

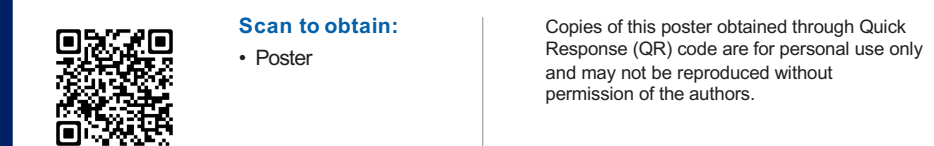
# Distant Disease-Free Survival Across Key Subgroups From the Phase 3 NATALEE Trial of Ribociclib Plus a Nonsteroidal Aromatase Inhibitor in Patients With HR+/HER2- Early Breast Cancer

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## KEY FINDINGS & CONCLUSIONS

- A 4-y landmark analysis was performed in NATALEE, when all patients were off RIB
- The combination of RIB + NSAI consistently reduced distant recurrence in patients with HR+/HER2- EBC, including patients with high-risk N0 disease
- The DDFS and DRFS benefits in the ITT population and the DDFS benefit across subgroups were maintained beyond the planned 3-y RIB duration
- In all subgroups, the absolute benefit with RIB + NSAI vs NSAI alone increased from 3 y to 4 y
- These findings support the use of RIB in combination with NSAI in the adjuvant setting to reduce the risk of distant recurrence in a broad population of high-risk patients with HR+/HER2- EBC



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## INTRODUCTION

- Despite improvements in outcomes in patients with hormone receptor (HR)+ early breast cancer (EBC), distant recurrence remains a major concern given that there is no cure for metastatic breast cancer<sup>1,2</sup>
- In the NATALEE trial, distant disease-free survival (DDFS) was improved with ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) vs NSAI alone in patients with stage II/III HR+/human epidermal growth factor receptor 2 (HER2)- EBC<sup>3-5</sup>
  - The DDFS benefit was maintained with all patients off RIB treatment (median follow-up, 44.2 mo; hazard ratio, 0.715 [95% CI: 0.604-0.847])<sup>5</sup>
- Given that risk of distant recurrence can depend on various disease features, assessing the effects of current adjuvant treatments on distant disease recurrence across patient subgroups, including by stage or nodal status, is important for treatment selection
- We present overall DDFS and distant recurrence-free survival (DRFS) as well as DDFS across clinically relevant subgroups from the 4-y landmark analysis of the NATALEE trial

## RESULTS

### Distant Recurrences in the ITT Population

- At the data cutoff of April 29, 2024, with all patients off RIB treatment, RIB + NSAI demonstrated a DDFS benefit in the ITT population (median duration of follow-up for DDFS, 44.2 mo) (Figure 2)
  - DRFS was also improved with RIB + NSAI vs NSAI alone (hazard ratio, 0.705 [95% CI: 0.589-0.844]; nominal P<.0001) in the ITT population
- The most common sites of distant recurrence were bone, liver, lung/pleura, and distant lymph nodes (Table 1)

Figure 2. DDFS and DRFS in the NATALEE ITT Population

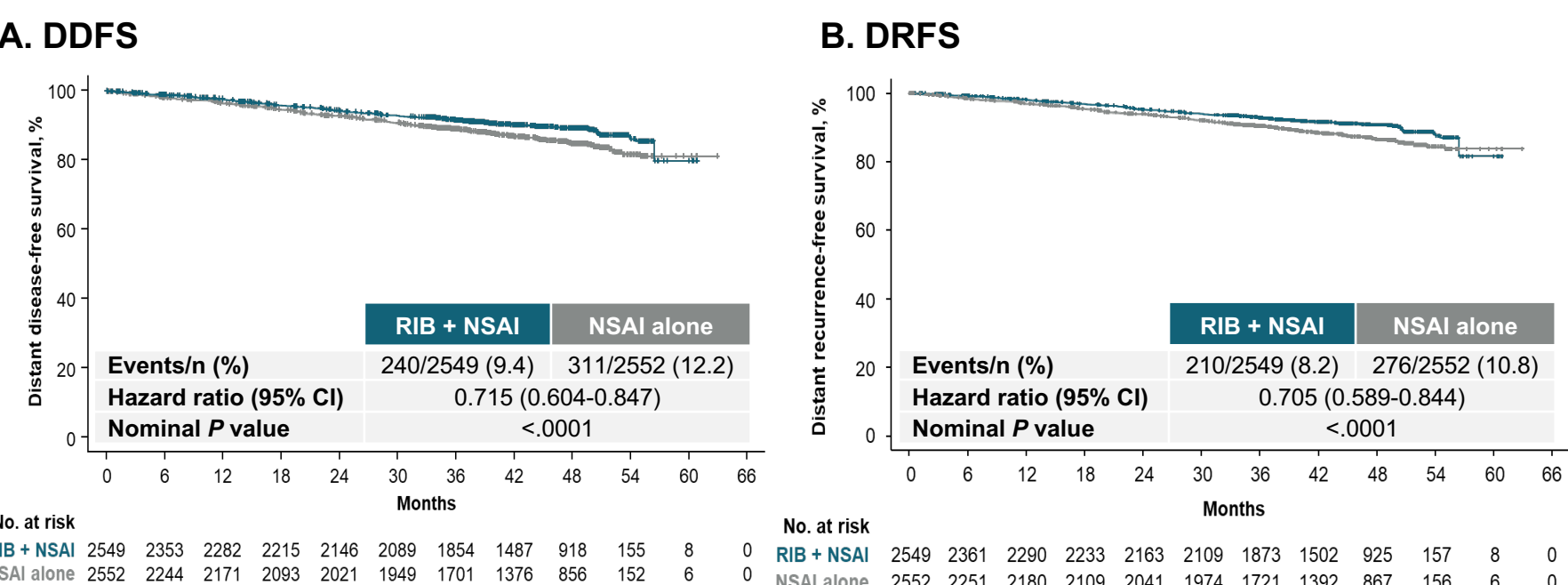


Table 1. Sites of Distant Recurrence in NATALEE

Site of DDFS recurrence event, n (%) <sup>a,b</sup>	RIB + NSAI n = 2549	NSAI alone n = 2552	Total N = 5101
Bone	109 (4.3)	142 (5.6)	251 (4.9)
Liver	52 (2.0)	82 (3.2)	134 (2.6)
Lung/pleura	37 (1.5)	58 (2.3)	95 (1.9)
Distant lymph nodes	28 (1.1)	40 (1.6)	68 (1.3)
Central nervous system	16 (0.6)	19 (0.7)	35 (0.7)
Other	12 (0.5)	15 (0.6)	27 (0.5)

<sup>a</sup> Excluding death and second primary nonbreast cancer. <sup>b</sup> Patients may have had multiple DDFS recurrence sites counted in the table, but distant recurrence was counted only once per patient.

## References

- Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 2024;404(10461):1407-1418. 2. Basaran GA, et al. *Cancer Treat Rev*. 2018;63:144-155. 3. Slamon D, et al. *N Engl J Med*. 2024;390(12):1080-1091. 4. Hortobagyi G, et al. *SABCS 2023*. Oral GS03-03. 5. Fasching PA, et al. *ESMO 2024*. Oral LBA113. 6. Tolaney SM, et al. *J Clin Oncol*. 2021;39:2720-2731.

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## METHODS

- Patients in NATALEE were randomized 1:1 to receive RIB (400 mg/d, 3 wk on/1 wk off for 3 y) + NSAI (anastrozole 1 mg/d or letrozole 2.5 mg/d for 5 y) or NSAI alone (Figure 1)
  - Men and premenopausal women in both arms also received goserelin
- Inclusion criteria were anatomical stage IIA (node negative [N0] with additional risk factors or N1 [1-3 axillary lymph nodes]), IIB, or III disease as defined by the American Joint Committee on Cancer guidelines (8th ed)
- DDFS was examined as a secondary end point in the intent-to-treat (ITT) population and across anatomical stage, nodal status, menopausal status, Ki67 score, age, and prior endocrine therapy (ET) duration subgroups
- DRFS was examined as an exploratory end point in the ITT population
- DDFS and DRFS were defined per Standardized Definitions for Efficacy End Points (STEEP) v2.0 criteria<sup>6</sup>

### DDFS by Stage

- A consistent DDFS benefit was observed regardless of anatomical stage and increased from 3 to 4 y (Figure 3, Table 2)

Figure 3. DDFS in NATALEE by Stage

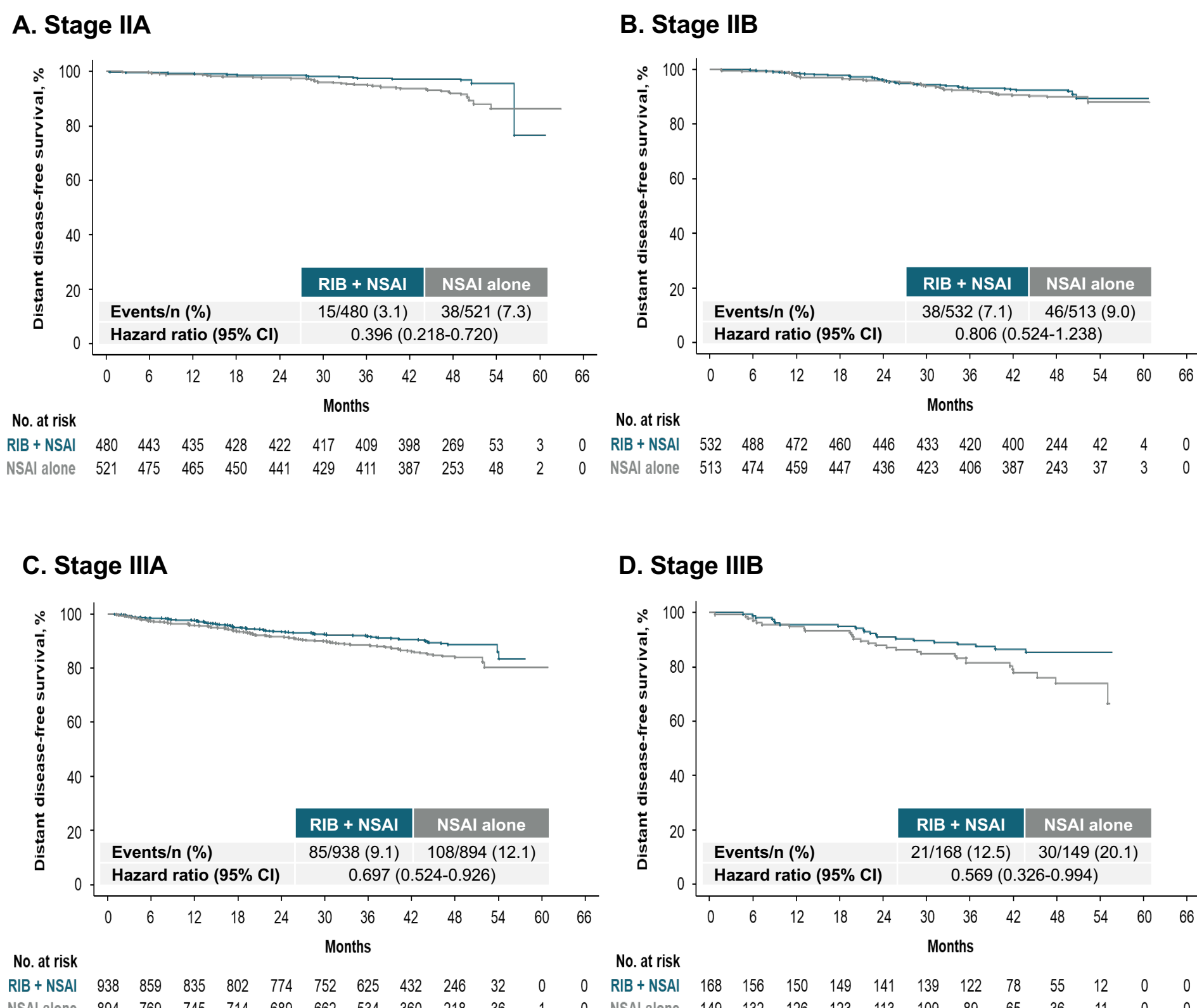
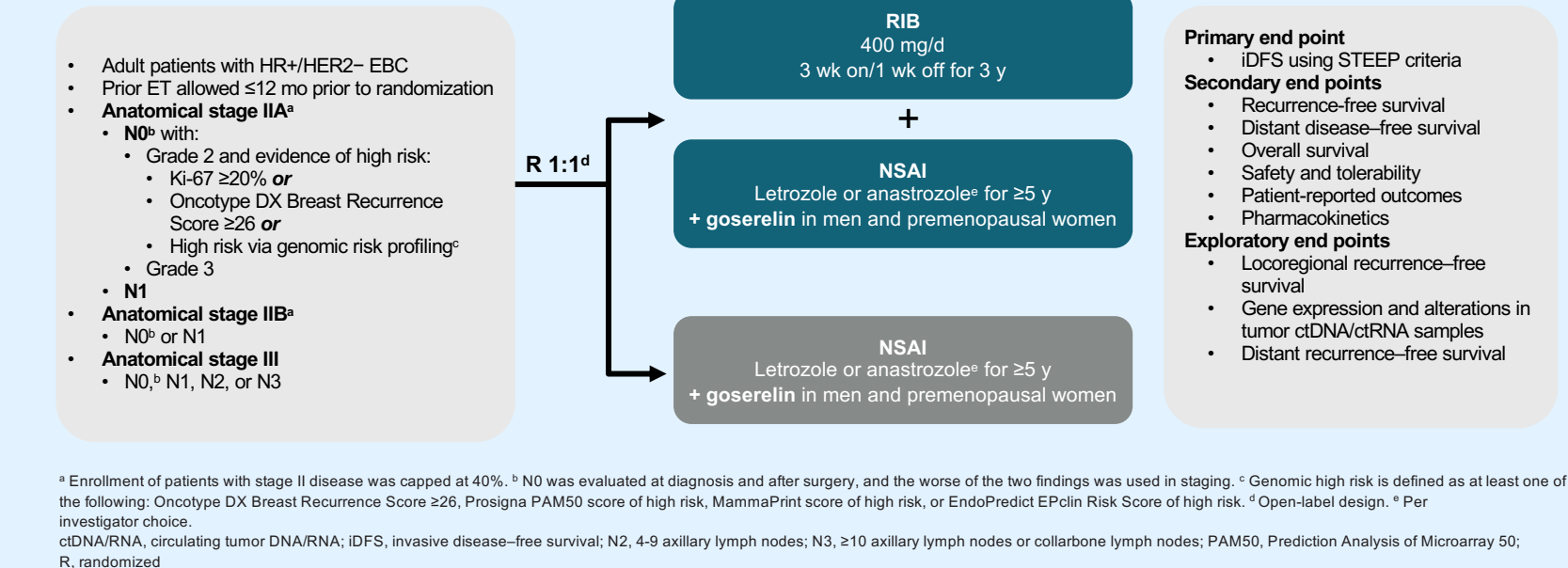


Table 2. Absolute DDFS Benefit by Stage

Stage	3-y DDFS rate, %		3-y abs. benefit	4-y DDFS rate, %		4-y abs. benefit
	RIB + NSAI	NSAI alone		RIB + NSAI	NSAI alone	
IIA	97.5	95.2	Δ2.3	97.2	92.1	Δ5.1
IIB	93.2	92.4	Δ0.8	92.5	89.9	Δ2.6
IIIA	91.7	88.6	Δ3.1	88.7	84.1	Δ4.6
IIIB	88.4	81.6	Δ6.8	85.4	74.0	Δ11.4
IIIC	84.4	82.0	Δ2.4	77.9	73.4	Δ4.5

## Figure 1. NATALEE Study Design



### DDFS by Nodal Status

- The DDFS benefit was consistent regardless of nodal status and increased from 3 to 4 y (Figure 4, Table 3)

Figure 4. DDFS in NATALEE by Nodal Status

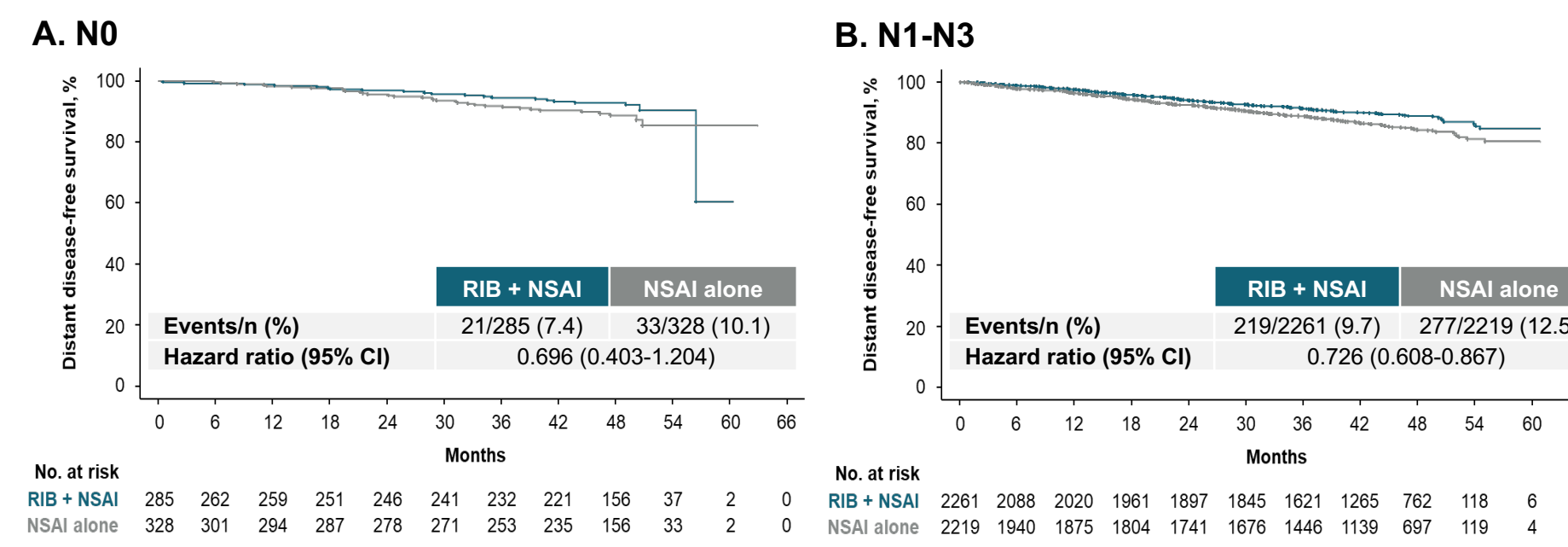


Table 3. Absolute DDFS Benefit by Nodal Status

Subgroup	3-y DDFS rate, %		3-y abs. benefit	4-y DDFS rate, %		4-y abs. benefit
	RIB + NSAI	NSAI alone		RIB + NSAI	NSAI alone	
Nodal status						
N0	94.5	91.8	Δ2.7	92.9	88.7	Δ4.2
N1-N3	91.3	88.9	Δ2.4	88.9	84.3	Δ4.6

### DDFS by Menopausal Status, Ki67 Status, Age Group, and Prior ET Duration

- RIB + NSAI demonstrated DDFS benefits regardless of menopausal status, Ki67 status, age, and prior duration of ET, with increasing absolute benefits from 3 to 4 y (Table 4)

Table 4. DDFS in NATALEE by Menopausal Status, Ki67 Status, Age Group, and Prior ET Duration

Subgroup	Events/n (%)		3-y DDFS rate, %		3-y abs. benefit	4-y DDFS rate, %		4-y abs. benefit	HR (95% CI)
	RIB + NSAI	NSAI alone	RIB + NSAI	NSAI alone		RIB + NSAI	NSAI alone		
Menopausal status									
Premenopausal <sup>a</sup>	88/1125 (7.8)	125/1132 (11.0)	92.8	90.0	Δ2.8	91.7	86.6	Δ5.1	0.658 (0.501-0.865)
Postmenopausal	152/1424 (10.7)	186/1420 (13.1)	90.7	88.6	Δ2.1	87.7	83.6	Δ4.1	0.771 (0.623-0.956)
Ki67 score									
≤20	95/1199 (7.9)	134/1236 (10.8)	92.7	90.7	Δ2.0	91.0	86.7	Δ4.3	0.699 (0.538-0.910)
>20	103/920 (11.2)	133/937 (14.2)	90.0	87.4	Δ2.6	87.3	82.2	Δ5.1	0.727 (0.562-0.940)
Age									
<40 y	24/250 (9.6)	38/293 (13.0)	92.2	86.7	Δ5.5	90.4	82.3	Δ8.1	0.593 (0.356-0.990)
≥40 y	216/2299 (9.4)	273/2259 (12.1)	91.6	89.5	Δ2.1	89.3	85.2	Δ4.1	0.745 (0.623-0.890)
<65 y	199/2142 (9.3)	248/2186 (11.3)	91.8	89.8	Δ2.0	89.8	86.1	Δ3.7	0.764 (0.634-0.921)
≥65 y	41/407 (10.1)	63/366 (17.2)	90.7	86.0	Δ4.7	87.4	78.3	Δ9.1	0.568 (0.383-0.841)
Prior ET									
<12 wk	64/747 (8.6)	86/718 (12.0)	92.4	90.0	Δ2.4	90.4	85.7	Δ4.7	0.665 (0.480-0.922)
≥12 but <26 wk	61/651 (9.4)	76/665 (11.4)	91.5	89.3	Δ2.2	89.6	85.3	Δ4.3	0.765 (0.545-1.075)
≥26 wk	32/358 (8.9)	42/352 (11.9)	92.5	89.7	Δ2.8	89.5	84.6	Δ4.9	0.682 (0.429-1.085)

<sup>a</sup> Also includes men.

## Disclosures

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