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Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2- early breast cancer: Primary results from the phase III NATALEE trial

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Disclosures

- Dr Slamon reports stock ownership from BioMarin, Pfizer, Amgen, Seagen, TORL BioTherapeutics, and 1200 Pharma; travel support from BioMarin, Pfizer, and Novartis; personal fees from Novartis and Eli Lilly; and grants from Pfizer and Novartis and is a founder of 1200 Pharma and TORL BioTherapeutics

Background

- While treatment for EBC is administered with curative intent, recurrences remain a significant problem
  - Patients with ER+ breast cancer, including those with node-negative disease, may experience disease recurrence up to decades after initial diagnosis, with the highest risk of recurrence occurring in the first 5 years[1,2]
- The significant PFS benefit and improved/maintained QOL with ribociclib + ET in HR+/HER2− ABC prompted investigation of ribociclib in the EBC setting[3-9]
- The Phase III NATALEE trial evaluated adjuvant ribociclib + NSAI in a broad population of patients with stage II or III HR+/HER2− EBC at risk of recurrence, including those with N0 disease
- We present results from the second prespecified interim efficacy analysis of the primary end point (iDFS) in NATALEE

ABC, advanced breast cancer; EBC, early breast cancer; ER, estrogen receptor; 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; PFS, progression-free survival; QOL, quality of life.

References: 1. Gomis RR and Gawrzak S, et al. *Mol Oncol*. 2017;11:62-78. 2. Pan H, et al. *N Engl J Med*. 2017;377:1836-1846. 3. Hortobagyi GN, et al. *N Engl J Med*. 2016;375:1738-1748. 4. Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-2472. 5. Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915. 6. Verma et al. *Breast Cancer Res Treat*. 2018;170:535-545. 7. Janni et al. *Breast Cancer Res Treat*. 2017;169:459-479. 8. Fasching P, et al. *Breast*. 2020;54:148-154. 9. Harbeck N, et al. *Ther Adv Med Oncol*. 2020;12:1758835920943065.

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

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

Primary End Point
- iDFS using STEEP criteria

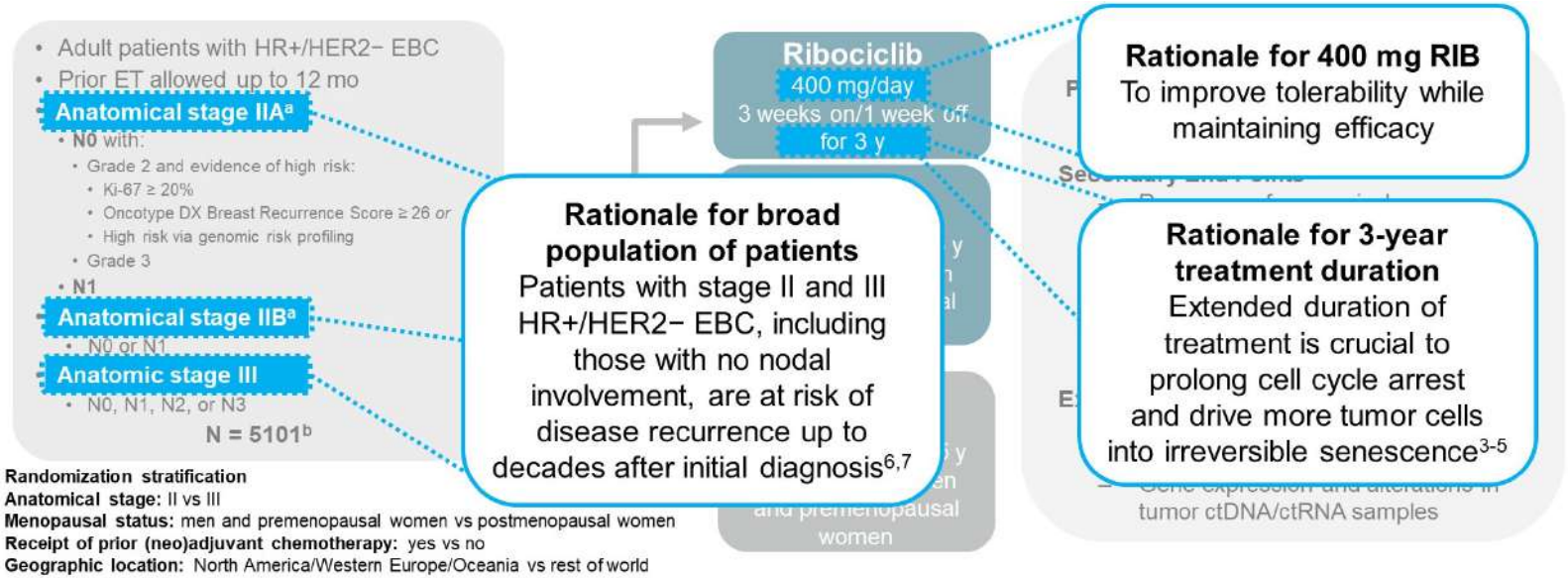
Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

[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]



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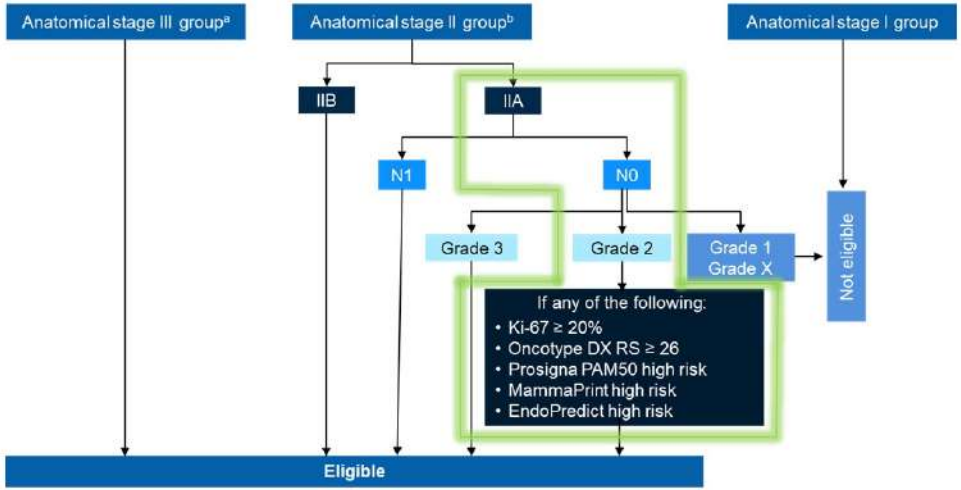
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl) [abstract TPS597]. 3. Kovatcheva M, et al. *Oncotarget*. 2015;6(10):8226-8243. 4. Rader J, et al. *Clin Cancer Res*. 2013;19(22):6173-6182. 5. Klein ME, et al. *Cancer Cell*. 2018;34:9-20. 6. Gomis RR and Gawrzak S, et al. *Mol Oncol*. 2017;11:62-78. 7. Pan H, et al. *N Engl J Med*. 2017;377:1836-1846.

NATALEE: eligible patients



AJCC anatomical staging[1]	TN (M0)	NATALEE[2,3]
Stage IA	T1N0	✗
Stage IB	T0N1mi	✗
	T1N1mi	✗
Stage IIA	T0N1	✓
	T1N1	✓
	T2N0	G3, or G2 with Ki-67 ≥ 20% or high genomic risk[c]
Stage IIB	T2N1	✓
	T3N0	✓
Stage IIIA	T0N2	✓
	T1N2	✓
	T2N2	✓
	T3N1	✓
	T3N2	✓
Stage IIIB	T4N0	✓
	T4N1	✓
	T4N2	✓
Stage IIIC	Any TN3	✓

AJCC, American Joint Committee on Cancer; G, grade; M, metastasis; N0, no nodal involvement;; N1mi, nodal micrometastases; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, ≥ 10 axillary lymph nodes or collarbone lymph nodes; RS, Recurrence Score; T, tumor; T0, no evidence of primary tumor; T1, tumor is 2cm or less; T2, Tumor is more than 2cm bu less than 5cm; T3, tumor is more than 5cm; T4, tumor of any size growing into the chest wall or skin, includes inflammatory breast cancer.
[a] Including stage IIIA (N1/N2), IIIB (N0/N1/N2), or IIIC (N3). [b] Capped at 40% (≈ 2000 patients). Simplified inclusion criteria are used in the illustration. [c] High risk as determined by Oncotype DX, Prosigna PAM50, MammaPrint, or EndoPredict EPclin Risk Score.

References: 1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017:587-636. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(suppl 15) [abstract TPS597]. 3. Data on file. NATALEE CLEE011O12301C (TRIO033). Clinical study protocol. V4.0. Novartis Pharmaceuticals Corp; August 27, 2020.

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

iDFS, invasive disease–free survival.

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 (%)			
Men[a] and premenopausal women	1126 (44)	1132 (44)	2258 (44)
Postmenopausal women	1423 (56)	1420 (56)	2843 (56)
Anatomical 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)

CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; N0, no nodal involvement; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, ≥ 10 axillary lymph nodes or infra- or supraclavicular lymph nodes; NSAI, nonsteroidal aromatase inhibitor; NX, regional nodes were not assessed; OFS, ovarian function suppression; RIB, ribociclib.
[a] In the RIB + NSAI arm, there were 11 men (0.4%); in the NSAI alone arm, there were 9 men (0.4%). [b] A total of 14 patients with stage I disease were included: 9 (0.4%) in the RIB + NSAI arm and 5 (0.2%) in the NSAI 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 patients (26.3%) in the RIB + NSAI arm and 620 (24.3%) in the NSAI alone arm.

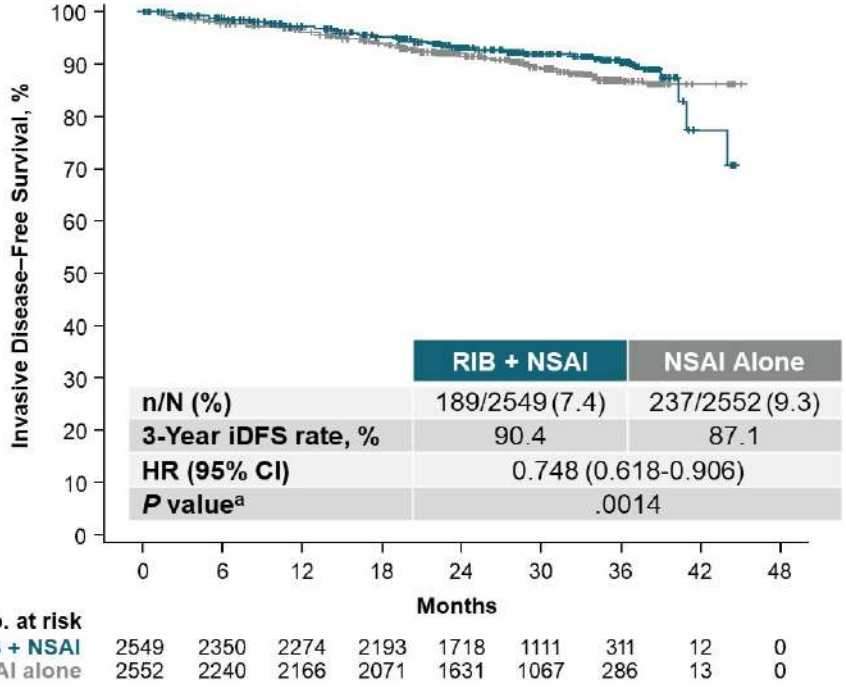
Patient disposition

Median follow-up of 34.0 months (minimum, 21 months)[a]

Parameter, n %	RIB + NSAI n = 2549	NSAI alone n = 2552
Patients treated	2526 (99)	2442 (96)
Patients with treatment ongoing[b]	1984 (78)	1826 (72)
Patients who discontinued NSAI	542 (21)	617 (24)
Primary reason for treatment discontinuation (NSAI)[c]		
Adverse Event	118 (5)	105 (4)
Patient/Physician decision	256 (10)	296 (12)
Disease relapse	142 (6)	186 (7)
Other[d]	13 (0.5)	15 (0.6)
Lost to follow-up	8 (0.3)	12 (0.5)
Death[e]	5 (0.2)	3 (0.1)
Patients who completed ribociclib treatment		
≥2 years (including ongoing)	1449 (57)	-
Completed 3 years RIB	515 (20)	-
Primary reason for early discontinuation of RIB[f]		-
Adverse Event	477 (19)	-

NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] Randomization to data cutoff of January 11, 2023. [b] In the RIB + NSAI arm, the treatment is considered ongoing if the patient is continuing either study treatment. [c] All components of treatment are discontinued if NSAI is discontinued. [d] Includes protocol deviations. [e] Causes of death in the RIB + NSAI arm were COVID-19 pneumonia, pulmonary embolism, and traffic accident, and in patients who had previously discontinued RIB but remained on NSAI, the causes of death were cardiac arrest and brain edema; for patients in the NSAI alone arm, the causes of death were myocardial infraction, sepsis, and unknown. [f] RIB could be discontinued early due to AEs, all other reasons for discontinuations would require both components be discontinued and are captured above.

Ribociclib achieved highly significant iDFS benefit



	RIB + NSAI	NSAI Alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-Year iDFS rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
P value[a]	.0014	

iDFS, invasive disease–free survival; IDMC, Independent Data Monitoring Committee; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] One-sided *P* value.

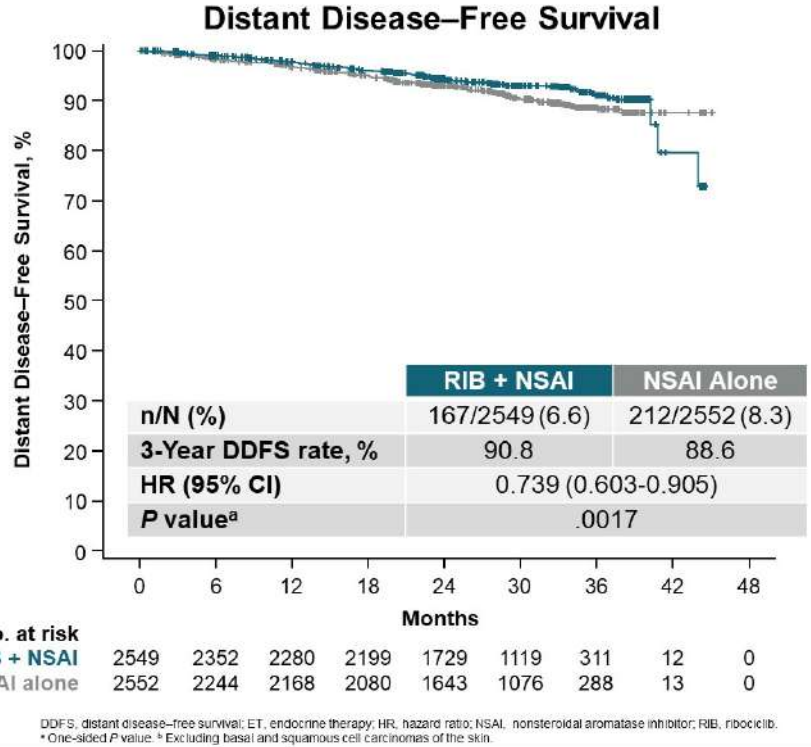
- Median follow-up for iDFS was 27.7 months
- Based on the *P* value of 0.0014, the IDMC concluded that the results met the criteria to demonstrate statistically significant and clinically superior efficacy
- Absolute iDFS benefit with RIB + NSAI at 3 years was 3.3%
- Risk of invasive disease was reduced by 25.2% with RIB + NSAI vs NSAI alone
- Ongoing patients will remain on treatment and follow-up will continue as prespecified

iDFS benefit was consistent across prespecified key subgroups

Subgroup	RIB + NSAI n = 2549	NSAI Alone n = 2552	HR	(95% CI)
Menopausal status				
Men and premenopausal women	71/1126	93/1132	0.722	(0.530-0.983)
Postmenopausal women	118/1423	144/1420	0.781	(0.613-0.997)
AJCC stage				
Stage II	49/1011	65/1034	0.761	(0.525-1.103)
Stage III	140/1528	172/1512	0.740	(0.592-0.925)
Prior CT				
Neoadjuvant	111/1085	132/1095	0.785	(0.610-1.011)
Adjuvant	63/1223	89/1220	0.671	(0.486-0.927)
Prior ET				
Yes	127/1824	157/1801	0.756	(0.598-0.955)
No	62/725	80/751	0.774	(0.556-1.079)
Region				
North America/Western Europe/Oceania	111/1563	139/1565	0.759	(0.591-0.974)
Rest of world	78/986	98/987	0.757	(0.562-1.019)
Histological grade at time of surgery				
Grade 1	9/213	12/217	0.778	(0.328-1.846)
Grade 2	102/1460	125/1432	0.749	(0.577-0.973)
Grade 3	61/684	78/702	0.776	(0.555-1.085)
Ki-67 status[a]				
Ki-67 ≤ 20%	76/1199	95/1236	0.801	(0.593-1.083)
Ki-67 > 20%	82/920	105/938	0.746	(0.559-0.996)
Nodal status[b,c]				
N0	16/285	28/328	0.630	(0.341-1.165)
N1-N3	173/2261	208/2219	0.771	(0.630-0.944)

AJCC, American Joint Committee on Cancer; CT, chemotherapy; ET, endocrine therapy; iDFS, invasive disease–free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] From archival tumor tissue. [b] Nodal status classification according to AJCC staging. [c] Nodal status is from the worse stage derived per surgical specimen or at diagnosis.

Consistent improvement in DDFS with ribociclib

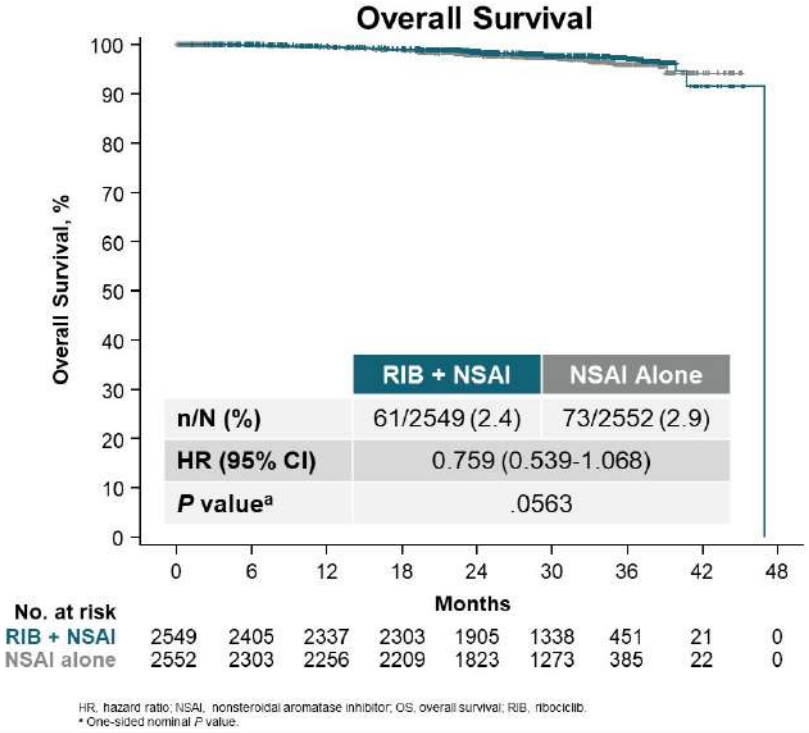


	RIB + NSAI	NSAI Alone
n/N (%)	167/2549 (6.6)	212/2552 (8.3)
3-Year DDFS rate, %	90.8	88.6
HR (95% CI)	0.739 (0.603-0.905)	
P value[a]	.0017	

DDFS, distant disease–free survival; ET, endocrine therapy; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] One-sided *P* value. [b] Excluding basal and squamous cell carcinomas of the skin.

- Distant disease–free survival is defined as the time from date of randomization to date of first event of distant recurrence, death (any cause), or second primary non-breast invasive cancer[b]
- The one-sided nominal *P* value was .0017
- Absolute distant disease–free survival benefit with RIB + NSAI at 3 years was 2.2%
- Risk of distant disease was reduced by 26.1% with RIB + NSAI vs NSAI alone

Ribociclib showed a trend for improved OS



HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.
[a] One-sided nominal *P* value.

- Median follow-up for OS was 30.4 months
- Additional follow-up for OS is planned

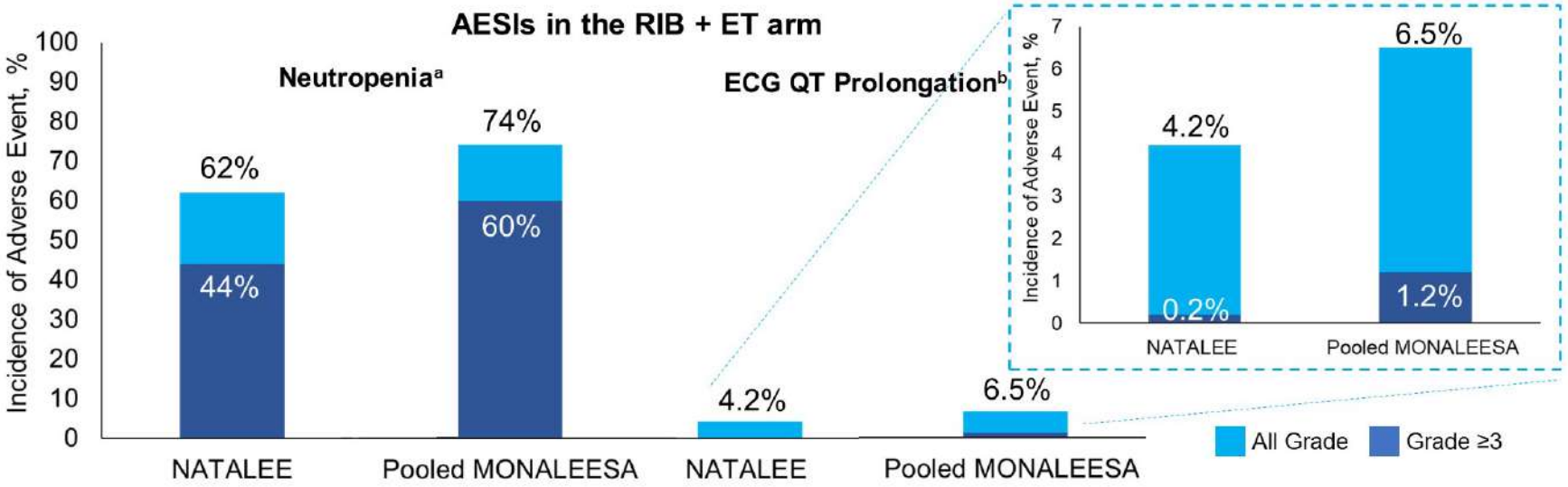
Ribociclib at the 400-mg dose was safe and well tolerated

	RIB + NSAI n = 2524		NSAI Alone n = 2444	
AESIs, %	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Neutropenia[a]	62.1	43.8	4.5	0.8
Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs[b]	25.4	8.3	10.6	1.5
QT interval prolongation	5.2	1.0	1.2	0.5
ECG QT prolonged	4.2	0.2	0.7	0
ILD pneumonitis[d]	1.5	0	0.8	0.1
Other clinically relevant AEs,%				
Arthralgia	36.5	1.0	42.5	1.3
Nausea	23.0	0.2	7.5	0.04
Headache	22.0	0.4	16.5	0.2
Fatigue	21.9	0.7	12.7	0.2
Diarrhea	14.2	0.6	5.4	0.1
VTE	1.4	0.6	0.6	0.2

- The most frequent all-grade AEs (RIB + NSAI vs NSAI alone) leading to discontinuation were:
  - Liver-related AEs: 8.9% vs 0.1%
  - Arthralgia: 1.3% vs 1.9%
- Most of the AE discontinuations of RIB occurred early in treatment
  - Median time of these discontinuations was 4 months

AE, adverse event; AESI, adverse event of special interest; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] This is a grouped term that combines neutropenia and neutrophil count decreased. [b] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [c] This is a grouped term. [d] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung disease.

Favorable safety profile with ribociclib 400 mg vs 600 mg



- Compared with RIB at a starting dose of 600 mg, the standard of care in the ABC setting, RIB at a 400-mg starting dose in the EBC setting showed lower rates of dose-dependent toxicities (neutropenia and QTc prolongation)[1]
- A new QTcF interval of > 500 ms was infrequent in both the RIB + NSAI and NSAI alone arms (0.1% vs < 0.1%), as was an increase from baseline of > 60 ms (0.8% vs 0.1%, respectively)[c]

ABC, advanced breast cancer; EBC, early breast cancer; ECG, electrocardiogram; ET, endocrine therapy; NSAI, nonsteroidal aromatase inhibitor; QTcF, QT interval corrected by Fridericia; RIB, ribociclib.
[a] This is a grouped term that combines neutropenia and neutrophil count decreased. [b] This is a preferred term. [c] The QTcF values reported in NATALEE are based on ECG abnormalities.
Reference: 1. Burris HA, et al. *Br J Cancer*. 2021;125:679-686.

Conclusions

- NATALEE met its primary end point at the second interim efficacy analysis, demonstrating a statistically significant and clinically meaningful improvement in iDFS with ribociclib + NSAI over NSAI alone
- iDFS benefit was consistent across prespecified key patient subgroups
- Results for secondary end points consistently favored ribociclib + NSAI over NSAI alone
- The 3-year regimen of ribociclib at a 400-mg starting dose in the adjuvant setting was well tolerated

NATALEE results support ribociclib + NSAI as a new treatment of choice in a broad population of patients with stage II or III HR+/HER2− EBC at risk of recurrence, including patients with node-negative disease

EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease–free survival; NSAI, nonsteroidal aromatase inhibitor.

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 MediTech Media, Ltd
- Ribociclib was discovered by Novartis Institutes for BioMedical Research in collaboration with Astex Pharmaceuticals

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