Received: 5 July 2022 | Revised: 12 September 2022 | Accepted: 14 September 2022

DOI: 10.1111/cas.15600

ORIGINAL ARTICLE

Cancer Science WILEY

Abemaciclib plus fulvestrant in East Asian women with HR+, HER2− advanced breast cancer: Overall survival from MONARCH 2

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Funding information
Eli Lilly and Company

Abstract

MONARCH 2 is a global, randomized, double-blind, phase 3 study of abemaciclib/placebo + fulvestrant in patients with hormone receptor positive, human epidermal growth factor receptor 2-negative advanced breast cancer. The East Asian population comprised 212 (31.7%) of the 669 intent-to-treat population in the MONARCH 2 trial. Consistent with the primary analysis, this subpopulation analysis of East Asian patients indicated progression-free survival benefit in the abemaciclib arm. The median overall survival was not reached in the abemaciclib arm and was 48.9 months in the placebo arm (hazard ratio 0.80; 95% confidence interval 0.52–1.24; $p = 0.377$). In addition, other efficacy endpoints, including time to chemotherapy, chemotherapy free survival, and time to second disease progression, indicated benefit in the abemaciclib arm. This analysis found no new safety concerns with longer follow-up. These findings support the positive benefit–risk balance of the MONARCH 2 regimen in East Asian patients with hormone receptor positive, human epidermal growth factor receptor 2-negative advanced breast cancer.

KEYWORDS
abemaciclib, breast cancer, cyclin-dependent kinase inhibitor, East Asia, metastatic

1 | INTRODUCTION

Abemaciclib is a small molecule, selective inhibitor of CDK4 & 6 and is approved in combination with fulvestrant for women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2−) advanced breast cancer (ABC) with disease progression following endocrine therapy (ET), in combination with an aromatase inhibitor as first-line ET in postmenopausal women with HR+, HER2− ABC and with adjuvant ET for patients with HR+, HER2−, high-risk early breast cancer.[1]

Abbreviations: ABC, advanced breast cancer; AE, adverse event; CBR, clinical benefit rate; CDK4 & 6, cyclin-dependent kinase 4 & 6; CFS, chemotherapy-free survival; CI, confidence interval; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; ILD, interstitial lung disease; ITT, intent-to-treat; mOS, median OS; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, time to second disease progression; TTC, time to chemotherapy; VTE, venous thromboembolism.

Trial registration: ClinicalTrials.gov, NCT02107703.

The approval of abemaciclib in combination with fulvestrant was based on positive progression-free survival (PFS) data from MONARCH 2. At the primary cutoff date of February 14, 2017, abemaciclib plus fulvestrant significantly extended PFS versus fulvestrant alone (median, 16.4 vs. 9.3 months; hazard ratio [HR], 0.553; 95% CI, 0.449 to 0.681; $p < 0.001$).[2] In a subgroup analysis of the East Asian patients (Japan, Korea, and Taiwan), consistent with the intent-to-treat (ITT) population, PFS benefit was observed in East Asian patients with a median PFS of 21.2 months for abemaciclib plus fulvestrant and 11.6 months for placebo plus fulvestrant (HR 0.52; 95% CI 0.36–0.75; $p < 0.001$).[3]

Later, based on data from the prespecified interim overall survival (OS) database lock, June 20, 2019, the combination also showed significantly improved OS in the ITT population of MONARCH 2 (46.7 months vs. 37.3 months, HR 0.76; 95% CI 0.61–0.95; $p = 0.01$).[4] In this report, we provide OS results for East Asian patients in the MONARCH 2 trial with additional data, including updated PFS, safety, and post-discontinuation therapy.

2 | METHODS

2.1 | Study design and treatment

The study design, procedures, and statistical methods for MONARCH 2 have been previously published in detail.[2] MONARCH 2 (NCT02107703) is a global, randomized, double-blind, phase III trial in women with HR+, HER2− ABC who progressed on ET. Patients received fulvestrant with either abemaciclib or placebo. Each center's institutional review board or independent ethics committee approved the trial. The study followed the guiding principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization. All patients provided written informed consent before enrolment.

2.2 | Study endpoints

The primary endpoint of MONARCH 2 was investigator-assessed PFS.[2] Key secondary endpoints previously reported for the ITT population include OS, overall response rate (ORR), clinical benefit rate (CBR), and safety and tolerability.[2,4] A subgroup analysis of the East Asian population of the trial previously reported PFS, ORR, CBR, safety, and pharmacokinetics.[5] In the present report, we provide OS, updated PFS, exploratory endpoints of the trial (including time to chemotherapy [TTC], chemotherapy-free survival [CFS], and time to second disease progression [PFS2]), and safety data in the East Asian subgroup.

2.3 | Statistical analysis

Detailed statistical methods have been previously published.[2,3] The East Asian population used for this subgroup analysis was defined by patients who were enrolled at sites in Japan, Korea, and Taiwan. The data are from the prespecified interim OS database lock from MONARCH 2, June 20, 2019. Efficacy endpoints were analyzed using Kaplan–Meier estimates and unstratified Cox proportional hazards models. All analyses are descriptive in nature, and quoted *p*-values were nominal.

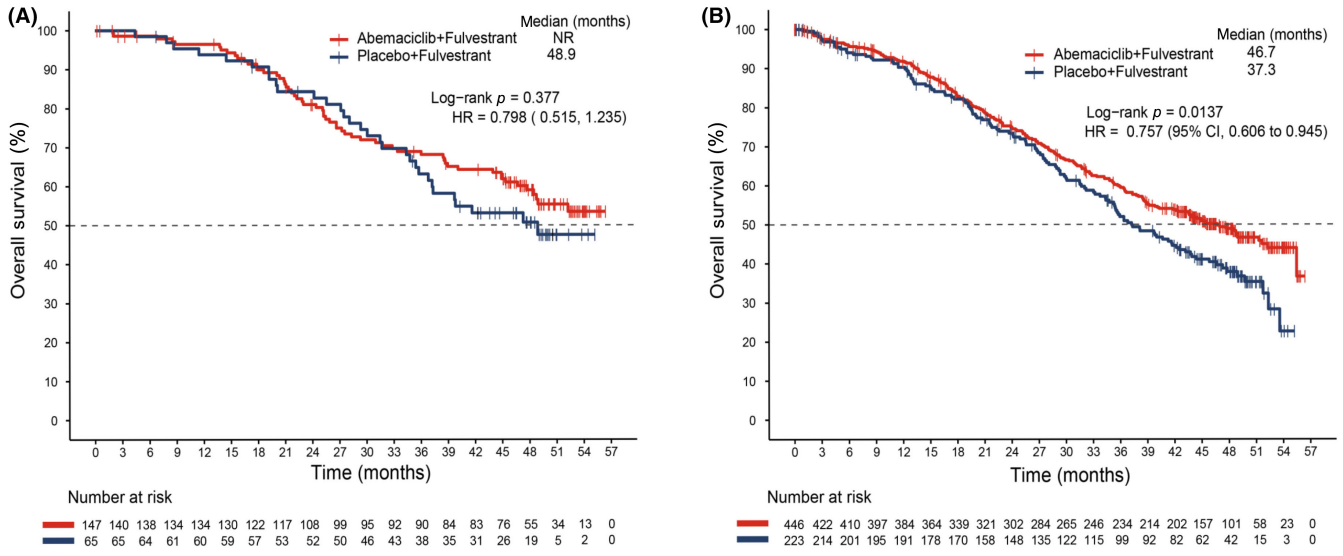


FIGURE 1 (A) Kaplan–Meier curve of overall survival (OS) in the East Asian population. Median OS (mOS) was not reached in the abemaciclib arm versus 48.9 months in the placebo arm. (B) In the ITT population, mOS was 46.7 months versus 37.3 months in the abemaciclib versus placebo arms. HR, hazard ratio; NR, not reached

3 | RESULTS

3.1 | Patients

Baseline characteristics of the East Asian and ITT populations of MONARCH 2 were previously reported.[2,3] A total of 669 patients were in the ITT population of the MONARCH 2 trial, of whom 212 (31.7%) were enrolled in East Asian countries and were randomly assigned to either abemaciclib plus fulvestrant (n = 147; 69.3%) or placebo plus fulvestrant (n = 65; 30.7%). At data cutoff, 35 (23.8%) and 2 (3.1%) patients in the abemaciclib arm and placebo arm, respectively, of the East Asian population were still on treatment. As the stratification at randomization was applied to the overall ITT population, patient baseline characteristics in the East Asian population were not completely balanced by treatment arm. Notably, 91 patients (61.9%) in the abemaciclib arm had visceral disease compared with 32 (49.2%) in the placebo arm.

3.2 | Overall survival

At the time of data cutoff, 89 deaths had occurred among 212 patients (abemaciclib arm, n = 58; placebo arm, n = 31) in the

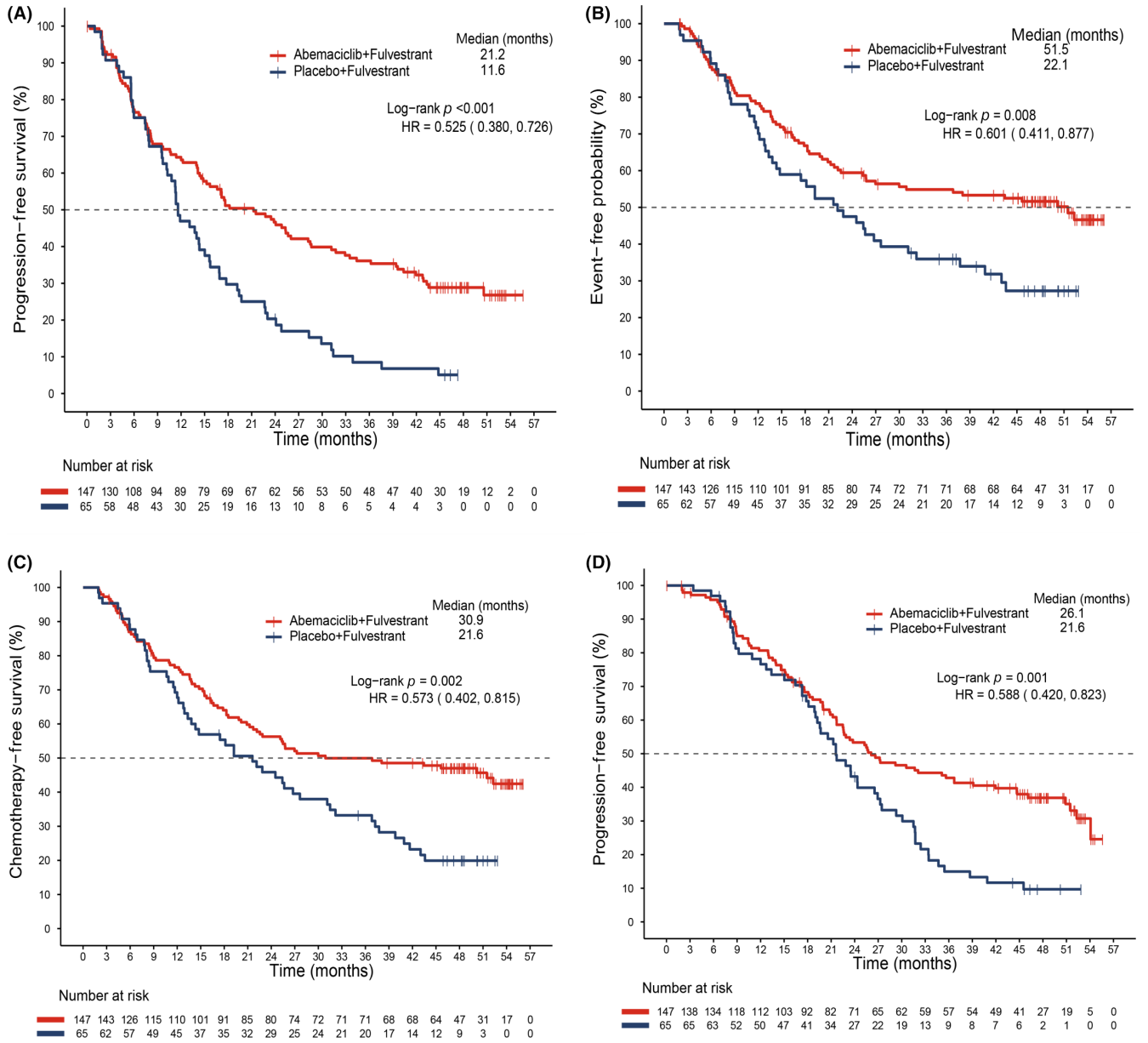


FIGURE 2 Kaplan–Meier curves of progression-free survival (PFS) and exploratory endpoints in the East Asian population. (A) Updated PFS. (B) Time to chemotherapy (censoring patients who died prior to receiving chemotherapy). (C) Chemotherapy-free survival (including both initiation of first post-discontinuation chemotherapy and death as events). (D) Time to second disease progression, defined as time from randomization to discontinuation of first subsequent post-discontinuation therapy or death (whichever is earlier). HR, hazard ratio

East Asian population. Median follow-up time was 49.6 months. Median OS (mOS) was not reached (NR) for patients receiving abemaciclib and was 48.9 months (HR 0.798; 95% CI 0.515–1.235; $p = 0.377$) for patients receiving placebo (Figure 1A).

3.3 | Updated progression-free survival

Consistent with the subgroup analysis of the East Asian population at primary cutoff, this analysis continues to show an improved PFS with the addition of abemaciclib to fulvestrant. Median PFS was 21.2 months in the abemaciclib arm and 11.6 months in the placebo arm (HR 0.525; 95% CI 0.380–0.726; $p < 0.001$) (Figure 2A).

3.4 | Exploratory endpoints

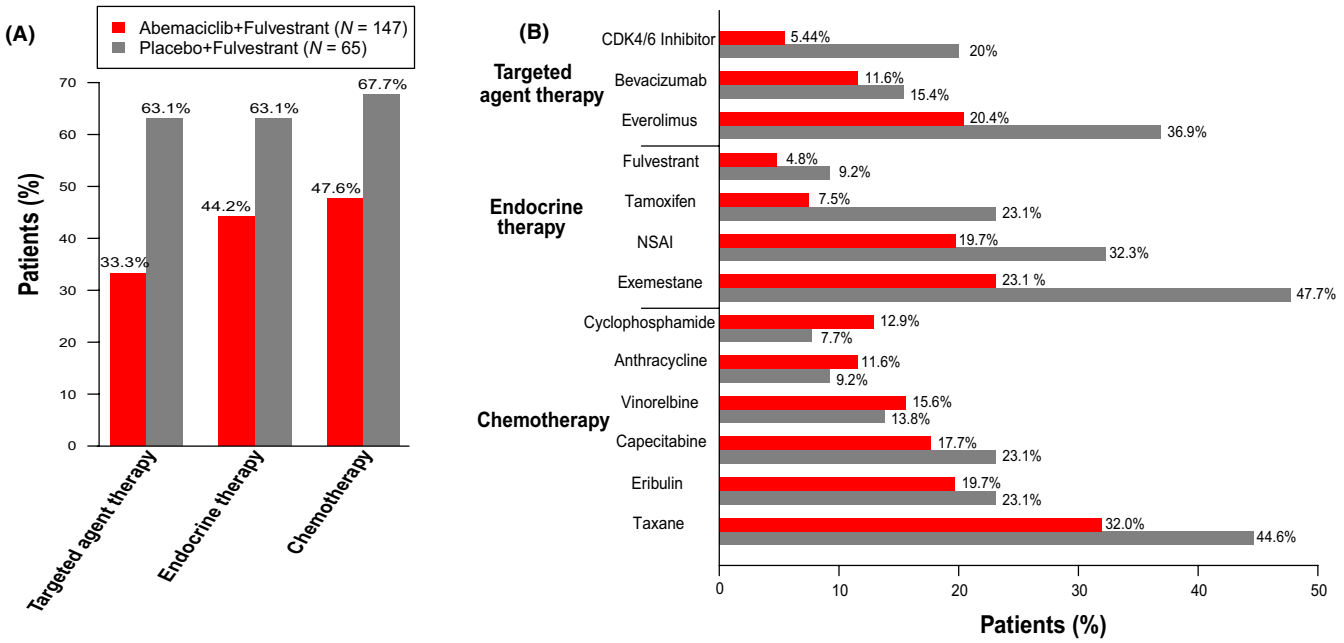
Time to chemotherapy, CFS, and PFS2 were all significantly prolonged with the addition of abemaciclib to fulvestrant (Figure 2B–D).

3.5 | Post-discontinuation therapy

A summary of post-discontinuation therapies administered is depicted in Figure 3A–C. Ninety-five (64.6%) East Asian patients in the abemaciclib arm and 59 (90.8%) in the placebo arm received any post-discontinuation therapy (Figure 3C). Of the 154 East Asian patients who received any post-discontinuation therapy, the first subsequent therapy was chemotherapy for 71 patients (46.1%), ET for 48 patients (31.2%), everolimus-based therapy for 23 patients (14.9%), and CDK4 & 6 inhibitor therapy for 7 patients (4.5%), with minimal differences between the treatment arms (Figure 3C) and slight changes compared with the ITT population (45.3%, 25.8%, 17.4%, and 6.7% respectively).

3.6 | Safety

No new safety signals were observed in the East Asian population compared to the previous report despite longer exposure to abemaciclib. The median duration of abemaciclib treatment was 66.2 weeks



(C)

First Subsequent Line of Post-Discontinuation Therapy	Abemaciclib+Fulvestrant (*n* = 95)	Placebo+Fulvestrant (*n* = 59)
Chemotherapy	45 (47.4)	26 (44.1)
Endocrine therapy	27 (28.4)	21 (35.6)
Everolimus-based therapy	14 (14.7)	9 (15.3)
CDK 4 & 6 inhibitor	5 (5.3)	2 (3.4)
Bevacizumab	4 (4.2)	1 (1.7)

FIGURE 3 Post-discontinuation therapy. (A) The most common subsequent systemic therapies used in the East Asian population. (B) The most common subsequent regimens. Percentages for panels A and B were calculated using number patients receiving each therapy out of the number of randomized patients in each treatment arm. (C) Summary of first line of post-discontinuation therapy. Subsequent systemic therapies were received by 95 (64.6%) patients in the abemaciclib arm and 59 (90.8%) in the placebo arm. Percentages for panel (C) were calculated using the number of patients receiving each therapy out of the number of patients who received post-discontinuation therapy in each treatment arm. *N*, number of patients

(range 0.1–237.0 weeks). At data cutoff, a total of 9 (6.1%) and 2 (3.1%) patients in the abemaciclib and placebo arms, respectively, discontinued any study drug due to an adverse event (AE). A higher incidence of grade ≥3 AEs and serious AEs was observed in those who received abemaciclib versus placebo (69.9% vs. 24.6% and 26.0% vs. 12.3%, respectively). No new deaths due to AE were reported after the primary subgroup analysis. Diarrhea of any grade was the most frequent AE in the abemaciclib arm (90.4%), with 16.4% Grade ≥3 (Table 1). Neutropenia was the most frequently reported Grade ≥3 AE in the abemaciclib arm (48.6%), although there were only 2 cases of febrile neutropenia (both Grade 3). As previously reported, ALT/AST increase was observed at a higher rate in the East Asian population compared with the ITT safety population, although no patients developed drug-induced liver injury (no patients fulfilled Hy's law criteria).[2,3,5] Interstitial lung disease (ILD) was reported in 4 patients (2.7%; all Grade ≤ 2) who received abemaciclib; of these, 2 were reported after the primary subgroup analysis. The rate is comparable to the ITT safety population, where 12 patients (2.7%) reported ILD (Grade ≤ 2, 2.0%; Grade ≥ 3, 0.7%). There were no new cases of venous thromboembolism (VTE) after the primary subgroup analysis (any grade 3.4%; Grade ≥ 3, 2.1%). The rates were lower than those observed in the ITT safety population of MONARCH 2, where 29 (6.6%) patients experienced VTE (any grade 6.6%; Grade ≥ 3, 2.9%).

4 | DISCUSSION

A significant OS benefit was observed in the abemacicilb arm of the ITT population. The current descriptive analysis further confirms the efficacy and safety of abemaciclib in East Asian women with HR+, HER2− ABC. This study of the East Asian subpopulation indicated a numerical OS benefit, consistent with the statistically significant OS improvement demonstrated in the ITT population, despite the higher percentage of East Asian patients with visceral disease in the abemaciclib arm. Additional efficacy analyses, including updated PFS, TTC, CSF, and PFS2, exhibit consistency with the ITT population in showing the benefit of adding abemaciclib to ET. There was no obvious difference between the study arms regarding the frequency of post-discontinuation treatment. Considering the higher number of patients still on treatment in the abemaciclib arm, the number of patients who received any post-discontinuation therapies appeared to be balanced across the two treatment arms. Irrespective of treatment, numerically longer OS and PFS were observed in the East Asian population compared with the ITT population, possibly due to differences in patient characteristics, most notably the higher percentage of patients with good performance status in the East Asian population.[4] Despite the extended follow-up in this analysis, no new

TABLE 1 Treatment-emergent adverse events in safety population and East Asian patients of MONARCH 2

	Safety population				East Asian population			
	Abemaciclib + Fulvestrant		Placebo + Fulvestrant		Abemaciclib + Fulvestrant		Placebo + Fulvestrant	
	n = 441		*n* = 223		*n* = 146		*n* = 65	
≥25% in either arm	All	≥G3	All	≥G3	All	≥G3	All	≥G3
Any, *n* (%)	435 (98.6)	300 (68.0)	203 (91.0)	62 (27.8)	144 (98.6)	102 (69.9)	62 (95.4)	16 (24.6)
Diarrhea	384 (87.1)	64 (14.5)	62 (27.8)	1 (0.4)	132 (90.4)	24 (16.4)	16 (24.6)	1 (1.5)
Neutropenia[a]	219 (49.7)	132 (29.9)	9 (4.0)	4 (1.8)	103 (70.5)	71 (48.6)	3 (4.6)	2 (3.1)
Leukopenia	146 (33.1)	49 (11.1)	4 (1.8)	0 (0.0)	65 (44.5)	23 (15.8)	2 (3.1)	0 (0.0)
Anemia	153 (34.7)	40 (9.1)	10 (4.5)	3 (1.3)	62 (42.5)	21 (14.4)	5 (7.7)	3 (4.6)
Nausea	217 (49.2)	12 (2.7)	56 (25.1)	5 (2.2)	59 (40.4)	3 (2.1)	12 (18.5)	1 (1.5)
Abdominal pain	164 (37.2)	14 (3.2)	37 (16.6)	2 (0.9)	47 (32.2)	2 (1.4)	11 (16.9)	0 (0.0)
Decreased appetite	127 (28.8)	5 (1.1)	30 (13.5)	2 (0.9)	45 (30.8)	4 (2.7)	10 (15.4)	0 (0.0)
Alanine aminotransferase increase	70 (15.9)	20 (4.5)	12 (5.4)	4 (1.8)	41 (28.1)	12 (8.2)	2 (3.1)	0 (0.0)
Headache	106 (24.0)	3 (0.7)	36 (16.1)	1 (0.4)	39 (26.7)	1 (0.7)	11 (16.9)	0 (0.0)
Stomatitis	77 (17.5)	2 (0.5)	24 (10.8)	0 (0.0)	39 (26.7)	1 (0.7)	10 (15.4)	0 (0.0)
Vomiting	127 (28.8)	4 (0.9)	26 (11.7)	5 (2.2)	39 (26.7)	2 (1.4)	7 (10.8)	0 (0.0)
Aspartate aminotransferase increase	69 (15.6)	12 (2.7)	16 (7.2)	7 (3.1)	38 (26.0)	8 (5.5)	3 (4.6)	1 (1.5)
Thrombocytopenia	77 (17.5)	15 (3.4)	6 (2.7)	1 (0.4)	37 (25.3)	12 (8.2)	2 (3.1)	1 (1.5)
Constipation	70 (15.9)	3 (0.7)	36 (16.1)	1 (0.4)	20 (13.7)	1 (0.7)	12 (18.5)	0 (0.0)

Note: Includes TEAEs reported in ≥25% of patients in any group within East Asian patients.

ITT, intent-to-treat; TEAEs, treatment-emergent adverse events.

[a]Two (1.4%) cases of febrile neutropenia (both Grade 3) in the East Asian abemaciclib arm.

safety signals emerged in the East Asian population compared to the previous analyses.[2,3]

In conclusion, the survival benefit and the lower risk of death in the abemaciclib group indicated the clinical benefit of the regimen in East Asian patients with HR+, HER2− ABC. Safety data with longer follow-up align with the generally tolerable and manageable safety profile for abemaciclib.

ACKNOWLEDGMENTS

We thank the patients and their caregivers for their participation in this study, the study investigators and their staff, and the clinical trial team. We thank Dr Antonio Llombart for his contributions to the trial. We would also like to acknowledge Declan O'Dea of Eli Lilly and Company for scientific communication expertise.

FUNDING INFORMATION

Funded by Eli Lilly and Company.

DISCLOSURE

S. Sakaguchi, N. Haddad, and G. van Hal are full-time employees of Eli Lilly and Company. W. Zhang was a full-time employee of Eli Lilly and Company at the time of this work. M. Toi has received honoraria for speaker's bureaus from Eli Lilly and Company and grants or funding from Astellas, Taiho, AstraZeneca, Kyowa-Kirin, Shimadzu, JBCRG assoc., AFI Technology, Yakult, Luxonus, GL Science, KBCRN assoc., Eisai, Nippon-Kayaku, and Chugai. M. Toi is assigned to the editorial board of *Cancer Science*. C-S Huang has received funding from Eli Lilly and Company, Pfizer, Novartis, Roche, AstraZeneca, EirGenix, OBI Pharma, MSD, and Daiichi Sankyo. J. Sohn received funding from MSD, Roche, Novartis, AstraZeneca, Eli Lilly and Company, Pfizer, GSK, Daiichi Sankyo, Sanofi, and Boehringer Ingelheim. G. W. Sledge received grants from Pfizer and Eli Lilly and Company, fees from Verseau Inc., Syndax, and Caris Life Sciences for consulting or advisory board membership, and is on the board of directors for Tessa Therapeutics. Y-H. Im has no conflicts of interest to declare. Approval of the research protocol: Each center's institutional review board or independent ethics committee approved the trial. All patients provided written informed consent before enrolment.

DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and the EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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How to cite this article: Toi M, Huang C-S, Im Y-H, et al. Abemaciclib plus fulvestrant in East Asian women with HR+, HER2− advanced breast cancer: Overall survival from MONARCH 2. *Cancer Sci*. 2023;114:221-226. doi: 10.1111/cas.15600