Poster 240P

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Efficacy and safety of ribociclib + nonsteroidal aromatase inhibitor in older patients with HR+/HER2− early breast cancer in NATALEE

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KEY FINDINGS & CONCLUSIONS

- This analysis of patients with HR+/HER2− EBC from the NATALEE trial showed a consistent iDFS, RFS, DRFS, and DDFS benefit with RIB + NSAI vs NSAI alone, regardless of age
- Safety was consistent with the overall population and no new safety signals were identified in patients aged 65 and older
  - A proportion of the patients aged 65 and older did not have a dose reduction before discontinuing RIB + NSAI due to AEs, presenting an opportunity to optimize AE management with dose modifications and maximize treatment benefits
- Regardless of age, there was no evidence of difference between arms for TTFD in physical functioning and GHS scores
- This analysis demonstrated that RIB + NSAI is effective and well-tolerated in a broad range of patients with HR+/HER2− EBC, including patients aged 65 and older

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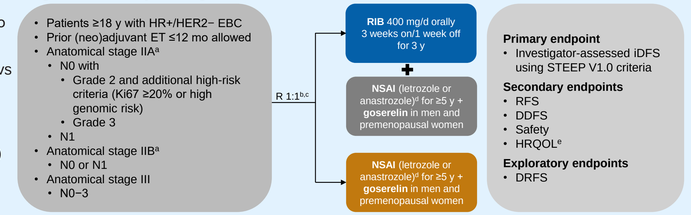
INTRODUCTION

- The phase III NATALEE trial demonstrated a statistically significant invasive disease–free survival (iDFS) benefit with ribociclib (RIB) 400 mg + nonsteroidal aromatase inhibitor (NSAI) compared with NSAI alone (hazard ratio [HR], 0.749; 95% CI, 0.628-0.892; *P*=.0006; data cutoff: July 21, 2023) in a broad population of patients with hormone-receptor positive, human epidermal growth factor receptor 2 negative (HR+/HER2−) early breast cancer (EBC)[1]
- Safety analyses have shown that RIB 400 mg was well tolerated in NATALEE[2]
  - RIB dose reductions due to adverse events (AEs) did not compromise efficacy
- Previous analyses demonstrated that the health-related quality of life (HRQOL) of patients in NATALEE was maintained with the addition of RIB to NSAI vs NSAI alone[3]
- Increased age is associated with comorbidities, highlighting the need for effective and tolerable treatment options in older patients[4,5]
- We present efficacy, safety, and HRQOL results for patients aged <65 and ≥65 y from the NATALEE trial

METHODS

- Men and pre/postmenopausal women with HR+/HER2− EBC were randomly assigned 1:1 to receive RIB + NSAI or NSAI alone (**Figure 1**)
- In this analysis, iDFS, recurrence–free survival (RFS), distant recurrence–free survival (DRFS), and distant disease–free survival (DDFS) were evaluated across age groups (<65 vs ≥65 y) using Kaplan-Meier methods
- Safety and HRQOL were also assessed across age groups
- Patient-reported outcomes (PROs) were collected via the European Organisation for Research and Treatment of Cancer questionnaire (EORTC QLQ-C30)
  - Time to first deterioration (TTFD) in physical functioning and global health status (GHS) scores were evaluated using Kaplan-Meier methods
- Relative dose intensity (RDI) is defined as dose intensity/planned dose intensity (PDI)
  - PDI is defined as planned cumulative dose/duration of exposure, where adjusted duration of exposure is used for RIB
  - PDI for RIB is 400 mg/day
- The data cutoff for this analysis was July 21, 2023

Figure 1. Study Design of the NATALEE Trial



DDFS, distant disease–free survival; DRFS, distant recurrence–free survival; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRQOL, health-related quality of life; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; R, randomized; RFS, recurrence-free survival; RIB, ribociclib; STEEP, standardized definitions for efficacy end points.
[a] Enrollment of patients with stage II disease was capped at 40%. [b] Open-label design. [c] 5101 patients were randomized from January 10, 2019, to April 20, 2021. [d] Per investigator choice. [e] Physical functioning score of the EORTC QLQ-C30 was the prespecified primary patient-reported outcome of interest

RESULTS

Baseline Characteristics and Exposure to Treatment

- Of the 5101 patients randomized in NATALEE, 4328 were <65 y (RIB + NSAI, n = 2142; NSAI alone, n = 2186) and 773 were ≥65 y (RIB + NSAI, n = 407; NSAI alone, n = 366)
- Baseline characteristics were generally well balanced across age groups, with minor differences observed (**Table 1**)
  - Compared with the ≥65 y group, the <65 y group had higher rates of prior chemotherapy (90.6% vs 74.0%) and endocrine therapy (72.3% vs 65.2%)
- Median RIB exposure was 33.0 mo in patients <65 y vs 28.4 mo in patients ≥65 y with a median duration of follow-up of 36.6 vs 39.4 mo, respectively
- RIB median RDI was 93.9% in patients <65 y and 94.0% in patients ≥65 y

Table 1. Demographics and Baseline Clinical Characteristics by Age

	<65 y		≥65 y	
	RIB + NSAI n = 2142	NSAI alone n = 2186	RIB + NSAI n = 407	NSAI alone n = 366
Age, years				
Median (range)	50 (24-64)	50 (24-64)	68 (65-90)	69 (65-89)
ECOG PS, n (%)[a]				
0	1814 (84.7)	1848 (84.5)	292 (71.7)	284 (77.6)
1	325 (15.2)	336 (15.4)	115 (28.3)	82 (22.4)
Anatomical stage, n (%)[a]				
Stage I	7 (0.3)	4 (0.2)	2 (0.5)	1 (0.3)
Stage II	833 (38.9)	877 (40.1)	178 (43.7)	157 (42.9)
Stage III	1302 (60.8)	1305 (59.7)	226 (55.5)	207 (56.6)
Nodal status at diagnosis, n (%)[b]				
NX	214 (10.0)	215 (9.8)	60 (14.7)	49 (13.4)
N0	579 (27.0)	599 (27.4)	116 (28.5)	138 (37.7)
N1	908 (42.4)	927 (42.4)	141 (34.6)	122 (33.3)
N2/3	403 (18.8)	414 (18.9)	79 (19.4)	53 (14.5)
Histological grade at diagnosis, n (%)[c]				
GX	25 (1.2)	28 (1.3)	6 (1.5)	4 (1.1)
G1	172 (8.0)	201 (9.2)	46 (11.3)	39 (10.7)
G2	1225 (57.2)	1243 (56.9)	234 (57.5)	208 (56.8)
G3	432 (20.2)	472 (21.6)	87 (21.4)	77 (21.0)
Not assessed	263 (12.3)	225 (10.3)	29 (7.1)	33 (9.0)
Ki67 category at diagnosis, n (%)[d]				
≤20%	791 (36.9)	799 (36.6)	147 (36.1)	155 (42.3)
>20%	790 (36.9)	845 (38.7)	133 (32.7)	108 (29.5)
Prior antineoplastic therapy, n (%)				
Chemotherapy	1940 (90.6)	1982 (90.7)	309 (75.9)	263 (71.9)
Endocrine therapy	1560 (72.8)	1567 (71.7)	266 (65.4)	238 (65.0)

ECOG PS, Eastern Cooperative Oncology Group performance status; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] In the ≥65 y group, stage was missing for 1 patient in each arm. [b] Nodal status was missing for 38 patients in the RIB + NSAI arm and 31 patients in the NSAI alone arm in the <65 y group and for 11 patients in the RIB + NSAI arm and 4 patients in the NSAI alone arm in the ≥65 y group. [c] Grade was missing for 25 patients in the RIB + NSAI arm and 17 patients in the NSAI alone arm for the <65 y group and for 5 patients in each arm in the ≥65 y group. [d] Ki67 category was missing for 561 patients in the RIB + NSAI arm and 542 patients in the NSAI alone arm in the <65 y group and for 127 patients in the RIB + NSAI arm and 103 patients in the NSAI alone arm for the ≥65 y group.

Efficacy With RIB + NSAI vs NSAI Alone by Age

- An iDFS benefit with RIB + NSAI vs NSAI alone was observed regardless of age (median iDFS follow-up for <65 y vs ≥65 y, 33.2 vs 34.6 mo; **Figure 2**)
  - The 3-year iDFS rates with RIB + NSAI vs NSAI alone were similar across age groups (90.8% vs 87.9% in patients <65 y and 89.6% vs 85.4% in patients ≥65 y)
- A consistent RFS (**Figure 3**), DRFS (**Figure 4**), and DDFS (**Figure 5**) benefit with RIB + NSAI vs NSAI alone was observed, regardless of age

Figure 2. iDFS by Age

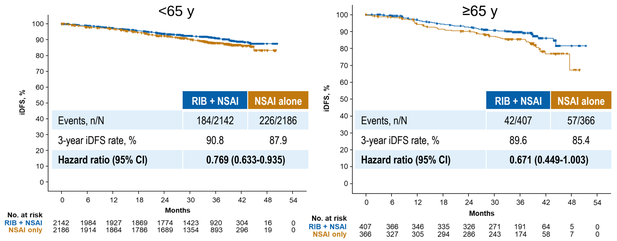


Figure 3. RFS by Age

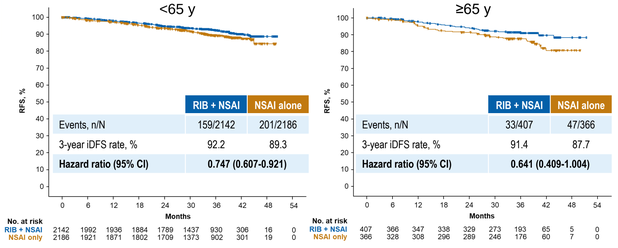


Figure 4. DRFS by Age

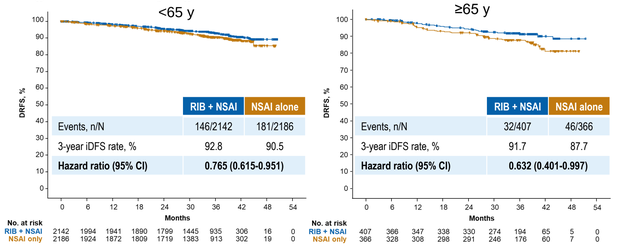
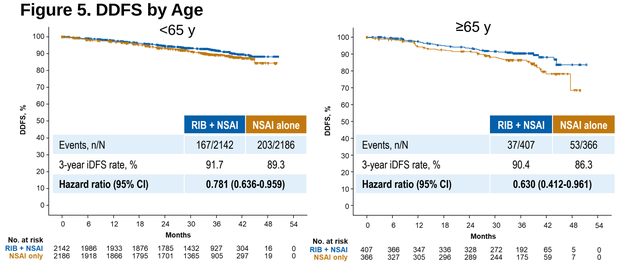


Figure 5. DDFS by Age



Safety With RIB + NSAI vs NSAI Alone by Age

- Rates of AEs were generally consistent across age groups (**Table 2**)
  - Within the ≥65 y age group, the most frequent AEs in the RIB + NSAI arm in patients aged ≥75 y were neutropenia (48.2%), nausea (35.7%), and arthralgia (26.8%)
- In the RIB arm, the proportion of patients who required ≥1 RIB dose reduction due to AEs was similar across age groups and was most commonly driven by neutropenia (**Table 3**)
- In the RIB arm, discontinuations of any study component due to AEs were primarily driven by alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations and arthralgia in both age groups (**Table 4**)
- A higher proportion of patients aged ≥65 y discontinued RIB due to AEs, including those without prior dose reduction
  - The most frequent AEs leading to RIB discontinuation without prior dose reduction in the <65 y and ≥65 y age groups were ALT (all grade 42% and 30%) and AST (17% and 11%) elevations

Table 2. AEs (≥20% in RIB + NSAI Arm [≥65 y]) by Age

Safety set, n (%)	<65 y				≥65 y			
	All grade		Grade 3/4		All grade		Grade 3/4	
	RIB + NSAI n = 2123	NSAI alone n = 2091	RIB + NSAI n = 2123	NSAI alone n = 2091	RIB + NSAI n = 402	NSAI alone n = 351	RIB + NSAI n=402	NSAI alone n=351
Neutropenia[a]	1346 (63.4)	103 (4.9)	969 (45.6)	21 (1.0)	233 (58.0)	10 (2.8)	149 (37.1)	1 (0.3)
Arthralgia	812 (38.2)	926 (44.3)	20 (0.9)	27 (1.3)	130 (32.3)	132 (37.6)	5 (1.2)	4 (1.1)
Fatigue	462 (21.8)	266 (12.7)	15 (0.7)	4 (0.2)	102 (25.4)	56 (16.0)	4 (1.0)	0
Nausea	491 (23.1)	165 (7.9)	5 (0.2)	1 (<0.1)	97 (24.1)	25 (7.1)	1 (0.2)	0
ALT increased	410 (19.3)	116 (5.5)	156 (7.3)	17 (0.8)	82 (20.4)	20 (5.7)	36 (9.0)	0

ALT, alanine aminotransferase; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] Includes neutropenia, febrile neutropenia, neutrophil count decreased, and granulocytopenia.

Table 3. RIB Dose Modifications and Discontinuations Due to AEs by Age

Safety set, n (%)	<65 y	≥65 y
	RIB + NSAI n = 2123	RIB + NSAI n = 402
Patients with ≥1 RIB interruption due to AEs	1421 (66.9)	250 (62.2)
Patients with ≥1 RIB reduction due to AEs	485 (22.8)	91 (22.6)
Patients with RIB discontinuation due to AEs	387 (18.1)[a]	111 (27.3)[a]
Without prior dose reduction	283 (13.3)	70 (17.4)

AE, adverse event; ITT, intent-to-treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] Based on the ITT set.

Table 4. AEs Leading to Discontinuation by Age

Safety set, n (%)	<65 y		≥65 y	
	RIB + NSAI n = 2123	NSAI alone n = 2091	RIB + NSAI n = 402	NSAI alone n = 351
AEs leading to discontinuation[a] (all grade)	409 (19.3)	111 (5.3)	115 (28.6)	23 (6.6)
ALT increased	145 (6.8)	2 (0.1)	35 (8.7)	0
AST increased	58 (2.7)	0	13 (3.2)	0
Arthralgia	30 (1.4)	46 (2.2)	7 (1.7)	3 (0.9)
Blood creatinine increased	2 (0.1)	0	6 (1.5)	0
Neutropenia	14 (0.7)	0	5 (1.2)	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] Discontinuation of any study component in >1% of patients in the RIB + NSAI arm (≥65 y).

HRQOL With RIB + NSAI vs NSAI Alone by Age

- TTFD in physical functioning and GHS scores were similar between treatment arms in both age groups (**Table 5**)

Table 5. TTFD of PROs by Age

PRO scale		<65 y		≥65 y	
		RIB + NSAI n = 2142	NSAI alone n = 2186	RIB + NSAI n = 407	NSAI alone n = 366
GHS	mTTFD, mo	13.8	13.8	11.2	16.6
	Hazard ratio (95% CI)	1.03 (0.95-1.11)		1.15 (0.96-1.39)	
Physical functioning	mTTFD, mo	27.6	24.7	16.8	19.4
	Hazard ratio (95% CI)	0.97 (0.89-1.06)		1.04 (0.86-1.26)	

GHS, global health status; mTTFD, median time to first deterioration; NSAI, nonsteroidal aromatase inhibitor; PRO, patient-reported outcome; RIB, ribociclib.

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1. Hortobagyi G, et al. Oral presented at: SABCS 2023. Oral GS03-03. **2.** Barrios C, et al. Oral presented at: ESMO Breast 2024. **3.** Fasching PA, et al. *Ann Oncol*. 2023; 34(10):951-953. **4.** Bergen ES, et al. *Breast Cancer Res Treat*. 2016; 157(1):91-99. **5.** Kartal M, et al. *BMC Womens Health*. 2013; 13:34.

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