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Treatment With Adjuvant Abemaciclib Plus Endocrine Therapy in Patients With High-risk Early Breast Cancer Who Received Neoadjuvant Chemotherapy

A Prespecified Analysis of the monarchE Randomized Clinical Trial

Miguel Martin, MD, PhD,[✉] [1] Roberto Hegg, MD, [2] Sung-Bae Kim, MD, PhD, [3] Michael Schenker, MD, PhD, [4] Daniela Grecea, MD, PhD, [5] Jose Angel Garcia-Saenz, MD, PhD, [6] Konstantinos Papazisis, MD, PhD, [7] QuChang Ouyang, MD, [8] Aleksandra Lacko, MD, PhD, [9] Berna Oksuzoglu, MD, [10] James Reeves, MD, [11] Meena Okera, MD, [12] Laura Testa, MD, [13] Chikako Shimizu, MD, PhD, [14] Neelima Denduluri, MD, [15] Hryhoriy Adamchuk, MD, [16] Shaker Dakhil, MD, [17] Ran Wei, PhD, [18] Tammy Forrester, [18] Maria Munoz Fernandez, PhD, [18] Annamaria Zimmermann, [18] Desiree Headley, [18] and Stephen R. D. Johnston, MD, PhD [19]

[1]Medical Oncology Service, Hospital General Universitario Gregorio Marañon, Universidad Complutense, Centro de Investigación Biomédica en Red-Cáncer, Grupo Español de Investigación en Cáncer de Mama, Madrid, Spain
[2]Clinica de Pesquisa e Centro São Paulo, São Paulo, Brazil
[3]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[4]Centrul de Oncologie Sf Nectarie SRL, University of Medicine and Pharmacy Craiova, Craiova, Romania
[5]Institutul Oncologic “Prof.Dr. Ion Chiricuta” Cluj-Napoca, Cluj-Napoca, Romania
[6]Medical Oncology Service, Hospital Clinico San Carlos, GEICAM, Madrid, Spain
[7]Euromedica, General Clinic of Thessaloniki, Thessaloniki, Greece
[8]Hunan Cancer Hospital, Changsha, China
[9]Dolnoslaskie Centrum Onkologii, Uniwersytet Medyczny we Wroclawiu, Wroclaw, Poland
[10]Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey
[11]Florida Cancer Specialists/Sarah Cannon Research Institute, Fort Myers
[12]Adelaide Cancer Centre, Kurralta Park, Australia
[13]Instituto D’Or de Pesquisa e Ensino, São Paulo, Brazil
[14]National Center for Global Health and Medicine, Tokyo, Japan
[15]Virginia Cancer Specialists, US Oncology Network, Arlington, Virginia
[16]Communal Enterprise “Kryvyi Rih oncology dispensary” Dnipr region, Kryvyi Rih, Ukraine
[17]Cancer Center of Kansas, Wichita, Kansas
[18]Eli Lilly and Company, Indianapolis, Indiana
[19]Royal Marsden National Health Service Foundation Trust, London, England
[✉]Corresponding author.

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Corresponding Author: Miguel Martin, MD, PhD, Medical Oncology Service, Hospital General Universitario Gregorio Marañon, Universidad Complutense, Centro de Investigación Biomédica en Red-Cáncer, GEICAM, Madrid, Spain (mmartin@geicam.org).

Author Contributions: Drs Martin and Johnston had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Martin, Denduluri, Headley, Johnston.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Martin, Schenker, Forrester, Munoz Fernandez, Zimmermann.

Critical revision of the manuscript for important intellectual content: Martin, Hegg, Kim, Schenker, Grecea, García-Sáenz, Papazisis, Ouyang, Lacko, Oksuzoglu, Reeves, Okera, Testa, Shimizu, Denduluri, Adamchuk, Dakhil, Wei, Forrester, Munoz Fernandez, Headley, Johnston.

Statistical analysis: Wei, Zimmermann.

Administrative, technical, or material support: Martin, Grecea, Ouyang, Oksuzoglu, Munoz Fernandez.

Supervision: Hegg, Schenker, Ouyang, Johnston.

Other - Served as PI for the trial for Virginia Cancer Specialists, enrolled most patients within The US Oncology Network: Denduluri.

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Key Points

Question

Can treatment with abemaciclib provide good clinical outcomes for patients with high-risk early breast cancer who received neoadjuvant chemotherapy?

Findings

In this prespecified analysis of the monarchE randomized clinical trial, treatment with abemaciclib and endocrine therapy demonstrated clinically meaningful benefit in invasive disease-free survival and distant relapse-free survival, with an absolute improvement of 6.6% in 2-year invasive disease-free survival rates and 6.7% in 2-year distant relapse-free survival rates. Consistent treatment benefit was observed by residual pathological breast tumor size or the number of positive lymph nodes at surgery.

Meaning

The results of this analysis of the monarchE randomized clinical trial found that treatment with adjuvant abemaciclib plus endocrine therapy demonstrated benefit for patients with hormone receptor–positive, ERBB2^{-}, node-positive, and high-risk early breast cancer who received neoadjuvant chemotherapy before trial enrollment.

Abstract

Importance

Patients selected to receive neoadjuvant chemotherapy (NAC) are usually those at higher risk of relapse, and there is a need to find better therapeutic options for these patients.

Objective

To determine the efficacy and safety outcomes for patients with hormone receptor (HR)–positive, ERBB2 (formerly HER2)$^{-}$, high-risk early breast cancer enrolled in the randomized clinical trial monarchE who received NAC.

Design, Setting, and Participants

The monarchE randomized clinical trial was a multicenter, phase 3, open-label study that evaluated adjuvant treatment with abemaciclib plus endocrine therapy (ET) compared with ET alone in patients with HR^{+}, ERBB2^{-}, and node-positive early breast cancer who were at high risk of recurrence. Patients were recruited between July 2017 and August 2019 from 603 sites in 38 countries. This subgroup analysis was performed with primary outcome data, with a cutoff date of July 8, 2020.

Intervention

Enrolled patients were randomized (1:1) to receive standard of care ET for at least 5 years with or without treatment with abemaciclib (150 mg, twice daily) for 2 years (treatment period) or until criteria were met for discontinuation.

Main Outcomes and Measures

Prior chemotherapy (NAC vs adjuvant vs none) was a stratification factor in monarchE, and and a prespecified exploratory analysis included outcomes in patients who received NAC. The data presented in this article are from the primary outcome analysis (395 invasive disease-free survival [IDFS] events; cutoff date, July 8, 2020; median follow-up 19 months [IQR, 15.6-23.9 months]). Invasive disease-free survival (the primary end point of monarchE) and distant relapse-free survival (DRFS) were evaluated using the Cox proportional hazard model and Kaplan-Meier method.

Results

Of the 5637 patients (mean [SD] age, 49.9 [10.6] years; 2046 women [99.5%]; 462 Asian [22.8%], 54 Black [2.7%], and 1473 White participants [70.8%]) enrolled in monarchE, 2056 (37%) received treatment with NAC. In this subgroup, treatment with abemaciclib and ET demonstrated clinically meaningful benefit in IDFS (hazard ratio, 0.61; 95% CI, 0.47-0.80) and DRFS (hazard ratio, 0.61; 95% CI, 0.46-0.81), which corresponded with an absolute improvement of 6.6% in 2-year IDFS rates and 6.7% in 2-year DRFS rates. A consistent treatment benefit was observed across subgroups of pathological breast tumor size or number of positive lymph nodes at surgery.

Conclusions and Relevance

In the randomized clinical trial monarchE, treatment with adjuvant abemaciclib combined with ET demonstrated a clinically meaningful improvement in IDFS and DRFS for patients with HR^+, $ERBB2^-$, node-positive, high-risk early breast cancer who received NAC before trial enrollment.

Trial Registration

ClinicalTrials.gov Identifier: NCT03155997

Introduction

Neoadjuvant chemotherapy (NAC) is often offered to patients with hormone receptor–positive (HR^+), ERBB2 (formerly HER2)$^-$, high-risk early breast cancer with higher disease burden to improve a patient's likelihood of undergoing breast-conserving surgery.[1] Residual disease in the breast and/or lymph nodes at surgery following NAC is known to be associated with poorer outcomes in all breast cancer subtypes, including HR^+, $ERBB2^-$ breast cancer.[2] In other breast cancer subtypes, like triple-negative and $ERBB2^+$, modern NAC has more than a 50% chance of inducing a pathological complete response (pCR), and subsequent treatment with adjuvant capecitabine or trastuzumab emtansine, respectively, has been shown to improve the outcomes in studies specifically designed to determine the effect of adjuvant therapy in patients with residual disease after treatment with NAC.[3,4]

In contrast, most patients with HR^+, $ERBB2^-$ breast cancer have residual disease after receiving NAC,[5] and although adjuvant endocrine therapy (ET) can reduce the risk of recurrence in these patients, a considerable risk remains. Novel therapeutic options are needed to prevent recurrences for these patients.

Based on results from the monarchE randomized clinical trial, abemaciclib, a cyclin-dependent kinase (CDK) 4 and 6 inhibitor, is the first CDK4 and 6 inhibitor approved for the adjuvant treatment of HR^+, $ERBB2^-$, node-positive, early breast cancer at high risk of recurrence.[6] In this article, we present efficacy and safety data from the primary outcome (PO) analysis for patients enrolled in monarchE who received NAC.

Methods

monarchE Study Design and Population

The monarchE study, an open-label, global, randomized, phase 3 clinical trial, investigated the addition of abemaciclib to ET in treating patients with HR^+, $ERBB2^-$, node-positive, high-risk early breast cancer (Supplement 1 and Supplement 2).[7] The study design was previously published[7] (eFigure 1 in Supplement 3). Patients who received NAC as initial prior chemotherapy were stratified as NAC. This study, including all amendments, was approved by institutional review boards at the study institutions and was conducted in accordance with consensus ethical principles derived from international ethical guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences and the International Conference on Harmonisation-Good Clinical Practice guidelines.

As patients were eligible for enrollment based on the lymph node status either at diagnosis or at surgery, collection of the lymph node status was required only at 1 of the time points, and lymph node status at the time of surgery was not available in all patients. Thus, pCR status in the breast and axillary lymph nodes (ALNs) could not be calculated.

Statistical Analysis

Study end points were previously described.[7] A subgroup analysis per prior chemotherapy was a prespecified exploratory analysis. This subgroup analysis was performed with PO data (395 invasive disease-free survival [IDFS] events; cutoff, July 8, 2020; median [IQR] follow-up time, 19 [15.6-23.9] months).

Among the patients who received NAC, the efficacy and safety of treatment with abemaciclib and ET was evaluated in terms of IDFS, distant relapse-free survival (DRFS), and adverse events (AEs). Exploratory analyses on IDFS and DRFS were performed by residual pathological tumor size and by the number of positive nodes in those patients from whom lymph nodes status at surgery was available. All efficacy analyses were unadjusted. Analyses were conducted using SAS (version 9.4; SAS Institute).

Results

Patients

In total, 2056 patients (36.5%) enrolled in monarchE received NAC (eTable 1 in Supplement 3). Most patients in the NAC subgroup received anthracycline/taxane–based regimens (eTable 1 in Supplement 3). Baseline characteristics of patients who received NAC are shown in eTables 1 and 2 in the Supplement 3.

Efficacy

Treatment with abemaciclib and ET demonstrated a 39% relative reduction in the risk of developing an IDFS event compared with ET alone (hazard ratio, 0.61; 95% CI, 0.47-0.80; nominal $P < .001$) in patients who received NAC. The 2-year IDFS rates reflected an absolute difference of 6.6% (Figure, A). In the NAC subgroup, the benefit of treatment with abemaciclib and ET in DRFS rates corresponded to a 39% relative risk reduction (hazard ratio, 0.61; 95% CI, 0.46-0.81; nominal $P < .001$) and an absolute improvement of 6.7% in 2-year DRFS rates (Figure, B).

Given the limited number of patients who had a pCR in the breast (1.6% in both arms) or no involved ALN at surgery (3.0% vs 2.9% between arms), efficacy analyses were not performed within those patients. Larger tumor size after treatment with NAC (>2 cm vs ≤2 cm) and more positive ALNs postsurgery (≥4 vs 1-3) were associated with a higher risk of developing an IDFS or DRFS event in the control arm. However, a consistent treatment benefit was observed in patients who received NAC regardless of the residual primary tumor size or number of positive ALNs at the time of surgical resection (Table).

Safety

Among the 2037 patients who received NAC and at least one dose of study treatment, the safety profile was consistent with the safety profile reported in the broader monarchE population. The abemaciclib and ET arm had higher incidence of treatment-emergent AEs (TEAEs), with the most frequent events being diarrhea, infections, neutropenia, and fatigue. The most common grade 3 or higher TEAEs were neutropenia and leucopenia. In the ET alone arm, the most frequent TEAEs were arthralgia, hot flashes, and fatigue (eTable 2 in Supplement 3).

Discussion

In this prespecified analysis of the monarchE randomized clinical trial, patients who received NAC had a poorer prognosis than the monarchE intent-to-treat population, as suggested by the higher risk of recurrence at 2 years (19% vs 11% in the control arms). For those patients, the magnitude of treatment benefit from abemaciclib and ET in IDFS and DRFS rates was clinically meaningful and numerically greater than that in the intent-to-treat population.

In the subgroup exploratory analyses by the extent of residual disease, patients with a larger residual pathological tumor size (>2 cm) and higher numbers of positive ALNs (≥4) had higher rates of disease recurrence. However, the benefit of treatment with abemaciclib and ET in IDFS and DRFS rates was consistently observed independently of the extent of residual disease.

In contrast with the outcome in the NAC subgroup in monarchE, Penelope-B, a study investigating the efficacy of palbociclib as adjuvant treatment of HR^+, $ERBB2^-$ early breast cancer in patients with residual disease after receiving NAC, did not show any treatment benefit with 42.8 months follow-up.[8] Differences in the schedules of administration and the pharmacological properties of both drugs may have influenced the different outcomes. Abemaciclib was administered continuously,[7] while palbociclib was administered for 21 days, followed by 7 days of no use.[8] The treatment duration also differed between monarchE and Penelope-B, with abemaciclib being administered for 2 years and palbociclib for 1 year.[7,8]

Abemaciclib has demonstrated in biochemical and cell-based assays a stronger inhibition of CDK4 vs CDK6 relative to palbociclib.[9,10] This differentiated pharmacological profile allows abemaciclib to be dosed continuously. In vitro studies have shown that continuous drug exposure of HR^+ BC cells is required for profound inhibition of DNA synthesis,[8] and a similar effect in patients could play a role in the sustained tumor growth inhibition of micrometastatic disease. Moreover, CDK4 has been shown to play an essential role in the development/growth of breast cancer in animal models.[11] Also, in breast cancer cell lines, abemaciclib was a more potent inducer of senescence and apoptosis than palbociclib.[12]

Limitations

The subgroup analyses are exploratory, as they were not sufficiently powered nor α controlled for statistical testing. Additionally, complete information on the tumor characteristics before and after NAC were not required; thus, further analyses by residual disease should be interpreted with caution. Despite these limitations, the treatment benefit of abemaciclib and ET within the NAC subgroup was statistically valid given the large size of this subgroup and prior chemotherapy being 1 stratification factor.

Conclusions

In the randomized clinical trial monarchE, treatment with abemaciclib combined with ET demonstrated a clinically meaningful improvement in IDFS and DRFS rates for patients with HR^+, $ERBB2^-$, node-positive, high-risk early breast cancer who received NAC. To our knowledge, abemaciclib is the first agent added to standard adjuvant ET that has been shown to reduce the risk of recurrence in patients with HR^+, $ERBB2^-$, early breast cancer with residual disease after NAC, and the efficacy was maintained regardless of residual tumor or nodal burden.

Notes

Supplement 1.

Trial protocol

Supplement 2.

Statistical analysis plan

Supplement 3.

eFigure 1. CONSORT Diagram in the ITT population

eTable 1. Patient Demographics and Disease Characteristics

eTable 2. Tumor characteristics and demographics by treatment arm in patients that received NAC

eTable 3. TEAEs in patients who received NAC

Supplement 4.

Data sharing statement

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Figures and Tables

Figure.

Kaplan-Meier Curves of Invasive Disease-Free Survival (IDFS)/Distant Relapse-Free Survival (DRFS) in Patients Who Received Neoadjuvant Chemotherapy (NAC)

Kaplan-Meier curves of IDFS (A), DRFS (B), and IDFS/DRFS (inset) to better visualize separation of the curves in patients who received NAC. The inset tables present the number of events per arm, unstratified hazard ratio (HR) in the NAC subgroup, and the 2-year rates in each arm (blue dotted lines). ET indicates endocrine therapy.

Table.

IDFS and DRFS Based on Tumor Size in Patients Who Received NAC

Characteristic	IDFS			DRFS		
	Abemaciclib + ET	ET alone	HR (95% CI)	Abemaciclib + ET	ET alone	HR (95% CI)
Residual pathological tumor size at surgery (post NAC)						
≤2 cm	NA	NA	0.56 (0.34-0.90)	NA	NA	0.48 (0.28-0.83)
Patients, No.	405	413	NA	405	413	NA
Events, No.	26	46	NA	19	39	NA
2-Year rates	91.4	82.2	NA	93.7	84.4	NA
>2 cm	NA	NA	0.61 (0.44-0.84)	NA	NA	0.64 (0.45-0.90)
Patients, No.	569	575	NA	569	575	NA
Events, No.	59	97	NA	52	82	NA
2-Year rates	85	79	NA	87.4	81.2	NA
No. of positive nodes assessed at surgery (post NAC)[a]						
1-3	NA	NA	0.73 (0.43-1.23)	NA	NA	0.76 (0.44-1.33)
Patients, No.	334	340	NA	334	340	NA
Events, No.	24	33	NA	22	29	NA
2-Year rates	90.8	87.6	NA	92.1	89	NA
≥4	NA	NA	0.57 (0.41-0.81)	NA	NA	0.57 (0.39-0.83)
Patients, No.	521	516	NA	521	516	NA
Events, No.	51	87	NA	42	73	NA
2-Year rates	85.1	77.2	NA	87.7	79.7	NA

Abbreviations: DRFS, distant relapse-free survival; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; NA, not applicable; NAC, neoadjuvant chemotherapy.

[a] Lymph node information after surgery was not available for all patients.