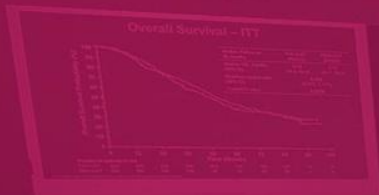
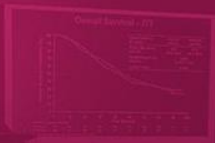


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REALIZAÇÃO



Potenciais conflitos de interesse

- Participo(ei) de estudos clínicos patrocinados pelas empresas: Eli-Lilly, AstraZeneca, Roche, Bayer, Daiichi Sankyo, Novartis, BMS, Puma Biotechnology, Gilead, AMGEN, MSD, Grupo Oncoclínicas
- Participo(ei) como speaker de eventos das empresas: Roche, Eli-Lilly, Novartis, AstraZeneca, Pfizer, United Medical, GSK, Gilead, Daichii-Sankyo;
- Sou (Fui) membro do advisory board das empresas: Daiichi Sankyo, MSD, Roche e GSK
- Não tenho ações de quaisquer destas companhias
- Minhas opiniões podem não representar a opinião do Grupo Oncoclínicas



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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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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 cancer⁴⁻¹²
- 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 trial¹³
- 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 Design¹⁻³

- 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 $\geq 20\%$
 - 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

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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

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%)

Ribociclib + NSAI, n=2549

- NSAI ongoing: 1914 (75.1%)
- RIB ongoing: 528 (20.7%)
- Stopped RIB: 1996 (79.3%)
 - Completed 3 years: 1091 (42.8%)
 - Early discontinuation: 905 (35.5%)
 - Discontinued due to AEs: 498 (19.5%)

NSAI alone, n=2552

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

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.

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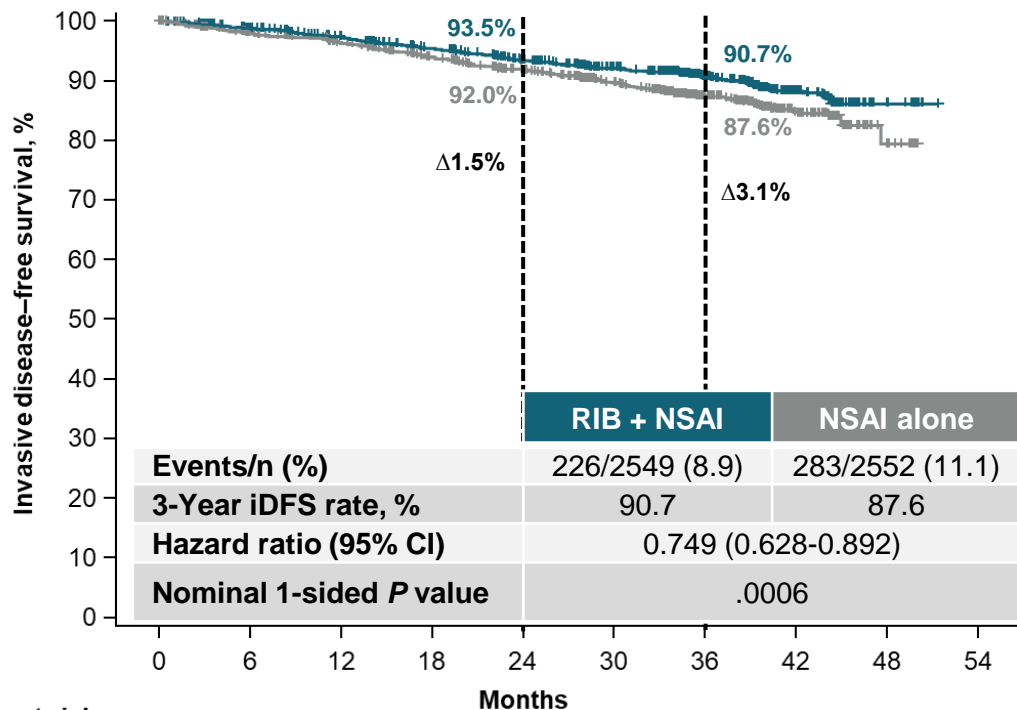
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Invasive Disease–Free Survival

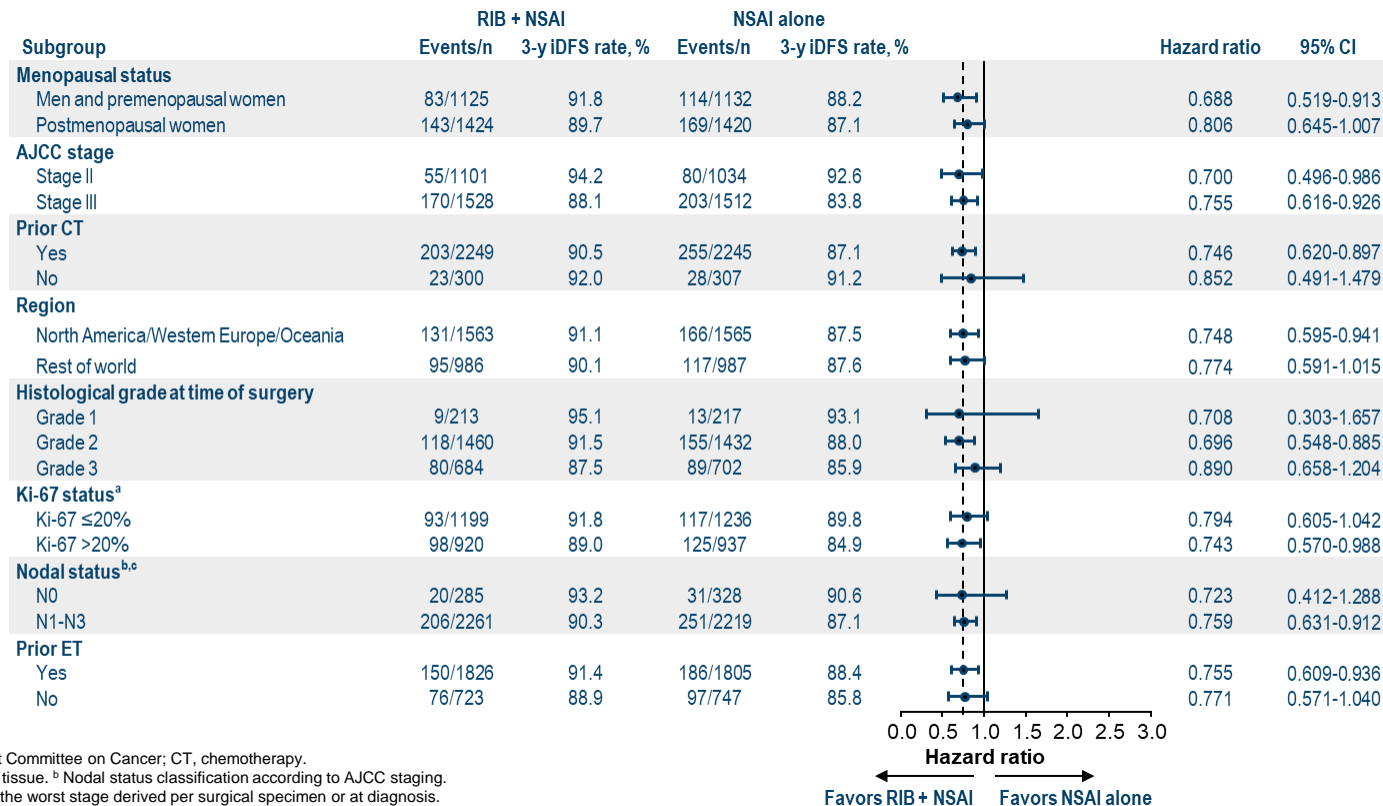


- The median follow-up for iDFS was 33.3 months (maximum, 51 months)—an additional 5.6 months from the second interim efficacy analysis¹
- The absolute iDFS benefit with ribociclib plus NSAI was 3.1% at 3 years
- The risk of invasive disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone

No. at risk	Months									
	0	6	12	18	24	30	36	42	48	54
RIB + NSAID	2549	2350	2273	2204	2100	1694	1111	368	21	0
NSAI alone	2552	2241	2169	2080	1975	1597	1067	354	26	0

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

iDFS Across Key Prespecified Subgroups



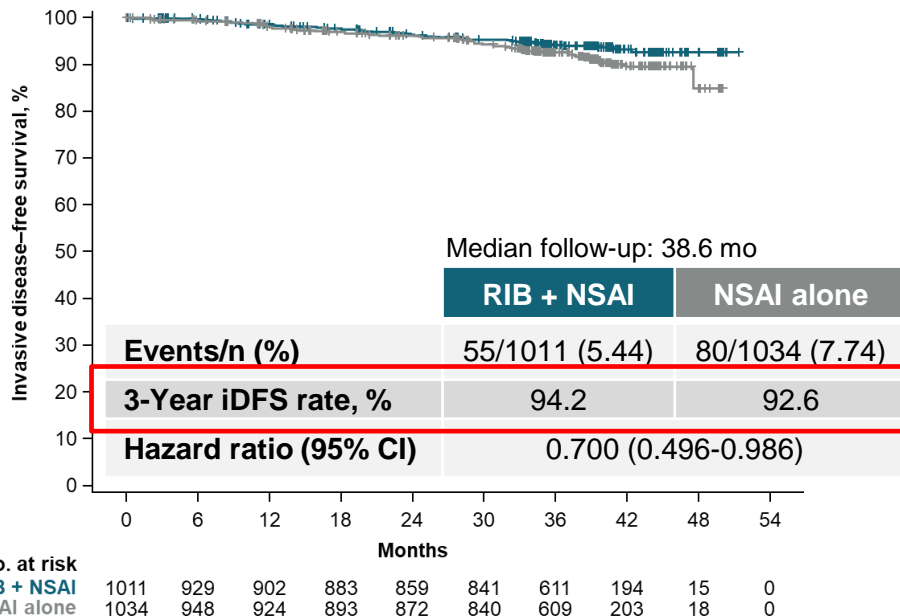
AJCC, American Joint Committee on Cancer; CT, chemotherapy.

^a From archival tumor tissue. ^b Nodal status classification according to AJCC staging.

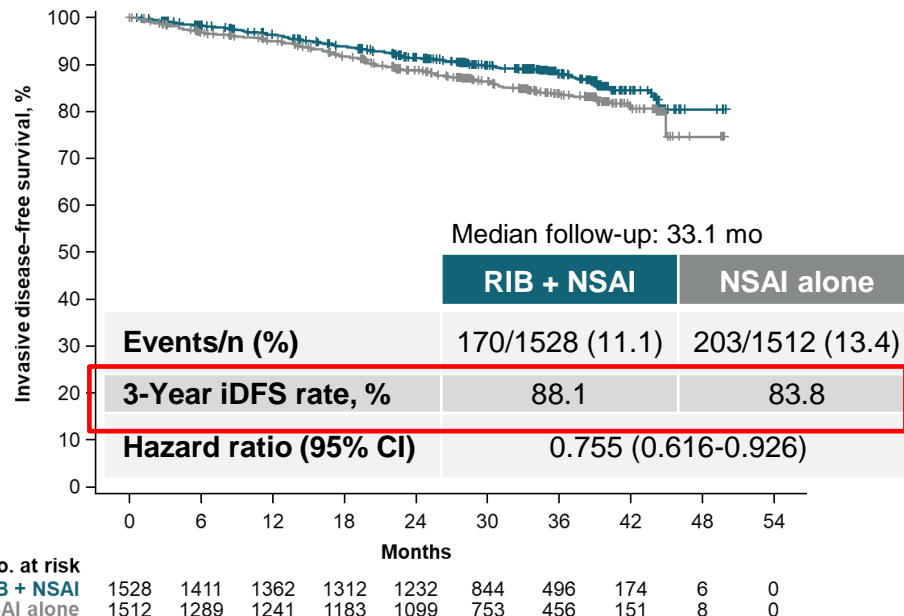
^c Nodal status is from the worst stage derived per surgical specimen or at diagnosis.

iDFS by Anatomical Stage

Stage II



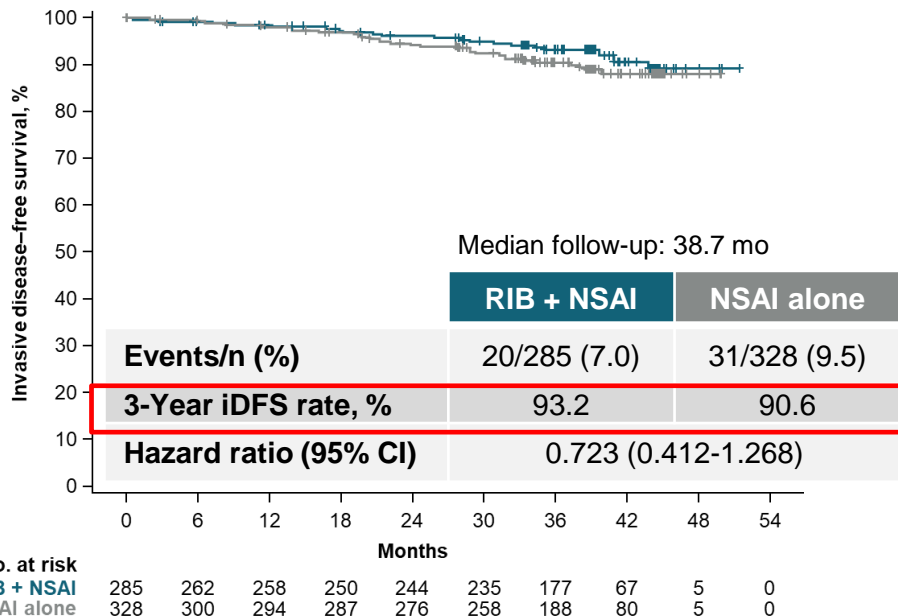
Stage III



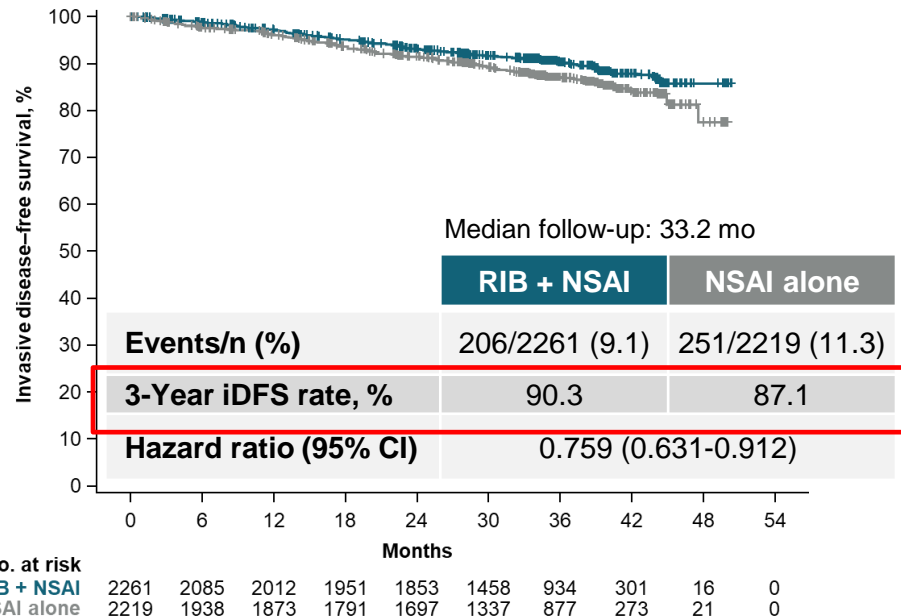
- The risk of invasive disease was reduced by 30.0% for stage II and by 24.5% for stage III disease with ribociclib plus NSA vs NSA alone

iDFS by Nodal Status

N0

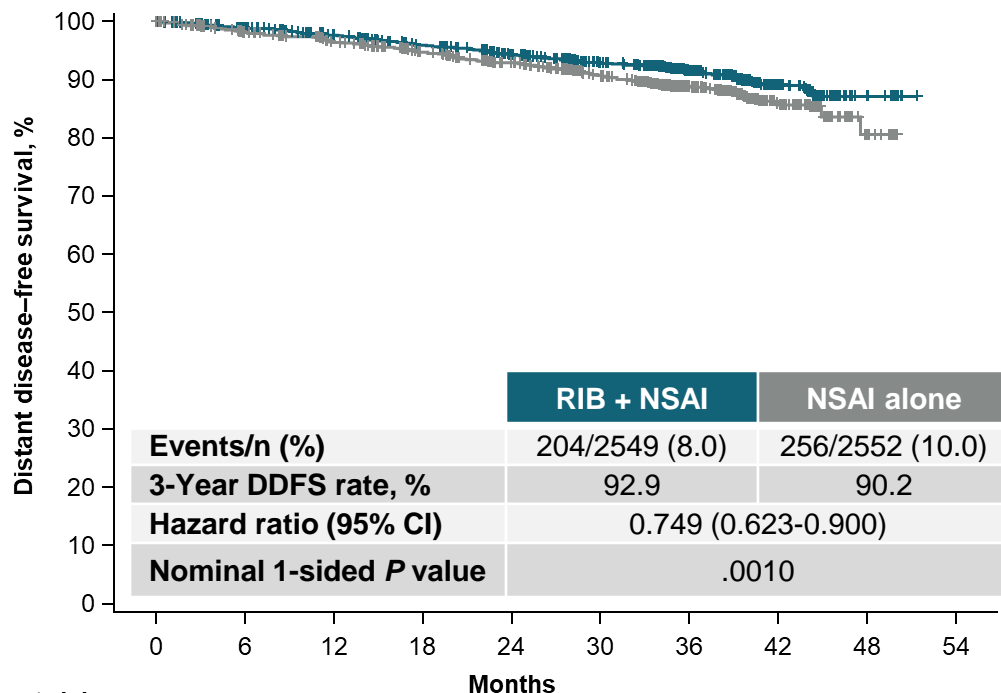


N1-N3



- 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



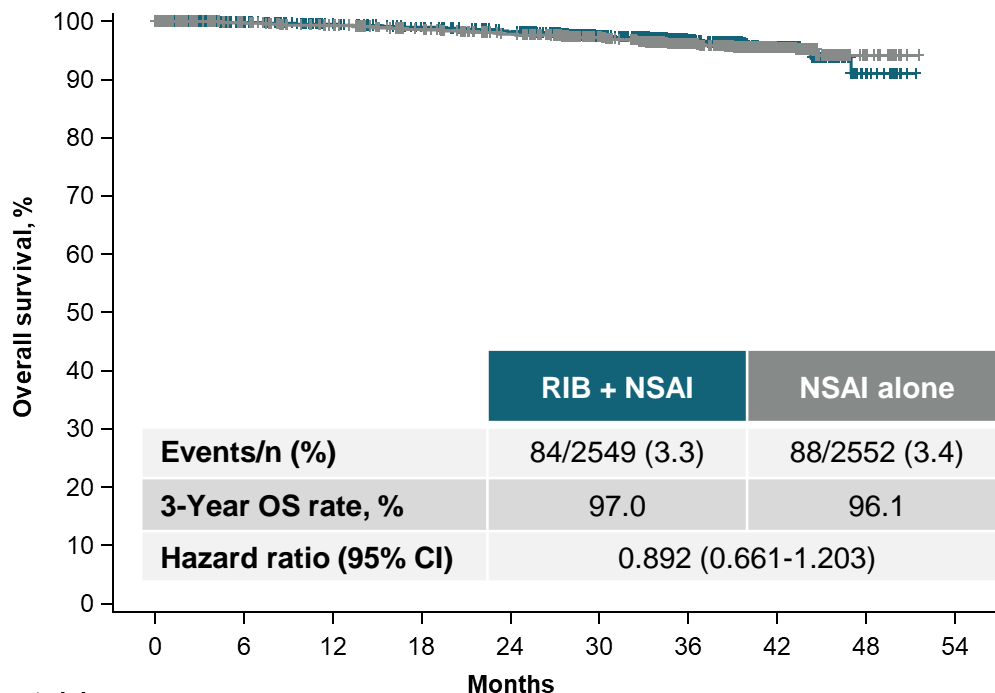
- The absolute DDFS^a benefit with ribociclib plus NSAI was 2.7% at 3 years
- The risk of distant disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone at the final analysis

No. at risk	0	6	12	18	24	30	36	42	48	54
RIB + NSAI	2549	2352	2280	2212	2113	1704	1119	369	21	0
NSAI alone	2552	2245	2171	2091	1990	1609	1080	356	26	0

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



- 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

No. at risk	Months									
	0	6	12	18	24	30	36	42	48	54
RIB + NSAI	2549	2405	2337	2305	2259	1902	1259	455	24	0
NSAI alone	2552	2302	2256	2209	2158	1815	1207	444	31	0

Safety Profile of Ribociclib at 400 mg

AEIS, %	RIB + NSAI n=2525		NSAI alone n=2442	
	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 AEIS or clinically relevant AEs increased >1% and only a 0.8% increase in discontinuations was observed in this updated analysis¹
- The most frequent reason for discontinuation of ribociclib was liver-related AEs

AEIS, 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 79.3% of patients no longer on ribociclib treatment at data cutoff¹
 - The iDFS benefit was consistent across key prespecified subgroups, including patients with stage II, III, node-negative, and node-positive disease²
 - 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 setting¹

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

Take home messages

- Análise final pré especificada de SLDi do NATALEE, com FUP 33.3 meses continua a mostrar ganho consistente com a adição de ribociclibe à IA não esteirodal quando comparado a IA não esteirodal em monoterapia (Δ 3.1 em 03 anos; HR: 0.749)
 - 79.3% dos pacientes não mais em uso do ribociclibe → 42.8% concluíram os 03 anos e 35.5% descontinuaram precocemente o ribociclibe (19% por EA).
- **Aguardemos a publicação do dados!!**
- **FUP mais longo (em especial, população N0)**

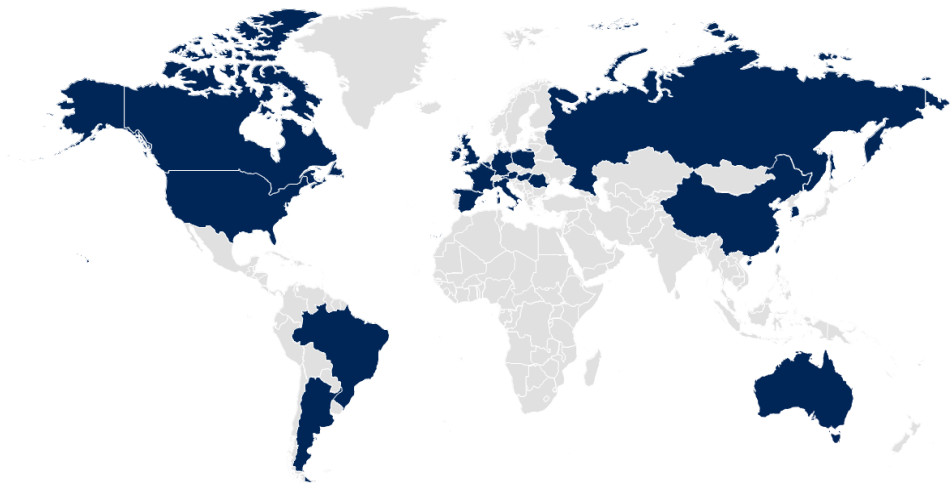
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 - 78% dos pacientes não mais em uso do ribociclibe → 42.8% concluíram os 03 anos e 35.5% descontinuaram precocemente o ribociclibe (19% por EA).
- **Aguardemos a publicação do dados**
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** Questões em aberto:

1. Qual duração ideal dos iCDK4/6 na adjuvância?
2. Qual será o perfil de toxicidades e adesão ao tratamento na prática diária?
3. Poderíamos oferecer apenas a combinação iCDK4/6 + IA (sem QT), para algum perfil de paciente?

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