SABCS SAN ANTONIO BREAST CANCER SYMPOSIUM®
DECEMBER 5-9, 2023 | @SABCSSanAntonio

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

Gabriel N. Hortobagyi,[1] Daniil Stroyakovskiy,[2] Denise A. Yardley,[3] Chiun-Sheng Huang,[4] Peter A. Fasching,[5] John Crown,[6] Aditya Bardia,[7] Stephen Chia,[8] Seock-Ah Im,[9] Miguel Martin,[10] Sherene Loi,[11] Binghe Xu,[12] Sara Hurvitz,[13] Carlos Barrios,[14] Michael Untch,[15] Rebecca Moroose,[16] Frances Visco,[17] Federico Parnizari,[18] Farhat Ghaznawi,[19] Zheng Li,[19] Sorcha Waters,[20] Arunava Chakravartty,[19] Dennis Slamon[21]

[1]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Moscow City Oncology Hospital No. 62 of Moscow Healthcare Department, Moscow Oblast, Russia; [3]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA; [4]National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei City, Taiwan; [5]University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Friedrich Alexander University Erlangen-Nuremberg, Erlangen, Germany; [6]St. Vincent's University Hospital, Dublin, Ireland; [7]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA; [8]British Columbia Cancer Agency, Vancouver, BC, Canada; [9]Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [10]Instituto de Investigación Sanitaria Gregorio Marañón, Centro de Investigación Biomédica en Red de Cáncer, Grupo Español de Investigación en Cáncer de Mama, Universidad Complutense de Madrid, Madrid, Spain; [11]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [12]Department of Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) & Peking Union Medical College (PUMC), Beijing, China; [13]University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [14]Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil; [15]Interdisciplinary Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; [16]UF Health Cancer Center – Orlando Health, Orlando, FL, USA; [17]National Breast Cancer Coalition (NBCC), Washington, DC, USA; [18]Translational Research in Oncology (TRIO), Montevideo, Uruguay; [19]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [20]Novartis Ireland, Dublin, Ireland; [21]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Disclosure Information

San Antonio Breast Cancer Symposium®
December 5-9, 2023 | San Antonio, TX | @SABCSSanAntonio

Gabriel N. Hortobagyi

Consultant/advisory role: Lilly, Merck, Novartis, and Roche

Grant/research support to institution: Novartis

Background

- 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

1. Iqbal J, et al. *JAMA*. 2015;313:165-173. 2. Pistilli B, et al. *Am Soc Clin Oncol Educ Book*. 2022;42:1-13. 3. Pan H, et al. *N Engl J Med*. 2017;377:1836-1846. 4. Tripathy D, et al. *Lancet Oncol*. 2018;7:904-915. 5. Slamon DJ, et al. *J Clin Oncol*. 2018;24:2465-2472. 6. Hortobagyi GN, et al. *Ann Oncol*. 2018;29:1541-1547. 7. Hortobagyi GN, et al. *N Engl J Med*. 2022;386:942-950. 8. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524. 9. Im SA, et al. *N Engl J Med*. 2019;381:307-316. 10. Verma S, et al. *Breast Cancer Res Treat*. 2018;170:535-545. 11. Fasching PA, et al. *Breast*. 2020;54:148-154. 12. Harbeck N, et al. *Ther Adv Med Oncol*. 2020;12:1758835920943065. 13. Slamon D, et al. ASCO 2023. Oral LBA500.

NATALEE Study Design[1-3]

- 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]

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

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

ct, circulating tumor; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; 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 Jan 10, 2019 to April 20, 2021. [c] Open-label design. [d] Per investigator choice.
1. Slamon D, et al. ASCO 2023. Oral LBA500. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl). Abstract TPS597. 3. Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:17588359231178125.

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

Patient Disposition

Second Interim Efficacy Analysis

Data cutoff: January 11, 2023
iDFS events: n=426

Ribociclib + NSAI, n=2549

- 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%)

NSAI alone, n=2552

- NSAI ongoing: 1826 (71.6%)
- Discontinued NSAI: 617 (24.2%)

Final iDFS Analysis

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

Ribociclib + NSAI, n=2549

- 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

- NSAI ongoing: 1748 (68.5%)
- Discontinued NSAI: 693 (27.2%)

AE, adverse event; RIB, ribociclib.
Slamon D, et al. ASCO 2023. Oral LBA500.

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
- 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%)

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

Ribociclib + NSAI, n=2549
- 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
- NSAI ongoing: 1748 (68.5%)
- Discontinued NSAI: 693 (27.2%)

AE, adverse event; RIB, ribociclib.
Slamon D, et al. ASCO 2023. Oral LBA500.

Patient Disposition

Second Interim Efficacy Analysis

Data cutoff: January 11, 2023
iDFS events: n=426

Ribociclib + NSAI, n=2549

- 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%)

NSAI alone, n=2552

- NSAI ongoing: 1826 (71.6%)
- Discontinued NSAI: 617 (24.2%)

Final iDFS Analysis

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

Ribociclib + NSAI, n=2549

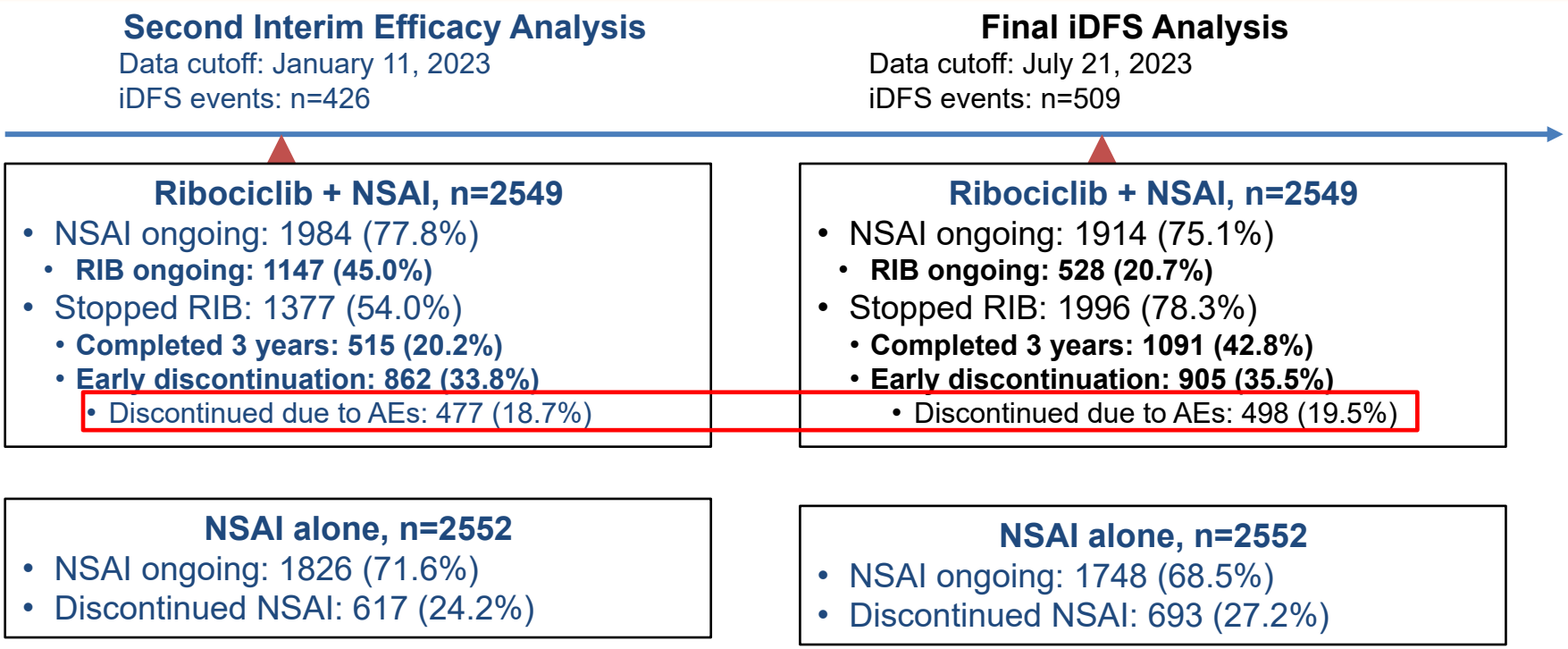
- NSAI ongoing: 1914 (75.1%)
  - **RIB ongoing: 528 (20.7%)**
- Stopped RIB: 1996 (78.3%)
  - **Completed 3 years: 1091 (42.8%)**
  - **Early discontinuation: 905 (35.5%)**
    - Discontinued due to AEs: 498 (19.5%)

NSAI alone, n=2552

- NSAI ongoing: 1748 (68.5%)
- Discontinued NSAI: 693 (27.2%)

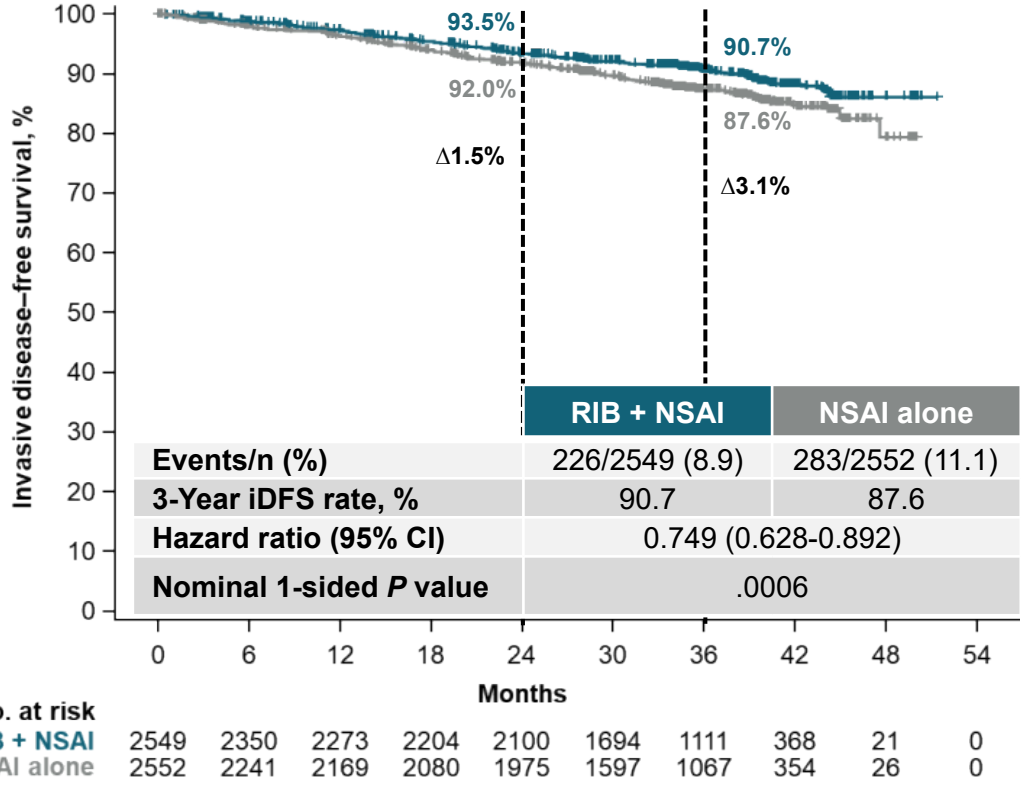
AE, adverse event; RIB, ribociclib.
Slamon D, et al. ASCO 2023. Oral LBA500.

Patient Disposition



AE, adverse event; RIB, ribociclib.
Slamon D, et al. ASCO 2023. Oral LBA500.

Invasive Disease–Free Survival



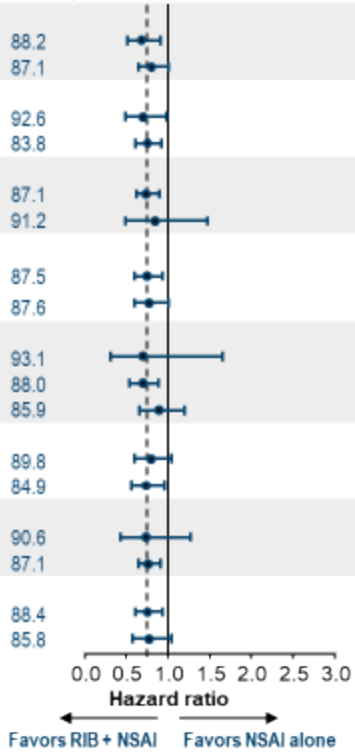
	RIB + NSAI	NSAI alone
Events/n (%)	226/2549 (8.9)	283/2552 (11.1)
3-Year iDFS rate, %	90.7	87.6
Hazard ratio (95% CI)	0.749 (0.628-0.892)	
Nominal 1-sided *P* value	.0006	

- The median follow-up for iDFS was 33.3 months (maximum, 51 months)—an additional 5.6 months from the second interim efficacy analysis[1]
- The absolute iDFS benefit with ribociclib plus NSAI was 3.1% at 3 years
- The risk of invasive disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone

1. Slamon D, et al. ASCO 2023. Oral LBA500.

iDFS Across Key Prespecified Subgroups

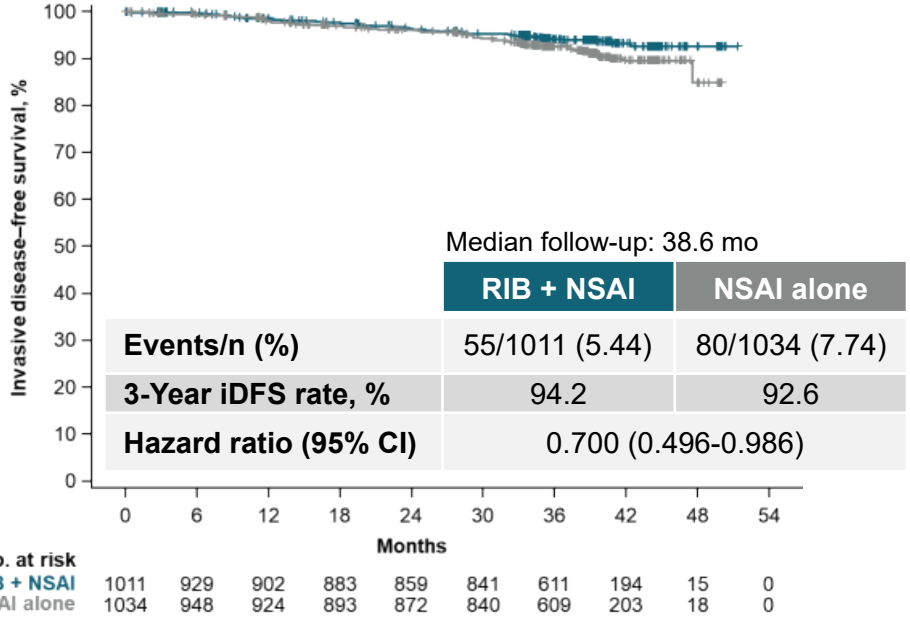
Subgroup	RIB + NSAI Events/n	RIB + NSAI 3-y iDFS rate, %	NSAI alone Events/n	NSAI alone 3-y iDFS rate, %	Hazard ratio	95% CI
Menopausal status						
Men and premenopausal women	83/1125	91.8	114/1132	88.2	0.688	0.519-0.913
Postmenopausal women	143/1424	89.7	169/1420	87.1	0.806	0.645-1.007
AJCC stage						
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.

iDFS by Anatomical Stage

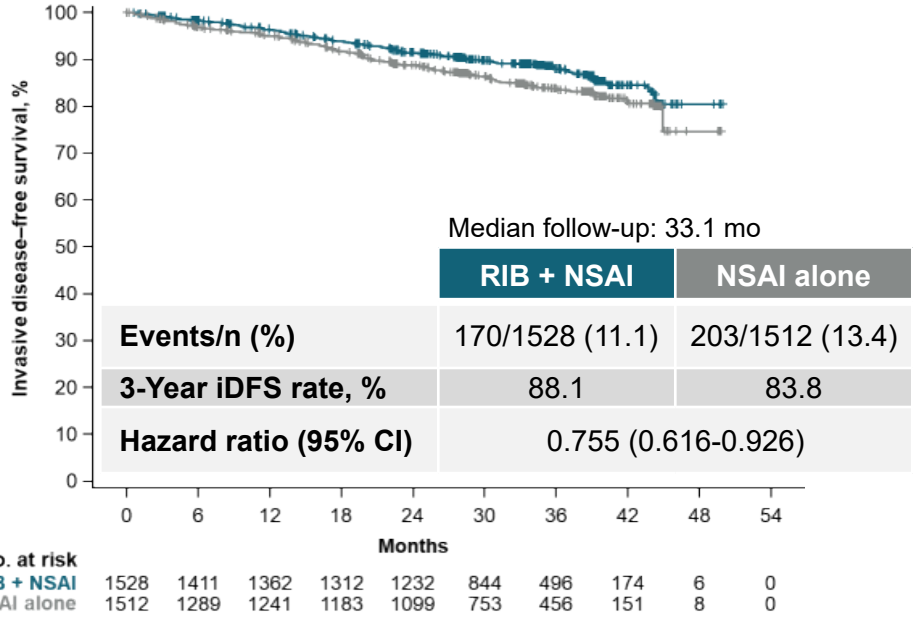
Stage II



Median follow-up: 38.6 mo

	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)	

Stage III



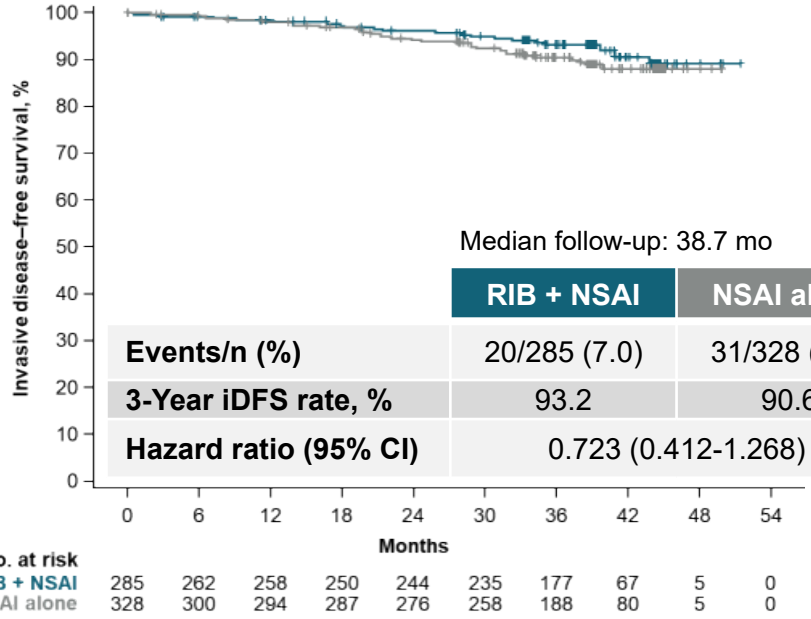
Median follow-up: 33.1 mo

	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)	

- 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

iDFS by Nodal Status

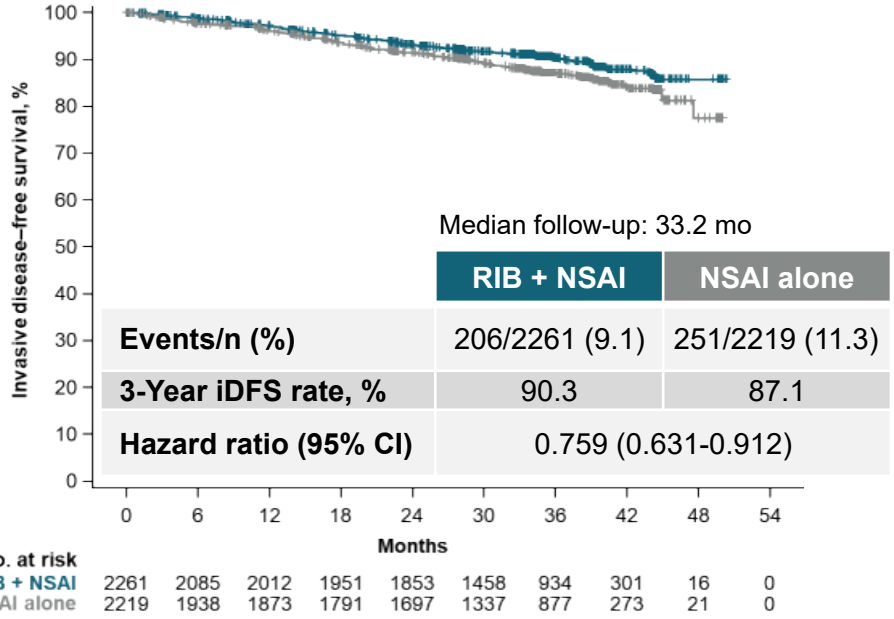
N0



Median follow-up: 38.7 mo

	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)	

N1-N3

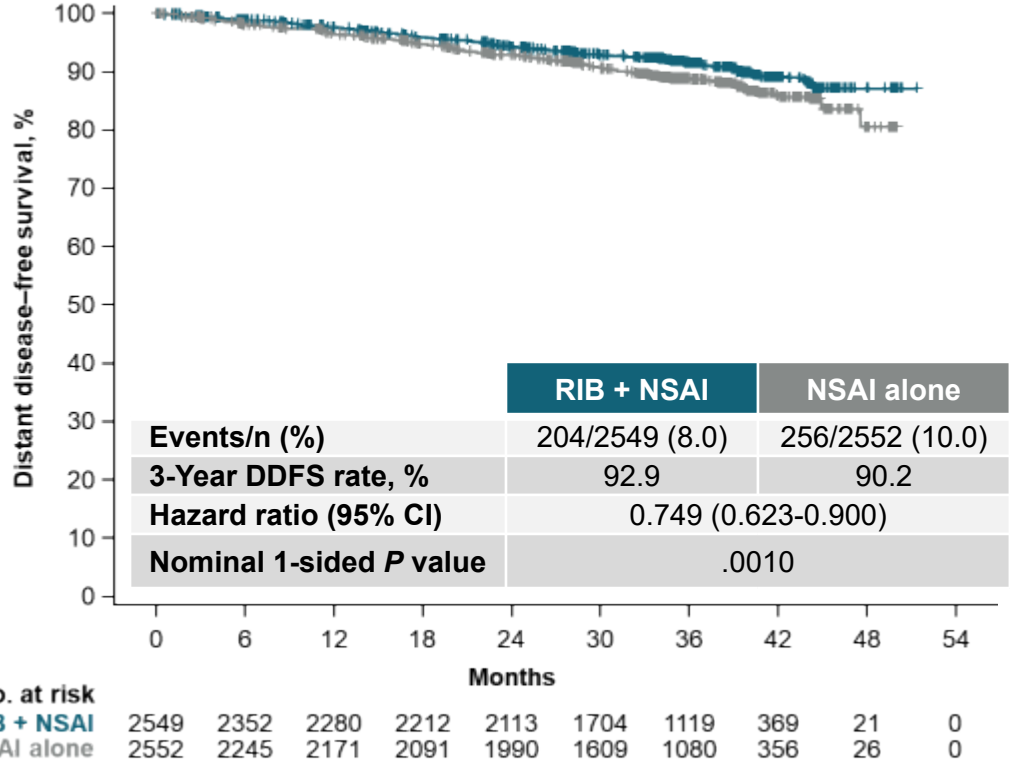


Median follow-up: 33.2 mo

	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)	

- 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

Distant Disease–Free Survival



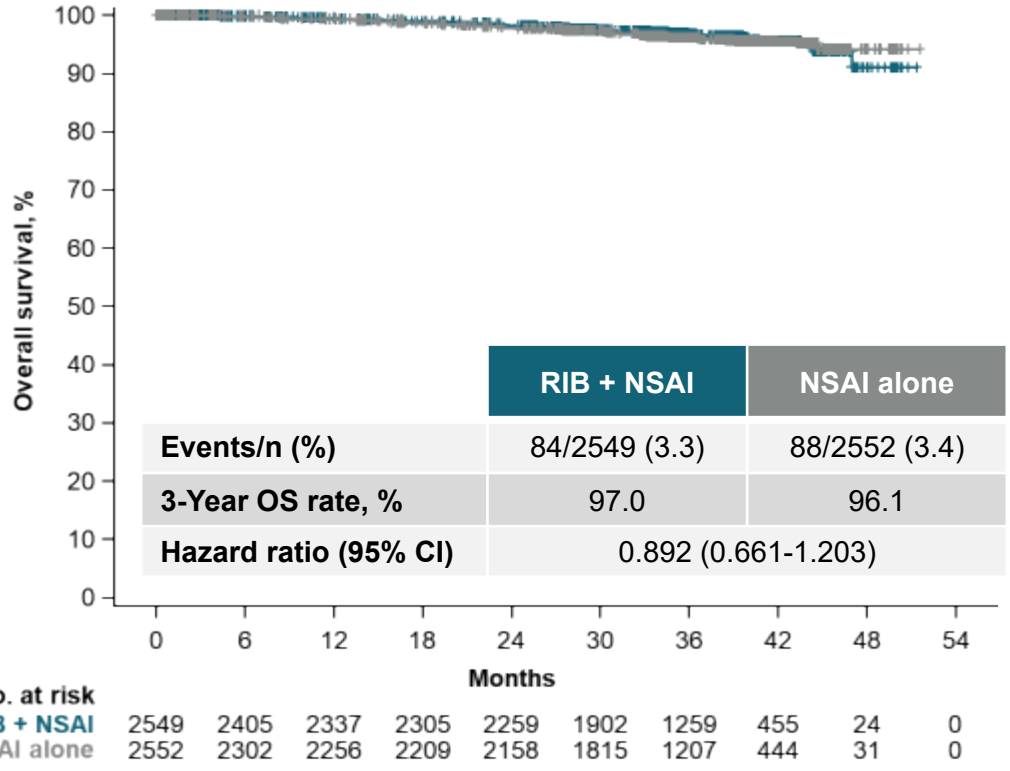
	RIB + NSAI	NSAI alone
Events/n (%)	204/2549 (8.0)	256/2552 (10.0)
3-Year DDFS rate, %	92.9	90.2
Hazard ratio (95% CI)	0.749 (0.623-0.900)	
Nominal 1-sided *P* value	.0010	

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

DDFS, distant disease–free survival.

[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).

Overall Survival



	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)	

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

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

- No AESIs or clinically relevant AEs increased >1% and only a 0.8% increase in discontinuations was observed in this updated analysis[1]
- The most frequent reason for discontinuation of ribociclib was liver-related AEs

AESI, adverse event of special interest; 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. ASCO 2023. Oral LBA500.

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[1]
  - The iDFS benefit was consistent across key prespecified subgroups, including patients with stage II, III, node-negative, and node-positive disease[2]
  - 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[1]

1. Slamon D, et al. ASCO 2023. Oral LBA500. 2. Bardia A, et al. ESMO 2023. Oral LBA23.

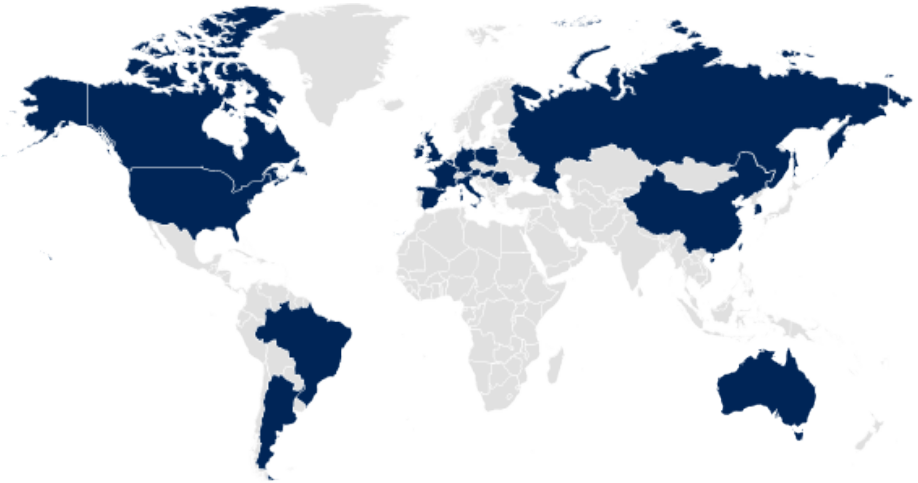
Conclusions

- 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[1]
  - The iDFS benefit was consistent across key prespecified subgroups, including patients with stage II, III, node-negative, and node-positive disease[2]
  - 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[1]

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

1. Slamon D, et al. ASCO 2023. Oral LBA500. 2. Bardia A, et al. ESMO 2023. Oral LBA23.

Acknowledgments



- We thank the 5101 patients who participated in this trial and their families and caregivers from 384 sites in 20 countries
- We also thank the data monitoring committee members, study steering committee members, and staff who assisted with the trial at each site
- Medical writing support was provided by Tara Wabbersen, PhD, and Casey Nielsen, PhD, of Nucleus Global
- Ribociclib was discovered by the Novartis Institutes for BioMedical Research in collaboration with Astex Pharmaceuticals

Scan QR Code Below for a Copy of This Presentation

Copies of this presentation obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from SABCS® and the author of this presentation.

https://bit.ly/HortobagyiGGS0303

Scan this QR code