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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: NATALEE assessed efficacy and tolerability of 3 years of adjuvant ribociclib plus a nonsteroidal aromatase inhibitor (NSAI) compared with an NSAI alone in a broad population of patients with hormone receptor (HR)-positive/human epidermal growth factor 2 (HER2)-negative early breast cancer, including a select group without nodal involvement. This is the final preplanned analysis of invasive disease-free survival (iDFS).

Patients and methods: Premenopausal/postmenopausal women and men were randomized 1 : 1 to ribociclib ($n = 2549$; 400 mg/day, 3 weeks on/1 week off for 36 months) plus NSAI (letrozole 2.5 mg/day or anastrozole 1 mg/day for 60 months) or NSAI alone ($n = 2552$). Men and premenopausal women also received goserelin (3.6 mg once every 28 days). Patients had anatomical stage IIA (N0 with additional risk factors or N1), IIB, or III disease. The primary endpoint was iDFS. Secondary efficacy endpoints were recurrence-free survival (RFS), distant DFS, and overall survival. This final iDFS analysis was planned after ∼500 events.

Results: At data cut-off (21 July 2023), ribociclib was stopped for 1996 patients (78.3%); 1091 (42.8%) completed 3 years of ribociclib, and ribociclib treatment was ongoing for 528 (20.7%). Median follow-up for iDFS was 33.3 months. Overall, 226 and 283 iDFS events occurred with ribociclib plus NSAI versus NSAI alone, respectively. Ribociclib plus NSAI demonstrated significant iDFS benefit over NSAI alone [hazard ratio 0.749, 95% confidence interval (CI) 0.628-0.892; $P = 0.0012$]. The 3-year iDFS rates were 90.7% (95% CI 89.3% to 91.8%) versus 87.6% (95% CI 86.1% to 88.9%). A consistent benefit was observed across prespecified subgroups, including stage (II/III) and nodal status (positive/negative). Distant DFS and RFS favored ribociclib plus NSAI. Overall survival data were immature. No new safety signals were observed.

Conclusions: With longer follow-up and most patients off ribociclib, NATALEE continues to demonstrate iDFS benefit with ribociclib plus NSAI over NSAI alone in the overall population and across key subgroups. Observed adverse events remained stable.

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INTRODUCTION

Breast cancer remains a leading cause of death among women and has surpassed lung cancer as the most diagnosed cancer worldwide.[1] Hormone receptor-positive, human epidermal growth factor 2-negative (HR-positive/HER2-negative) breast cancer is the most common type, representing nearly three-quarters of all cases.[2] For most patients diagnosed with HR-positive/HER2-negative early breast cancer (EBC), current practice guidelines recommend surgical excision and adjuvant endocrine therapy (ET), while the addition of radiotherapy and chemotherapy may be appropriate depending on individual risk factors.[3] The inclusion of ET as a systemic treatment has shown disease-free survival (DFS) and overall survival (OS) benefit in patients with endocrine receptor-positive (ER-positive) tumors.[4] The benefit of adjuvant ET, particularly nonsteroidal aromatase inhibitors (NSAIs),[5] is evident in the first 5 years of treatment, and the reduction in recurrence risk attributed to ET is sustained over time.[4]

Despite this benefit, current standard-of-care treatment that includes adjuvant ET does not eliminate the risk of disease recurrence. Contemporary clinical trials in patients with HR-positive/HER2-negative EBC receiving ET as part of the standard of care found that up to 13% of patients experience disease recurrence within 3 years of starting ET.[6-8] Unlike in patients with other solid tumors, recurrence risk in patients with ER-positive breast cancer does not decrease over time, and up to half of patients experience a metastatic event within 20 years, depending on disease characteristics at initial diagnosis.[9,10] It is well established that a variety of anatomical, pathological, and genomic characteristics impact recurrence risk,[9-14] and therefore, escalation of adjuvant treatment is warranted in this group of patients.

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have emerged as effective therapeutic interventions for patients with HR-positive/HER2-negative breast cancer and have since become the standard of care for patients with metastatic disease.[15] Ribociclib is a CDK4/6 inhibitor that has demonstrated statistically significant benefit in progression-free survival and OS as a first-line or second-line treatment for patients with HR-positive/HER2-negative advanced breast cancer (ABC).[16-21] This benefit prompted investigations into the use of ribociclib in the adjuvant setting in combination with ET. Currently, only two phase III trials using CDK4/6 inhibitors have shown positive efficacy for invasive disease-free survival (iDFS) in patients with HR-positive/HER2-negative EBC: the monarchE trial, evaluating abemaciclib plus ET,[22-24] and the NATALEE trial, evaluating ribociclib plus an NSAI.[8]

The monarchE trial compared 2 years of adjuvant abemaciclib plus ET versus ET alone in patients with HR-positive/HER2-negative EBC who presented with high-risk disease, defined as at least four positive pathological axillary lymph nodes or one to three positive axillary lymph nodes and one of the following: tumor size $\geq$5 cm, histological grade 3 disease, or centrally assessed Ki-67 $\geq$20%.[25] Abemaciclib plus ET demonstrated significant iDFS benefit, which led to regulatory approval for patients with HR-positive/HER2-negative EBC at a high risk of recurrence.[26] There remains an unmet need, however, to provide effective treatment options for a broader range of at-risk patients with HR-positive/HER2-negative EBC.

The NATALEE trial was designed to evaluate the efficacy and tolerability of ribociclib plus an NSAI with a 3-year treatment duration in a population of patients with stage II and III HR-positive/HER2-negative EBC, including a select group of patients without nodal involvement. To improve tolerability, NATALEE assessed a lower daily dose of ribociclib (400 mg) in patients with EBC compared with the starting dose that is approved in ABC (600 mg).[27] Results from the second prespecified interim efficacy analysis of NATALEE found a statistically significant 25% reduction in iDFS events in patients receiving ribociclib plus an NSAI compared with NSAI alone [hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.62-0.91; $P = 0.003$].[8] In this manuscript, we report efficacy and safety results from the protocol-specified final analysis of iDFS in the NATALEE trial.

METHODS

Study design and patients

NATALEE (ClinicalTrials.gov ID: NCT03701334) study design, eligibility criteria, and methods have been published previously.[28] This was an international, randomized, open-label, phase III trial in patients with HR-positive/HER-negative EBC. Eligible patients were aged $\geq$18 years, had locally assessed histological confirmation of HR-positive/HER-negative EBC, and had stage II or stage III disease per anatomical classification in the American Joint Committee on Cancer's (AJCC's) *Cancer Staging Manual*, eighth edition. Patients were randomized 1 : 1 to receive ribociclib (400 mg/day once daily, days 1-21 of a 28-day cycle, over a duration of 36 months) together with an NSAI (letrozole 2.5 mg or anastrozole 1 mg once daily continuously for 60 months) or an NSAI alone. Men and premenopausal women also received subcutaneously administered goserelin (3.6 mg once every 28 days). Patients were considered to be on trial treatment as long as they were continuing on NSAI (up to 5 years), regardless of ribociclib discontinuation. Randomization was stratified by menopausal status

(premenopausal women and men or postmenopausal women), anatomical stage (II or III), prior neoadjuvant and/or adjuvant chemotherapy (yes or no), and geographic location (North America, Western Europe, Oceania, or rest of the world).

The trial was conducted in accordance with the International Council for Harmonisation — Good Clinical Practice guidelines, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki. The study protocol was approved by the institutional review board or ethics committee for each participating center. An independent data monitoring committee reviewed safety and efficacy data per study protocol. All patients provided written informed consent.

Endpoints

The primary objective was iDFS per Standardized Definitions for Efficacy End Points (STEEP) criteria, version 1.0, as assessed by the investigator. Secondary objectives were recurrence-free survival (RFS) and distant DFS (DDFS) using STEEP criteria, OS, health-related quality of life (HRQoL), safety and tolerability of the treatment regimen, and pharmacokinetics. Treatment-emergent adverse events (AEs) were monitored for 36 months from randomization plus an additional 30-day follow-up and are referred to as AEs throughout this analysis. Serious adverse events were monitored until the end of the trial. AEs and serious AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical analysis

At the prespecified second interim efficacy analysis carried out at 426 iDFS events (data cut-off, 11 January 2023), the study met its primary endpoint of iDFS.[8] This final analysis was conducted after the planned ∼500 iDFS events were documented (data cut-off, 21 July 2023). iDFS between the two treatment arms was compared using a stratified log-rank test based on the randomization stratification factors. Primary and secondary endpoints were estimated using the Kaplan—Meier (KM) method. The HR was calculated using a stratified Cox proportional hazards model, along with 95% CIs. *P* values were two-sided and were not adjusted for multiple comparison in this analysis. Efficacy analyses were conducted in the intent-to-treat (ITT) population. The OS distribution was estimated using the KM method. Safety analyses were conducted in patients who received at least one dose of ribociclib or ET.

RESULTS

This multicenter trial conducted across 20 countries randomized 5101 patients to receive ribociclib plus NSAI (n = 2549) or NSAI alone (n = 2552) between 10 January 2019 and 20 April 2021. Demographic and clinical characteristics at baseline were well balanced between treatment arms and have been previously reported.[8] At data cut-off for the final analysis, the median duration of iDFS follow-up (from randomization to last completed recurrence assessment) was 33.3 months, an additional 5.6 months of iDFS follow-up since the previous preplanned interim analysis. At the current data cut-off, 1996 patients (78.3%) had stopped receiving ribociclib; 1091 (42.8%) completed the planned 3-year ribociclib treatment and 905 (35.5%) discontinued ribociclib early. In the ribociclib plus NSAI arm, 1914 patients (75.1%) remained on study treatment as of the data cut-off date; 528 patients (20.7%) remained on ribociclib. A total of 1748 patients (68.5%) remained on study treatment in the NSAI arm. The primary reason for early discontinuation of ribociclib was AEs, which occurred in 498 patients (19.5%). The median duration of exposure to study treatment was 36.2 months in the ribociclib plus NSAI arm and 35.9 months in the NSAI-alone arm. The median duration of exposure to ribociclib alone was 32.9 months.

The final efficacy analysis for iDFS occurred after 509 iDFS events were documented, which provided an additional 83 iDFS events since the second interim efficacy analysis. Of the 509 iDFS events, 226 (8.9%) were with ribociclib plus NSAI versus 283 (11.1%) with NSAI alone. There was a 25.1% reduction in the risk of iDFS events in the ribociclib plus NSAI arm compared with the NSAI-alone arm (HR 0.749, 95% CI 0.628-0.892; two-sided P = 0.0012) (Figure 1). The 3-year iDFS rates were 90.7% (95% CI 89.3% to 91.8%) with ribociclib plus NSAI and 87.6% (95% CI 86.1% to 88.9%) with NSAI alone, an absolute benefit of 3.1%.

A consistent benefit was observed with ribociclib combination treatment in key subgroups, including stage II disease (HR 0.700, 95% CI 0.496-0.986), stage III disease (HR 0.755, 95% CI 0.616-0.926), node-positive disease (HR 0.759, 95% CI 0.631-0.912), and node-negative disease (HR 0.723, 95% CI 0.412-1.268) (Figures 2 and 3). KM estimates of 3-year iDFS rates favored ribociclib plus NSAI versus NSAI alone in patients with stage II disease [94.2% (95% CI 92.4% to 95.6%) versus 92.6% (95% CI 90.6% to 94.1%)], stage III disease [88.1% (95% CI 86.1% to 89.9%) versus 83.8% (95% CI 81.5% to 85.8%)], node-negative disease [93.2% (95% CI

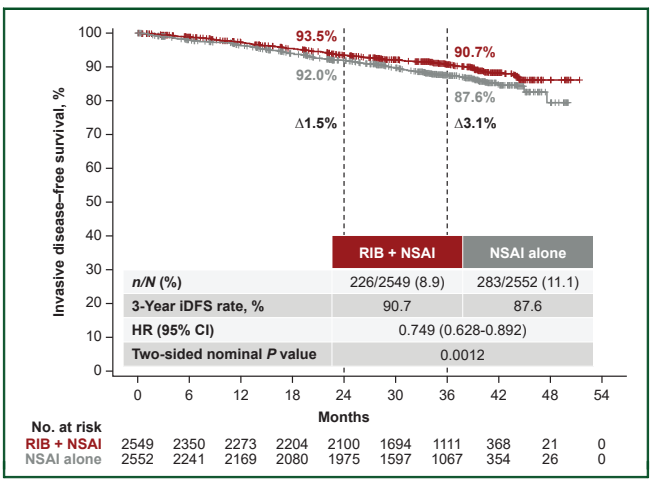

Figure 1. iDFS in the ITT population.
CI, confidence interval; HR, hazard ratio; iDFS, invasive disease—free survival; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

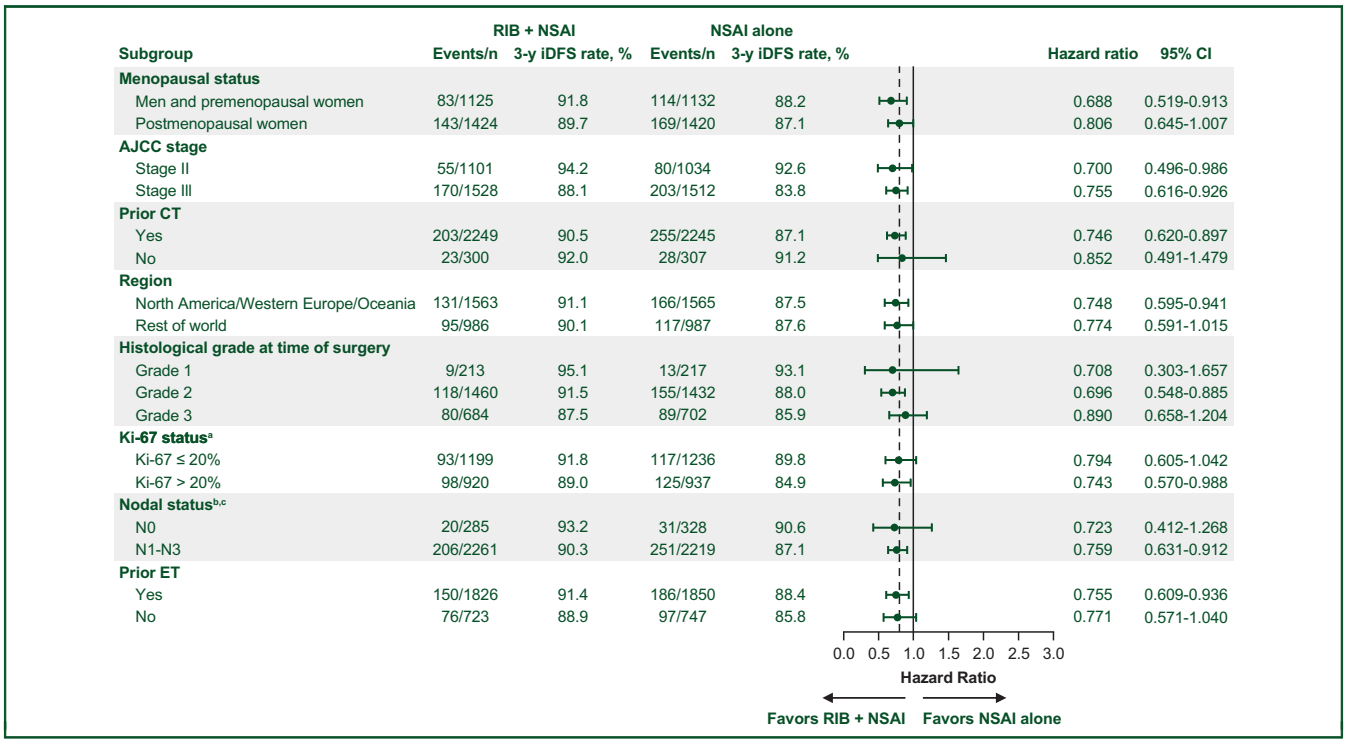

Figure 2. iDFS across key prespecified subgroups.
AJCC, American Joint Committee on Cancer; CI, confidence interval; CT, chemotherapy; ET, endocrine therapy; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a]From archival tumor tissue.
[b]Nodal status classification according to AJCC staging.
[c]Nodal status is from the worst stage derived per surgical specimen or at diagnosis.

89.2% to 95.7%) versus 90.6% (95% CI 86.5% to 93.4%)], and node-positive disease [90.3% (95% CI 88.9% to 91.6%) versus 87.1% (95% CI 85.5% to 88.6%)] (Figure 2).

There was a benefit with ribociclib for the secondary endpoints of RFS (HR 0.727, 95% CI 0.602-0.877; two-sided $P = 0.0008$) (Figure 4A) and DDFS (HR 0.749, 95% CI 0.623-0.900; two-sided $P = 0.0020$) (Figure 4B). The most common sites of disease recurrence were bone and liver in both treatment arms (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.10.015). OS events occurred in 172 patients (84 in the ribociclib arm and 88 in the NSAI-alone arm). OS data were not mature at the time of this analysis; 3-year OS rates were 97.0% with ribociclib plus NSAI and 96.1% with NSAI (HR 0.892, 95% CI 0.661-1.203) (Figure 4C).

Safety was analyzed in 2525 patients in the ribociclib arm and 2442 in the NSAI-alone arm (Table 1). At least one treatment-emergent AE occurred in 2474 patients (98.0%) in the ribociclib arm and 2145 (87.8%) in the NSAI-alone arm. Serious AEs occurred in 357 patients (14.1%) in the ribociclib arm and 256 (10.5%) in the NSAI-alone arm.

The most common AEs of any grade were neutropenia (62.5% with ribociclib plus NSAI versus 4.6% with NSAI alone), arthralgia (37.3% versus 43.3%, respectively), and nausea (23.3% versus 7.8%, respectively). The most common grade $\geq$3 event was neutropenia (44.3% with ribociclib plus NSAI versus 0.9% with NSAI alone). Grade $\geq$3 liver-related adverse events occurred in 8.6% of patients in the ribociclib plus NSAI arm and 1.7% in the NSAI-alone arm. The median time to onset of grade $\geq$3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase was 2.9 months in the ribociclib arm. The median duration of grade $\geq$3 liver-related adverse events (from time of onset to resolution to grade $\leq$1) was 0.7 months (95% CI 0.7-0.9 months) in the ribociclib arm and 1.4 months (95% CI 1.0-2.7 months) in the NSAI-alone arm. At the time of this report, 89.2% of patients with grade $\geq$3 ALT or AST elevations in the ribociclib arm resolved to grade $\leq$1. QT interval prolongation events were more commonly observed in the ribociclib plus NSAI arm compared with the NSAI-alone arm (5.3% versus 1.4%), although grade $\geq$3 events were uncommon in both arms (1.0% versus 0.6%, respectively).

AEs leading to ribociclib discontinuation and dose reduction occurred in 19.5% and 22.8% of patients, respectively. The median times to ribociclib discontinuations (4.17 months) and first dose reduction (3.15 months) due to AEs were low and occurred early in the treatment period. The most frequent any-grade AEs leading to discontinuation were ALT increased (7.1% with ribociclib plus NSAI versus 0.1% with NSAI alone), AST increased (2.8% versus 0%, respectively), and arthralgia (1.5% versus 2.0%, respectively). Neutropenia and fatigue contributed to discontinuation in $<$1%

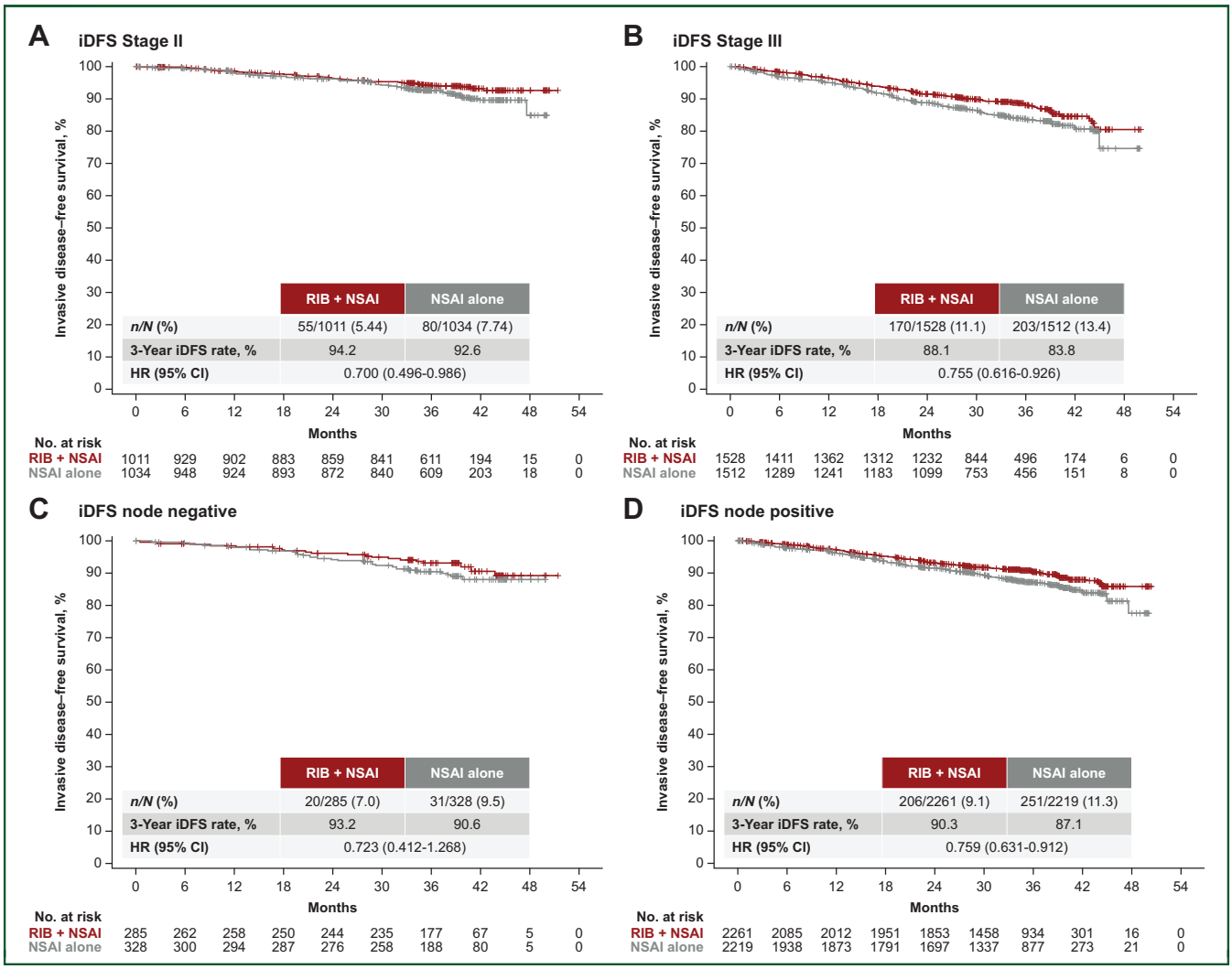

Figure 3. iDFS by stage and nodal status.
CI, confidence interval; HR, hazard ratio; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

of patients in either treatment arm. Rates of NSAI discontinuation due to AEs were similar between the two arms (5.1% in the ribociclib arm and 4.4% in the NSAI-alone arm).

Since the primary analysis, overall deaths due to any cause remain more frequent in the NSAI-alone arm [89 patients (3.6%)] compared with the ribociclib plus NSAI arm [83 patients (3.3%)]. Deaths without disease progression or recurrence occurred in 25 patients in the ribociclib plus NSAI arm and in 16 patients in the NSAI-alone arm. On-treatment deaths were defined as occurring on or after the treatment start date and up to 30 days after 36 months of treatment or earlier treatment discontinuation. On-treatment deaths occurred in 20 patients (0.8%) in the ribociclib plus NSAI arm and in 9 patients (0.4%) in the NSAI-alone arm, which represents an additional 3 on-treatment deaths since the primary analysis (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.10.015). Among these on-treatment deaths, 12 occurred within 30 days after the last dose of ribociclib. Six on-treatment deaths occurred due to coronavirus disease 2019 (COVID-19) in the ribociclib arm compared with one death due to COVID-19 in the NSAI-alone arm. There was no preceding or concurrent severe myelosuppression at the time of the COVID-19 in any of these six patients. Most other on-treatment deaths in both arms were single occurrence events with no clustering around a single AE type. No on-treatment deaths were considered related to ribociclib.

DISCUSSION

This protocol-specified final analysis of iDFS provided an additional 5.6 months of iDFS follow-up, with a majority of patients off ribociclib treatment (78.3% had stopped ribociclib at the time of this analysis versus 54.0% in previous analysis).[8] Consistent with the prior interim efficacy analysis,[8] this analysis of NATALEE demonstrated a 25% reduction in the risk of iDFS events with ribociclib plus NSAI (HR 0.749, 95% CI 0.628-0.892; $P = 0.0012$). There was a clear separation of the iDFS KM curves between the study arms in favor of ribociclib plus NSAI, demonstrating a sustained benefit through the ribociclib treatment window and at

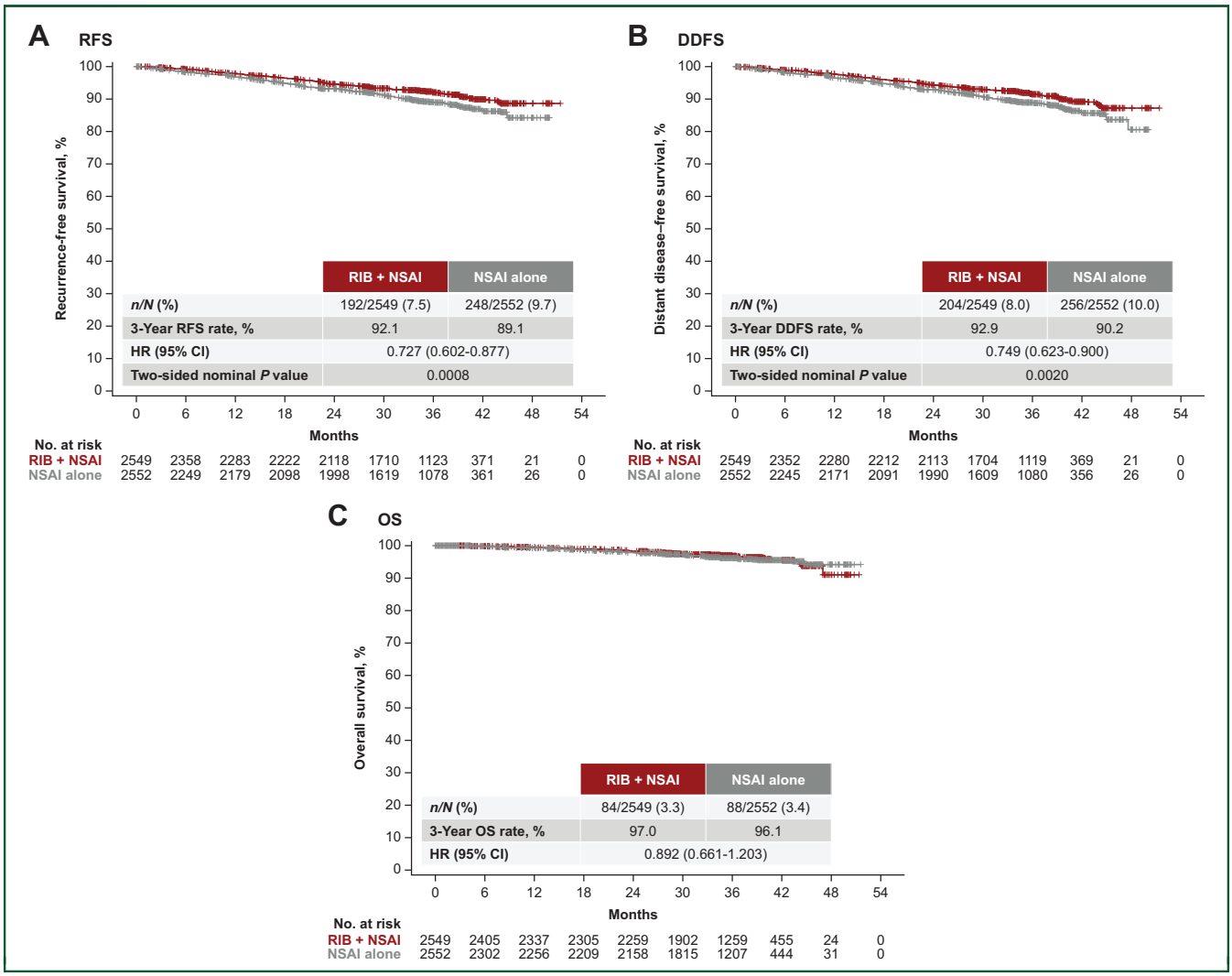

Figure 4. RFS, DDFS, and OS in the ITT population.
CI, confidence interval; DDFS, distant disease-free survival; HR, hazard ratio; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RFS, recurrence-free survival; RIB, ribociclib.

subsequent follow-up. The secondary endpoints of RFS and DDFS also favored ribociclib plus NSAI, while OS data were immature at the time of this analysis. Since the previous interim analysis, the incidence rates of the most frequently observed AEs remained stable, and the absolute increase for any AE of special interest or clinically relevant AE was

Table 1. Adverse events

	Ribociclib + NSAI (n = 2525)				NSAI only (n = 2442)			
≥15% In either arm, n (%)	All grades	Grade 3	Grade 4	Grade 5	All grades	Grade 3	Grade 4	Grade 5
No. of patients with ≥1 TEAE	2474 (98.0)	1463 (57.9)	133 (5.3)	11 (0.4)	2145 (87.8)	425 (17.4)	40 (1.6)	4 (0.2)
Neutropenia[a]	1579 (62.5)	1065 (42.2)	53 (2.1)	0	113 (4.6)	19 (0.8)	3 (0.1)	0
Arthralgia	942 (37.3)	25 (1.0)	0	0	1058 (43.3)	31 (1.3)	0	0
Nausea	588 (23.3)	6 (0.2)	0	0	190 (7.8)	1 (<0.1)	0	0
Headache	575 (22.8)	11 (0.4)	0	0	415 (17.0)	4 (0.2)	0	0
Fatigue	564 (22.3)	19 (0.8)	0	0	322 (13.2)	4 (0.2)	0	0
SARS-CoV-2 test positive	532 (21.1)	0	0	0	332 (13.6)	0	0	0
COVID-19	537 (21.3)	18 (0.7)	0	3 (0.1)	345 (14.1)	11 (0.5)	0	1 (<0.1)
ALT increased	492 (19.5)	159 (6.3)	33 (1.3)	0	136 (5.6)	16 (0.7)	1 (<0.1)	0
Hot flush	486 (19.2)	6 (0.2)	0	0	489 (20.0)	3 (0.1)	0	0
Asthenia	428 (17.0)	14 (0.6)	0	0	291 (11.9)	3 (0.1)	0	0
AST increased	426 (16.9)	100 (4.0)	18 (0.7)	0	139 (5.7)	13 (0.5)	0	0
Alopecia	380 (15.0)	0	0	0	109 (4.5)	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus 2019; NSAI, nonsteroidal aromatase inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TEAE, treatment-emergent adverse event.
[a]This is a grouped term that combines neutropenia and neutrophil count decreased.

<1%.[8] Similarly, discontinuations due to AEs only increased by 0.8%, despite more than three-quarters of patients off ribociclib at the time of this updated analysis.

The efficacy of ribociclib plus NSAI was favorable in all prespecified subgroups and was consistent with the overall results. HRs for all prespecified subgroups favored ribociclib plus NSAI versus NSAI alone (HR, range 0.688-0.890) (Figure 2). In addition, the 3-year iDFS rates showed a treatment benefit with ribociclib plus NSAI versus NSAI alone across menopausal status, AJCC stage, prior chemotherapy, geographic region, tumor grade, Ki-67 status, nodal status, and prior ET use (absolute benefit, range 0.8% to 4.3%). The 95% CIs remained wide for subgroups with low numbers of events, but the iDFS HRs continued to narrow toward the ITT estimates in this updated analysis. This improvement was particularly evident in patients with stage II disease. While this subgroup had a lower event rate, there was an increase in iDFS benefit since the previous interim analysis (HR 0.70 versus 0.76, respectively) and a narrowing of the CI to exclude unity with the longer follow-up. Additional follow-up data are planned to fully evaluate the efficacy among subgroups with fewer iDFS events in NATALEE, but the current iDFS benefit across subgroups suggests that the overall efficacy of ribociclib plus NSAI in the ITT sample is not driven by any single patient subtype.

There were no new safety signals in this final analysis, and the rates of AEs of special interest, including neutropenia, arthralgia, and elevated liver enzymes, showed minimal change with additional follow-up. Compared with the 600 mg starting dose of ribociclib in the MONALEESA ABC trials, the 400 mg starting dose in the EBC setting was associated with lower rates of dose-dependent toxicities. Any-grade neutropenia (grouped term including neutrophil count decreased) occurred in 62.5% of patients in the ribociclib arm of the NATALEE study in an adjuvant setting, which was lower than the 74% seen in a pooled sample of patients receiving ribociclib in the MONALEESA-2, -3, and -7 studies in metastatic breast cancer.[29] Similarly, only 1% of patients in the NATALEE ribociclib arm experienced grade ≥3 QT prolongation, which was <1.8% to 4.5% incidence rates of grade ≥3 QT prolongation reported in the MONALEESA trials.[16-18] Collectively, these findings further demonstrate that the 3-year regimen of ribociclib 400 mg in the adjuvant setting was well tolerated.

Ribociclib discontinuations and dose reductions due to AEs occurred early in treatment (median 4.17 and 3.15 months, respectively), and there was a <1% absolute increase in new treatment discontinuations due to AEs since the last analysis (18.7% versus 19.5%).[8] This was a small change in light of a substantial majority of patients off ribociclib and a median relative dose intensity of 94.0% for ribociclib in this updated analysis. In the monarchE trial of adjuvant abemaciclib, a similar rate of 18.5% was observed for patients who discontinued the drug or all treatment due to AEs despite a shorter treatment duration.[30] While patients in monarchE primarily discontinued due to diarrhea,[30] ALT and AST elevation were the primary AEs leading to discontinuation in NATALEE, most of which occurred without concurrent elevations in bilirubin. ALT and AST elevations in NATALEE occurred early in the course of care (median 2.9 months for grade ≥3) and resolved in ∼3 weeks. While the mechanisms driving the elevation of ALT and AST are likely multifactorial and not fully understood, these liver-related events resolved with protocol-guided dose modifications.

While efficacy was the primary aim of the study, understanding the safety profile and its impact on HRQoL is essential when making clinical decisions in a population that requires several years of therapy. A previous analysis of NATALEE demonstrated that overall HRQoL was maintained with the addition of ribociclib to NSAI in all prespecified HRQoL measures, including the protocol-defined endpoint of physical functioning.[31]

CDK4/6 inhibition has become standard treatment in ABC, but efficacy has not been consistent across all CDK4/6 inhibitors in patients with HR-positive/HER2-negative EBC. Palbociclib failed to meet efficacy targets in the adjuvant setting,[7,32,33] while abemaciclib[6,22-24] and ribociclib,[8] each in combination with ET, have shown benefit in iDFS, albeit in different patient populations. There are notable differences between the monarchE and NATALEE studies, including the treatment duration (2 versus 3 years), ET partner (tamoxifen versus NSAI), and patient population.[22] monarchE did not include patients with node-negative disease,[22,24] while NATALEE included a population of patients with N0 disease and additional high-risk features. A recent real-world study in which most patients received standard of care ET found that patients with N0 disease and high-risk features had a recurrence risk that was similar to patients with N1 disease at a median follow-up of 79.1 months; this risk was significantly greater than patients with N0 disease without high-risk features.[34] These real-world data, together with the high risk of recurrence at 3 years in the control arm of patients with N0 disease (9.4%; Figure 3C) and consistent treatment benefit across nodal subgroups in this study, highlight the benefit of ribociclib plus NSAI for patients with node-positive and node-negative disease at high risk of recurrence.

When evaluating results from positive adjuvant trials of CDK4/6 inhibitors, it is also important to consider the median follow-up. monarchE had 54 months of follow-up and has shown improved benefit over time,[24] suggesting that the benefit of CDK4/6 inhibition extends well beyond the treatment window. Since the previous analysis, the absolute treatment benefit in NATALEE has been maintained and the CIs continue to narrow in the overall population and prespecified subgroups. This improving benefit is consistent with preclinical data that have shown that CDK4/6 inhibitors may exert their effect not only through cell cycle inhibition during treatment but also through tumor senescence and beneficial modulation of the immune response and microenvironment.[35-37] The significant and persistent benefit of CDK4/6 inhibitors in existing trials is encouraging. Future analyses, including biomarker studies, will hopefully extend our understanding of ribociclib benefit and responsive patient populations. Given that the economic impact of

adjuvant treatments is an important consideration, future value assessments will be needed and are planned.

In this protocol-prespecified final iDFS analysis, adjuvant ribociclib plus NSAI demonstrated a sustained treatment benefit in iDFS compared with NSAI alone in in patients with stage II or III HR-positive/HER2-negative EBC. The majority of AEs were asymptomatic with this additional follow-up, and the safety profile remained consistent with that observed in previous interim analyses of ribociclib plus NSAI in patients with EBC. Future analyses are planned and will continue to elucidate the sustained benefit of ribociclib plus NSAI for long-term outcomes and among specific subgroups of interest.

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