BERLIN 2025 ESMO congress

Adjuvant Ribociclib Plus Nonsteroidal Aromatase Inhibitor Therapy in Patients With HR+/HER2− Early Breast Cancer: NATALEE 5-Year Outcomes

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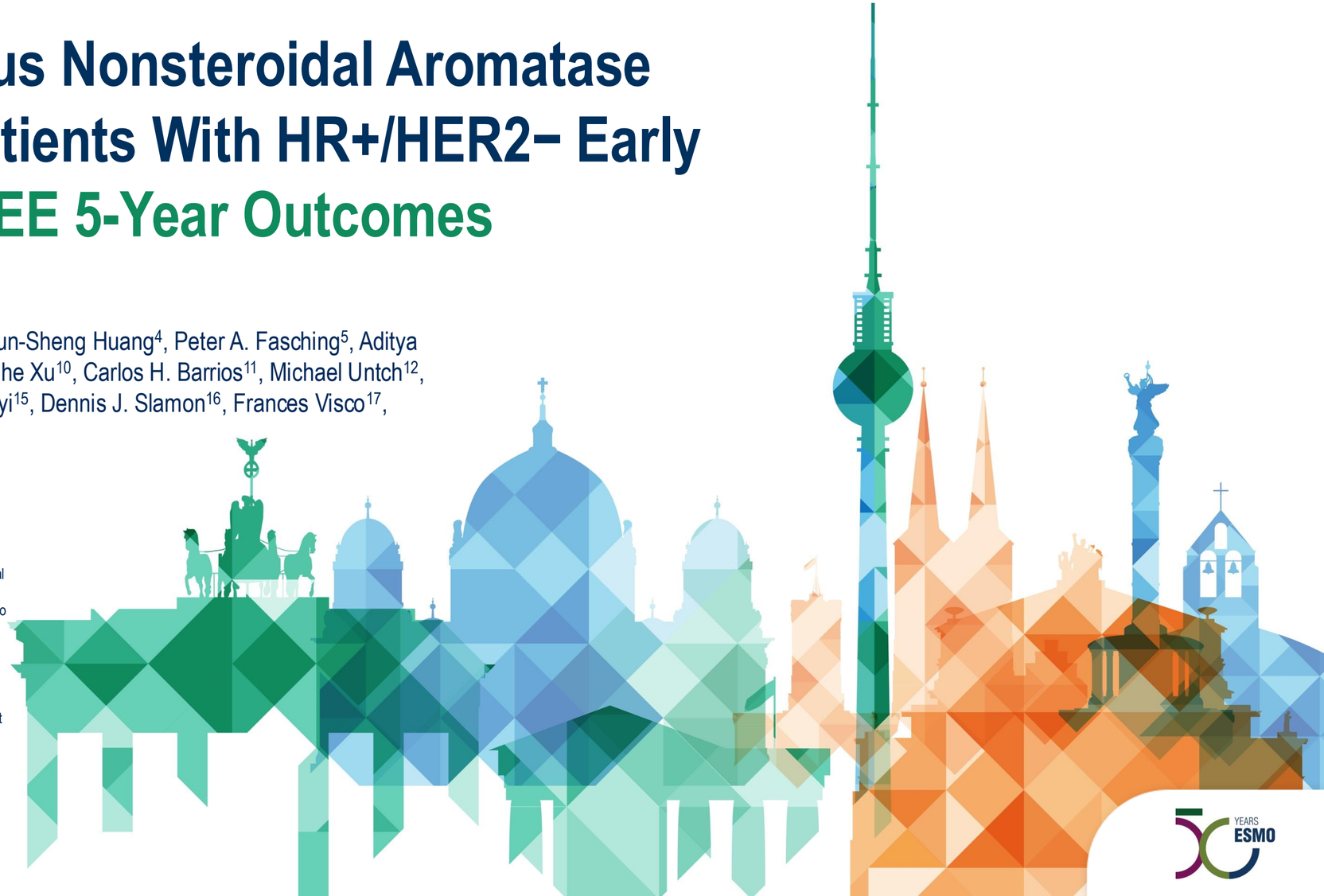
Speaker: John Crown, M.D.



50 YEARS ESMO

Declarations of Interest

John Crown reports:

- Personal fees from Pierre Fabre, Immunocore, Novartis, AstraZeneca, and Regeneron
- Stock from OncoAssure and Akkure
- Travel support to meetings from Novartis, MSD Oncology, Pfizer, Roche, AstraZeneca, and Regeneron
- A patent for WO2020011770 (A1) - A method of predicting response to treatment in cancer patients

Background

- Ribociclib (RIB), in combination with an aromatase inhibitor, is indicated as adjuvant treatment for patients with stage II or III HR+/HER2− EBC at high risk of recurrence[1,2]
- Treatment with RIB + a nonsteroidal aromatase inhibitor (NSAI) demonstrated statistically significant improvement in invasive disease–free survival (iDFS) vs NSAI alone in patients with HR+/HER2− EBC at the primary analysis of NATALEE (median iDFS follow-up, 27.7 months; HR, 0.75; 2-sided *P*=.003)[3]
- The NATALEE trial was specifically designed to include a broad patient population with high risk of recurrence, and results from a 4-year follow-up show sustained iDFS improvement with increasing absolute benefit
- We report updated efficacy and key safety outcomes from a prespecified 5-year analysis of NATALEE with all patients being off ribociclib treatment for a median of 2 years (data cutoff: May 28, 2025; median iDFS-follow-up, 55.4 months)

EBC, early breast cancer; HR, hazard ratio; HR+/HER2−, hormone receptor positive, human epidermal growth factor receptor 2 negative.

1. Ribociclib. Summary of product characteristics. Novartis Pharmaceuticals. 2. Ribociclib. Prescribing information. Novartis Pharmaceuticals Corp. 3. Slamon D et al. *N Engl J Med*. 2024;390(12):1080-1091.

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Study Design: NATALEE

An open-label, multicenter, randomized, phase 3 trial[1,2]

Adult patients with stage II and III HR+/HER2− EBC

- Prior ET allowed up to 12 months
- **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

R
1:1

RIB
400 mg/day
3 weeks on/1 week off for **3 y**
+
NSAI
Letrozole or anastrozole[b] for **≥5 y**
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[b] for **≥5 y**
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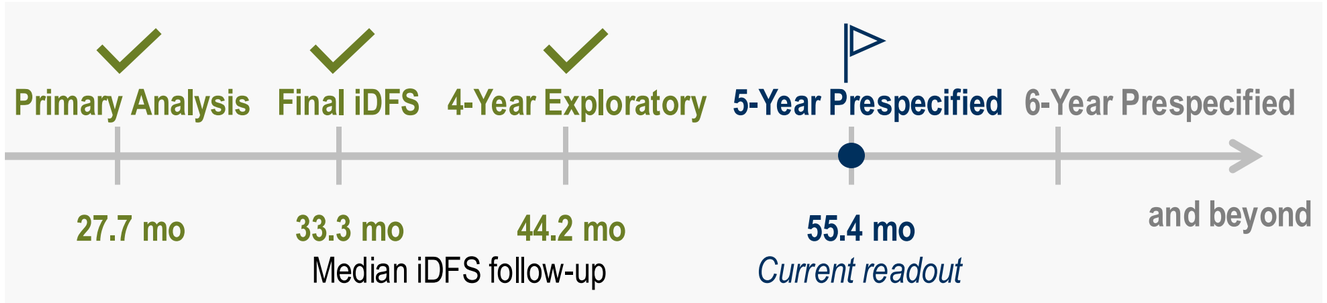
Primary End Point
iDFS using STEEP criteria

Secondary End Points
- RFS, DDFS, OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- DRFS
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Efficacy outcomes for the 5-year analysis were estimated by the Kaplan-Meier method, and results are descriptive. The Cox proportional hazards model was used to estimate the HRs and 95% CIs.



[a] Enrollment of patients with stage II disease was capped at 40%. [b] Per investigator choice.
ctDNA/RNA, circulating tumor DNA/RNA; DDFS, distant disease–free survival; DRFS, distant recurrence–free survival; EBC, early breast cancer; ET, endocrine therapy; HR, hazard ratio; iDFS, invasive disease–free survival; ITT, intention to treat; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcomes; RIB, ribociclib; RFS, recurrence-free survival; STEEP, Standardized Definitions for Efficacy End Points.

1. ClinicalTrials.gov. Accessed November 8, 2023. https://clinicaltrials.gov/study/NCT03701334.
2. Slamon D et al. *Ther Adv Med Oncol.* 2023;15:1-16.

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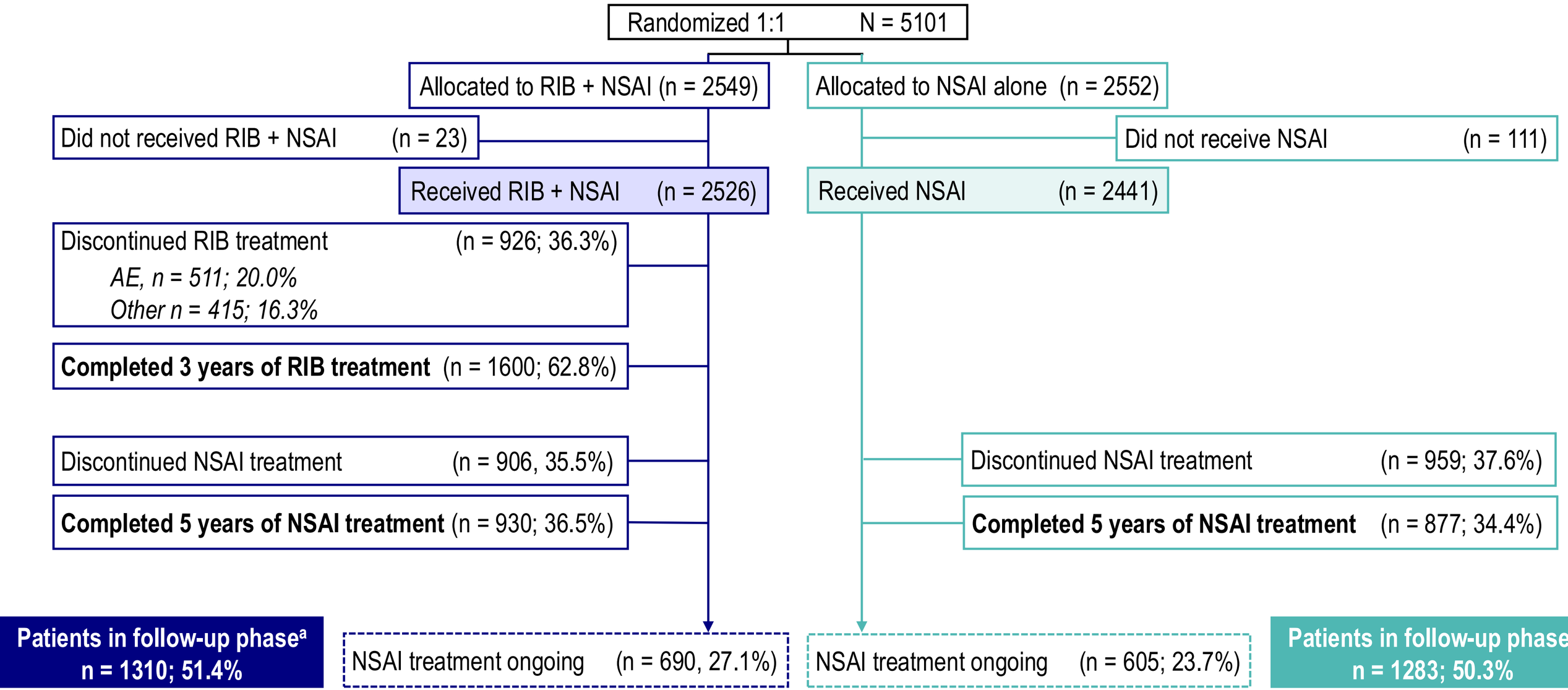
Updated Disposition: All Patients Off RIB Treatment for a Median of 2 Years



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[a] Patients are either in follow-up or are awaiting their first follow-up appointment post treatment cessation (discontinuation or completion of regimen).
AE, adverse event; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

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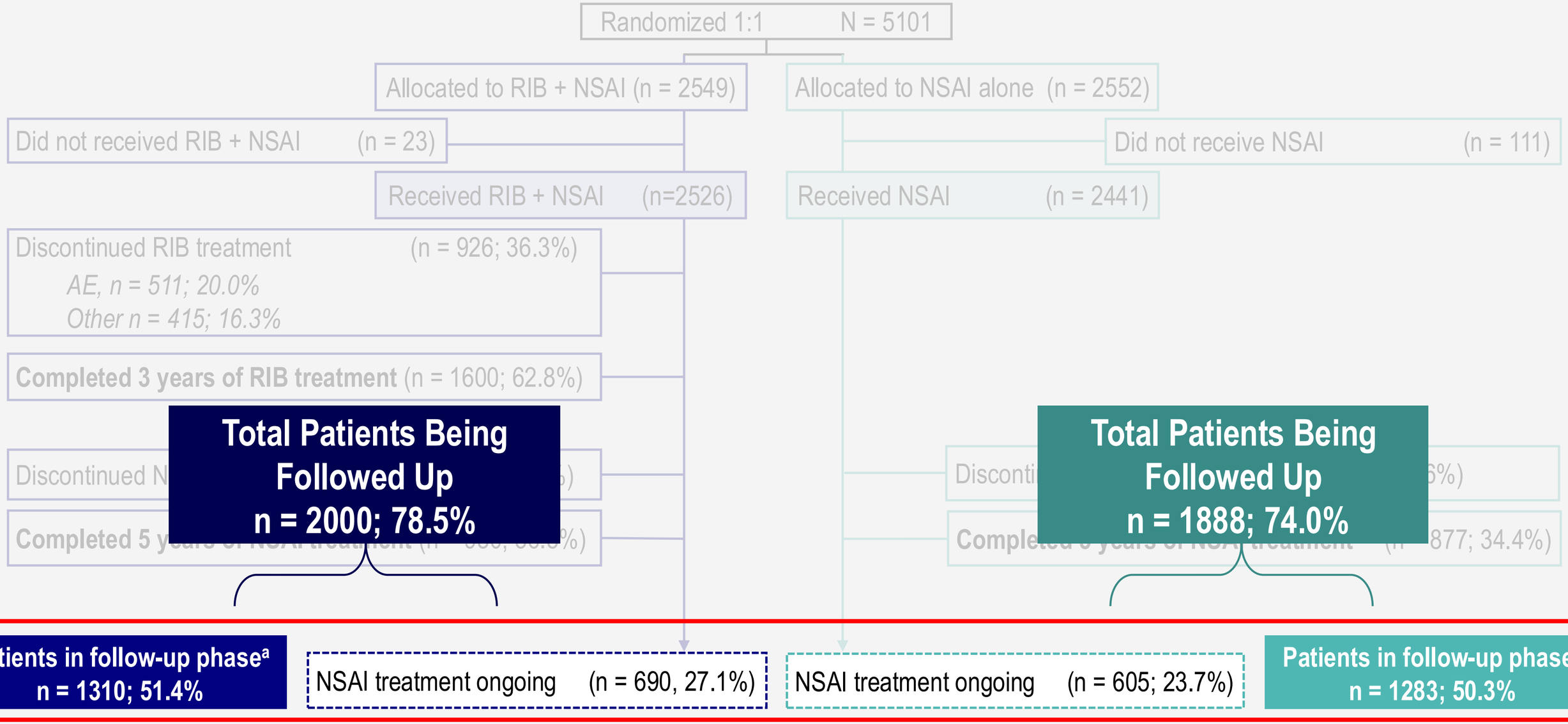

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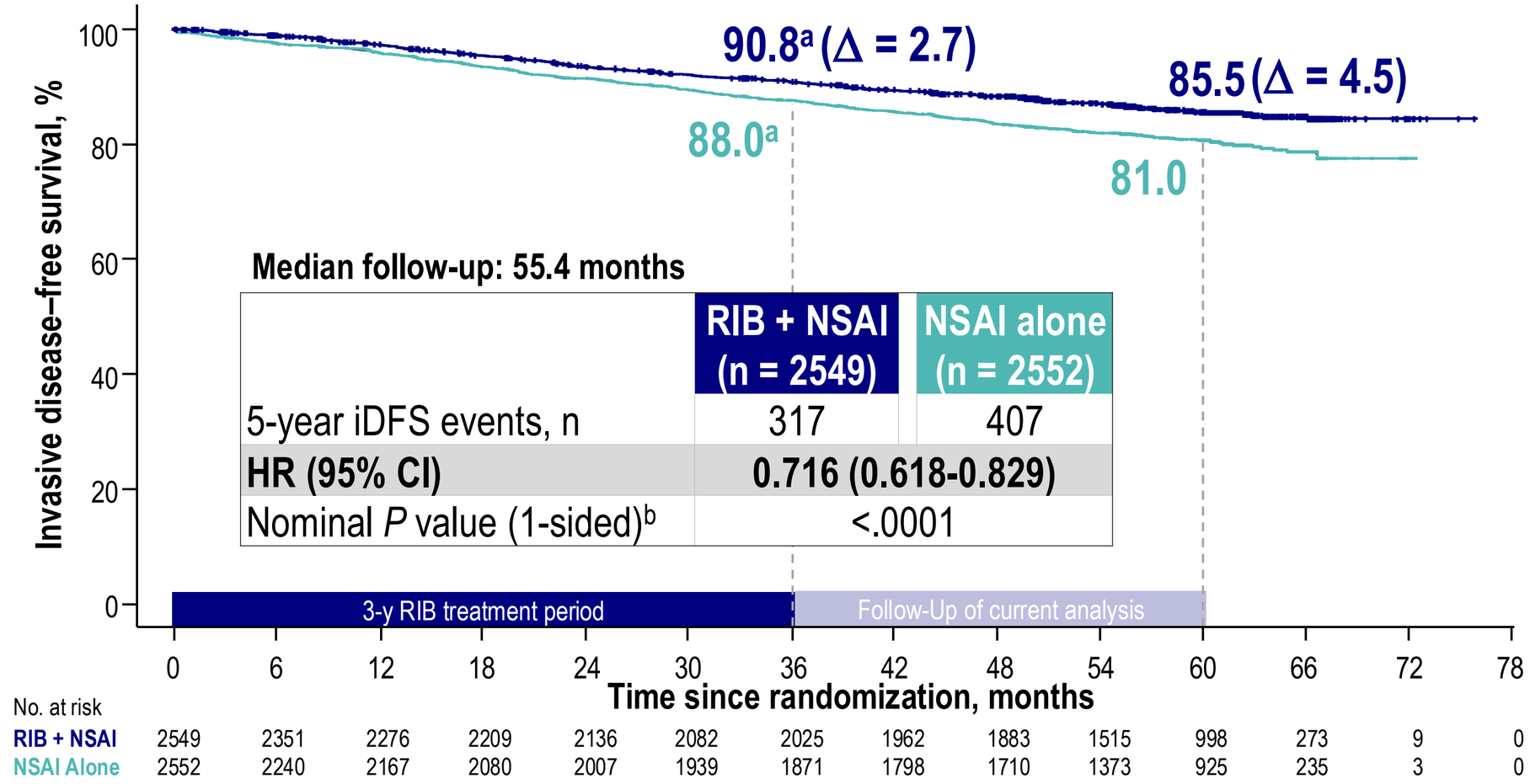
iDFS in the ITT Population

With 55.4 months of follow-up, RIB continues to demonstrate a durable iDFS benefit



[a] The difference between percentages does not equal 2.7 due to rounding. [b] Comparison of survival between treatment arms was generated by stratified log-rank test (1-sided *P* value, informational and not preplanned).
HR, hazard ratio; IDFS, invasive disease–free survival; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

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RIB + NSAI Reduces Distant Disease

***Most iDFS events were distant recurrences*, which were more common in the NSAI-alone arm**

ITT Population	RIB + NSAI n = 2549	NSAI Alone n = 2552
iDFS event type, n (%)		
Distant recurrence	**207 (8.1)**	**290 (11.4)**
Local/regional invasive recurrence	29 (1.1)	56 (2.2)
Second primary nonbreast cancer	49 (1.9)	52 (2.0)
Death	23 (0.9)	14 (0.5)
Invasive contralateral breast tumor	14 (0.5)	14 (0.5)
Invasive ipsilateral breast tumor	8 (0.3)	11 (0.4)

[a] One patient may have multiple iDFS recurrence sites.
iDFS, invasive disease–free survival; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

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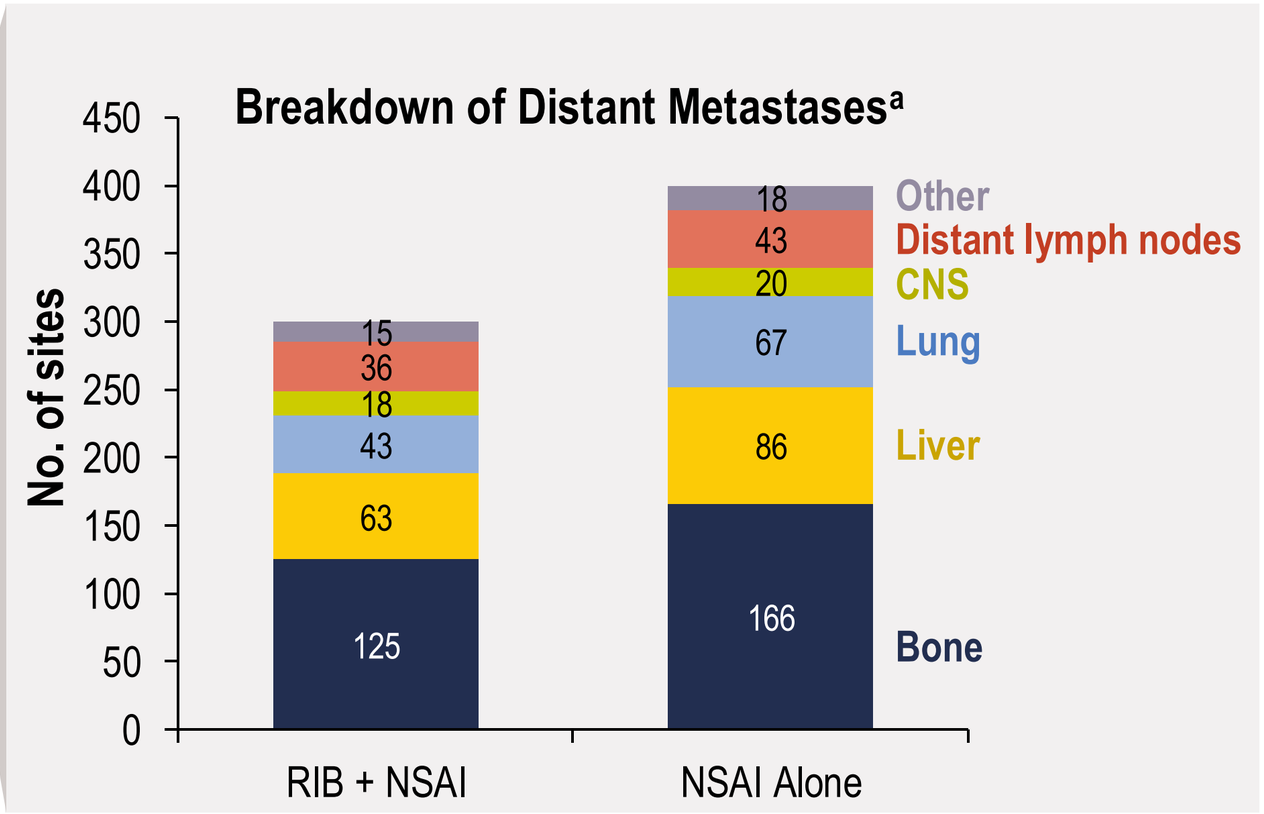

[a] One patient may have multiple iDFS recurrence sites.
CNS, central nervous system; iDFS, invasive disease–free survival; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

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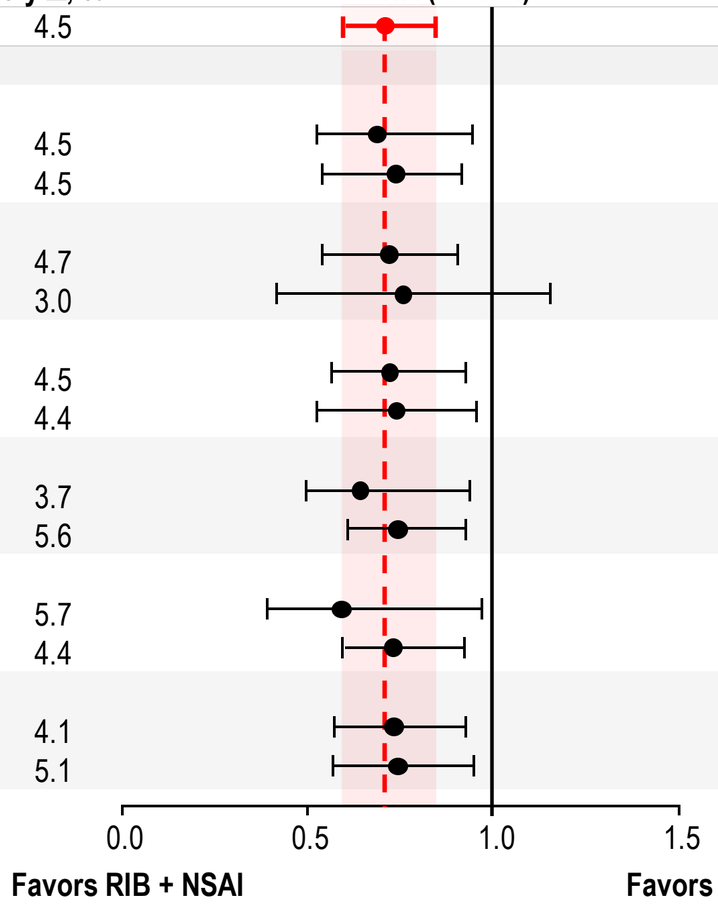
Consistent iDFS Outcomes Across Key Prespecified Subgroups

	RIB + NSAI		NSAI alone					
	Events/n	5-y iDFS rate, %	Events/n	5-y iDFS rate, %	5-y Δ, %	HR (95% CI)	HR	95% CI
ITT	317/2549	85.5	407/2552	81.0	4.5		0.716	0.618-0.829
SUBGROUPS								
Menopausal status								
Premenopausal women and men	124/1126	87.1	162/1132	82.6	4.5		0.714	0.565-0.902
Postmenopausal women	193/1423	84.3	245/1420	79.7	4.5		0.734	0.608-0.887
Prior CT[a]								
Yes	290/2249	84.9	370/2245	80.2	4.7		0.722	0.619-0.842
No	27/300	89.6	37/307	86.6	3.0		0.744	0.453-1.222
Prior ET								
Yes	220/1832	85.8	278/1807	81.3	4.5		0.726	0.608-0.867
No	97/717	84.6	129/745	80.3	4.4		0.730	0.561-0.950
AJCC stage								
Stage II	75/1012	91.7	113/1034	87.9	3.7		0.660	0.493-0.884
Stage III	241/1527	81.2	294/1512	75.6	5.6		0.730	0.615-0.865
Nodal status[b]								
N0	25/285	90.3	46/329	84.6	5.7		0.606	0.372-0.986
N1-N3	292/2261	84.9	360/2218	80.5	4.4		0.737	0.631-0.860
Ki-67 status[c]								
Ki-67 ≤20%	132/1200	87.0	177/1241	83.0	4.1		0.730	0.583-0.915
Ki-67 >20%	138/919	83.2	172/932	78.1	5.1		0.743	0.594-0.930



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

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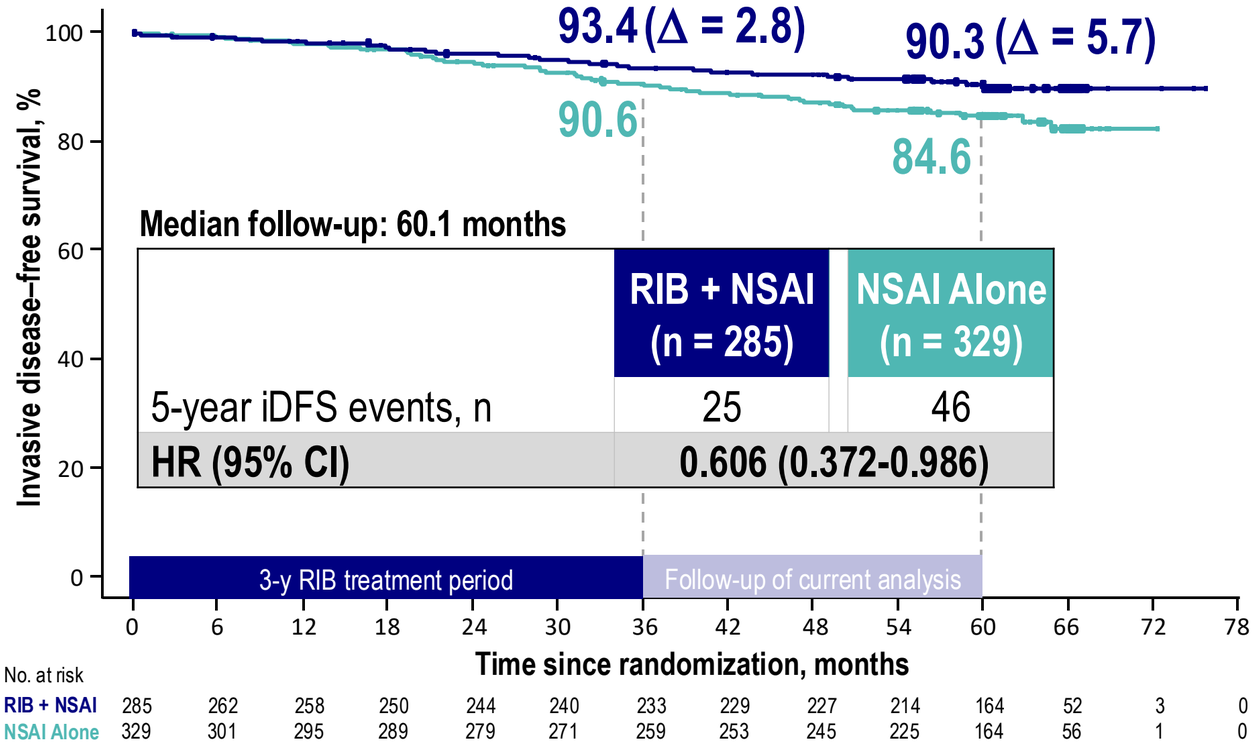
iDFS by Nodal Status

With a median of 2 years off RIB treatment, ***RIB continues to demonstrate persistent benefit in patients with high-risk N0 disease and N+ disease***

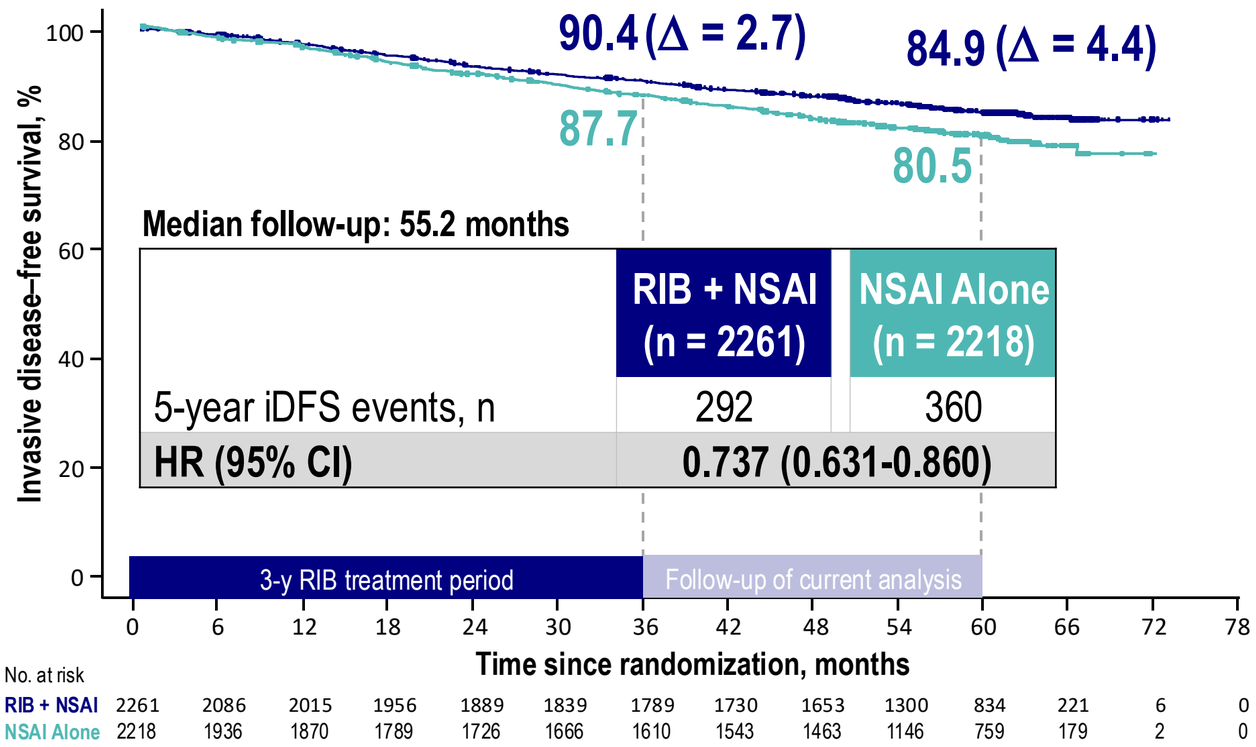
N0



No. at risk

RIB + NSAI	285	262	258	250	244	240	233	229	227	214	164	52	3	0
NSAI Alone	329	301	295	289	279	271	259	253	245	225	164	56	1	0

N+



No. at risk

RIB + NSAI	2261	2086	2015	1956	1889	1839	1789	1730	1653	1300	834	221	6	0
NSAI Alone	2218	1936	1870	1789	1726	1666	1610	1543	1463	1146	759	179	2	0

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

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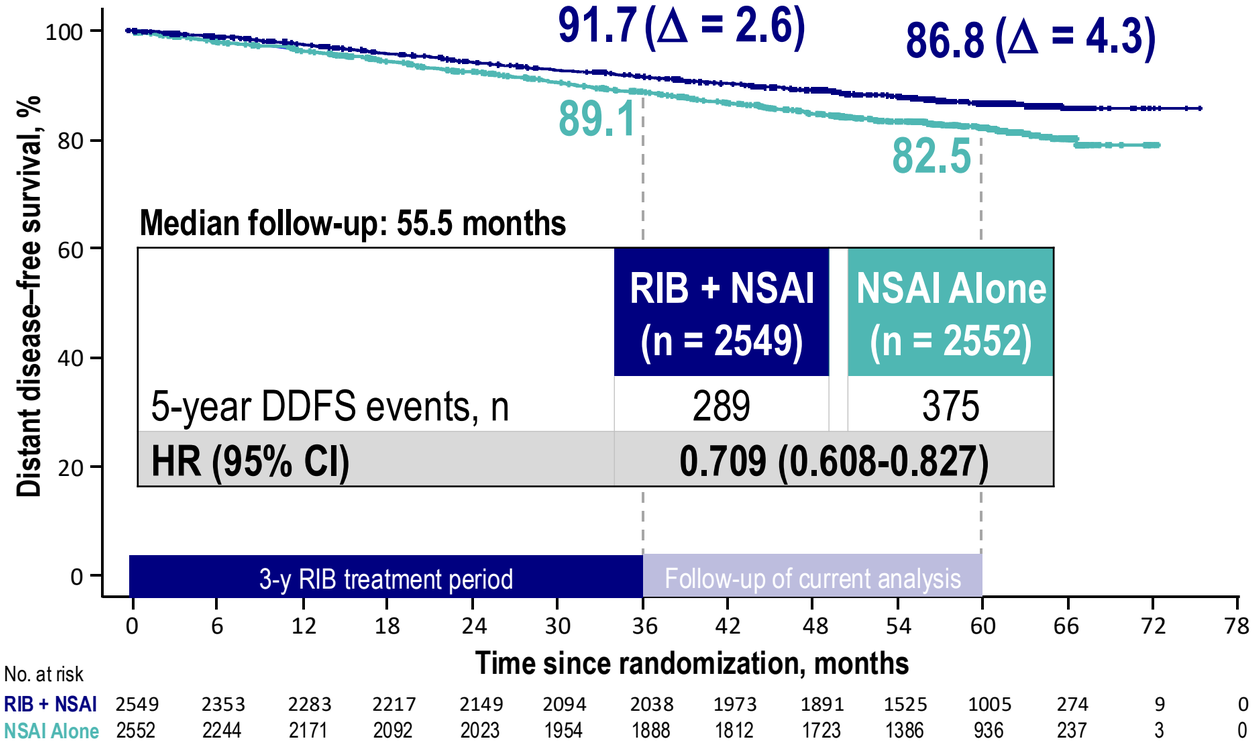
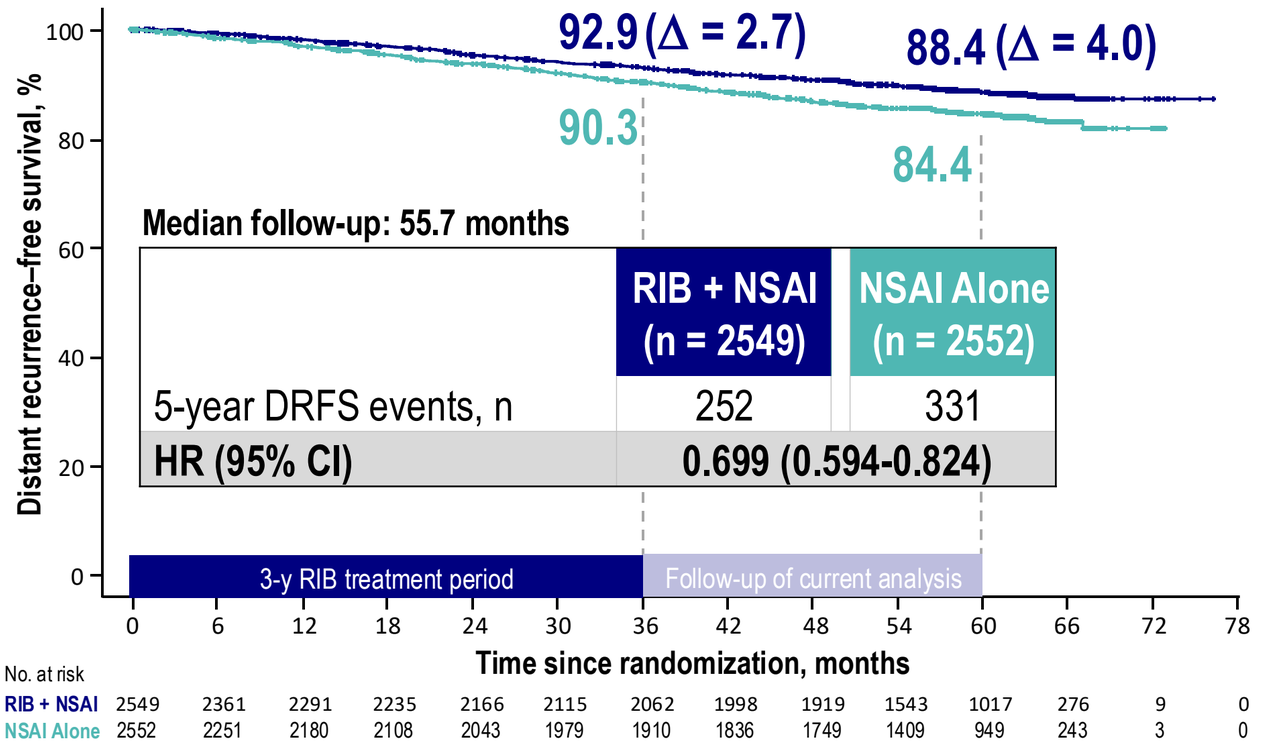
Secondary and Exploratory Endpoints

RIB + NSAI demonstrated continued benefit in DDFS and DRFS

DDFS



DRFS



DDFS, distant disease–free survival; DRFS, distant recurrence–free survival; HR, hazard ratio; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

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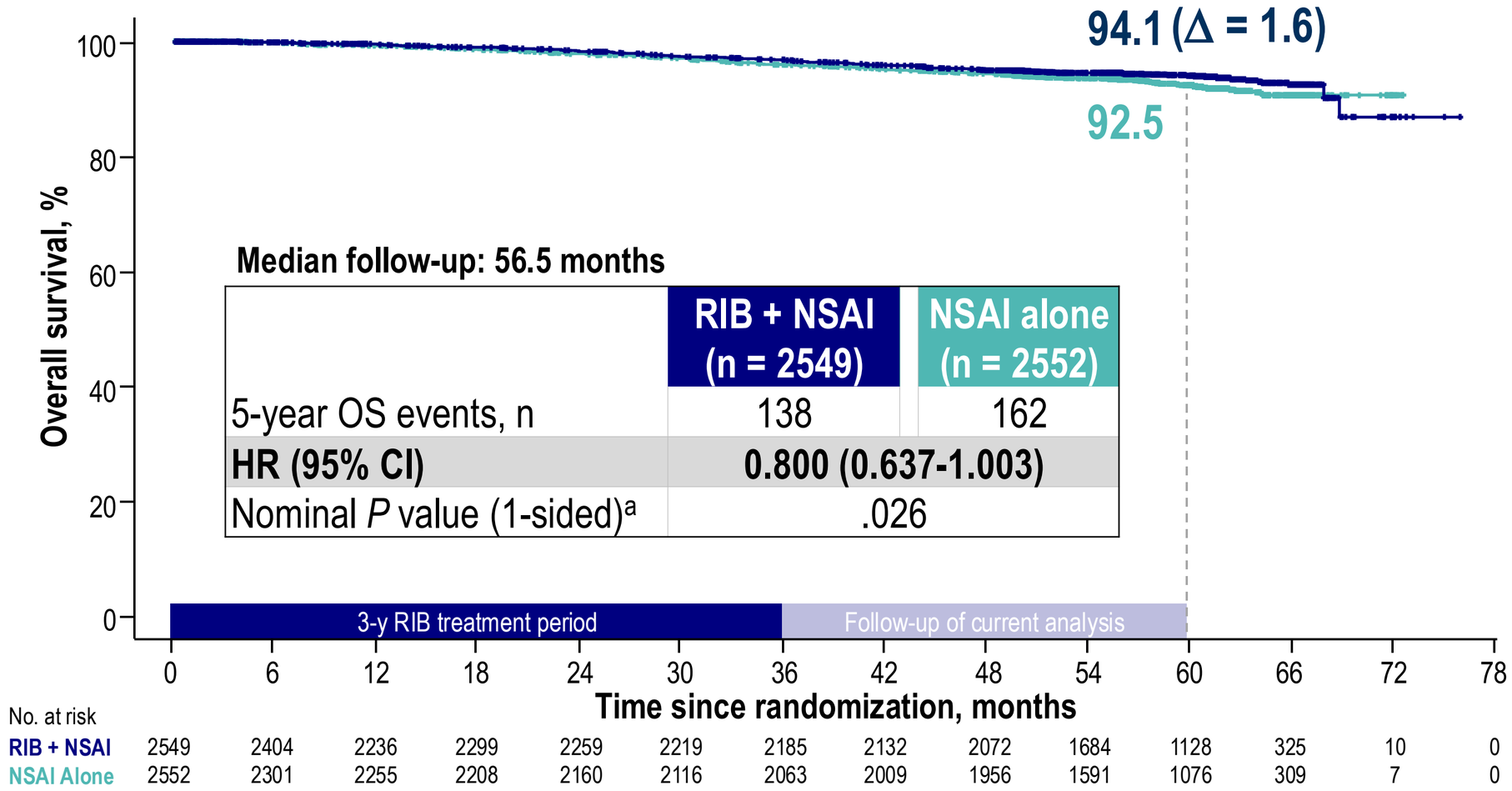
OS in the ITT Population

As OS data matures, a positive trend favoring RIB + NSAI treatment continues to emerge



[a] Comparison of survival between treatment arms was generated by stratified log-rank test (1-sided *P* value, informational and not preplanned).
HR, hazard ratio; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.

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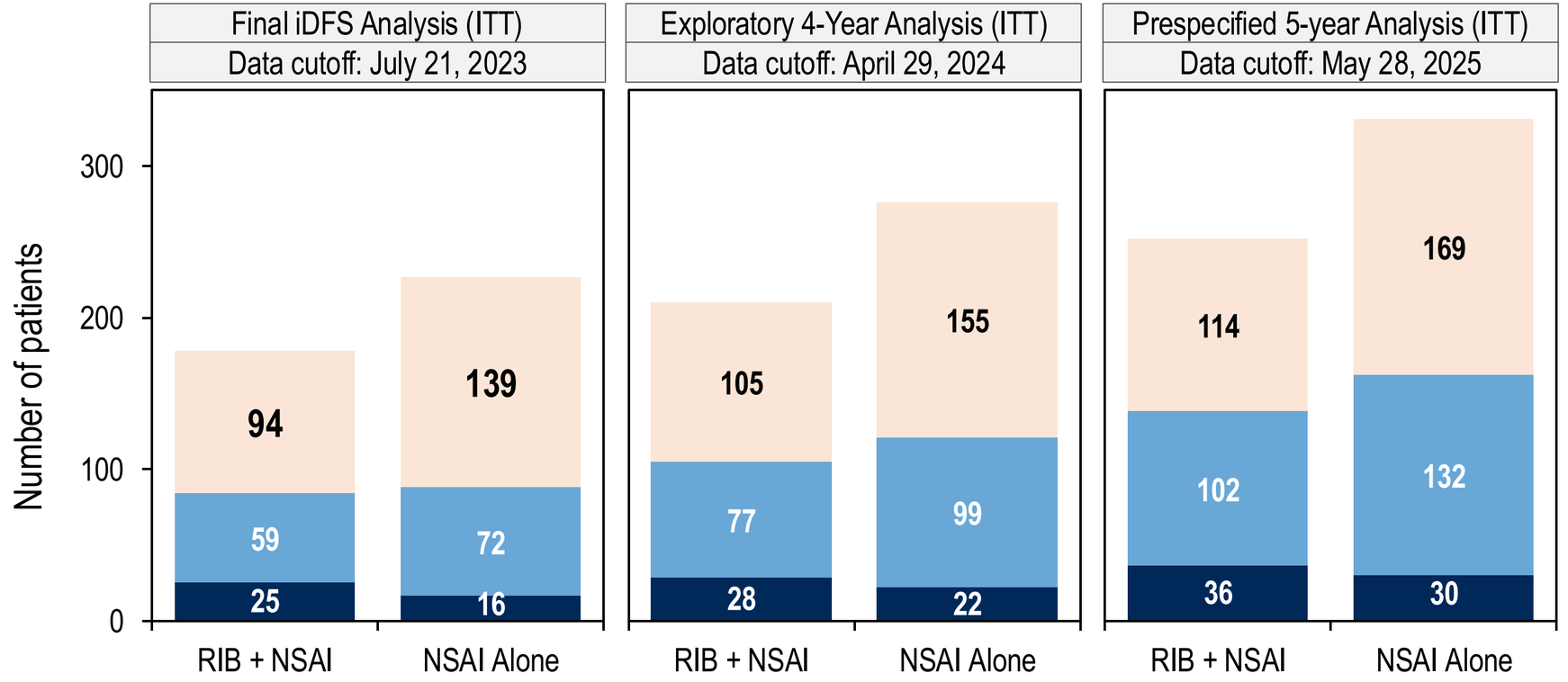
Survival Status Over Time: Fewer BC-Related Deaths in RIB Arm

A positive OS signal in favor of RIB + NSAI treatment has been observed at earlier timepoints



Approximate median follow-up (months)	36	44	57
OS HR (95% CI)	0.89 (0.66-1.20)	0.83 (0.64-1.07)	0.800 (0.637-1.003)

BC, breast cancer; HR, hazard ratio; iDFS, invasive disease–free survival; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib; OS, overall survival.

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Deaths and Key Safety Assessments

With all patients off ribociclib treatment for a median of 2 years, no new safety signals were identified

With 12.9 months of additional follow-up since the prior 4-year exploratory analysis:

- 5 new deaths due to AEs occurred—these deaths were not considered related to study treatment
  - 3 patients in the RIB + NSAI arm (brain hemorrhage, myocardial infarction, gastric adenocarcinoma)
  - 2 in the NSAI-alone arm (rectal adenocarcinoma, aortic aneurysm rupture)

- The proportion of patients who developed secondary primary malignancies was similar in the 2 arms (RIB + NSAI: 67 patients [2.7%]; NSAI alone: 74 patients [3.0%])

AE, adverse event; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

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Conclusions

- RIB + NSAI demonstrated durable iDFS benefit vs NSAI alone, with a 28% relative reduction in the risk of recurrence or death after a median of 2 years post RIB treatment
  - —Absolute iDFS improvement between treatment arms was Δ4.5% for 5-year rates
- Sustained iDFS benefit with RIB + NSAI was observed across subgroups, including those with high-risk N0 disease, with the upper boundary of the CI for N0 below 1 for the first time
- At the 5-year analysis, RIB + NSAI also demonstrated a clinically meaningful reduction in the risk of distant recurrence or death: 29.1% with DDFS and 30.1% for DRFS
- RIB + NSAI showed a continued numerical trend for improved OS, as data continue to mature
- No new safety signals were identified

At this 5-year follow-up of NATALEE, RIB + NSAI continues to reduce the risk of recurrence beyond the 3-year treatment window, supporting its use as adjuvant therapy in patients with HR+/HER2− EBC at high risk of recurrence, including those with high-risk N0 disease

DDFS, distant disease–free survival; DRFS, distant recurrence–free survival; EBC, early breast cancer; HR+/HER2−, hormone receptor positive, human epidermal growth factor receptor 2 negative; iDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.

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ORIGINAL ARTICLE

Adjuvant ribociclib plus nonsteroidal aromatase inhibitor therapy in patients with HR-positive/HER2-negative early breast cancer: 5-year follow-up of NATALEE efficacy outcomes and updated overall survival

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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 Anjeza Petersen, PhD, of Nucleus Global
- Ribociclib was discovered by the Novartis Institutes for BioMedical Research in collaboration with Astex Pharmaceuticals

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Thank you!

Danke schön!

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