bjclub breast Journal club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

7-8 MARZO 2025
NAPOLI
Hotel Royal Continental
Via Partenope, 38

Disclosures:

- **GNH reports receiving consulting or advisory role fees from Agendia, Lilly, Merck, Novartis, Peregrine Pharmaceuticals, and Roche and travel expenses from Novartis, and his institution has received research funding from Novartis.** JS reports research grant/funding (institution) from Merck Sharp & Dohme (MSD), Roche, Novartis, AstraZeneca, Lilly, Pfizer, GlaxoSmithKline (GSK), Daiichi Sankyo, Sanofi, Boehringer Ingelheim, stock/immediate family member from Daiichi Sankyo. MRB reports speaker fees from Pfizer, Novartis, AstraZeneca; consulting or advisory role from Pfizer, Novartis, Pierre Fabre. YHP reports grants and/or personal fees from MSD, Pfizer Roche, Novartis, AstraZeneca, Gencurix, Genome Insight, Daiichi Sankyo, Gilead, Lilly. DAY reports research funding to institution from Daiichi Sankyo/Lilly, Eisai, Genentech/Roche, Novartis, AbbVie, AstraZeneca, Clovis Oncology, Immunomedics, InventisBio, Lilly, MedImmune, Medivation, Merck, Oncothyreon, Pfizer, Syndax, Tesaro; personal fees from Biotheranostics, Bristol Myers Squibb, Celgene, Daiichi Sankyo/Lilly, Eisai, Genentech/Roche, Novartis, NanoString Technologies. CSH reports grants to institution from Novartis, Daiichi Sankyo, AstraZeneca, EirGenix, Eli Lilly, MSD, OBI Pharma, Pfizer, Roche; personal fees from Novartis, Daiichi Sankyo, AstraZeneca, Eli Lilly, Pfizer, Roche; non-financial support from AstraZeneca, EirGenix, Eli Lilly, OBI Pharma, Roche, Novartis. PAF reports personal fees from Novartis, Pfizer, DaiichiSankyo, AstraZeneca, Eisai, MSD, Lilly, Pierre Fabre, Seagen, Roche, Hexal, Agendia, Sanofi Aventis, Gilead; institutional funding from BioNTech, Pfizer, Cepheid; research grant from Pfizer. AB reports research grants to institution from Genentech, Novartis, Pfizer, Merck, Sanofi, Radius Health, Immunomedics, Mersana, Innocrin; personal fees from Biotheranostics Inc., Pfizer, Novartis, Genentech, Merck, Radius Health, Immunomedics, Spectrum Pharma, Taiho, Sanofi, Daiichi Pharma, Puma. SC reports personal fees and grants to institution from Novartis, Pfizer, Hoffman LaRoche, Eli Lilly. SAI reports personal fees from AstraZeneca, Novartis, Hanmi, Pfizer, Eisai, Amgen, Roche, Lilly, GSK, MSD; research grants from AstraZeneca, Pfizer, Eisai, Roche, Daewoong Pharm. MM reports personal fees from Lilly, Pfizer, AstraZeneca, personal fees and grants from Novartis, Roche-Genentech, GSK, PharmaMar, Taiho Oncology, Menarini. SL reports research funding grants to institution from Novartis, Bristol Myers Squibb, Merck, Puma Biotechnology, Eli Lilly, Nektar Therapeutics, AstraZeneca, Roche-Genentech, Seattle Genetics; uncompensated consultant for Seattle Genetics, Novartis, Bristol Myers Squibb, Merck, AstraZeneca, Eli Lilly, Pfizer, Gilead Therapeutics, Roche-Genentech; consultant with fees paid to institution from Aduro Biotech, Novartis, GSK, RocheGenentech, AstraZeneca, Silverback Therapeutics, G1 Therapeutics, PUMA Biotechnologies, Pfizer, Gilead Therapeutics, Seattle Genetics, Daiichi Sankyo, Merck, Amunix, Tallac Therapeutics, Eli Lilly, Bristol Myers Squibb. BX reports personal fees from Novartis, AstraZeneca, Pfizer, Roche, Eisai. SH reports grants from Ambryx, Amgen, AstraZeneca, Arvinas, Bayer, CytomX, Daiichi Sankyo, Dignitana, Genentech/Roche, Gilead, GSK, Immunomedics, Lilly, MacroGenics, Novartis, OBI Pharma, Pfizer, Pieris, Puma, Radius, Sanofi, Seattle Genetics, Zymeworks, Phoenix Molecular Designs; other from Lilly. CB reports institutional research grants from Pfizer, Pharma Mar, Polyphor, Henlius Biotech, Shanghai, Merck KGaA, Millennium, LEO Pharm, ImClone Systems, Exelixis, Medivation, Asana Biosciences, AB Science, Abraxis Biosciences, Daiichi Sankyo, Bristol Myers Squibb, BioMarin, Astellas Pharma, AbbVie, Merck (MSD), Merrimack, Mylan, Taiho Pharmaceutical, Sanofi, GSK, Roche/Genentech, Lilly, Boehringer Ingelheim, Novartis, AstraZeneca, Amgen, Pfizer; personal fees from Boehringer-Ingelheim, Sanofi, Lilly, Zodiac, AstraZeneca, MSD, Bayer, Eisai, Roche/Genentech, Pfizer, Novartis, GSK, Daiichi Sankyo; stock from MedSIR, Thummi. RM reports personal fees from Gilead, Lilly, Pfizer, Seattle Genetics, Genentech, Johnson & Johnson. FP reports TRIO is contracted by Novartis as CRO conducting the NATALEE trial and I am a TRIO employee. JPZ, ZL, SW, AC report employment and stock ownership from Novartis. DS reports stock ownership from BioMarin, Pfizer, Amgen, Seattle Genetics, TORL BioTherapeutics, 1200 Pharma; travel support from BioMarin, Pfizer, Novartis; personal fees from Novartis, Eli Lilly; grants from Pfizer, Novartis; founder of 1200 Pharma, TORL BioTherapeutics. All other authors have declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

A phase III trial of adjuvant ribociclib plus endocrine therapy versus endocrine therapy alone in patients with HR-positive/HER2-negative early breast cancer: final invasive disease-free survival results from the NATALEE trial

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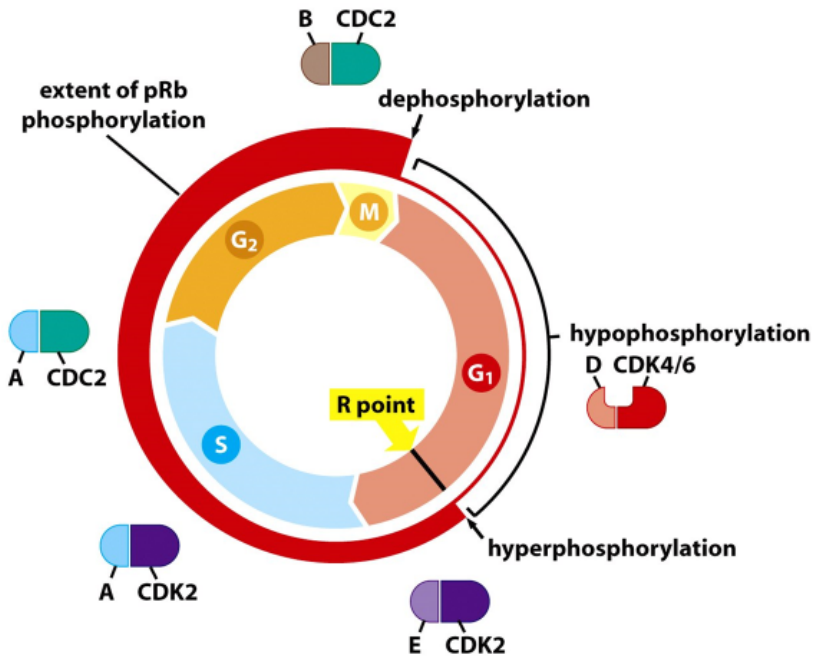
Background

- The majority of breast cancer cases are diagnosed at early stages (stage I-III)[1]
- The current standard-of-care therapy for patients with HR+/HER2− EBC is surgery with or without chemotherapy or radiation, followed by 5 to 10 years of adjuvant endocrine therapy[2]
- The goal of treatment in the EBC setting is curative; however, even after receiving adjuvant endocrine therapy, one-third of patients with stage II and more than half of patients with stage III HR+/HER2− EBC will experience disease recurrence within two decades after diagnosis[3]
- Ribociclib is a CDK4/6 inhibitor that improved progression-free and overall survival while maintaining or improving quality of life in patients with HR+/HER2− advanced breast cancer (stage IV)[4-9]
- The NATALEE study was designed to assess ribociclib plus standard-of-care endocrine therapy in patients with HR+/HER2− EBC with the aim of addressing the unmet need for this broad patient population

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. Hortobagyi GN, et al. N Engl J Med 2022;386:942-50. 5. Slamon DJ, et al. N Engl J Med. 2020;382:514-24. 6. Im SA, et al. N Engl J Med. 2019;381:307-316. 7. Verma S, et al. Breast Cancer Res Treat. 2018;170:535-545. 8. Fasching PA, et al. Breast. 2020;54:148-154. 9. Harbeck N, et al. Ther Adv Med Oncol. 2020;12:1758835920943065.

Rb as a Master Regulator of the G1/S Checkpoint[1]



- Protein kinases control cell cycle progression and rely on associations with regulatory subunits called cyclins
- Cyclin-dependent kinases (CDK) 4/6 associate with cyclin D and hyperphosphorylate Rb
- Hyperphosphorylation of Rb inactivates Rb and allows the cell to progress from G1 to S phase
- P16 inhibits the CDK4/6-cyclin D complex
- CDK4/6 inhibition has been demonstrated to lead to cellular senescence in preclinical studies

Can inhibiting CDK4/6-cyclin D prevent hyperphosphorylation of Rb and thereby prevent cell cycle progression?

Randomized Trials with cdk4/6-Inhibitors in First-Line Metastatic, HR+ Breast Cancer

Study	No. of patients	ORR	CBR	mPFS in mos (95% CI)	HR PFS	*P*	*HR OS*	*P*
PALOMA-1								
- Letrozole	81	33 (39)	58	10.2 (5.7-12.6)	**0.488** (0.319-0.748)	0.0004	0.90 (0.62-1.29)	0.281
- Letrozole + palbociclib	84	43 (56)	81	20.2 (13.8-27.5)				
PALOMA-2								
- Letrozole + placebo	222	35 (44)	71	14.5 (12.9-17.1)	**0.58** (0.46-0.72)	<0.0001	0.96 0.78-1.18	0.34
- Letrozole + palbociclib	444	42 (55)	84	24.8 (22.1-NR)				
MONALEESA-2								
- Letrozole + placebo	334	28 (37)	72	14.7 (13.0-16.5)	**0.556** (0.429-0.720)	0.00000329	**0.76** (0.63-0.93)	**0.004**
- Letrozole + ribociclib	334	41 (53)	80	NR (19.3-NR)				
MONALEESA-3								
- Fulvestrant + placebo	238	N/A	N/A	18.3 (N/A)	**0.577** (0.415-0.802)	N/A, but **<0.05**	**0.64** (0.46-0.88)	N/A, but **<0.05**
- Fulvestrant + ribociclib	129	N/A	N/A	NR (N/A)				
MONALEESA-7								
- Tamoxifen/NSAI + GnRH + placebo	337	30 (36)	67	13.0 (11.0-16.4)	**0.553** (0.441-0.694)	0.000000098	**0.76** (0.61-0.96)	**0.0097**
- Tamoxifen/NSAI + GnRH + ribociclib	335	41 (51)	80	23.8 (19.2-NR)				
MONARCH-3								
- NSAI + placebo	165	35 (44)	72	14.7	**0.543** (0.409-0.723)	0.000021	**0.80**	**0.0664**
- NSAI + abemaciclib	328	48 (59)	78	NR				

Finn RS, et al. Lancet Oncol, 16(1):25 - 35, 2015; Finn RS, et al. NEJM 375(20):1925-36, 2016; Hortobagyi GN, et al. NEJM 375(18):1738-48, 2016; Goetz MP, et al. J Clin Oncol 35(32):3638-3646, 2017; Tripathy D, et al. SABCS 2017 GS2-05; Slamon DS, et al. Ann Oncol 32(8):1015-24, 2021

EarLEE-1: Adjuvant Therapy For High-Risk Early Breast Cancer

EarLEE-1 is a double-blind, randomized, placebo-controlled, multicenter, international phase 3 study of ribociclib + endocrine therapy (Target N ~ 2,000)

- HR+, HER2– EBC
- Men and pre- and postmenopausal women
- High risk of recurrence
  - AJCC 8th ed, Prognostic Stage Group III
  - Residual disease in LN(s) and breast tissue after neoadjuvant chemotherapy

→ Endocrine therapy[a] + Ribociclib (600 mg/d, 3 weeks on/1 week off × 26 cycles [24 mo])

→ Endocrine therapy + Placebo (3 weeks on/1 week off × 26 cycles [24 mo])

End Points

Primary:
iDFS

Secondary:
RFS
DDFS
OS
QoL
Safety

[a] Endocrine therapy can be started up to 12 weeks before randomization and continue for at least 60 months.

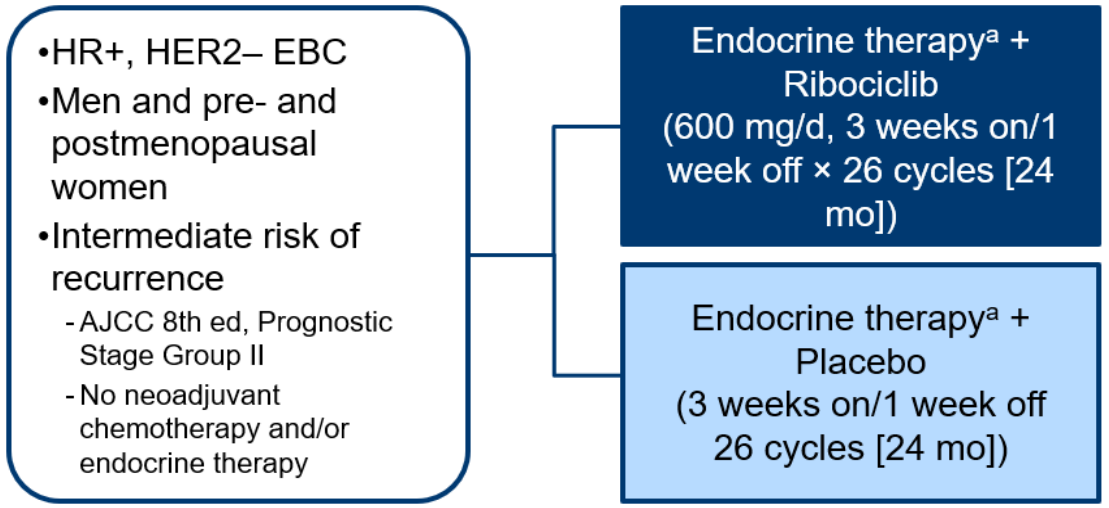
Randomization stratification factors:
Menopausal status: men and premenopausal women vs postmenopausal women
Risk group: IIIA vs IIIB/C vs residual disease after neoadjuvant chemotherapy
Geographical region: North America/Europe/Australia vs rest of the world

AJCC, American Joint Committee on Cancer; EBC, early breast cancer; DDFS, distant disease-free survival; HER2–, human epidermal growth factor receptor-2–negative; HR+, hormone receptor-positive; iDFS, invasive disease-free survival; LN, lymph node; NACT, neoadjuvant chemotherapy; OS, overall survival; QoL, quality of life; RFS, recurrence-free survival.

NCT03078751.

EarLEE-2: Adjuvant Therapy For Intermediate-Risk Early Breast Cancer

EarLEE-2 is a double-blind, randomized, placebo-controlled, multicenter, international phase 3 study of ribociclib + endocrine therapy (Target N ~ 4,000)



End Points

Primary:
iDFS

Secondary:
RFS
DDFS
OS
QoL
Safety

[a] Endocrine therapy can be started up to 12 weeks before randomization and continue for at least 60 months.

Randomization stratification factors:
Menopausal status: men and premenopausal women vs postmenopausal women
Risk group: IIA vs IIB
Geographical region: North America/Europe vs rest of the world
Prior adjuvant therapy: yes/no

AJCC, American Joint Committee on Cancer; EBC, early breast cancer; DDFS, distant disease-free survival; HER2–, human epidermal growth factor receptor-2–negative; HR+, hormone receptor-positive; iDFS, invasive disease-free survival; LN, lymph node; OS, overall survival; QoL, quality of life; RFS, recurrence-free survival.
NCT03081234.

5 June 2017

NATALEE study design[1,2]

- 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/day
3 weeks on/1 week 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

[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.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol.* 2019;37(15 suppl) [abstract TPS597].

NATALEE study design: unique features[1,2]

- 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]

Ribociclib
400 mg/day
3 weeks on/1 week off
for 3 y

Rationale for broad population of patients
Patients with stage II and III HR+/HER2− EBC, including those with no nodal involvement, are at risk of disease recurrence up to decades after initial diagnosis[3,4]

Rationale for 400 mg RIB
To improve tolerability while maintaining efficacy

Rationale for 3-year treatment duration
Extended duration of treatment is crucial to prolong cell cycle arrest and drive more tumor cells into irreversible senescence[5-7]

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

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1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol.* 2019;37(15 suppl) [abstract TPS597]. 3. Gomis RR and Gawrzak S, et al. *Mol Oncol*. 2017;11:62-78. 4. Pan H, et al. *N Engl J Med*. 2017;377:1836-1846. 5. Kovatcheva M, et al. *Oncotarget*. 2015;6:8226-8243; 6. Rader J, et al. *Clin Cancer Res*. 2013;19:6173-6182; 7. Klein ME, et al. *Cancer Cell*. 2018;34:9-20.

Statistical methods

- The study was powered at ≈ 85%, assuming a hazard ratio of 0.76 for a one-sided alpha level controlled at 0.025
  - Two interim efficacy analyses were planned at ≈ 350 events and ≈ 425 events, with the final analysis planned to take place at ≈ 500 events

- At the data cutoff (January 11, 2023) for the second interim efficacy analysis of iDFS, 426 iDFS events were documented

- Statistical comparison was made by a stratified log-rank test, with a protocol-defined Lan-DeMets (O'Brien-Fleming) stopping boundary of a one-sided P < .0128 for superior efficacy

Baseline characteristics

Parameter	RIB + NSAI n = 2549	NSAI alone n = 2552	All patients N = 5101
Age, median (min-max), years	52 (24-90)	52 (24-89)	52 (24-90)
Menopausal status, n (%)			
Premenopausal women and men[a]	1126 (44)	1132 (44)	2258 (44)
Postmenopausal women	1423 (56)	1420 (56)	2843 (56)
Anatomic stage[b,c], n (%)			
Stage IIA	479 (19)	521 (20)	1000 (20)
Stage IIB	532 (21)	513 (20)	1045 (20)
Stage III	1528 (60)	1512 (59)	3040 (60)
Nodal status at diagnosis, n (%)			
NX	272 (11)	264 (10)	536 (11)
N0	694 (27)	737 (29)	1431 (28)
N1	1050 (41)	1049 (41)	2099 (41)
N2/N3	483 (19)	467 (18)	950 (19)
Prior ET, n (%)[d]			
Yes	1824 (72)	1801 (71)	3625 (71)
Prior (neo)adjuvant CT, n (%)			
Yes	2249 (88)	2245 (88)	4494 (88)
ECOG PS, n (%)			
0	2106 (83)	2132 (84)	4238 (83)
1	440 (17)	418 (16)	858 (17)

[a] In the RIB+NSAI arm there were 11 men (0.4%) and in the NSAI alone arm there were 9 men (0.4%). [b] A total of 14 patients with Stage I disease were included: 9 pts (0.4%) in the RIB + ET arm and 5 pts (0.2%) in the ET alone arm. [c] Stage is derived using TNM from surgery for patients having not received (neo)adjuvant treatment, or as worst stage derived using TNM at diagnosis and TNM from surgery for patients having received (neo)adjuvant treatment. [d] Prior OFS was received by 670 pts (26.3%) in the RIB + NSAI arm and 620 pts (24.3%) in the NSAI alone arm.

CT, chemotherapy; ET, endocrine therapy; N0, no nodal involvement; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, 10 or more axillary lymph nodes or collarbone lymph nodes; NSAI, nonsteroidal aromatase inhibitor; NX, regional nodes were not assessed.

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

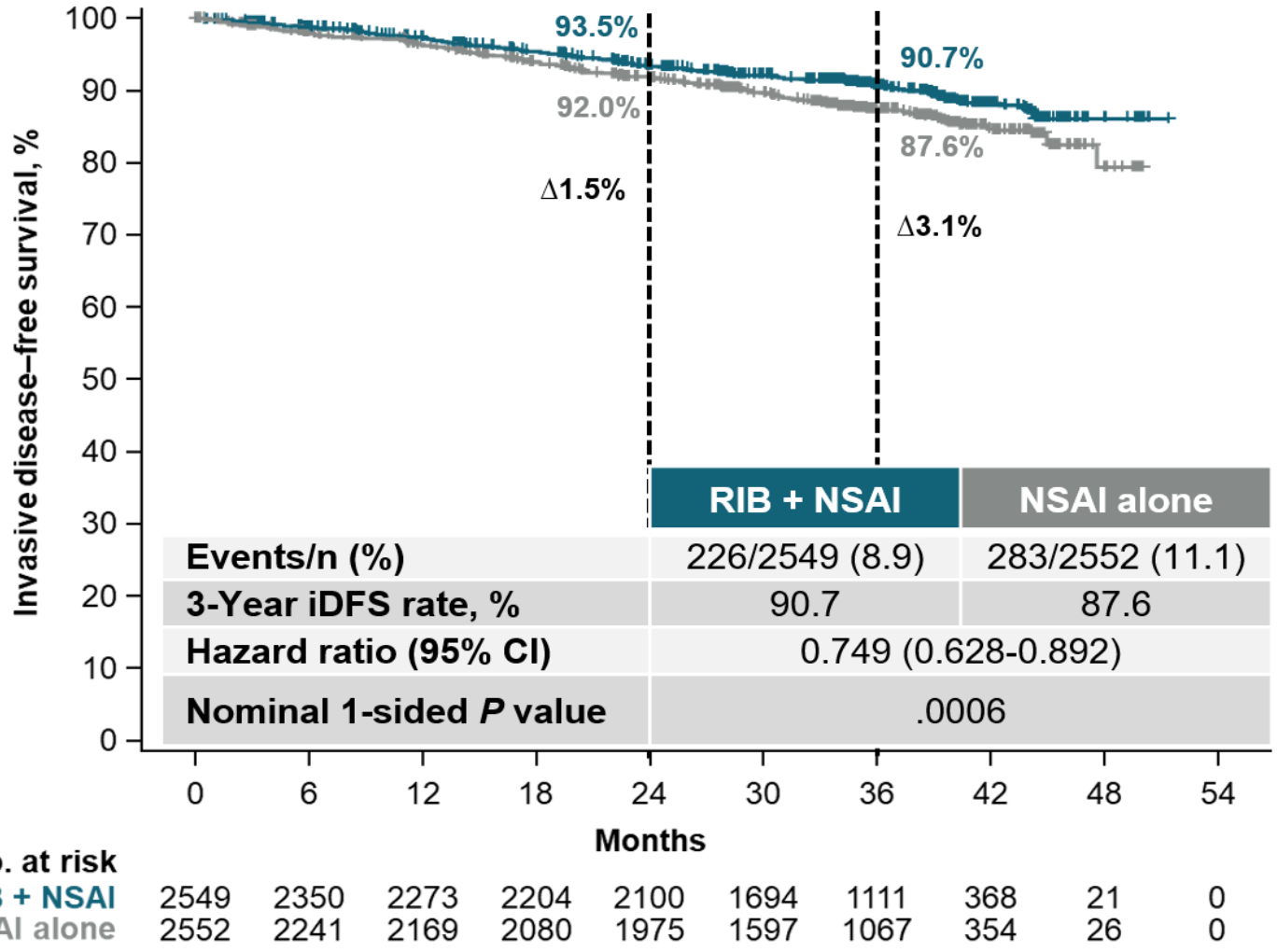
- NSAI ongoing: 1914 (75.1%)
  - **RIB ongoing: 528 (20.7%)**
- Stopped RIB: 1996 (78.3%)
  - **Completed 3 years: 1091 (42.8%)**
  - **Early discontinuation: 905 (35.5%)**
    - Discontinued due to AEs: 498 (19.5%)

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.

Invasive Disease–Free Survival

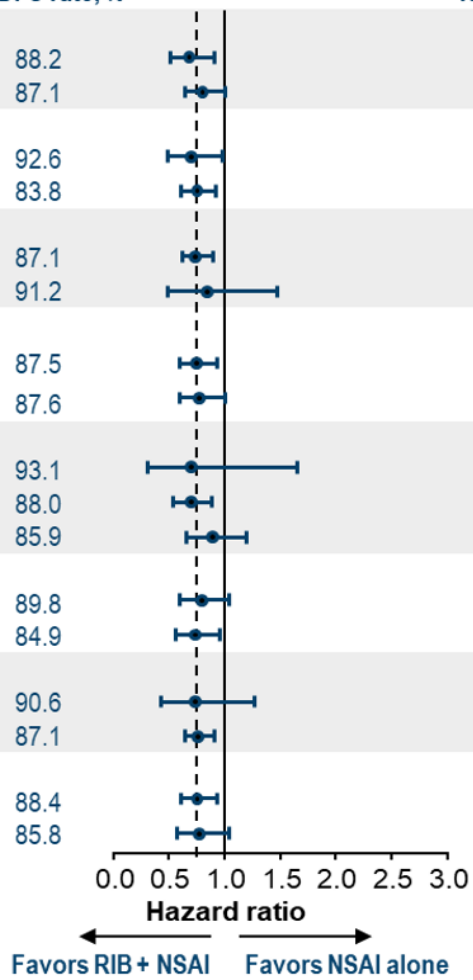


1. Slamon D, et al. ASCO 2023. Oral LBA500.

- 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

iDFS Across Key Prespecified Subgroups

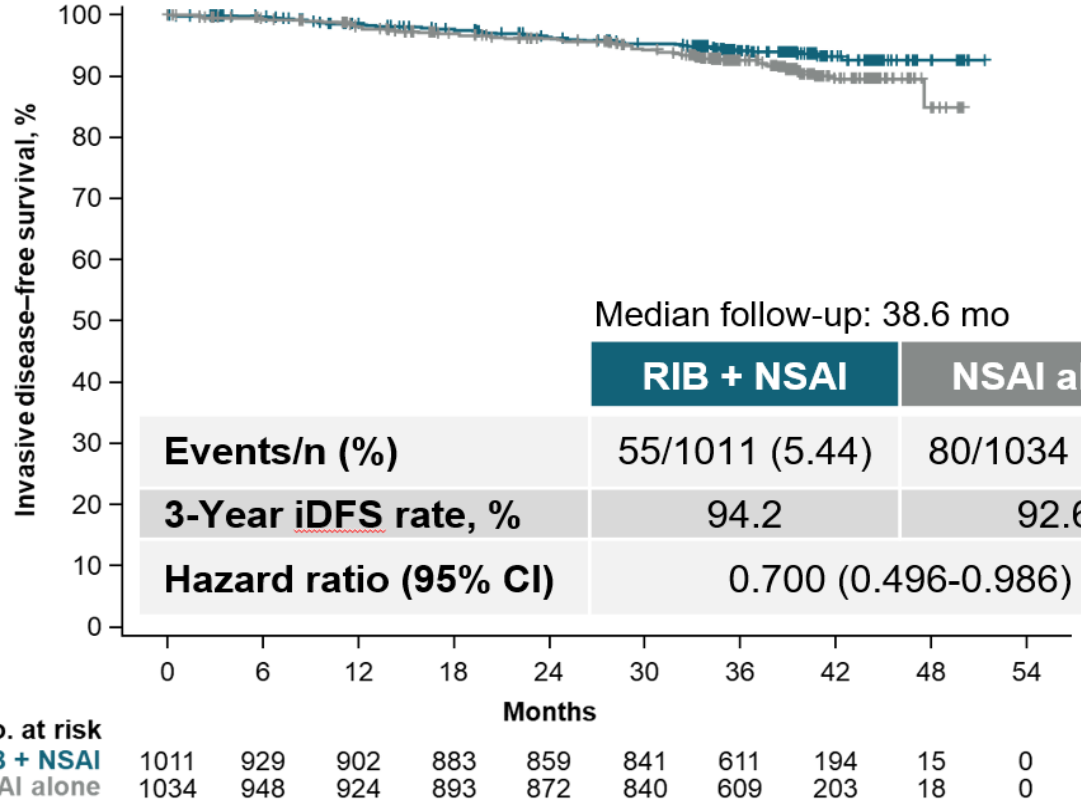
Subgroup	RIB + NSAI Events/n	RIB + NSAI 3-y iDFS rate, %	NSAI alone Events/n	NSAI alone 3-y iDFS rate, %	Hazard ratio	95% CI
Menopausal status						
Men and premenopausal women	83/1125	91.8	114/1132	88.2	0.688	0.519-0.913
Postmenopausal women	143/1424	89.7	169/1420	87.1	0.806	0.645-1.007
AJCC stage	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

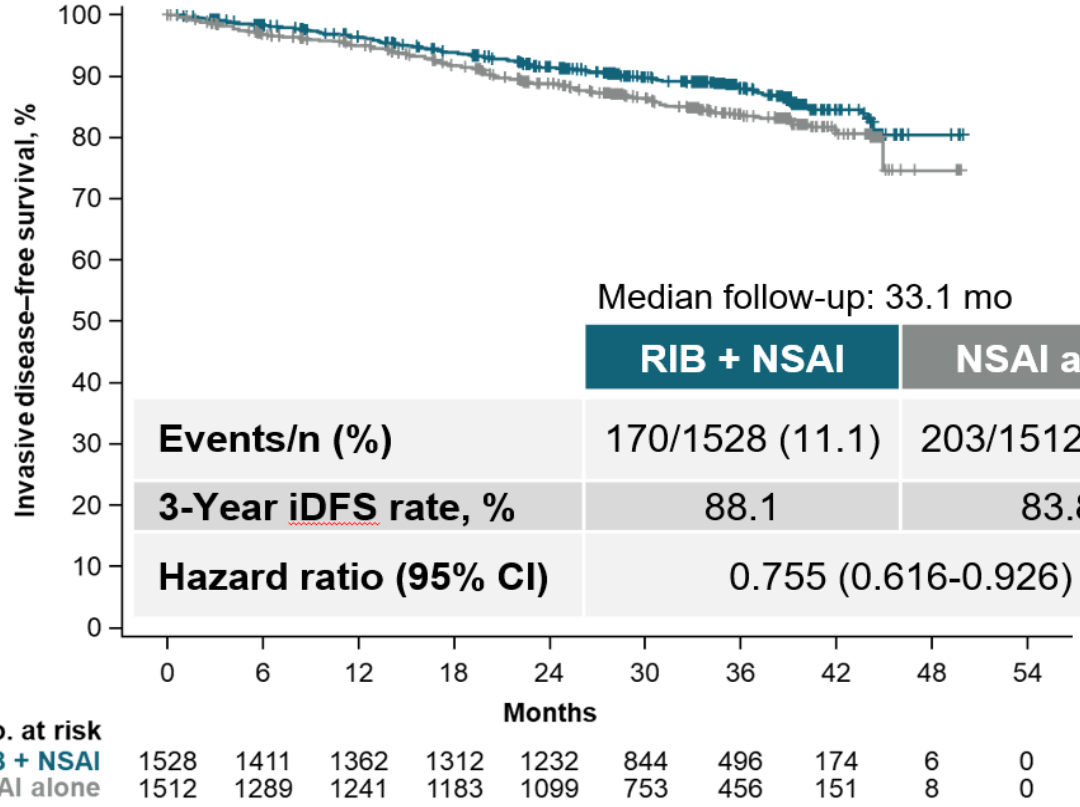


Median follow-up: 38.6 mo

	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)	

No. at risk										
RIB + NSAI	1011	929	902	883	859	841	611	194	15	0
NSAI alone	1034	948	924	893	872	840	609	203	18	0

Stage III



Median follow-up: 33.1 mo

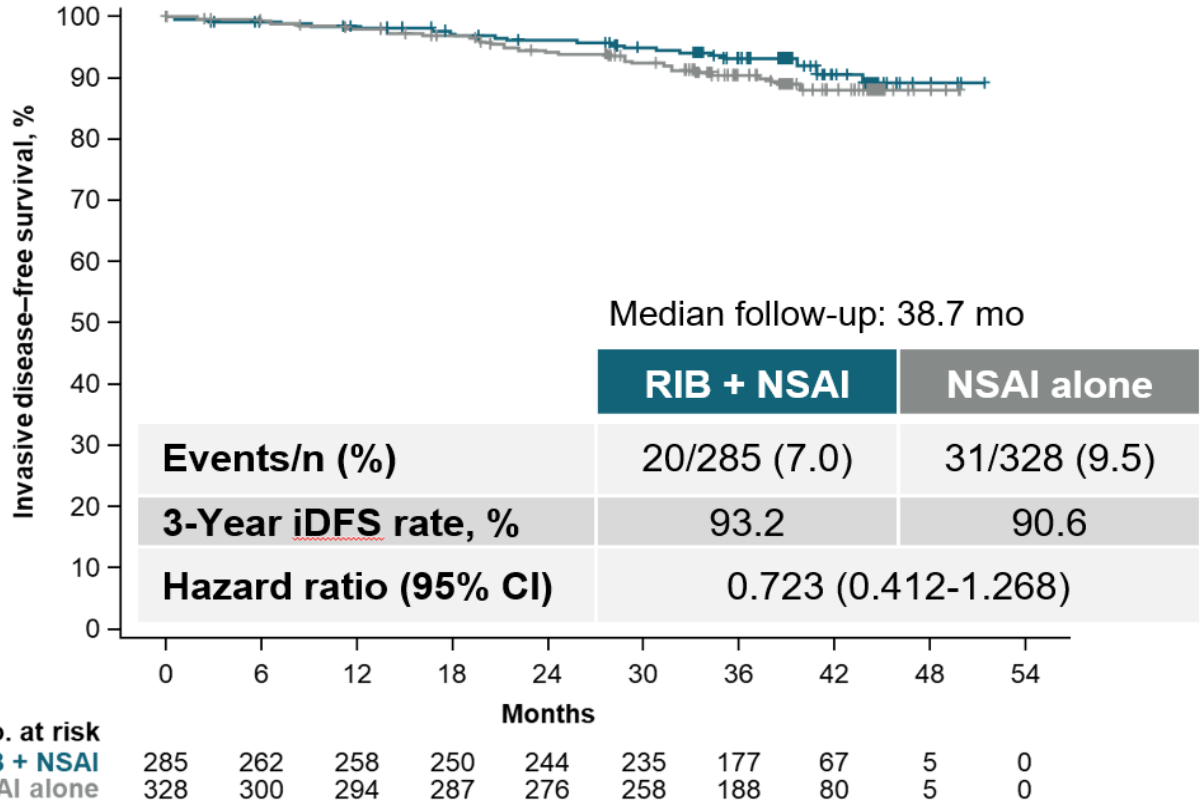
	RIB + NSAI	NSAI alone
Events/n (%)	170/1528 (11.1)	203/1512 (13.4)
3-Year iDFS rate, %	88.1	83.8
Hazard ratio (95% CI)	0.755 (0.616-0.926)	

No. at risk										
RIB + NSAI	1528	1411	1362	1312	1232	844	496	174	6	0
NSAI alone	1512	1289	1241	1183	1099	753	456	151	8	0

- 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

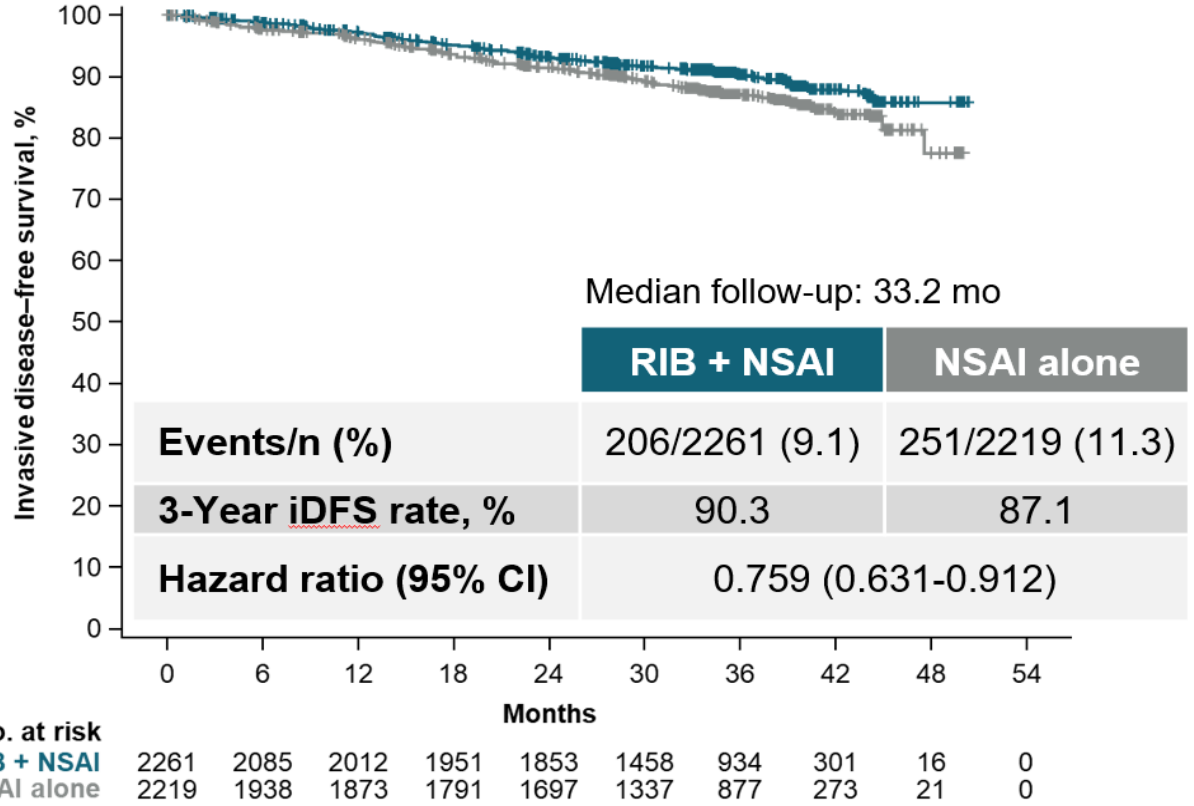


Median follow-up: 38.7 mo

	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)	

No. at risk										
RIB + NSAI	285	262	258	250	244	235	177	67	5	0
NSAI alone	328	300	294	287	276	258	188	80	5	0

N1-N3



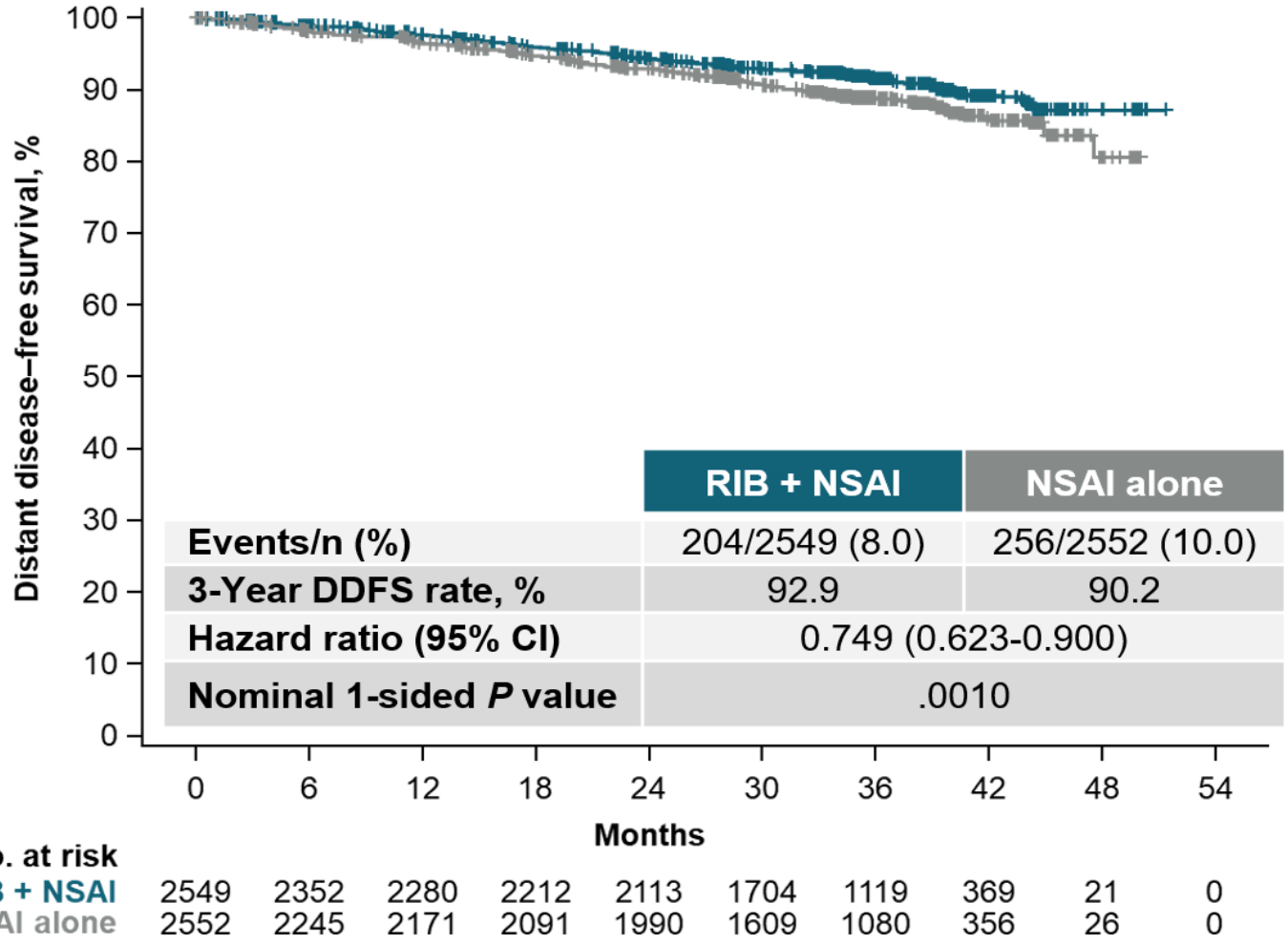
Median follow-up: 33.2 mo

	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)	

No. at risk										
RIB + NSAI	2261	2085	2012	1951	1853	1458	934	301	16	0
NSAI alone	2219	1938	1873	1791	1697	1337	877	273	21	0

- 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	

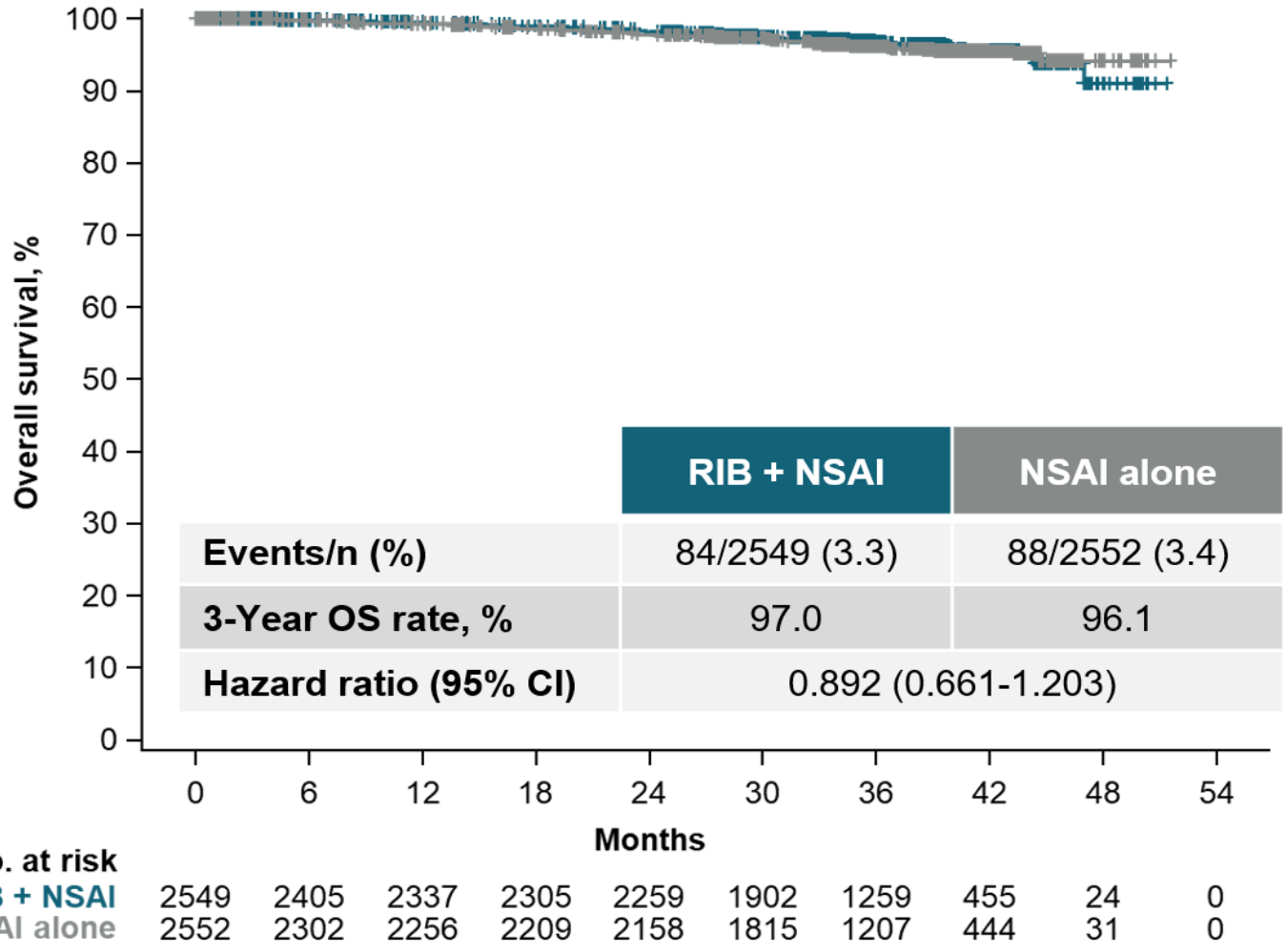
No. at risk										
RIB + NSAI	2549	2352	2280	2212	2113	1704	1119	369	21	0
NSAI alone	2552	2245	2171	2091	1990	1609	1080	356	26	0

- 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)	

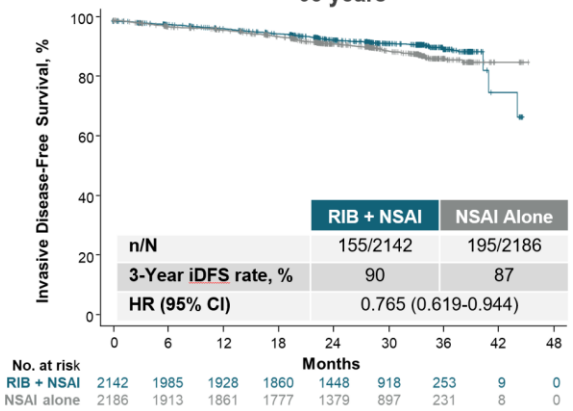
No. at risk										
RIB + NSAI	2549	2405	2337	2305	2259	1902	1259	455	24	0
NSAI alone	2552	2302	2256	2209	2158	1815	1207	444	31	0

- 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

NATALEE iDFS by age

iDFS benefit with ribociclib + NSAI across age groups

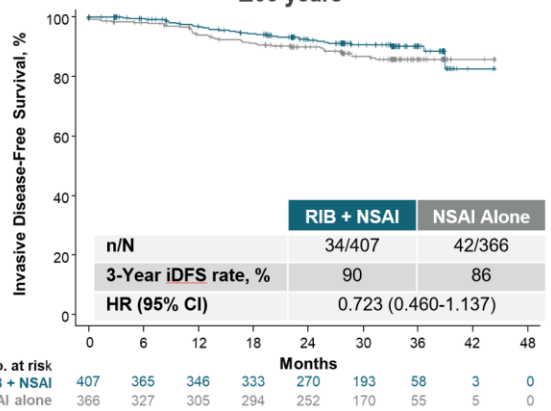
<65 years



	RIB + NSAI	NSAI Alone
n/N	155/2142	195/2186
3-Year iDFS rate, %	90	87
HR (95% CI)	0.765 (0.619-0.944)	

No. at risk									
RIB + NSAI	2142	1985	1928	1860	1448	918	253	9	0
NSAI alone	2186	1913	1861	1777	1379	897	231	8	0

≥65 years



	RIB + NSAI	NSAI Alone
n/N	34/407	42/366
3-Year iDFS rate, %	90	86
HR (95% CI)	0.723 (0.460-1.137)	

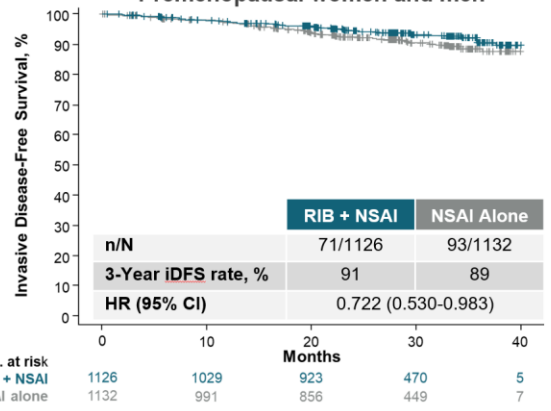
No. at risk									
RIB + NSAI	407	365	346	333	270	193	58	3	0
NSAI alone	366	327	305	294	252	170	55	5	0

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

NATALEE iDFS by menopausal status

iDFS benefit with ribociclib + NSAI across pre- and postmenopausal patients

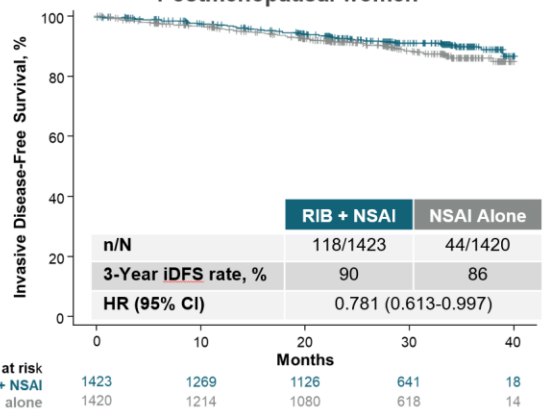
Premenopausal women and men



	RIB + NSAI	NSAI Alone
n/N	71/1126	93/1132
3-Year iDFS rate, %	91	89
HR (95% CI)	0.722 (0.530-0.983)	

No. at risk					
RIB + NSAI	1126	1029	923	470	5
NSAI alone	1132	991	856	449	7

Postmenopausal women



	RIB + NSAI	NSAI Alone
n/N	118/1423	44/1420
3-Year iDFS rate, %	90	86
HR (95% CI)	0.781 (0.613-0.997)	

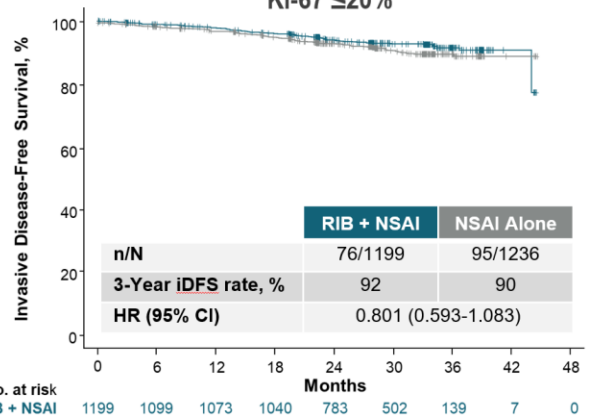
No. at risk					
RIB + NSAI	1423	1269	1126	641	18
NSAI alone	1420	1214	1080	618	14

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

NATALEE iDFS by local Ki-67

Ribociclib + NSAI prolonged iDFS regardless of Ki-67 score[a]

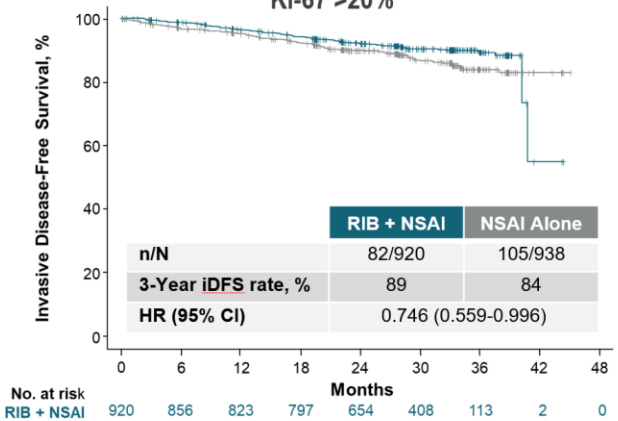
Ki-67 ≤20%



	RIB + NSAI	NSAI Alone
n/N	76/1199	95/1236
3-Year iDFS rate, %	92	90
HR (95% CI)	0.801 (0.593-1.083)	

No. at risk									
RIB + NSAI	1199	1099	1073	1040	783	502	139	7	0
NSAI alone	1236	1107	1077	1037	802	521	130	4	0

Ki-67 >20%



	RIB + NSAI	NSAI Alone
n/N	82/920	105/938
3-Year iDFS rate, %	89	84
HR (95% CI)	0.746 (0.559-0.996)	

No. at risk									
RIB + NSAI	920	856	823	797	654	408	113	2	0
NSAI alone	938	813	784	745	604	383	106	6	0

[a] Locally tested

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

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 the protocol-specified final iDFS analysis of NATALEE, ribociclib plus NSAI demonstrated a statistically significant improvement in iDFS over NSAI alone, with 78.3% of patients no longer on ribociclib treatment at data cutoff
  - The iDFS benefit was consistent across key prespecified subgroups, regardless of stage, nodal status, age, menopausal status and Ki67
  - Ki67Results 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

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 Jan 2023	21 July 2023	29 April 2024
Median follow-up for iDFS, months	27.7	33.3	44.2
iDFS events	426	509	603
Off RIB treatment	54.0%	78.3%	100%
Completed 3 years of RIB treatment	20.2%	42.8%	62.8%

Fasching P, et al., ESMO, 24 September 2024

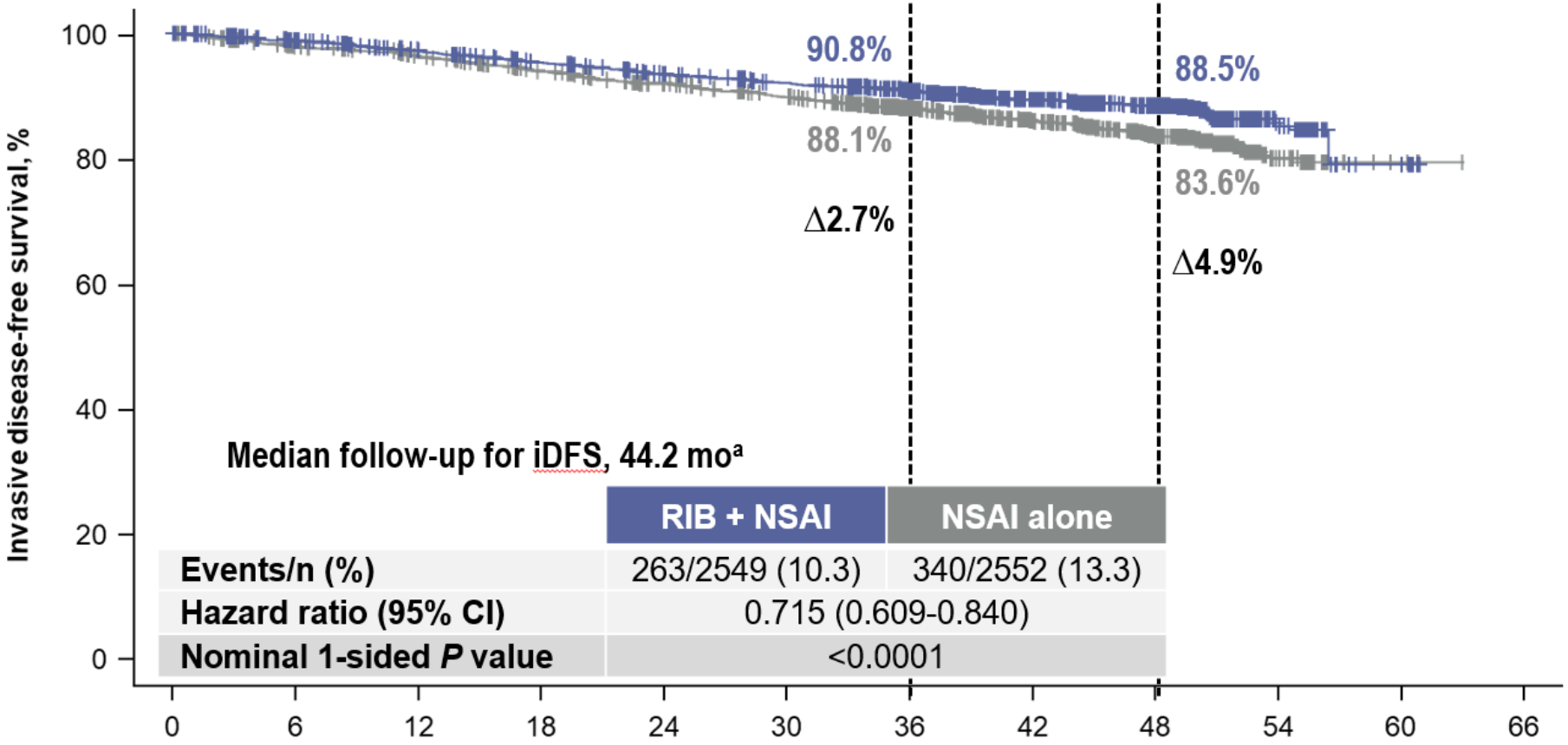
Patient Disposition

All patients are off ribociclib and 62.8% completed 3-years

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 3y RIB treatment	1601 (62.8)		-
	RIB	NSAI	NSAI
Early discontinuation	923 (36.2)	732 (28.7)	813 (31.9)
Primary reason for early discontinuation			
Disease relapse	127 (5.0)	196 (7.7)	267 (10.5)
AE	509 (20.0)	136 (5.3)	124 (4.9)
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)	6 (0.2)	6 (0.2)
Other[a]	114 (4.5)	169 (6.6)	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

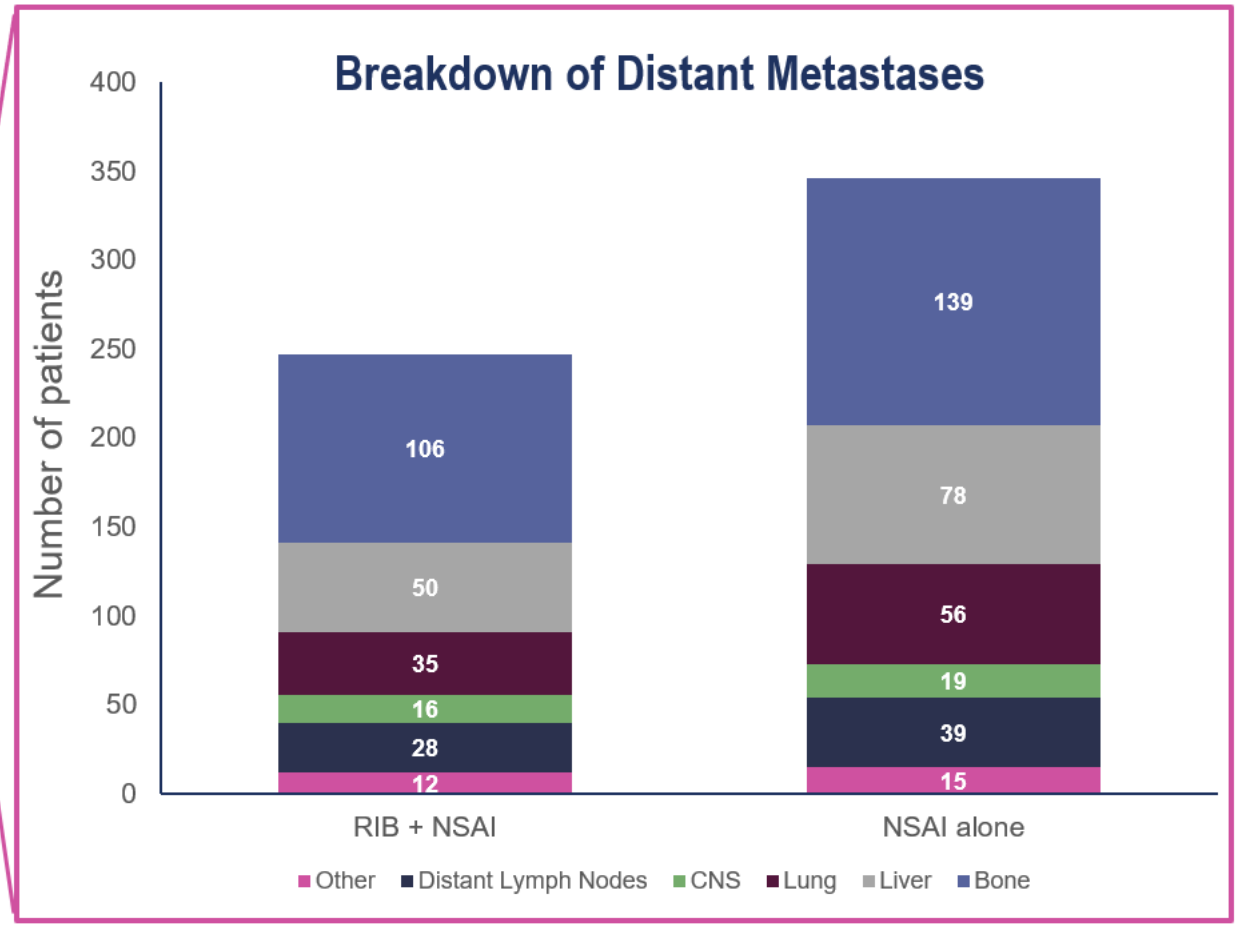
NATALEE – iDFS in the Intent-to-treat Population



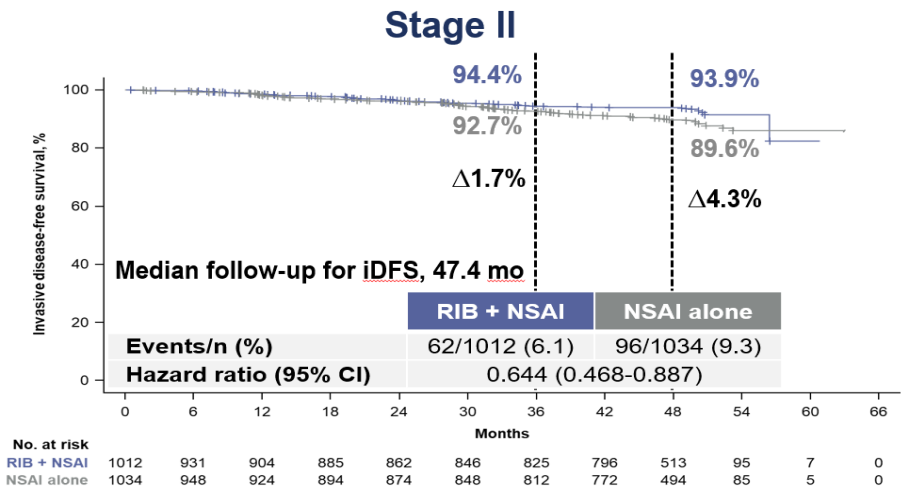
NATALEE – iDFS in the Intent-to-treat Population

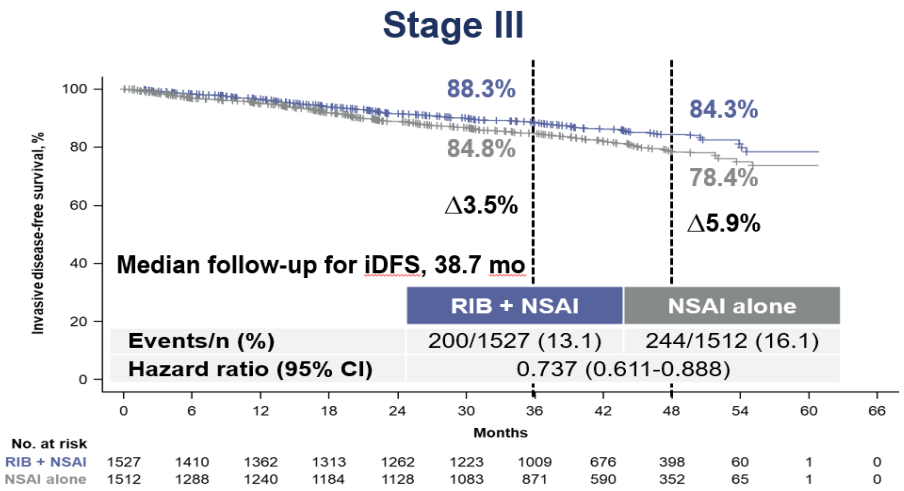
The majority of iDFS events were distant recurrences which were more common in the NSAI only arm

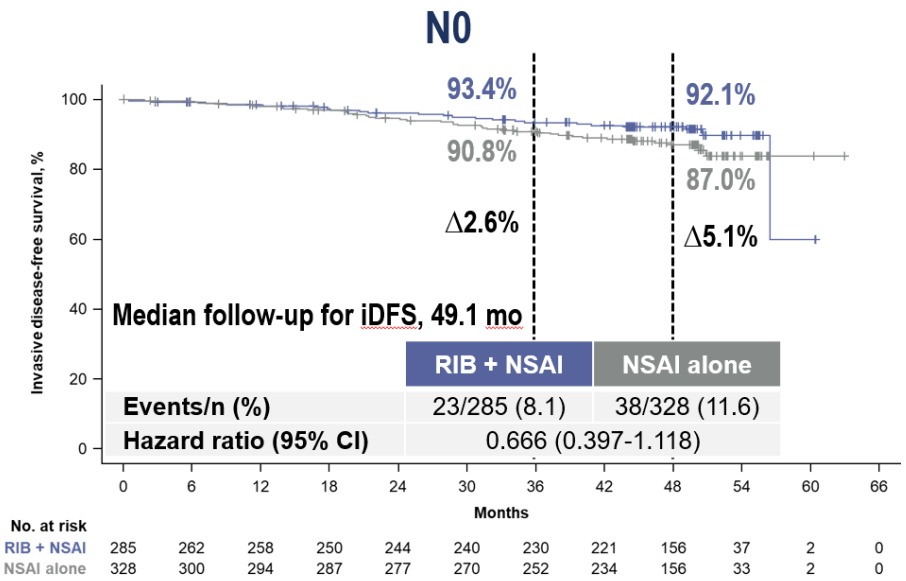
Type and Site of First iDFS Event, n (%)	RIB + NSAI n=2549	NSAI Alone n=2552
Invasive ipsilateral breast tumor	8 (0.3)	9 (0.4)
Invasive contralateral breast tumor	11 (0.4)	10 (0.4)
Local/regional invasive recurrence	25 (1.0)	49 (1.9)
Distant recurrence	176 (6.9)	246 (9.6)
Second primary non-breast cancer	39 (1.5)	40 (1.6)
Death	17 (0.7)	11 (0.4)

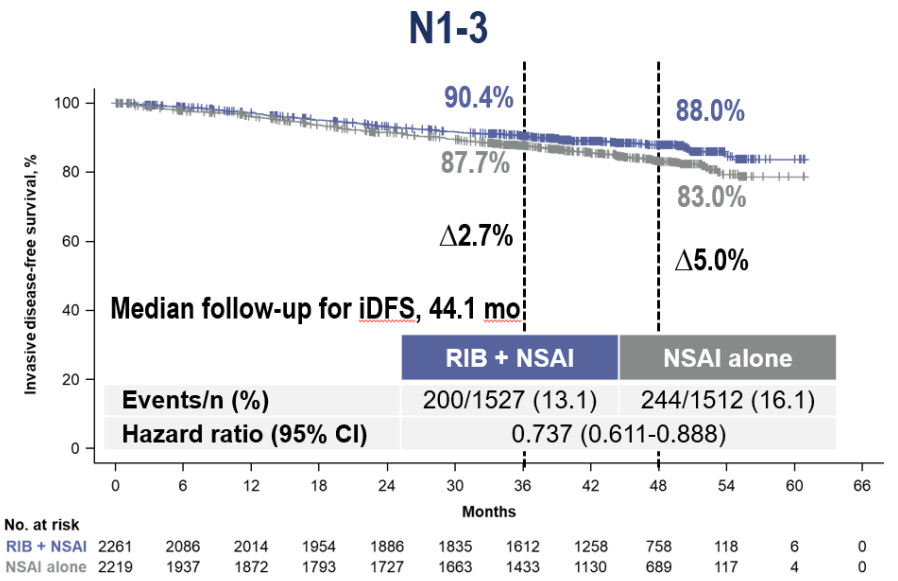


NATALEE – iDFS Subgroup Analysis



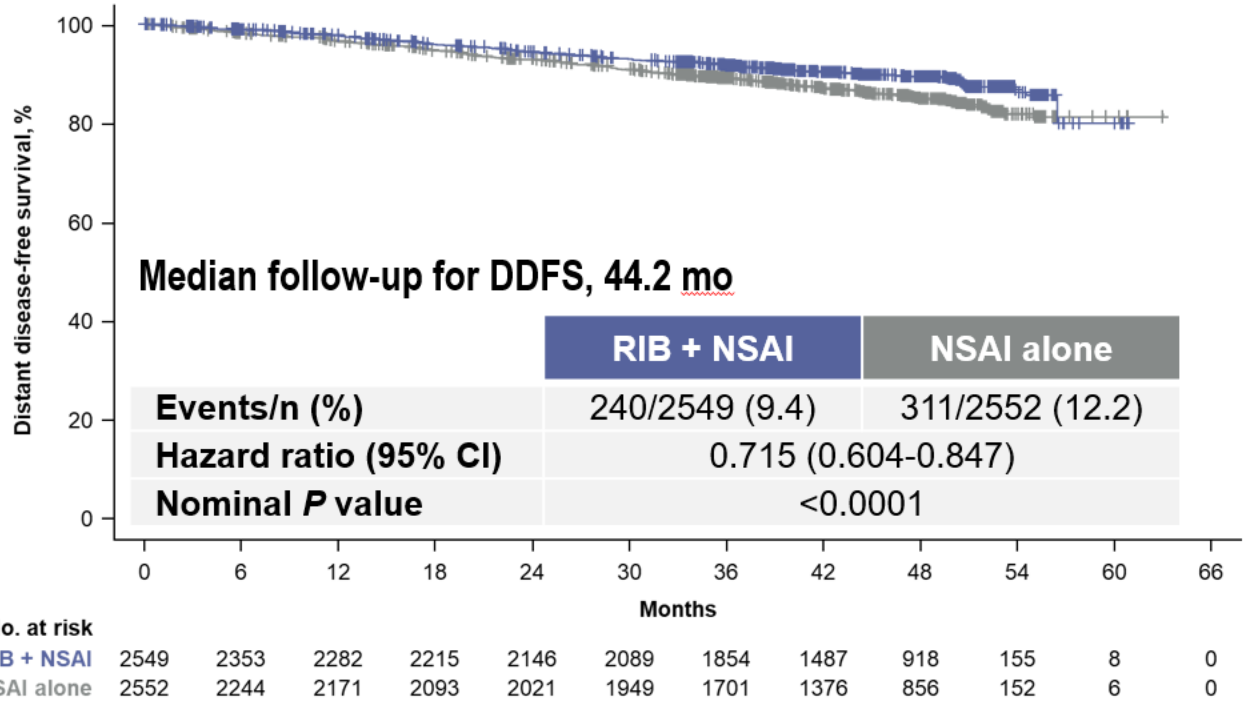






Key Secondary Efficacy Endpoints

DDFS

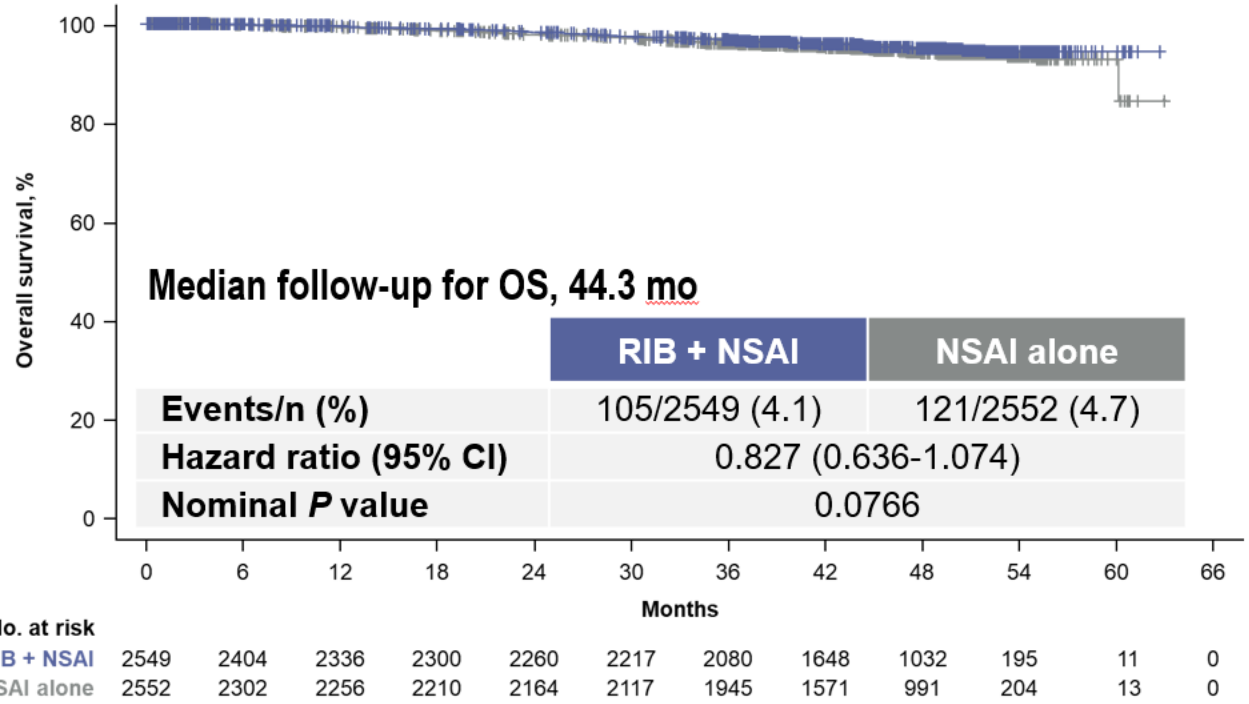


Median follow-up for DDFS, 44.2 mo

	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	

No. at risk												
RIB + NSAI	2549	2353	2282	2215	2146	2089	1854	1487	918	155	8	0
NSAI alone	2552	2244	2171	2093	2021	1949	1701	1376	856	152	6	0

OS



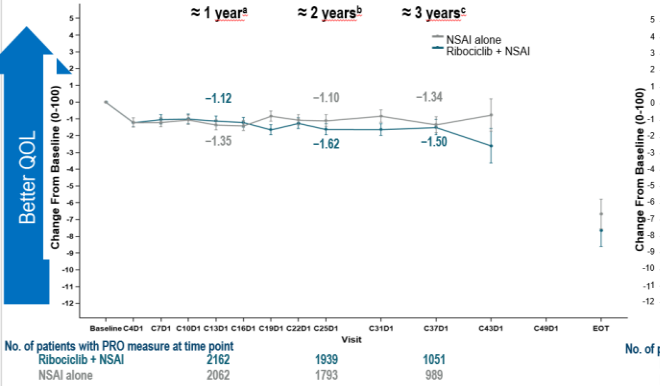
Median follow-up for OS, 44.3 mo

	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	

No. at risk												
RIB + NSAI	2549	2404	2336	2300	2260	2217	2080	1648	1032	195	11	0
NSAI alone	2552	2302	2256	2210	2164	2117	1945	1571	991	204	13	0

PRIMARY HRQOL OF INTEREST—EORTC QLQ-C30: PHYSICAL FUNCTIONING

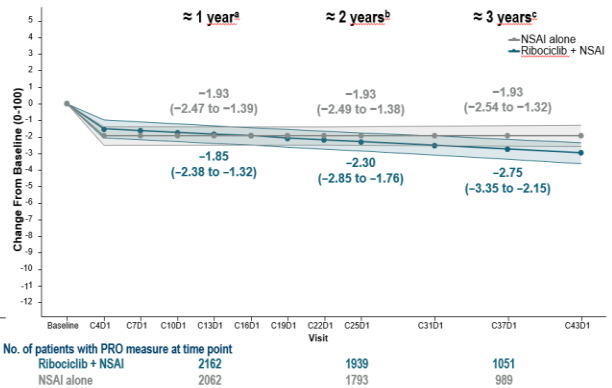
Descriptive Analysis



No. of patients with PRO measure at time point

Ribociclib + NSAI	2162	1939	1051
NSAI alone	2062	1793	989

Model-Based Analyses



No. of patients with PRO measure at time point

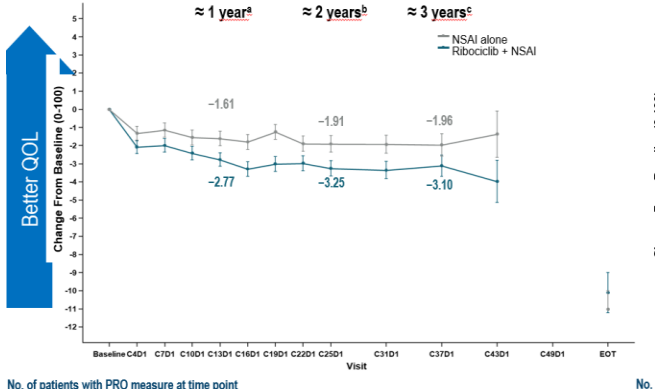
Ribociclib + NSAI	2162	1939	1051
NSAI alone	2062	1793	989

- Based on regression analysis, physical functioning scores were higher in premenopausal women and men vs postmenopausal women and those who received prior (neo)adjuvant CT vs no prior (neo)adjuvant CT and were not impacted by the treatment arm

Physical functioning was maintained with the addition of ribociclib to standard-of-care NSAI[1,d,e]

EORTC QLQ-C30: GLOBAL HEALTH STATUS

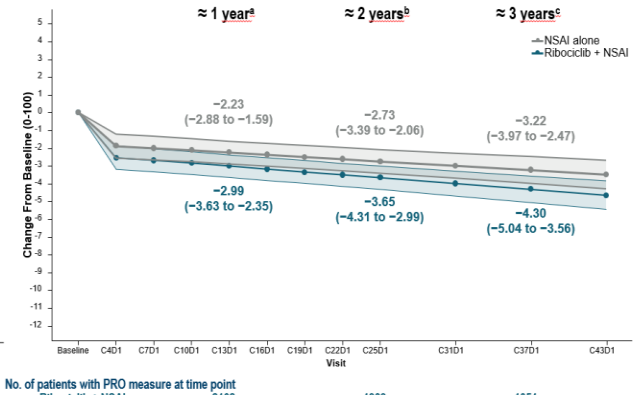
Descriptive Analysis



No. of patients with PRO measure at time point

Ribociclib + NSAI	2165	1939	1052
NSAI alone	2061	1797	991

Model-Based Analyses



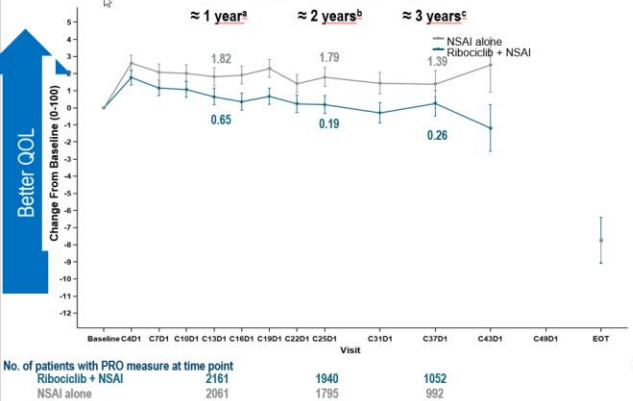
No. of patients with PRO measure at time point

Ribociclib + NSAI	2162	1939	1051
NSAI alone	2062	1793	989

Global health status was not impacted over time in both arms[1,d,e]

EORTC QLQ-C30: SOCIAL FUNCTIONING

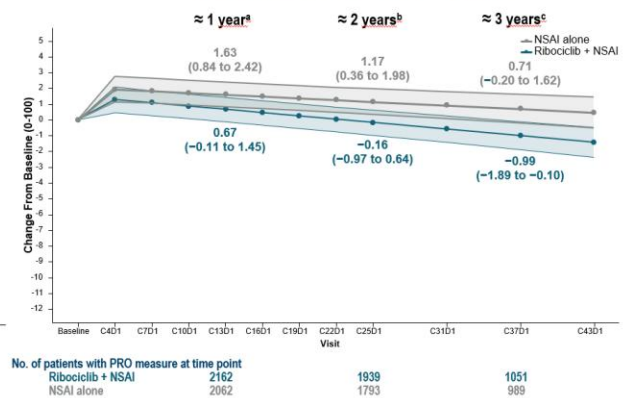
Descriptive Analysis



No. of patients with PRO measure at time point

Ribociclib + NSAI	2161	1940	1052
NSAI alone	2061	1795	992

Model-Based Analyses



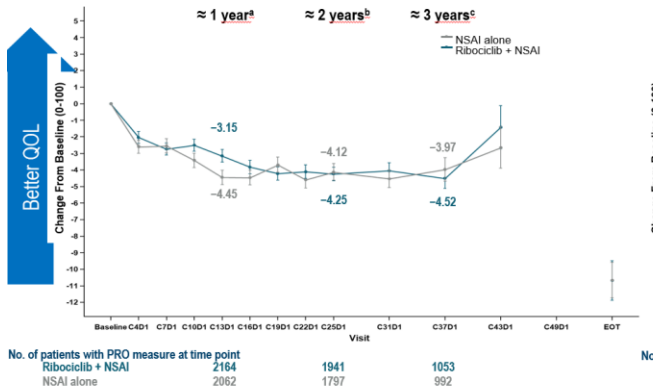
No. of patients with PRO measure at time point

Ribociclib + NSAI	2162	1939	1051
NSAI alone	2062	1793	989

No difference in social functioning from baseline was observed in both arms[1,d,e]

EORTC QLQ-C30: EMOTIONAL FUNCTIONING

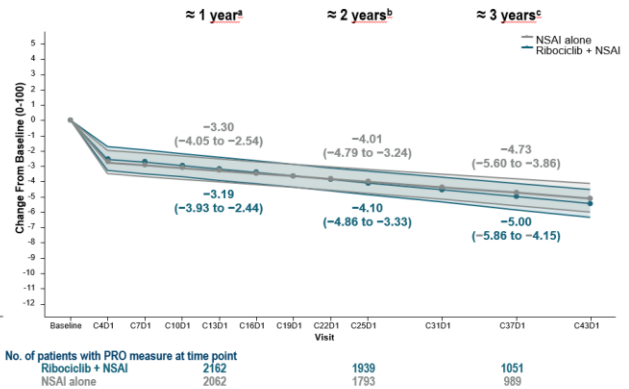
Descriptive Analysis



No. of patients with PRO measure at time point

Ribociclib + NSAI	2164	1941	1053
NSAI alone	2062	1797	992

Model-Based Analyses



No. of patients with PRO measure at time point

Ribociclib + NSAI	2162	1939	1051
NSAI alone	2062	1793	989

A small deterioration in emotional functioning from baseline was observed in both arms[1,d,e]
No difference was observed between patients treated with ribociclib + NSAI vs NSAI alone

NATALEE – Outcomes over time

Outcome	2 years	3 years	HR (95% CI)	4 years	
iDFS delta	1.5%	3.1%	0.749 (0.628-0.892)	4.9%	0.715 (0.609-0.840)
iDFS delta					
Stage II		1.6%	0.700 (0.496-0.986)	4.3%	0.644 (0.468-0.887)
Stage III		4.3%	0.755 (0.616-0.926)	5.9%	0.737 (0.611-0.888)
iDFS delta					
N0		2.6%	0.723 (0.412-1.268)	5.1%	0.666 (0.397-1.118)
N1-N3		3.2%	0.759 (0.631-0.912)	5.0%	0.737 (0.611-0.888
DDFS		2.7%	0.749 (0.623-0.900	2.8%	0.715 (0.604)-0.847)
OS		0.9%	0.892 (0.661-1.203	0.6%	0.827 (0.636-1.074)

bjclub breast Journal club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

Comparison of results of adjuvant trials

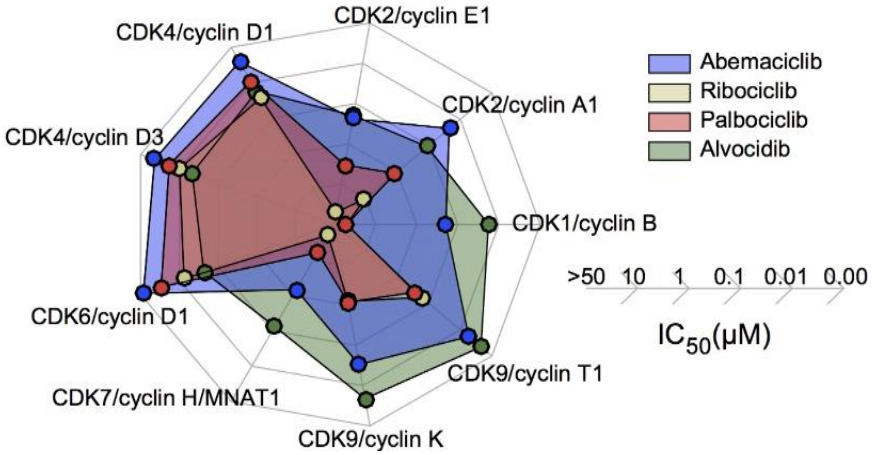
	Penelope-B	PALLAS	MonarchE	NATALEE
Sample size	1708	5761	5637	5101
Study population	HR+/HER2- without pCR after NACT and CPS-EG≥3 or ≥2 with pN+	Stage II-III HR+/HER2- (**48.6% Stage III**)	Cohort 1: ≥4 LND+ or 1-3 LND and grade 3, ≥5cm Cohort 2: 1-3 LND+ and Ki-67≥20% (**74% stage III**)	Stage II—III: N0-G2 if Ki-67≥20%, Oncotype >25 or high-risk genomic profiling, and all N0-G3, and Stage III N0
Study drug	Palbociclib (1 year)	Palbociclib (2 years)	Abemaciclib (2 years)	Ribociclib (3 years)
Results, Hazar Ratio (95% CI)	iDFS 3-year: 81.2% *vs.* 77.7% **0.93** (0.74 to 1.17)	iDFS 4-year: 84.2% vs. 84.5%, **0.96** (0.81-1.14)	iDFS 5-year: 83.6% vs. 76%, **0.680** (0.599-0.772)	iDFS 4-year: 88.5% vs. 83.6%, **0.715** (0.609-0.840)
% Discontinuation	17.5%	44.9%	16.6%	18.9%
Duration of follow up (median)	42.8 months	31 months	54 months	44 months

Rationale for 3 years

- Mainly because we are treating occult metastases, treatment duration should be longer than the 28 months median PFS under CDK4/6 inhibitor therapy in 1st line metastatic breast cancer. Results of the NATALEE trial with ribociclib given for 3 years might clarify this aspect.
- To prolong cell-cycle arrest and induce irreversible senescence.
- We used the lower dose of ribociclib—400 mg/d—than that used in the MONALEESA trials to improve tolerability and treatment adherence.

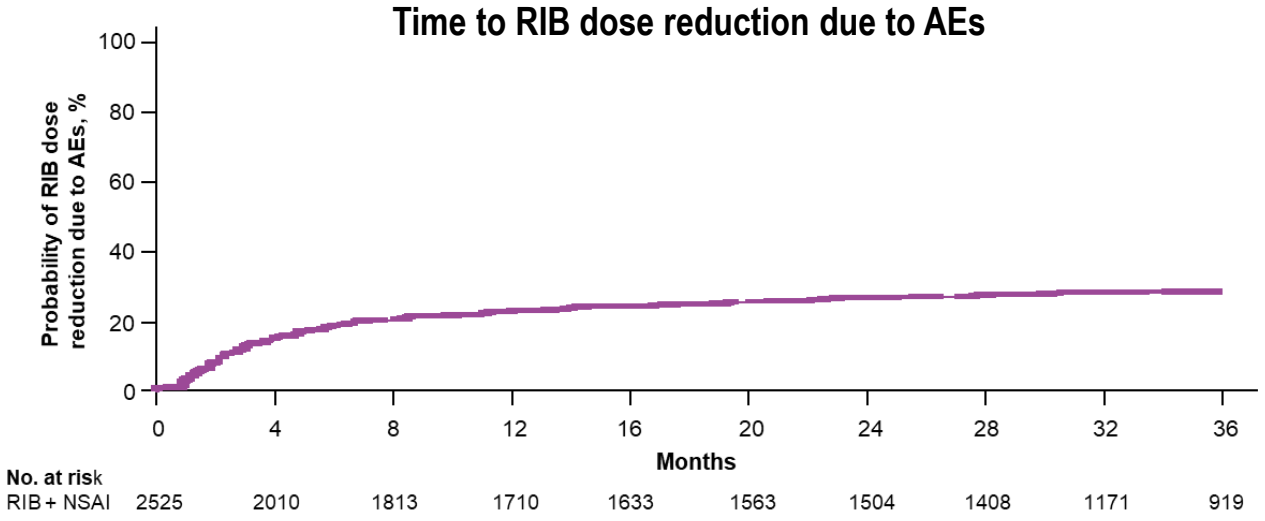
Properties of Approved CDK4/6 Inhibitors

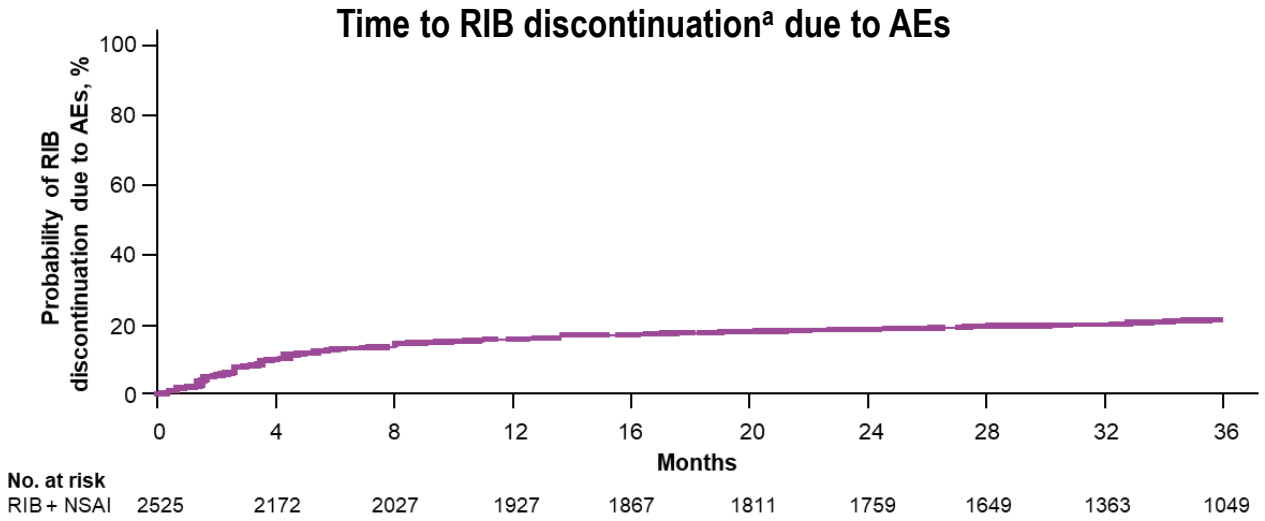
	Ribociclib	Palbociclib	Abemaciclib
IC_{50} (nM) – on target CDKs			
CDK4–cyclin D1	10	11	2
CDK6–cyclin D1/2/3	39	16	10
IC_{50} (nM) – on other CDKs			
CDK1–cyclin B	113,000	>10,000	1627
CDK2–cyclin A/E	76,000	>10,000	504
CDK5–p25	43,900	>10,000	355
CDK9–cyclin T	NR	NR	57
Kinase partition index	0.99	0.96	0.88
Lipophilicity (cLogP)	2.3	2.7	5.5
IC_{50} against bone marrow mononuclear cells (nM)	1700 ± 231	240 ± 43	230 ± 27
Half-life	33–42 hr	26–27 hr	17–38 hr
T_{max}	1–5 hr	6–12 hr	4–6 hr



Tripathy D, et al. Clin Cancer Res 2017

NATALEE: AE-RELATED DOSE REDUCTION AND DISCONTINUATION





- AE-related RIB dose reductions occurred in 22.8% of patients
  - Most commonly due to neutropenia (8.5%) and neutrophil count decreased (5.6%)
- Median time to AE-related RIB dose reduction: 3.15 months (range: 0.26-34.17)
- Median RDI during RIB treatment: 94%

- Most common AEs leading to discontinuation: ALT increased (7.1%) and AST increased (2.8%)
- Of 19.7% who discontinued due to AEs, 14.0% discontinued without prior dose reduction and 5.7% dose-reduced before discontinuing
- Median time to AE-related RIB discontinuation: 4.17 months (range: 0.10–35.75)

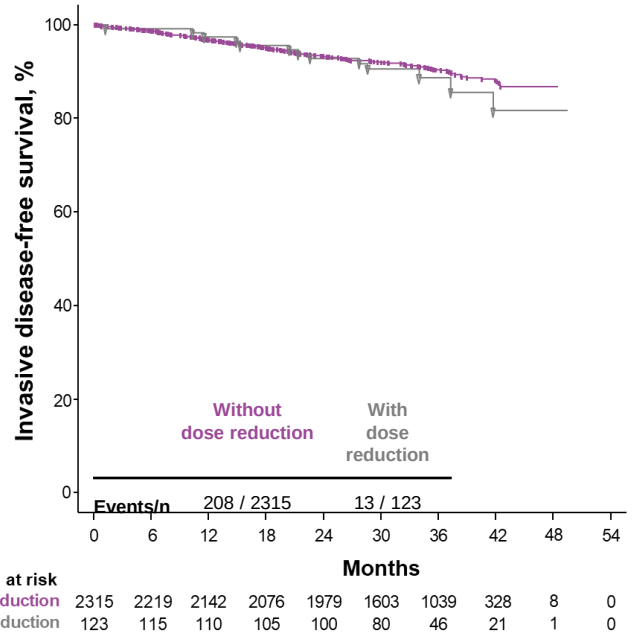
[a] Protocol required discontinuation for RIB dose interruption >28 days, or grade ≥4 AEs (except neutropenia and thrombocytopenia), or recurrent high-grade AEs
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; RDI, relative dose intensity; RIB, ribociclib.

Carlos Barrios, MD

NATALEE: IDFS BY DOSE REDUCTIONS

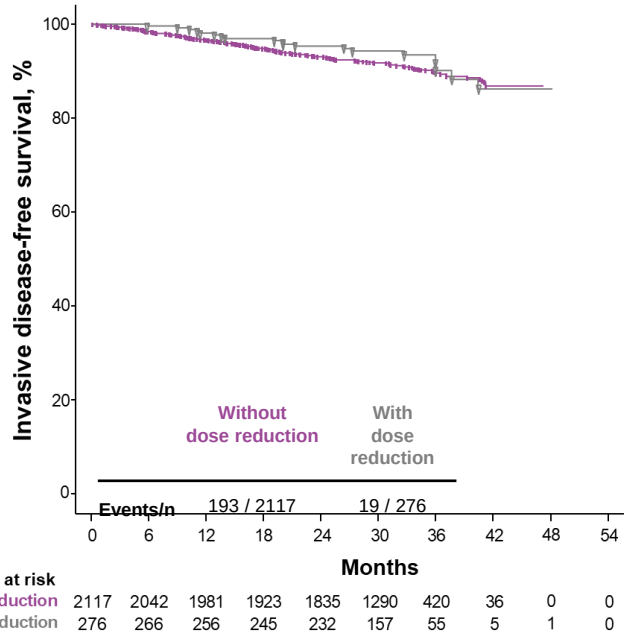
Landmark analysis revealed that RIB dose reduction due to AEs did not impact efficacy

iDFS by dose reduction at 25th percentile[a] (1.87 mo.)



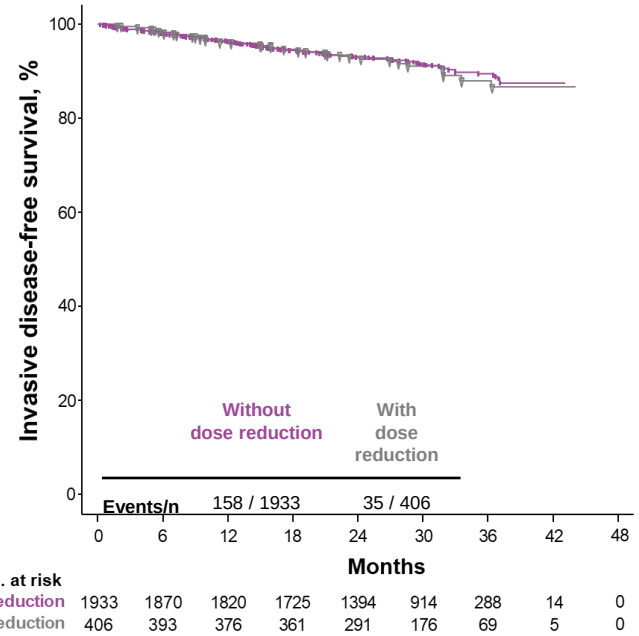
No. at risk										
Without dose reduction	2315	2219	2142	2076	1979	1603	1039	328	8	0
With dose reduction	123	115	110	105	100	80	46	21	1	0

iDFS by dose reduction at 50th percentile[a] (3.17 mo.)



No. at risk										
Without dose reduction	2117	2042	1981	1923	1835	1290	420	36	0	0
With dose reduction	276	266	256	245	232	157	55	5	1	0

iDFS by dose reduction at 75th percentile[a] (7.28 mo.)



No. at risk									
Without dose reduction	1933	1870	1820	1725	1394	914	288	14	0
With dose reduction	406	393	376	361	291	176	69	5	0

[a] Of dose reduction time, calculated from randomization.

AE, adverse event; CI, confidence interval; HR, hazard ratio; iDFS, invasive disease-free survival; RIB, ribociclib.

Carlos Barrios, MD