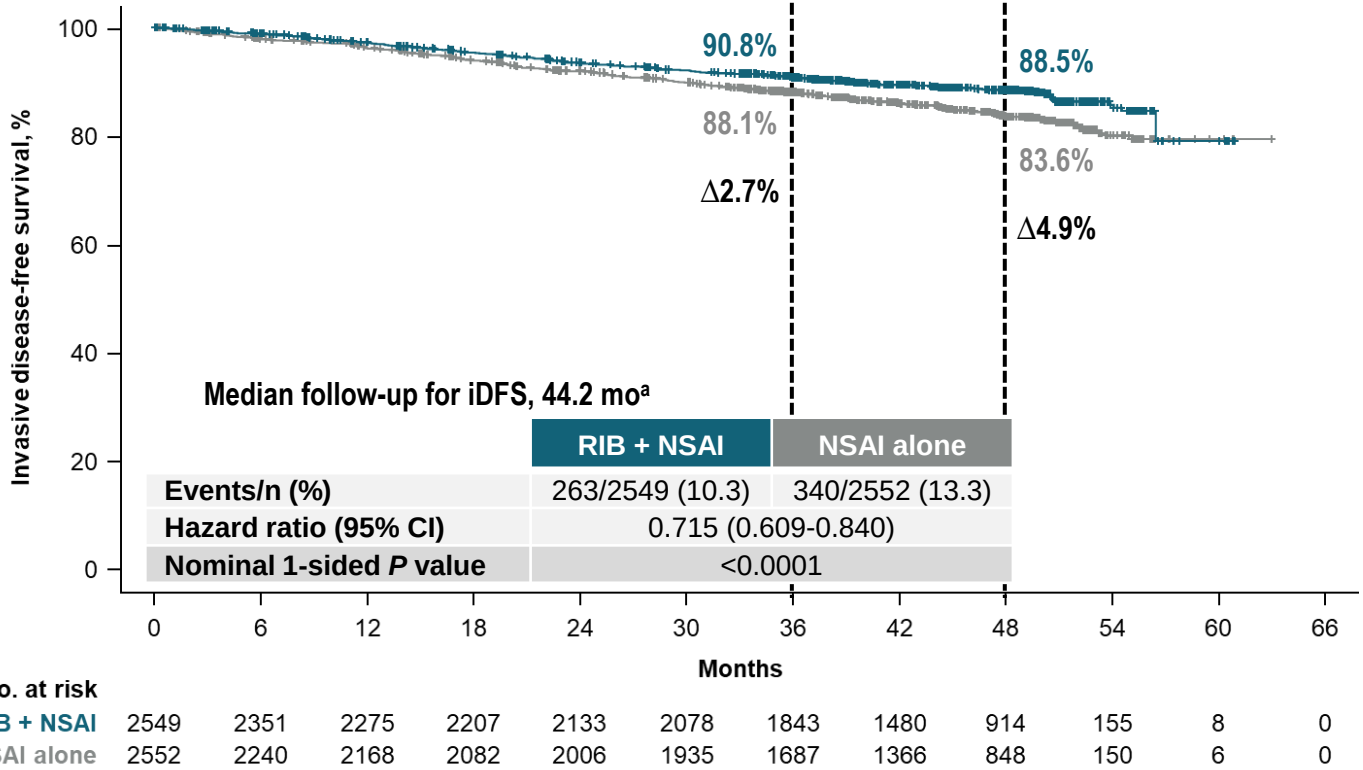
n (%)	RIB + NSAI n=2549		NSAI alone n=2552
Randomized	2549 (100)		2552 (100)
Treated	2526 (99.1)		2441 (95.7)
NSAI treatment ongoing	1794 (70.4)		1628 (63.8)
Completed 3 y RIB treatment	1601 (62.8)		–
Completed 5y study treatment	10 (0.4)		9 (0.4)
	RIB	NSAI	NSAI
Early discontinuation	923 (36.2)	722 (28.3)	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	5 (0.2)	9 (0.4)	6 (0.2)
Other[a]	114 (4.5)	160 (6.2)	197 (7.7)

- At the data cutoff, median duration of exposure to study treatment was 45.1 months in the RIB + NSAI arm vs 45.0 months in the NSAI alone arm

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

iDFS in ITT Population

Significant iDFS benefit with RIB + NSAI after the planned 3-year treatment

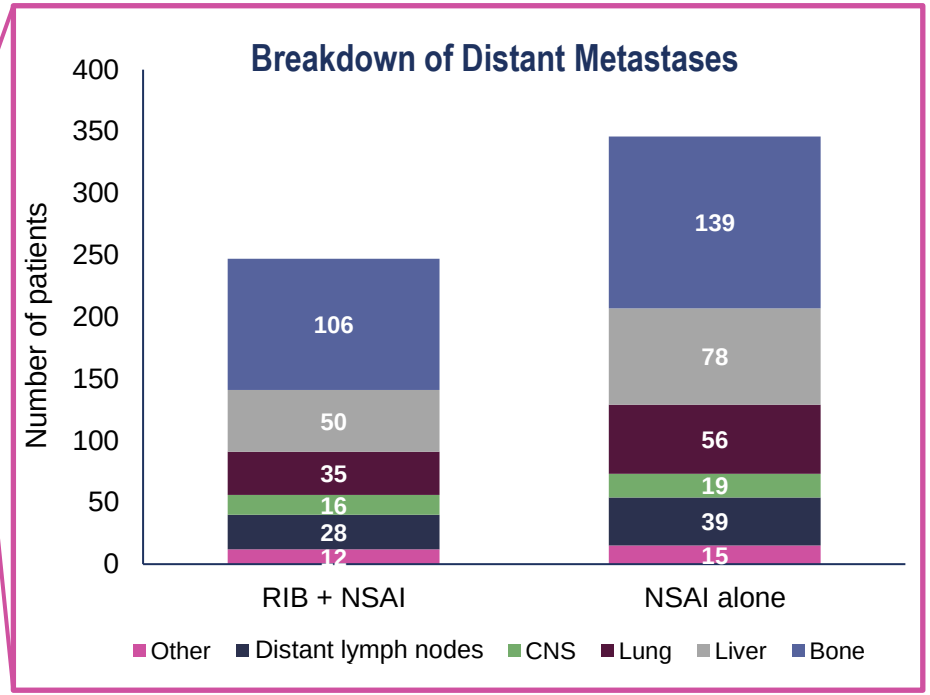


iDFS, invasive disease–free survival; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] An additional 10.9 months of follow-up compared with the protocol-specified final iDFS analysis.

iDFS Events in ITT Population

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	176 (6.9)	246 (9.6)
Local/regional invasive recurrence	25 (1.0)	49 (1.9)
Second primary nonbreast cancer	39 (1.5)	40 (1.6)
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)



CNS, central nervous system; iDFS, invasive disease–free survival; ITT, intent to treat; NE, not estimable; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

iDFS Across Key Prespecified Subgroups

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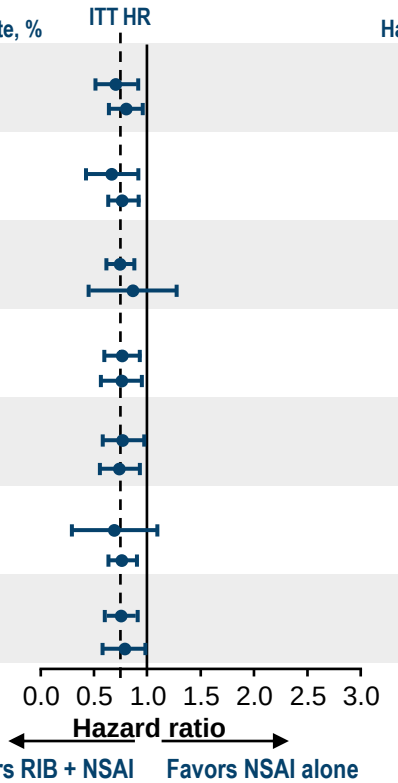
Consistent iDFS benefit across subgroups

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



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.

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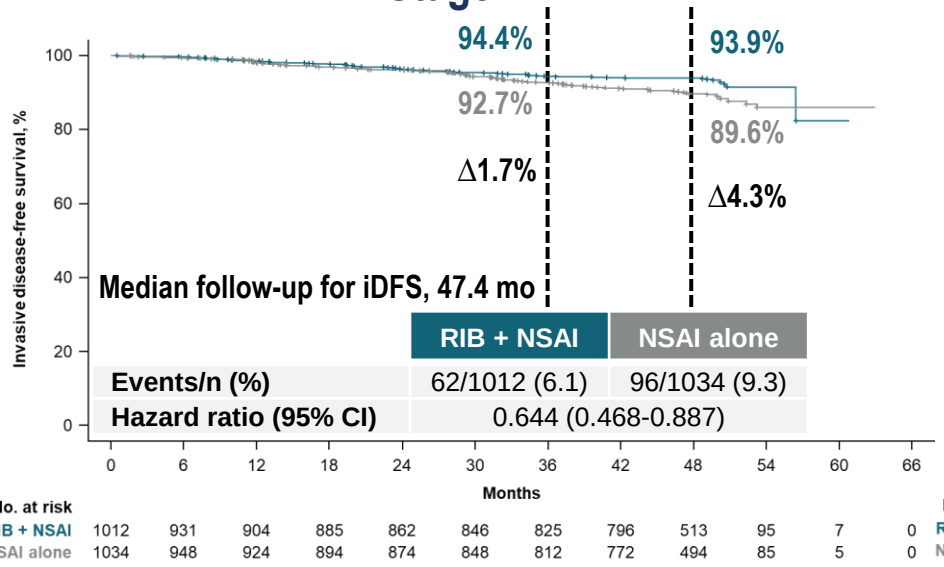
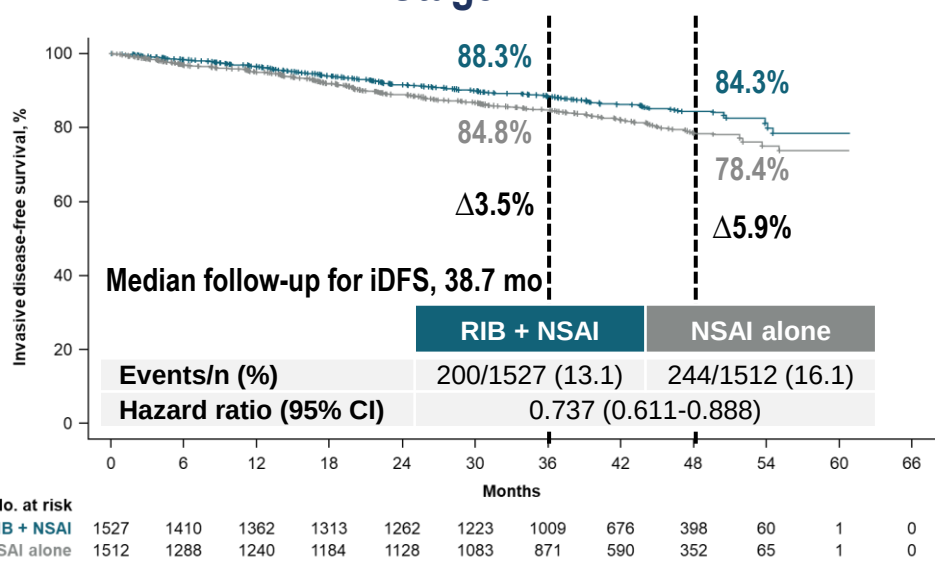
iDFS by Stage

RIB + NSAI demonstrated an increasing magnitude of iDFS benefit over time for stage II/III disease

Stage II



Stage III

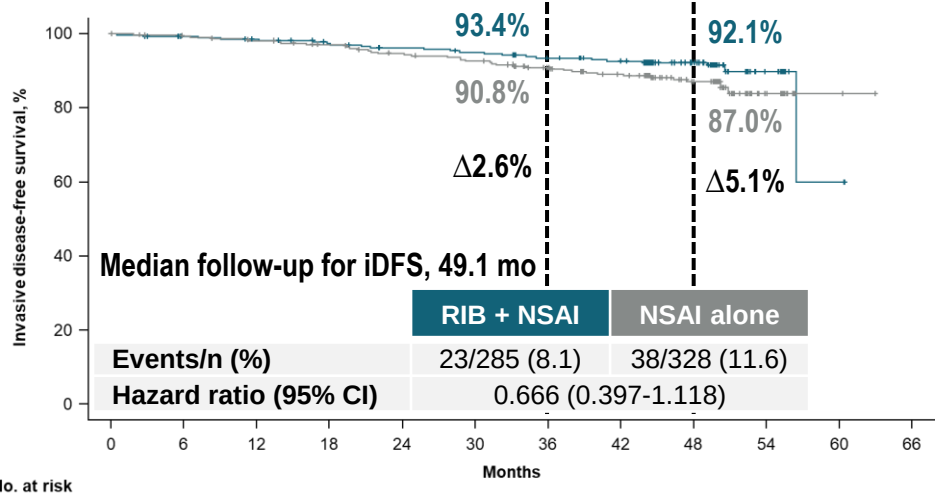


iDFS, invasive disease–free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

iDFS by Nodal Status

RIB + NSAI showed an increasing magnitude of iDFS benefit over time for patients with N0 or N1-3 disease

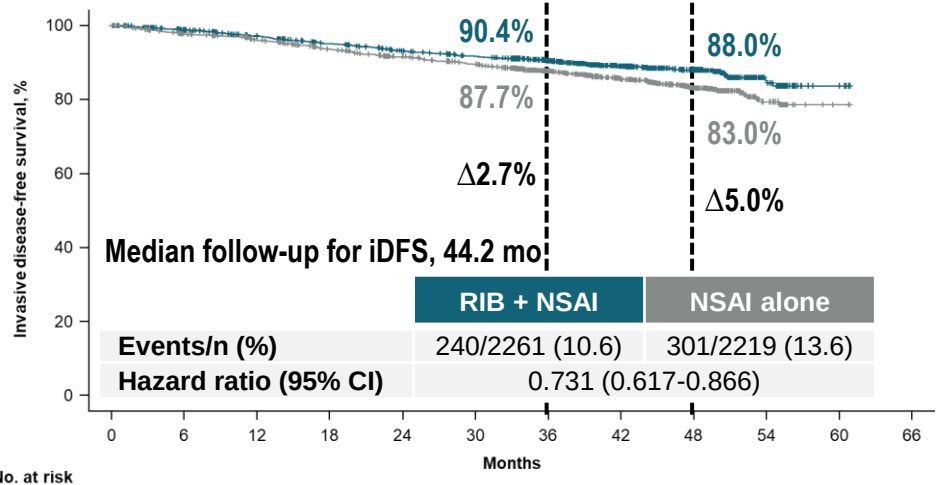
N0



	RIB + NSAI	NSAI alone
Events/n (%)	23/285 (8.1)	38/328 (11.6)
Hazard ratio (95% CI)	0.666 (0.397-1.118)	

No. at risk												
RIB + NSAI	285	262	258	250	244	240	230	221	156	37	2	0
NSAI alone	328	300	294	287	277	270	252	234	156	33	2	0

N1-3



	RIB + NSAI	NSAI alone
Events/n (%)	240/2261 (10.6)	301/2219 (13.6)
Hazard ratio (95% CI)	0.731 (0.617-0.866)	

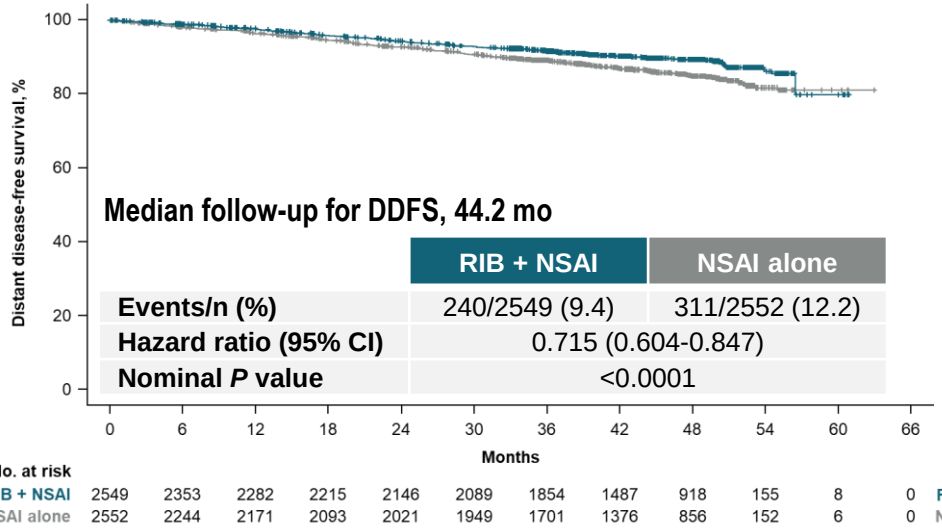
No. at risk												
RIB + NSAI	2261	2086	2014	1954	1886	1835	1612	1258	758	118	6	0
NSAI alone	2219	1937	1872	1793	1727	1663	1433	1130	689	117	4	0

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

Key Secondary Efficacy Endpoints

RIB + NSAI continued to improve DDFS and showed a positive trend for OS

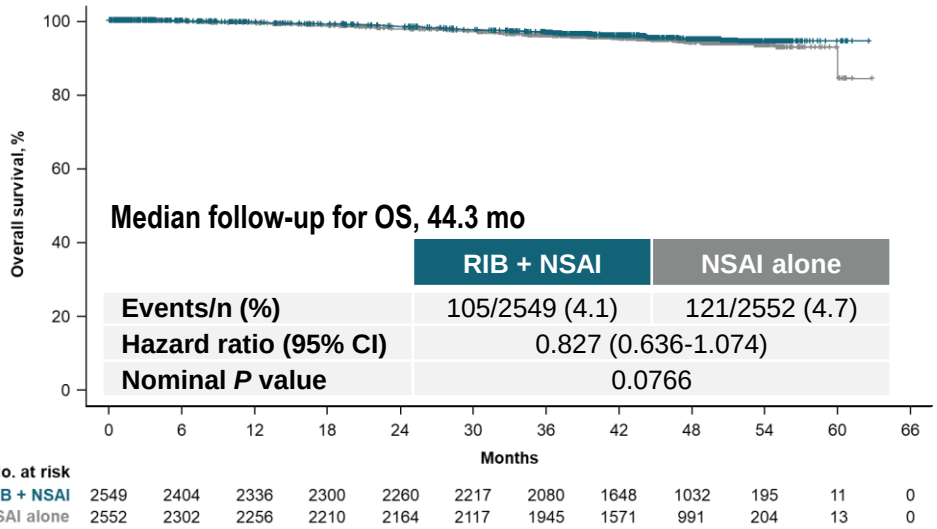
DDFS



Median follow-up for DDFS, 44.2 mo

	RIB + NSAI	NSAI alone
Events/n (%)	240/2549 (9.4)	311/2552 (12.2)
Hazard ratio (95% CI)	0.715 (0.604-0.847)	
Nominal *P* value	<0.0001	

OS



Median follow-up for OS, 44.3 mo

	RIB + NSAI	NSAI alone
Events/n (%)	105/2549 (4.1)	121/2552 (4.7)
Hazard ratio (95% CI)	0.827 (0.636-1.074)	
Nominal *P* value	0.0766	

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

Safety

Incidence of AEs remained stable from prior analyses

	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	8.6	11.4	1.7
QT interval prolongation[c]	5.4	1.0	1.6	0.7
ECG QT prolonged	4.4	0.2	0.8	<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	7.9	<0.1
Headache	22.9	0.4	17.2	0.2
Fatigue	22.8	0.8	13.5	0.2
Diarrhea	14.6	0.6	5.5	0.1
VTE[e]	1.1	0.6	0.5	0.3

- 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[1,2]
- Liver-related AEs were predominantly ALT/AST elevations without concomitant bilirubin increase

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.
1. Slamon D, et al. *N Eng J Med*. 2024;390(12):1080-1091. **2.** Hortobagyi G, et al. Oral presentation at: SABCS 2023. Oral GS03-03.

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

DDFS, distant disease–free survival; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease–free survival; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival.

Acknowledgments

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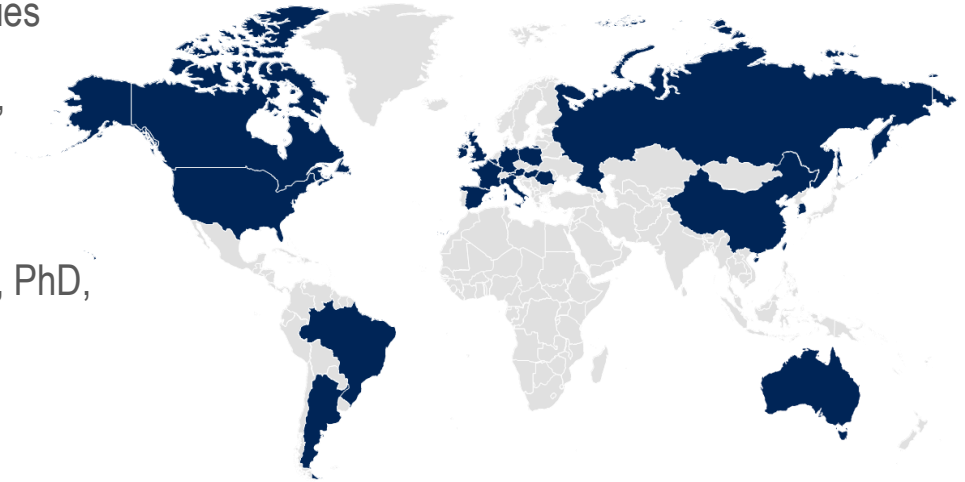

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