Gruppo A - Coordinatori: Catia Angiolini, Alessandra Fabi, Giovanni L. Pappagallo

Quesito clinico 1: *Nelle pazienti con carcinoma mammario HR+/ HER2-negativo stadio IIA-IIIC è raccomandabile l'aggiunta di inibitori di CDK4/6 (ribociclib/abemaciclib) all'endocrinoterapia adiuvante?*

- Sintesi delle evidenze e problematiche emerse dal lavoro di gruppo - Giulia Borghesani
- Quale impatto nella pratica clinica? - Luisa Carbognin

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The efficacy and safety of CDK4/6 inhibitors combined with endocrine therapy versus endocrine therapy alone in the adjuvant treatment of patients with high-risk invasive HR+/HER2-early breast cancer: A comprehensive updated meta-analysis of randomized clinical trials

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ABSTRACT

Background: This paper aimed to evaluate the effectiveness of incorporating CDK 4/6 inhibitors (CDK4/6i) into ET for the adjuvant treatment of HR + HER2-resected early-stage breast cancer (ESBC) patients, employing meta-analysis.

Methods: In this paper, we compiled randomized clinical trials focusing on CDK4/6i used in the adjuvant treatment of high-risk invasive HR-positive and HER2-ESBC patients. A meta-analysis was performed in line with the PRISMA guidelines.

Results: We identified four clinical trials that met our inclusion criteria and were published between 2020 and 2024. These trials involved a combined sample size of 17,749 patients diagnosed with breast cancer. The data obtained from the pooled analysis revealed a remarkable beneficial trend in terms of invasive disease-free survival (iDFS) for the use of ET in combination with CDK4/6i compared to the group receiving ET alone (HR = 0.81, 95 % CI: 0.67–0.98, $p = 0.03$). Of note, CDK4/6 inhibitors demonstrated a notably beneficial effect in both grade 2 (HR = 0.69, 95 % CI: 0.59–0.81, $p < 0.001$) and grade 3 (HR = 0.76, 95 % CI: 0.65–0.89, $p < 0.001$). Significant improvements were noted in terms of distant relapse-free survival (dRFS) in the groups treated with abemaciclib and ribociclib (HR = 0.65, 95 % CI: 0.56–0.76, $p < 0.001$; HR = 0.72, 95 % CI: 0.58–0.89, $p = 0.003$, respectively). CDK4/6i didn't yield a statistically significant difference in overall survival (OS) (HR = 0.96, 95 % CI: 0.77–1.19, $p = 0.69$). The use of CDK4/6i with ET was associated with an increased risk of adverse events, particularly anemia and neutropenia, compared with ET alone (OR = 9.12, 95 % CI = 5.04–16.48, $p < 0.001$).

Conclusion: The findings of this paper demonstrate a significant improvement in iDFS when ET is combined with CDK4/6i, compared to ET alone. Specifically, treatments with abemaciclib and ribociclib showed notable enhancements in dRFS.

1. Introduction

Approximately 70 % of early-stage breast cancers are comprised of hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) patients [1,2]. In this group of patients, treatment strategies including surgery, radiotherapy, adjuvant or neo-adjuvant chemotherapy, and endocrine therapy (ET) are employed based on risk characteristics. Endocrine therapy constitutes the

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[1] The authors' contribution to the work is equal. The authors were identified as the first authors.

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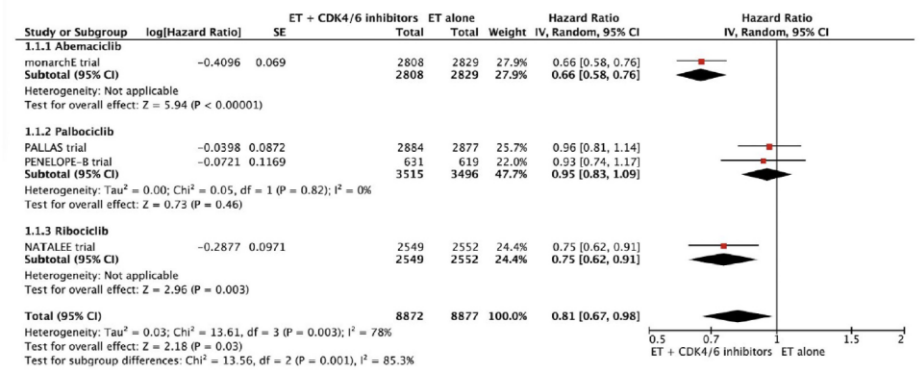

Fig. 3. The forest plot of the impact of CDK4/6 inhibitors with endocrine therapy compared to endocrine therapy alone on invasive disease-free survival. CI = confidence interval.

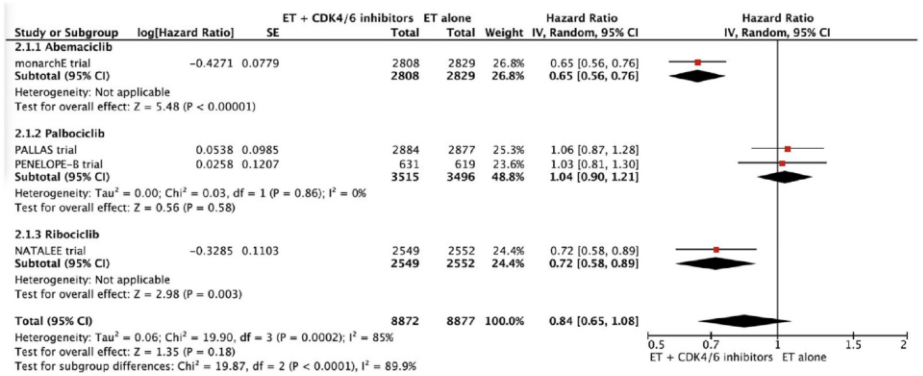

Fig. 4. The forest plot of the impact of CDK4/6 inhibitors with endocrine therapy compared to endocrine therapy alone on distant relapse-free survival. CI = confidence interval.

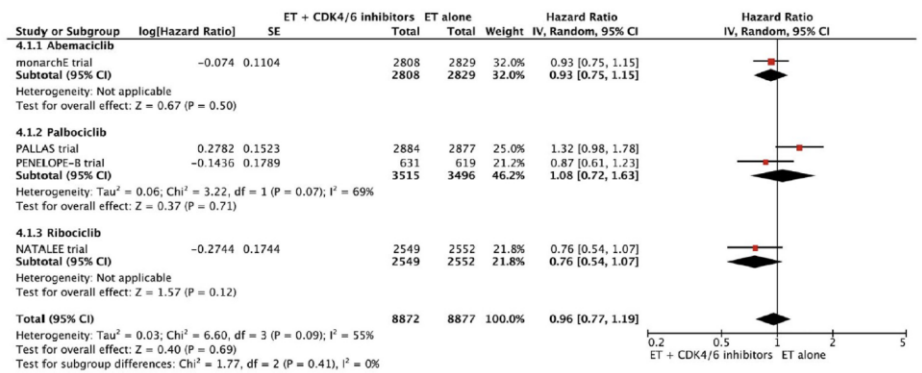

Fig. 5. The forest plot of the impact of CDK4/6 inhibitors with endocrine therapy compared to endocrine therapy alone on overall survival. CI = confidence interval.

Clinical Trial Updates

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Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes

Priya Rastogi, MD[1]; Joyce O'Shaughnessy, MD[2]; Miguel Martin, MD[3]; Frances Boyle, MD[4]; Javier Cortes, MD[5]; Hope S. Rugo, MD[6]; Matthew P. Goetz, MD[7]; Erika P. Hamilton, MD[8]; Chiun-Sheng Huang, MD[9]; Elzbieta Senkus, MD[10]; Alexey Tryakin, MD[11]; Irfan Cicin, MD[12]; Laura Testa, MD[13]; Patrick Neven, MD[14]; Jens Huober, MD[15]; Zhimin Shao, MD[16]; Ran Wei, PhD[17]; Valérie André, PhD[17]; Maria Munoz, PhD[17]; Belen San Antonio, PhD[17]; Ashwin Shahir, MD[17]; Nadia Harbeck, MD[18]; and Stephen Johnston, MD[19]

DOI https://doi.org/10.1200/JCO.23.01994

ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical trial updates provide an opportunity to disseminate additional results from studies, published in JCO *or elsewhere, for which the primary end point has already been reported.*

Two years of adjuvant abemaciclib combined with endocrine therapy (ET) resulted in a significant improvement in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) that persisted beyond the 2-year treatment period in patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative, node-positive, high-risk early breast cancer (EBC). Here, we report 5-year efficacy results from a prespecified overall survival (OS) interim analysis. In the intent-to-treat population, with a median follow-up of 54 months, the benefit of abemaciclib was sustained with hazard ratios of 0.680 (95% CI, 0.599 to 0.772) for IDFS and 0.675 (95% CI, 0.588 to 0.774) for DRFS. This persistence of abemaciclib benefit translated to continuous separation of the curves with a deepening in 5-year absolute improvement in IDFS and DRFS rates of 7.6% and 6.7%, respectively, compared with rates of 6% and 5.3% at 4 years and 4.8% and 4.1% at 3 years. With fewer deaths in the abemaciclib plus ET arm compared with the ET-alone arm (208 *v* 234), statistical significance was not reached for OS. No new safety signals were observed. In conclusion, abemaciclib plus ET continued to reduce the risk of developing invasive and distant disease recurrence beyond the completion of treatment. The increasing absolute improvement at 5 years is consistent with a carryover effect and further supports the use of abemaciclib in patients with high-risk EBC.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

Patients with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–), node-positive early breast cancer (EBC) are at high risk of recurrence (up to 30% at 5 years[1]) and need intensification of treatment. Two years of adjuvant abemaciclib in combination with endocrine therapy (ET) is an internationally approved standard of care with National Comprehensive Cancer Network category 1[2] and European Society for Medical Oncology–Magnitude of Clinical Benefit Scale score A[3] recommendation for patients with HR+, HER2–, node-positive EBC at high risk of recurrence. With a median follow-up of 42 months, abemaciclib demonstrated a persistent benefit in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) beyond the 2-year treatment period, with all patients off treatment. While overall survival (OS) remained immature, the lower number of deaths in the abemaciclib arm compared with the ET arm suggested that a survival signal favoring abemaciclib was emerging.[4] Here, we present efficacy results from a prespecified OS interim analysis that provides 5-year estimates of IDFS and DRFS and updated OS evaluation.

METHODS

A total of 5,637 patients in the monarchE phase III global trial were assigned to one of two cohorts. Cohort 1 (n = 5,120 [91%]) included patients with either at least four positive

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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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Available online 21 October 2024

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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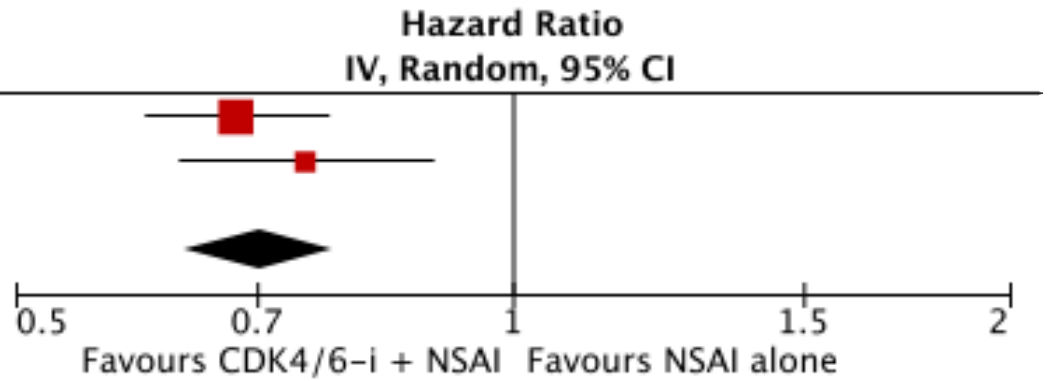
iDFS

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Monarch-E	-0.3857	0.0647	65.9%	0.68 [0.60, 0.77]
Natalee	-0.289	0.0899	34.1%	0.75 [0.63, 0.89]
Total (95% CI)			**100.0%**	**0.70 [0.63, 0.78]**

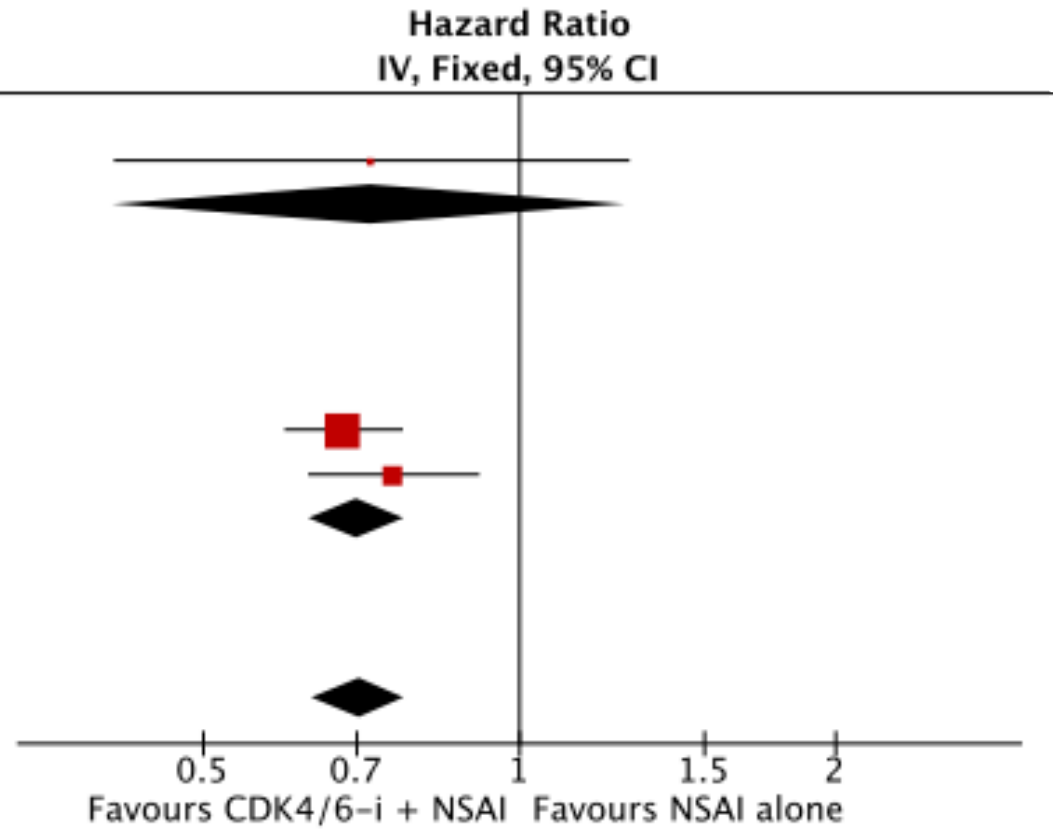
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.76$, df = 1 (P = 0.38); $I^2 = 0\%$

Test for overall effect: Z = 6.72 (P < 0.00001)



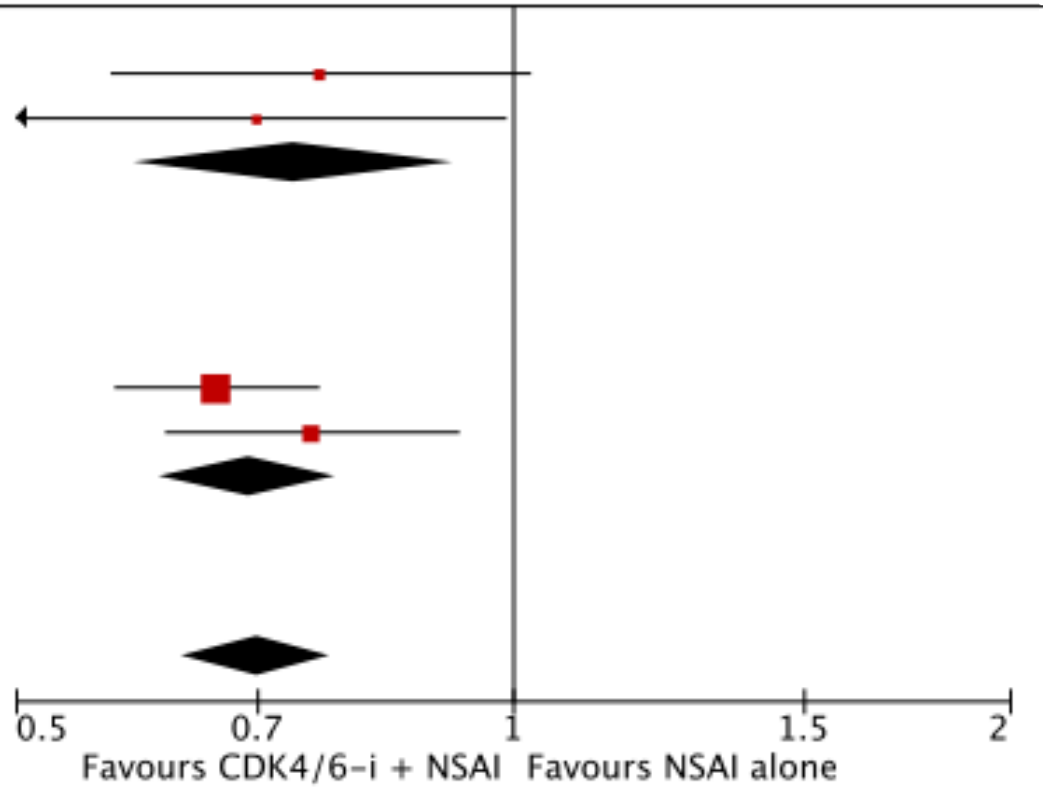
iDFS by l.n. involvement

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
1.3.1 N(-)				
Natalee N(-)	-0.3243	0.2869	3.3%	0.72 [0.41, 1.27]
Subtotal (95% CI)			**3.3%**	**0.72 [0.41, 1.27]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.13 (P = 0.26)				
1.3.2 N(+)				
Monarch-E	-0.3857	0.0647	65.7%	0.68 [0.60, 0.77]
Natalee N(+)	-0.2758	0.0942	31.0%	0.76 [0.63, 0.91]
Subtotal (95% CI)			**96.7%**	**0.70 [0.63, 0.78]**
Heterogeneity: $Chi^2 = 0.92$, df = 1 (P = 0.34); $I^2 = 0\%$				
Test for overall effect: Z = 6.57 (P < 0.00001)				
Total (95% CI)			**100.0%**	**0.70 [0.64, 0.78]**
Heterogeneity: $Chi^2 = 0.93$, df = 2 (P = 0.63); $I^2 = 0\%$				
Test for overall effect: Z = 6.67 (P < 0.00001)				
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.93), $I^2 = 0\%$				



iDFS by disease stage

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.2.1 Stage II				
Monarch-E Stage II	-0.2692	0.1486	12.5%	0.76 [0.57, 1.02]
Natalee Stage II	-0.3567	0.1758	8.9%	0.70 [0.50, 0.99]
Subtotal (95% CI)			**21.4%**	**0.74 [0.59, 0.92]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.14$, df = 1 (P = 0.70); $I^2 = 0\%$				
Test for overall effect: Z = 2.69 (P = 0.007)				
1.2.2 Stage III				
Monarch-E Stage III	-0.414	0.072	53.1%	0.66 [0.57, 0.76]
Natalee Stage III	-0.281	0.1038	25.5%	0.76 [0.62, 0.93]
Subtotal (95% CI)			**78.6%**	**0.69 [0.61, 0.78]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.11$, df = 1 (P = 0.29); $I^2 = 10\%$				
Test for overall effect: Z = 5.84 (P < 0.00001)				
Total (95% CI)			**100.0%**	**0.70 [0.63, 0.78]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.51$, df = 3 (P = 0.68); $I^2 = 0\%$				
Test for overall effect: Z = 6.80 (P < 0.00001)				
Test for subgroup differences: $Chi^2 = 0.23$, df = 1 (P = 0.63), $I^2 = 0\%$				

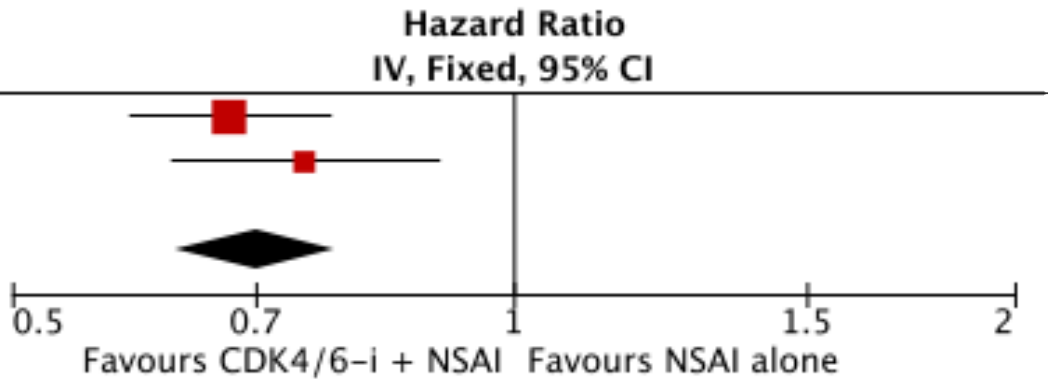


DRFS

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Monarch-E	-0.393	0.0704	64.1%	0.68 [0.59, 0.77]
Natalee	-0.289	0.094	35.9%	0.75 [0.62, 0.90]
Total (95% CI)			**100.0%**	**0.70 [0.63, 0.78]**

Heterogeneity: $Chi^2 = 0.78$, $df = 1$ ($P = 0.38$); $I^2 = 0\%$

Test for overall effect: $Z = 6.31$ ($P < 0.00001$)

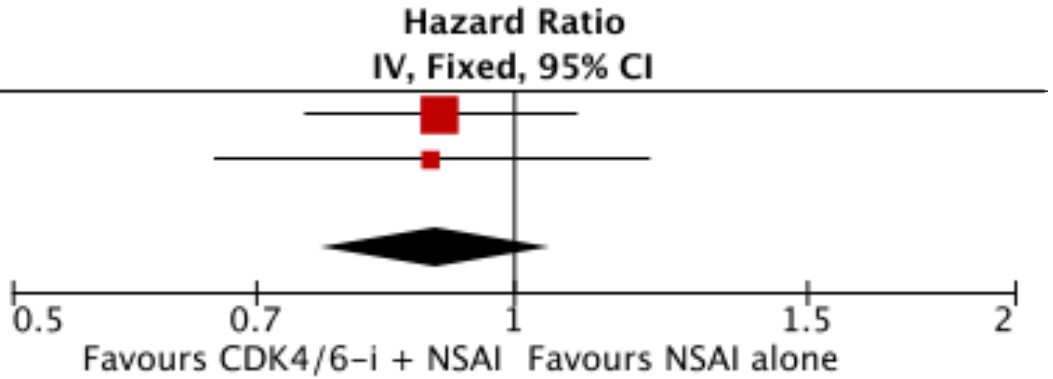


OS

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Monarch-E	-0.102	0.0954	72.0%	0.90 [0.75, 1.09]
Natalee	-0.1143	0.1529	28.0%	0.89 [0.66, 1.20]
Total (95% CI)			**100.0%**	**0.90 [0.77, 1.05]**

Heterogeneity: $Chi^2 = 0.00$, $df = 1$ ($P = 0.95$); $I^2 = 0\%$

Test for overall effect: $Z = 1.30$ ($P = 0.19$)



Author(s): Giovanni L. Pappagallo (27-Mar-2025)
Question: CDK4/6-inhibitor + NSAI compared to NSAI alone for patients with HR-positive/HER2-negative early breast cancer
Bibliography: Monarch-E: Johnston SRD, et al. J Clin Oncol 2020; 38:3987-3998 & Rastogi P, et al. J Clin Oncol 2024; 42:987-993
Natalee: Slamon D, et al. N Engl J Med 2024;390:1080-91 & Hortobagyi GN, et al. Ann Oncol. 2025 Feb;36(2):149-157.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CDK4/6-inhibitor + NSAI	NSAI alone	Relative (95% CI)	Absolute (95% CI)		
iDFS (assessed with Kaplan-Meier product limit estimate)												
2[a]	RND	serious [b]	not serious [c]	not serious [d]	not serious [e]	none	5357 -	5381 baseline risk 16.0%	**HR 0.70** (0.63 to 0.78)	**5 fewer per 100** (from 6 fewer to 3 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
DRFS (assessed with Kaplan-Meier product limit estimate)												
2[a]	RND	serious [b]	not serious [f]	not serious [d]	not serious [e]	none	5357 -	5381 baseline risk 14.0%	**HR 0.70** (0.63 to 0.78)	**4 fewer per 100** (from 5 fewer to 3 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
OS (assessed with Kaplan-Meier product limit estimate)												
2[a]	RND	not serious [g]	not serious [h]	not serious [d]	not serious [e]	none	5357 -	5381 baseline risk 6.0%	**HR 0.90** (0.77 to 1.05)	**1 fewer per 100** (from 1 fewer to 0 fewer)	⨁⨁⨁⨁ High	CRITICAL

a. pooled analysis of Monarch-E and Natalee studies
b. serious risk of detection bias (investigator's assessment)
c. Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.76$, df = 1 (P = 0.38); $I^2 = 0\%$
d. NSAI alone as adequate comparator
e. 95%CI of absolute effect consistent with a unique clinical interpretation
f. Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.78$, df = 1 (P = 0.38); $I^2 = 0\%$
g. not a serious risk of detection bias for OS endpoint
h. Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.95); $I^2 = 0$

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rapid communications abstract

Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2−, Node-Positive, High-Risk, Early Breast Cancer (monarchE)

Stephen R. D. Johnston, MD, PhD[1]; Nadia Harbeck, MD, PhD[2]; Roberto Hegg, MD, PhD[3]; Masakazu Toi, MD, PhD[4]; Miguel Martin, MD, PhD[5]; Zhi Min Shao, MD[6]; Qing Yuan Zhang, MD, PhD[7]; Jorge Luis Martinez Rodriguez, MD[8]; Mario Campone, MD, PhD[9]; Erika Hamilton, MD[10]; Joohyuk Sohn, MD, PhD[11]; Valentina Guarneri, MD, PhD[12]; Morihito Okada, MD, PhD[13]; Frances Boyle, MD, MBBS, PhD[14]; Patrick Neven, MD, PhD[15]; Javier Cortés, MD, PhD[16]; Jens Huober, MD[17]; Andrew Wardley, MD, MBChB[18]; Sara M. Tolaney, MD, MPH[19]; Irfan Cicin, MD[20]; Ian C. Smith, MD[21,22]; Martin Frenzel, PhD[23]; Desirée Headley, MSc[23]; Ran Wei, PhD[23]; Belen San Antonio, PhD[23]; Maarten Hulstijn, PhD[23]; Joanne Cox, MD[23]; Joyce O'Shaughnessy, MD[23]; and Priya Rastogi, MD[24]; on behalf of the monarchE Committee Members and Investigators

PURPOSE Many patients with HR+, HER2− early breast cancer (EBC) will not experience recurrence or have distant recurrence with currently available standard therapies. However, up to 30% of patients with high-risk clinical and/or pathologic features may experience distant recurrence, many in the first few years. Superior treatment options are needed to prevent early recurrence and development of metastases for this group of patients. Abemaciclib is an oral, continuously dosed, CDK4/6 inhibitor approved for HR+, HER2− advanced breast cancer (ABC). Efficacy and safety of abemaciclib in ABC supported evaluation in the adjuvant setting.

METHODS This open-label, phase III study included patients with HR+, HER2−, high-risk EBC, who had surgery and, as indicated, radiotherapy and/or adjuvant/neoadjuvant chemotherapy. Patients with four or more positive nodes, or one to three nodes and either tumor size ≥ 5 cm, histologic grade 3, or central Ki-67 ≥ 20%, were eligible and randomly assigned (1:1) to standard-of-care adjuvant endocrine therapy (ET) with or without abemaciclib (150 mg twice daily for 2 years). The primary end point was invasive disease-free survival (IDFS), and secondary end points included distant relapse–free survival, overall survival, and safety.

RESULTS At a preplanned efficacy interim analysis, among 5,637 randomly assigned patients, 323 IDFS events were observed in the intent-to-treat population. Abemaciclib plus ET demonstrated superior IDFS versus ET alone ($P = .01$; hazard ratio, 0.75; 95% CI, 0.60 to 0.93), with 2-year IDFS rates of 92.2% versus 88.7%, respectively. Safety data were consistent with the known safety profile of abemaciclib.

CONCLUSION Abemaciclib when combined with ET is the first CDK4/6 inhibitor to demonstrate a significant improvement in IDFS in patients with HR+, HER2− node-positive EBC at high risk of early recurrence.

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ASSOCIATED CONTENT

See accompanying editorial on page 3977

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

More than 90% of patients with breast cancer are diagnosed with early-stage disease, of whom approximately 70% have cancers that are hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2−).[1,2] Standard treatment varies depending on risk of recurrence but includes combinations of surgery, radiotherapy, adjuvant/neoadjuvant chemotherapy, and endocrine therapy (ET).[3,4] Adjuvant ET (aromatase inhibitors [AIs] and/or antiestrogens with or without ovarian suppression) is standard treatment of HR+, HER2− early breast cancer (EBC) and has been associated with a significant reduction in risk of recurrence and death.[4] Although many patients with HR+, HER2− disease will not experience recurrence or have distant recurrence with standard therapies alone, up to 20% of patients may experience disease recurrence in the first 10 years, often with distant metastases, at which time the disease is incurable.[5] For those patients with high-risk clinical and/or pathologic features, risk of recurrence is higher, especially during the first few years on adjuvant ET.[6] It is therefore critical to optimize adjuvant therapy to prevent early recurrences and metastases for these patients.

Abemaciclib is an oral, continuously dosed, cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor approved in combination with ET for the treatment of HR+, HER2− advanced breast cancer (ABC) on the basis of significant improvements in progression-free survival (PFS) and overall survival (OS) in combination with fulvestrant[7,8] and in PFS in combination with

ORIGINAL ARTICLE

Ribociclib plus Endocrine Therapy in Early Breast Cancer

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ABSTRACT

BACKGROUND
Ribociclib has been shown to have a significant overall survival benefit in patients with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer. Whether this benefit in advanced breast cancer extends to early breast cancer is unclear.

METHODS
In this international, open-label, randomized, phase 3 trial, we randomly assigned patients with HR-positive, HER2-negative early breast cancer in a 1:1 ratio to receive ribociclib (at a dose of 400 mg per day for 3 weeks, followed by 1 week off, for 3 years) plus a nonsteroidal aromatase inhibitor (NSAI; letrozole at a dose of 2.5 mg per day or anastrozole at a dose of 1 mg per day for ≥5 years) or an NSAI alone. Premenopausal women and men also received goserelin every 28 days. Eligible patients had anatomical stage II or III breast cancer. Here we report the results of a prespecified interim analysis of invasive disease–free survival, the primary end point; other efficacy and safety results are also reported. Invasive disease–free survival was evaluated with the use of the Kaplan–Meier method. The statistical comparison was made with the use of a stratified log-rank test, with a protocol-specified stopping boundary of a one-sided P-value threshold of 0.0128 for superior efficacy.

RESULTS
As of the data-cutoff date for this prespecified interim analysis (January 11, 2023), a total of 426 patients had had invasive disease, recurrence, or death. A significant invasive disease–free survival benefit was seen with ribociclib plus an NSAI as compared with an NSAI alone. At 3 years, invasive disease–free survival was 90.4% with ribociclib plus an NSAI and 87.1% with an NSAI alone (hazard ratio for invasive disease, recurrence, or death, 0.75; 95% confidence interval, 0.62 to 0.91; P=0.003). Secondary end points — distant disease–free survival and recurrence-free survival — also favored ribociclib plus an NSAI. The 3-year regimen of ribociclib at a 400-mg starting dose plus an NSAI was not associated with any new safety signals.

CONCLUSIONS
Ribociclib plus an NSAI significantly improved invasive disease–free survival among patients with HR-positive, HER2-negative stage II or III early breast cancer. (Funded by Novartis; NATALEE ClinicalTrials.gov number, NCT03701334.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Slamon can be contacted at dslamon@mednet.ucla.edu or at the David Geffen School of Medicine at the University of California, Los Angeles, 885 Tiverton Dr., Los Angeles, CA 90095.

A list of the investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

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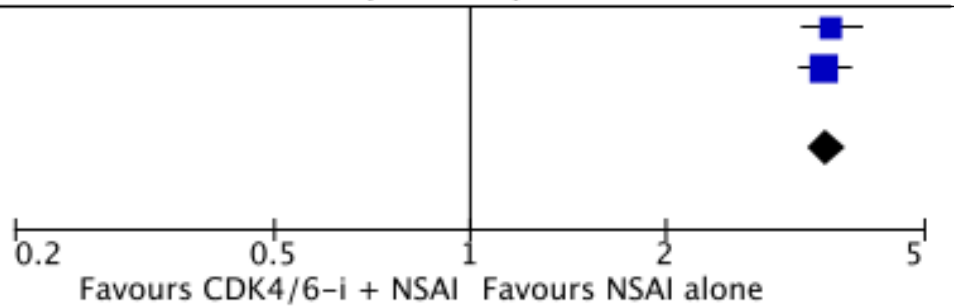
CME at NEJM.org

TEAE of CTCAE Grade 3-4

Study or Subgroup	CDK4/6-i + NSAI Events	Total	NSAI alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Monarch-E	1270	2791	354	2800	42.6%	3.60 [3.24, 4.00]
Natalee	1567	2524	432	2444	57.4%	3.51 [3.21, 3.85]
Total (95% CI)		**5315**		**5244**	**100.0%**	**3.55 [3.31, 3.80]**
Total events	2837		786			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0\%$

Test for overall effect: Z = 36.07 (P < 0.00001)

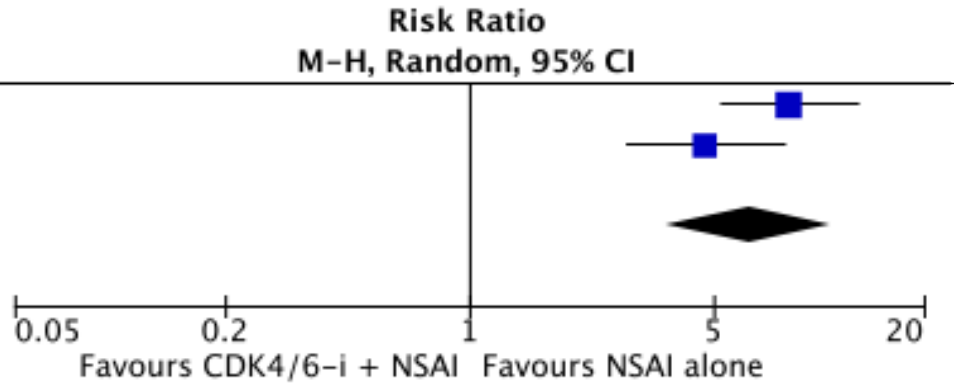


TEAE leading to discontinuation of all drugs

Study or Subgroup	CDK4/6-i + NSAI Events	Total	NSAI alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Monarch-E	172	2791	21	2800	52.8%	8.22 [5.24, 12.89]
Natalee	83	2524	17	2444	47.2%	4.73 [2.81, 7.94]
Total (95% CI)		**5315**		**5244**	**100.0%**	**6.33 [3.68, 10.90]**
Total events	255		38			

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 2.51$, df = 1 (P = 0.11); $I^2 = 60\%$

Test for overall effect: Z = 6.66 (P < 0.00001)

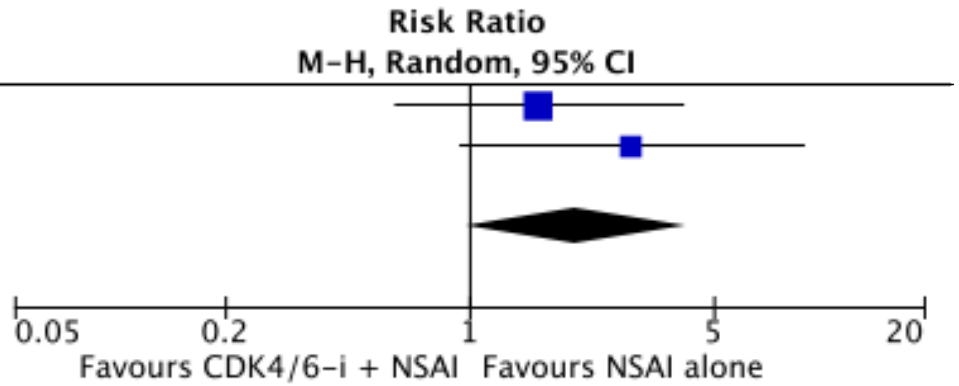


TEAE leading to death

Study or Subgroup	CDK4/6-i + NSAI Events	Total	NSAI alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Monarch-E	11	2791	7	2800	58.8%	1.58 [0.61, 4.06]
Natalee	12	2524	4	2444	41.2%	2.90 [0.94, 8.99]
Total (95% CI)		**5315**		**5244**	**100.0%**	**2.03 [0.98, 4.19]**
Total events	23		11			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.66$, df = 1 (P = 0.42); $I^2 = 0\%$

Test for overall effect: Z = 1.91 (P = 0.06)



Author(s): Giovanni L. Pappagallo (27-Mar-2025)
Question: CDK4/6-inhibitor + NSAI compared to NSAI alone for patients with HR-positive/HER2-negative early breast cancer
Bibliography: Monarch-E: Johnston SRD, et al. J Clin Oncol 2020; 38:3987-3998 & Rastogi P, et al. J Clin Oncol 2024; 42:987-993
Natalee: Slamon D, et al. N Engl J Med 2024;390:1080-91 & Hortobagyi GN, et al. Ann Oncol. 2025 Feb;36(2):149-157.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CDK4/6-inhibitor + NSAI	NSAI alone	Relative (95% CI)	Absolute (95% CI)		
TEAE of CTCTAE Grade 3-4 (assessed with:cumulative incidence)												
2[a]	RND	serious [b]	not serious [c]	not serious [d]	not serious [e]	none	2837/5315 (53.4%)	786/5244 (15.0%)	**RR 3.55** (3.31 to 3.80)	**38 more per 100** (from 35 more to 42 more)	⨁⨁⨁◯ Moderate	IMPORTANT
TEAE leading to discontinuation of all drugs (assessed with:cumulative incidence)												
2[a]	RND	serious [b]	not serious [f]	not serious [d]	not serious [e]	none	255/5315 (4.8%)	38/5244 (0.7%)	**RR 6.33** (3.68 to 10.90)	**4 more per 100** (from 2 more to 7 more)	⨁⨁⨁◯ Moderate	CRITICAL
TEAE leading to death (assessed with:cumulative incidence)												
2[a]	RND	serious [b]	not serious [g]	not serious [d]	not serious [e]	none	23/5315 (0.4%)	11/5244 (0.2%)	**RR 2.03** (0.98 to 4.19)	**0 fewer per 100** (from 0 fewer to 1 more)	⨁⨁⨁◯ Moderate	IMPORTANT

a. pooled analysis of Monarch-E and Natalee studies
b. serious risk of detection/performance bias (investigator assessment)
c. Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0\%$
d. NSAI alone as adequate comparator
e. 95%CI of absolute effect consistent with a unique clinical interpretation
f. Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 2.51$, df = 1 (P = 0.11); $I^2 = 60\%$
g. Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.66$, df = 1 (P = 0.42); $I^2 = 0\%$

Criterio	Giudizio Sintetico
I benefici attesi sono sostanziali?	❑ No ❑ Probabilmente No ❑ Incertezza ✅ Probabilmente Si ❑ Si
Gli effetti indesiderati attesi sono sostanziali?	❑ No ❑ Probabilmente No ❑ Incertezza ✅ Probabilmente Si ❑ Si
I benefici superano gli effetti indesiderati?	❑ No ❑ Probabilmente No ❑ Incertezza ✅ Probabilmente Si ❑ Si
Esistono incertezze / variabilità sul valore attribuito dai pazienti agli outcome considerati?	❑ No ❑ Probabilmente No ✅ Probabilmente Si ❑ Si

Criterio	Giudizio Sintetico
Qual è l'impatto dell'intervento in termini di risorse addizionali?	✅ Importante incremento ❑ Moderato incremento ❑ Trascurabile ❑ Moderato risparmio ❑ Importante risparmio ❑ n.d.
Impatto dell'intervento sulla equità in sanità?	❑ Riduzione disparità ❑ Probabile riduzione disparità ✅ Non impatto ❑ Probabile aumento disparità ❑ Aumento disparità
Accettabilità dell'intervento da parte degli stakeholders?	❑ No ❑ Probabilmente No ✅ Incertezza ❑ Probabilmente Si ❑ Si
Fattibilità della implementazione dell'intervento?	❑ No ❑ Probabilmente No ❑ Incertezza ❑ Probabilmente Si ✅ Si