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

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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.

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

CONTEXT

Key Objective

Does adding a CDK4/6 inhibitor to endocrine therapy (ET) in the adjuvant setting provide additional benefit for patients with HR+, HER2− early breast cancer (EBC)? monarchE is a global, randomized, phase III trial that evaluated the combination of the CDK4/6 inhibitor abemaciclib and standard ET among 5,637 randomly assigned patients with HR+, HER2−, node-positive EBC at high risk of early recurrence.

Knowledge Generated

The results showed that abemaciclib added to ET significantly improved invasive disease-free survival (IDFS) in patients with high-risk EBC in the adjuvant setting. There was a 25% reduction in the risk of developing an IDFS event relative to ET alone and a 3.5% absolute improvement in 2-year IDFS rates (92.2% v 88.7%). Safety was consistent with the known safety profile of abemaciclib.

Relevance

If approved, abemaciclib added to standard adjuvant ET could become a new standard of care for patients with HR+, HER2− high-risk EBC.

nonsteroidal AIs.[9,10] As such, exploration of the combination of abemaciclib with ET is warranted in the adjuvant setting.

monarchE is an open-label, global, randomized, phase III trial that investigated the addition of abemaciclib to standard adjuvant ET in patients with HR+, HER2−, node-positive, high-risk EBC. The design of monarchE was motivated by large clinical datasets in EBC, which all noted a subset of HR+, HER2− patients with high-risk clinical features and/or highly proliferative disease that were likely to experience recurrence quickly.[6,11-13] The goal in monarchE was to treat the patients with primary endocrine-resistant disease who were likely to experience recurrence earlier in the course of their disease, especially in the first 5 years. This report describes the first results from monarchE following a preplanned interim analysis.

METHODS

Trial Oversight

This study was funded by the sponsor (Eli Lilly) and designed together with members of the study Executive Committee. The study was performed in compliance with the Declaration of Helsinki. The study protocol and all amendments received approval from ethical/institutional review boards before implementation, and all patients gave written informed consent. All authors contributed to the writing and review of the manuscript and were involved in the interpretation of the data. Executive and Global Steering Committees provided oversight of the conduct of the trial, and an independent data monitoring committee reviewed the safety data approximately every 6 months and efficacy data at prespecified interim analyses. Although this was an open-label study, the sponsor and all investigative sites remained blinded to treatment group assignments for

aggregate data until the study was confirmed as positive. A complete list of all committee members and investigators is available in the Data Supplement (online only).

Patients

Female (any menopausal status) and male patients ≥ 18 years of age with HR+[14] and HER2−[15] disease were eligible. High risk was defined as patients with four or more positive pathologic axillary lymph nodes or one to three positive axillary lymph nodes and at least one of the following: tumor size ≥ 5 cm, histologic grade 3, or centrally assessed Ki-67 ≥ 20% (please refer to the Data Supplement, online only, for details on Ki-67 methodology).

Patients may have received up to 12 weeks of ET after the last non-ET before randomization and must have been randomly assigned within 16 months of definitive breast cancer surgery.

Radiotherapy and both adjuvant and neoadjuvant chemotherapy were allowed, but not required. Patients with occult breast cancer, metastatic disease, or node-negative breast cancer, and, after a protocol amendment, patients with inflammatory breast cancer, were excluded. Patients who had received treatment with ET for breast cancer prevention, raloxifene, and/or a CDK4/6 inhibitor, and those with a history of venous thromboembolic events (VTEs) were also excluded.

An interactive Web response system was used to randomly assign patients (1:1) to receive either abemaciclib (150 mg twice daily on a continuous dosing schedule) plus ET or ET alone. Stratification factors included previous chemotherapy (neoadjuvant, adjuvant, or none), menopausal status (as determined at the time of breast cancer diagnosis), and region (North America/Europe, Asia, or other). Patients were treated for 2 years (treatment period) or until meeting criteria for discontinuation. After the treatment period, all

patients continued ET for 5 to 10 years, as clinically indicated (Data Supplement). The 2-year treatment duration was chosen based on historical studies indicating recurrence events first peaked at 2 years for patients with EBC.[16] Post-discontinuation treatment was at the discretion of the investigator. Crossover was not permitted at any time.

Trial Procedures

Visits occurred every 2 weeks for the first 2 months, monthly from months 3-6, and then every 3 months until the end of year 2. Thereafter, visits were every 6 months until year 5 and then annually from years 6-10.

All randomly assigned patients were followed for local/regional and distant recurrence and OS. At each visit, patients were assessed by a medically qualified individual for adverse events (AEs) and any signs or symptoms of recurrence. At clinic visits, central chemistry and hematology laboratories were drawn, performance status was assessed, and physical examinations were conducted. Tests to confirm recurrence after detection of signs or symptoms were performed at the discretion of the treating medically qualified individual.

Statistical Analysis

The primary end point was invasive disease-free survival (IDFS) per the Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials (STEEP) criteria[17] and was measured from the date of randomization to the date of first occurrence of ipsilateral invasive breast tumor recurrence, local/regional invasive breast cancer recurrence, distant recurrence, death attributable to any cause, contralateral invasive breast cancer, or second primary nonbreast invasive cancer. Confirmation by biopsy or imaging was required, when possible. All patients who experienced local recurrence continued to be followed for distant recurrence. Distant relapse–free survival (DRFS), a secondary end point, was defined as the time from randomization to distant recurrence or death from any cause, whichever occurred first. Patients for whom no event was observed were censored on the day of their last assessment for recurrence or date of randomization if no post-baseline assessment for recurrence occurred. Other secondary end points included OS, safety, pharmacokinetics (PK), and patient-reported outcomes (PROs). PK and PRO data will be reported separately.

The study was powered at approximately 85% to detect the superiority of abemaciclib plus ET versus ET in terms of IDFS, assuming a hazard ratio (HR) of 0.73 at a cumulative two-sided α level of .05, with a 5-year IDFS rate of 82.5% in the control arm for this high-risk population.[6,12,13] This required approximately 390 IDFS events in the intent-to-treat (ITT) population at the time of the primary analysis. There were two planned efficacy interim analyses at approximately 50% and 75% of the total required events. The overall type I error for the preplanned interim analyses and primary analysis was maintained using the Lan-DeMets method with an O'Brien-Fleming stopping boundary.

Efficacy analyses were performed on the ITT population. The primary objective was to test the superiority of abemaciclib plus ET versus ET on IDFS using a log-rank test stratified by randomization factors. A stratified Cox proportional hazard model with treatment arm as a variable was used to estimate the HR and the corresponding 95% CI. The Kaplan-Meier method was used to estimate the 2-year IDFS rates in each treatment arm. Similar analyses were performed on DRFS, but there was no α control for statistical significance on this end point. All reported P values are two-sided.

Subgroup analyses of IDFS in the ITT population were performed for potential prognostic subgroup variables prespecified in the statistical analysis plan, including stratification factors and some clinicopathological features. HR estimates were reported within each subgroup, with P values for interaction tests across subgroups.

Safety was analyzed in all randomly assigned patients who received at least one dose of study treatment (defined as either abemaciclib or ET after randomization). Investigator-reported terms were mapped to MedDRA terms, and AEs were graded according to Common Terminology Criteria Adverse Events v4.0. Please refer to the protocol, included in the Data Supplement, for additional details on statistical methods and analyses.

RESULTS

Patients and Treatment

From July 2017 to August 2019, 5,637 patients from 603 sites in 38 countries were randomly assigned 1:1 to receive either abemaciclib plus ET or ET alone (Fig 1). Baseline characteristics were balanced between study arms (Table 1). The population had a median age of 51.0 years (12.6% patients < 40 years) and was predominantly female (99.4%), and postmenopausal (56.5%) at the time of diagnosis. Nearly 60% of patients were eligible on the basis of four or more nodes. Details on the specific high-risk clinical and/or pathologic feature(s) that made patients eligible are described in the Data Supplement. A total of 95.4% of patients had received radiotherapy, and 95.4% of patients had received prior chemotherapy (37.0% neoadjuvant, 58.3% adjuvant, 3.5% received both, and all patients who received both were counted in the neoadjuvant total). AIs were prescribed as the first ET on study treatment in 68.3% of patients (including 14.2% treated with AI plus ovarian function suppression), and tamoxifen in 31.4% (including 7.6% treated with tamoxifen plus ovarian function suppression; Table 1).

At the time of the data cutoff (March 16, 2020), 707 (12.5%) patients had completed the 2-year treatment period, and 4,101 (72.8%) patients were still in the 2-year treatment period. Median follow-up time was approximately 15.5 months in both arms.
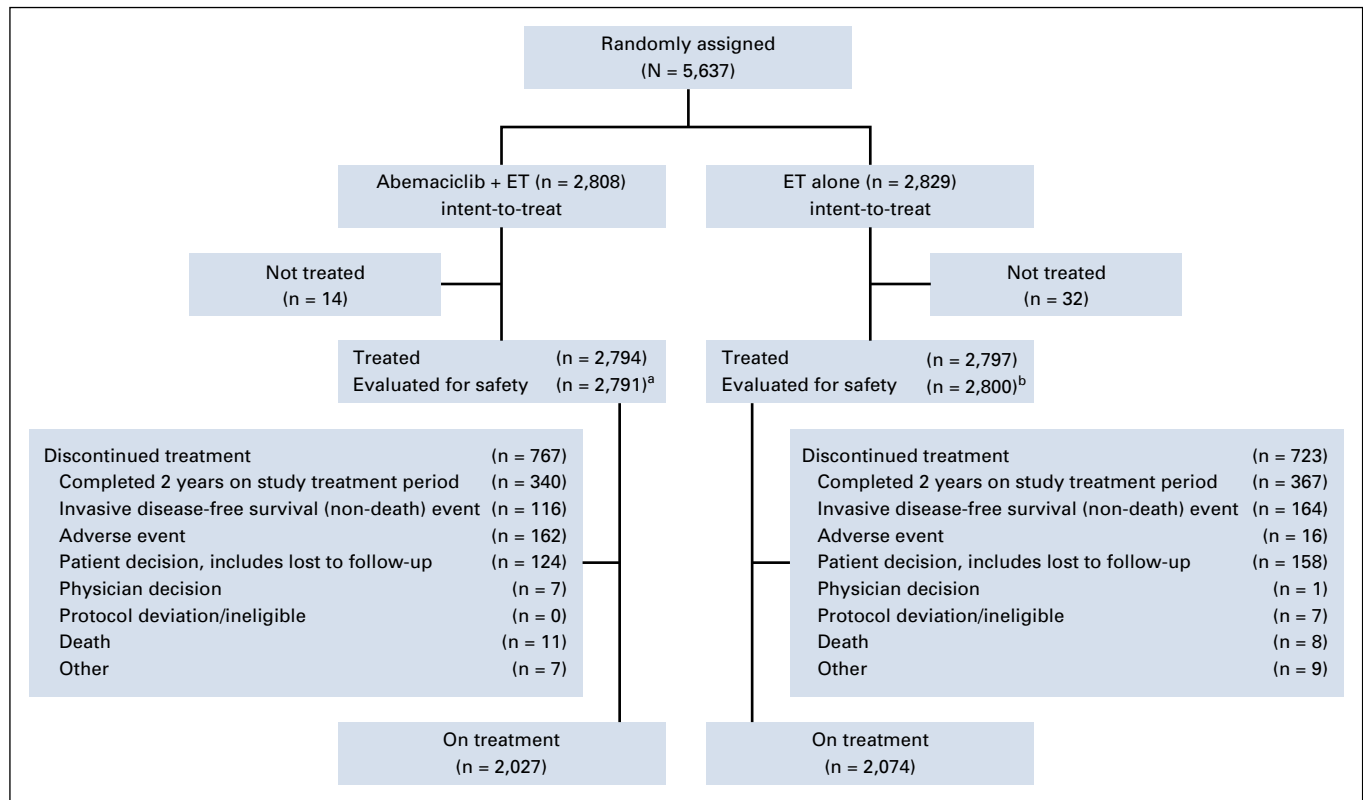
FIG 1. CONSORT diagram. (ᵃ) Four patients randomly assigned to the abemaciclib arm only received endocrine therapy (ET) and were evaluated for safety in the control arm. (ᵇ) One patient randomly assigned to the control arm received abemaciclib and was evaluated for safety in the abemaciclib arm.

Efficacy

With a total of 323 IDFS events observed at the second efficacy interim analysis, the two-sided *P* value boundary for positive efficacy was .026. At the time of data cutoff, there were 136 (4.8%) IDFS events in the abemaciclib arm and 187 (6.6%) in the control arm. Abemaciclib plus ET demonstrated a statistically significant improvement in IDFS versus ET alone (*P* = .01; HR, 0.75; 95% CI, 0.60 to 0.93), with 2-year IDFS rates of 92.2% (abemaciclib arm) versus 88.7% (control arm; Fig 2). Most IDFS events were distant recurrences (87 in the abemaciclib arm and 138 in the control arm; Table 2). The addition of abemaciclib to ET also resulted in an improvement in DRFS compared with ET alone (nominal *P* = .01; HR, 0.72; 95% CI, 0.56 to 0.92), with 2-year DRFS rates of 93.6% (abemaciclib arm) and 90.3% (control arm; Fig 3A). Common sites of distant recurrence were bone, liver, and lung (Table 2). HRs within prespecified subgroups are presented in Figure 2B (IDFS) and Figure 3B (DRFS).

OS data were immature, with 39 (1.4%) deaths observed in the abemaciclib arm and 37 (1.3%) observed in the control arm. The study will continue to a final analysis of OS.

Safety

A total of 5,591 patients (2,791 in the abemaciclib arm and 2,800 in the control arm) were included in the safety analysis. The median duration of ET was approximately 15 months in each arm. The median duration of abemaciclib was 14 months. Abemaciclib dose adjustments due to AEs occurred in 1,901 patients (68.1%), with 56.9% having dose omissions and 41.2% having reductions. In the abemaciclib arm, 463 patients (16.6%) discontinued abemaciclib because of AEs, of whom 306 remained on ET when abemaciclib was discontinued. A total of 172 patients (6.2%) discontinued both treatments (157 at the same time) because of AEs. In the control arm, 21 patients (0.8%) discontinued ET because of AEs.

A total of 5,141 patients experienced at least one treatment-emergent AE (97.9% in the abemaciclib arm and 86.1% in control arm). The most frequent AEs were diarrhea, neutropenia, and fatigue in the abemaciclib arm and arthralgia, hot flush, and fatigue in the control arm (Table 3). VTEs were reported in 2.3% of patients in the abemaciclib arm and 0.5% in the control arm (pulmonary embolism, 0.9% *v* 0.1%). Details on VTEs are in the Data Supplement. Interstitial lung disease (ILD) occurred in 2.7% of patients in the abemaciclib arm (0.3% grade 3) and 1.2% of patients in the control arm (one patient with grade 3; Table 3).

Grade ≥ 3 AEs occurred in 45.9% of patients in the abemaciclib arm and 12.9% of patients in the control arm. Serious adverse events (SAEs) occurred in 12.3% of patients in the abemaciclib arm and 7.2% of patients in the

TABLE 1. Baseline Characteristics

Category	Abemaciclib + ET (n = 2,808)	ET Alone (n = 2,829)
Age, median years (range)	51 (23-89)	51 (22-86)
< 65	2,371 (84.4)	2,416 (85.4)
≥ 65	437 (15.6)	413 (14.6)
Female	2,787 (99.3)	2,814 (99.5)
Male	21 (0.7)	15 (0.5)
Hormone receptor status		
Estrogen receptor positive	2,782 (99.1)	2,807 (99.2)
Estrogen receptor negative	16 (0.6)	17 (0.6)
Progesterone receptor positive	2,421 (86.2)	2,453 (86.7)
Progesterone receptor negative	298 (10.6)	294 (10.4)
Menopausal status[a,b]		
Premenopausal	1,221 (43.5)	1,232 (43.5)
Postmenopausal	1,587 (56.5)	1,597 (56.5)
Prior chemotherapy[a]		
Neoadjuvant chemotherapy	1,039 (37.0)	1,048 (37.0)
Adjuvant chemotherapy	1,642 (58.5)	1,647 (58.2)
No chemotherapy	127 (4.5)	134 (4.7)
Region[a]		
North American/Europe	1,470 (52.4)	1,479 (52.3)
Asia	574 (20.4)	582 (20.6)
Other	764 (27.2)	768 (27.1)
Positive axillary lymph nodes		
0	7 (0.2)	7 (0.2)
1-3	1,119 (39.9)	1,143 (40.4)
≥ 4	1,680 (59.8)	1,679 (59.3)
Histopathological grade at diagnosis		
Grade 1	209 (7.4)	215 (7.6)
Grade 2	1,373 (48.9)	1,395 (49.3)
Grade 3	1,090 (38.8)	1,066 (37.7)
Grade cannot be assessed	126 (4.5)	140 (4.9)
Pathologic tumor size, cm		
< 2	780 (27.8)	765 (27.0)
2-5	1,369 (48.8)	1,419 (50.2)
≥ 5	610 (21.7)	612 (21.6)
Ki-67 index, %		
< 20	953 (33.9)	973 (34.4)
≥ 20	1,262 (44.9)	1,233 (43.6)
TNM stage (derived)		
IA	2 (0.1)	1 (0.0)
IIA	323 (11.5)	353 (12.5)
IIB	389 (13.9)	387 (13.7)
IIIA	1,027 (36.6)	1,024 (36.2)
IIIB	104 (3.7)	91 (3.2)
IIIC	950 (33.8)	962 (34.0)
(continued on following page)		

TABLE 1. Baseline Characteristics (continued)

Category	Abemaciclib + ET (n = 2,808)	ET Alone (n = 2,829)
Prior radiotherapy	2,680 (95.4)	2,700 (95.4)
Neoadjuvant	71 (2.5)	82 (2.9)
Adjuvant	2,620 (93.3)	2,628 (92.9)
Prior chemotherapy		
Neoadjuvant		
Taxane only	49 (1.7)	38 (1.3)
Anthracycline only	71 (2.5)	58 (2.1)
Taxane and anthracycline	904 (32.2)	931 (32.9)
Adjuvant		
Taxane only	168 (6.0)	152 (5.4)
Anthracycline only	80 (2.8)	85 (3.0)
Taxane and anthracycline	1,445 (51.5)	1,451 (51.3)

Category	Abemaciclib + ET (n = 2,791)	ET Alone (n = 2,800)
First on-study ET		
Tamoxifen	857 (30.7)	898 (32.1)
Plus ovarian suppression (any time)	192 (6.9)	232 (8.3)
Toremifene	6 (0.2)	11 (0.4)
Aromatase inhibitors	1,928 (69.1)	1,891 (67.5)
Plus ovarian suppression (any time)	410 (14.7)	386 (13.8)
Letrozole	1,092 (39.1)	1,046 (37.4)
Anastrozole	611 (21.9)	617 (22.0)
Exemestane	225 (8.1)	228 (8.1)
Ovarian suppression (any time)	606 (21.7)	627 (22.4)
Bone-modifying agents (any time)	387 (13.9)	443 (15.8)

NOTE. Data are presented as No. (%) unless otherwise noted. Where values do not add up to 100%, remaining data are missing, unavailable, or could not be assessed.

Abbreviation: ET, endocrine therapy.

[a]Per interactive web response system.

[b]Menopausal status is at the time of diagnosis, and all males are considered postmenopausal.

control arm, with the most frequently reported SAE in both arms being pneumonia (0.8% and 0.5%, respectively). Although the number of grade ≥ 3 AEs was higher in the abemaciclib arm, this did not translate into proportional increases in SAEs.

Deaths on study treatment or within 30 days of discontinuation were balanced between the arms, with 14 (0.5%) in each arm. In the abemaciclib arm, 11 were due to AEs (two, diarrhea and pneumonitis, considered possibly related to study treatment by the investigator) versus seven as a result of AEs in the control arm.

DISCUSSION

In this global, open-label, randomized phase III trial in patients with HR+, HER2−, node-positive, high-risk EBC, the addition of abemaciclib to standard adjuvant ET resulted in a statistically significant improvement in IDFS. All patients had primary breast surgery, and despite > 95% of patients having received prior chemotherapy and radiotherapy, the estimated 2-year IDFS rate in the monarchE control arm indicates that 11.3% of patients with high-risk clinicopathological features will develop an invasive disease event within 2 years. The addition of abemaciclib resulted in a 25% reduction in the risk of developing an IDFS event relative to ET alone and an absolute improvement of 3.5% in 2-year IDFS rates. This is a clinically meaningful result, and the treatment effect was observed in all prespecified subgroups. Of note, among the 43.5% of patients who were premenopausal at diagnosis, there was a significant 37% reduction in the risk of recurrence relative to ET alone. This is relevant because there have been very few treatment advances in adjuvant therapy for HR+, HER2− EBC for nearly 20 years.

Early recurrence within the first 2 years of adjuvant ET in HR+ breast cancer is known to represent primary endocrine resistance.[18] More than 75% of the early recurrences seen

A

Invasive Disease–Free Survival (%)

(Inset) Invasive Disease–Free Survival (%)

P = .01
HR (95% CI): 0.75 (0.60 to 0.93)

	No. Patients	No. Events
Abemaciclib + ET	2,808	136
ET alone	2,829	187

Time (months)[a]

No. at risk:

2,808	2,676	2,613	2,543	1,996	1,371	918	566	245	3	1	0
2,829	2,699	2,649	2,562	2,013	1,405	932	586	262	7	6	0

B

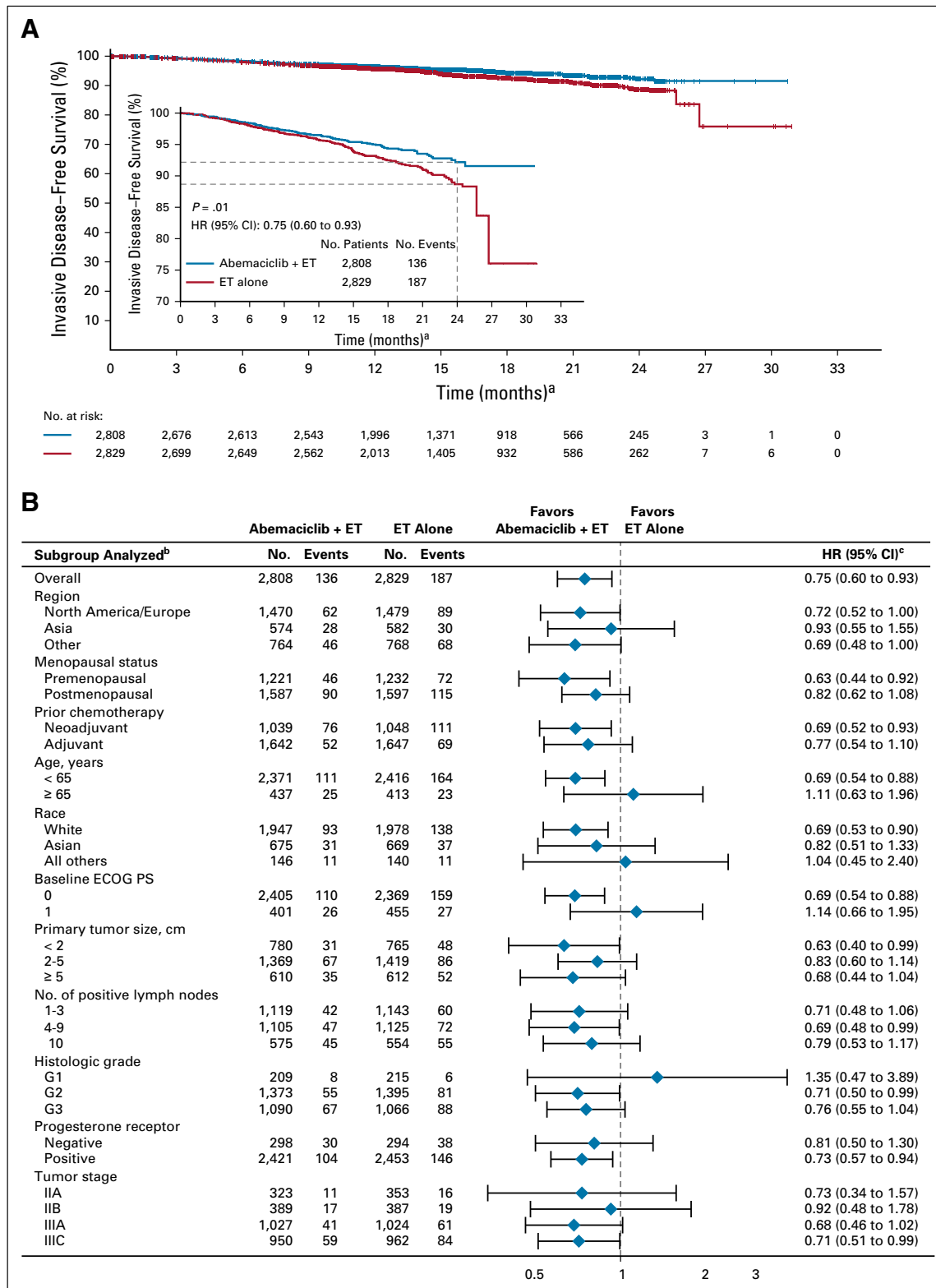| Subgroup Analyzed[b]	Abemaciclib + ET No.	Events	ET Alone No.	Events	Favors Abemaciclib + ET / Favors ET Alone	HR (95% CI)[c]
Overall	2,808	136	2,829	187		0.75 (0.60 to 0.93)
Region						
North America/Europe	1,470	62	1,479	89		0.72 (0.52 to 1.00)
Asia	574	28	582	30		0.93 (0.55 to 1.55)
Other	764	46	768	68		0.69 (0.48 to 1.00)
Menopausal status						
Premenopausal	1,221	46	1,232	72		0.63 (0.44 to 0.92)
Postmenopausal	1,587	90	1,597	115		0.82 (0.62 to 1.08)
Prior chemotherapy						
Neoadjuvant	1,039	76	1,048	111		0.69 (0.52 to 0.93)
Adjuvant	1,642	52	1,647	69		0.77 (0.54 to 1.10)
Age, years						
< 65	2,371	111	2,416	164		0.69 (0.54 to 0.88)
≥ 65	437	25	413	23		1.11 (0.63 to 1.96)
Race						
White	1,947	93	1,978	138		0.69 (0.53 to 0.90)
Asian	675	31	669	37		0.82 (0.51 to 1.33)
All others	146	11	140	11		1.04 (0.45 to 2.40)
Baseline ECOG PS						
0	2,405	110	2,369	159		0.69 (0.54 to 0.88)
1	401	26	455	27		1.14 (0.66 to 1.95)
Primary tumor size, cm						
< 2	780	31	765	48		0.63 (0.40 to 0.99)
2-5	1,369	67	1,419	86		0.83 (0.60 to 1.14)
≥ 5	610	35	612	52		0.68 (0.44 to 1.04)
No. of positive lymph nodes						
1-3	1,119	42	1,143	60		0.71 (0.48 to 1.06)
4-9	1,105	47	1,125	72		0.69 (0.48 to 0.99)
10	575	45	554	55		0.79 (0.53 to 1.17)
Histologic grade						
G1	209	8	215	6		1.35 (0.47 to 3.89)
G2	1,373	55	1,395	81		0.71 (0.50 to 0.99)
G3	1,090	67	1,066	88		0.76 (0.55 to 1.04)
Progesterone receptor						
Negative	298	30	294	38		0.81 (0.50 to 1.30)
Positive	2,421	104	2,453	146		0.73 (0.57 to 0.94)
Tumor stage						
IIA	323	11	353	16		0.73 (0.34 to 1.57)
IIB	389	17	387	19		0.92 (0.48 to 1.78)
IIIA	1,027	41	1,024	61		0.68 (0.46 to 1.02)
IIIC	950	59	962	84		0.71 (0.51 to 0.99)

0.5   1   2   3

FIG 2. Invasive disease-free survival (IDFS). (A) Kaplan-Meier curves of IDFS and IDFS zoomed in to better visualize separation of the curves in the intent-to-treat population. (B) IDFS of patient subgroups. Hazard ratios (HRs) are stratified in overall population and unstratified in subgroups for abemaciclib plus endocrine therapy (ET) versus ET alone. HR estimates for IDFS are indicated by diamonds, and 95% CIs are indicated by the crossing horizontal lines. ([a]) Curves should not be interpreted beyond 24 months because of the limited follow-up. ([b]) If a subgroup consists of < 5% of randomly assigned patients, analysis within that subgroup was omitted. ([c]) The width of CIs in subgroups has not been adjusted for multiplicity; thus, the subgroup results are exploratory in nature. ECOG PS, Eastern Cooperative Oncology Group performance status.

TABLE 2. Recurrence Events

Recurrence Event	Abemaciclib + ET (n = 2,808)	ET Alone (n = 2,829)
IDFS events		
Total IDFS events	136	187
Patients with invasive disease, first occurrence	123	181
Local/regional recurrence	17	26
Distant recurrence	87	138
Contralateral recurrence	4	9
Second primary neoplasm	16	12
Death from any cause without invasive disease	13	6
DRFS events		
Total DRFS events	106	152
Patients with distant relapse, any time	92	142
Bone	32	81
Liver	29	42
Lung	21	21
Brain	13	16
Lymph node	7	13
Pleura	6	7
CNS	4	2
Soft tissue	1	1
Skin	1	0
Peritoneum	0	1
Other[a]	11	7
Death from any cause without distant recurrence	14	10

NOTE. Some patients were counted more than once in subcategories if they had recurrence at different locations (for example, if a patient had local/regional recurrence and distant recurrence at the same time, or if a patient had liver and bone metastases).

Abbreviations: DRFS, distant relapse-free survival; IDFS, invasive disease-free survival.

[a]Includes ovarian (two), suprarenal, left scapula, abdomen, submandibular lesion, spleen, epidural, left adnexal mass, neck, fallopian tubes, adrenal (two), pericardial effusion, left orbit, spine, colon, gallbladder.

in the control arm were distant recurrence. Overcoming endocrine resistance and reducing the risk of distant metastasis is an essential objective for any novel therapy in HR+ EBC. Abemaciclib is an approved CDK4/6 inhibitor in HR+, HER2− ABC, with clinical efficacy both as monotherapy in pretreated ABC[19] and in combination with ET.[8,9] Significant improvement in OS was reported in patients with endocrine-resistant disease, including patients with visceral metastases.[7] The effect now seen in the EBC adjuvant setting in monarchE indicates a similar impact on preventing early primary endocrine resistant recurrences and on reducing the risk of metastatic recurrence by a clinically meaningful 28%

relative to ET alone, especially in bone and liver metastases (Table 2). Of note, the Kaplan-Meier curves for both IDFS and DRFS separate at 9-12 months (Figs 2 and 3), which may indicate the need for early treatment of very-high-risk patients who may have subclinical micrometastatic disease at diagnosis.

The ability to conclude the statistically significant benefit of adding abemaciclib to ET is dependent on the number of IDFS events observed. By enrolling patients whose cancer is at high risk of early recurrence, monarchE reached the target number of events for the efficacy assessment faster relative to a patient population at a lower risk of recurrence. At this preplanned interim analysis, 323 events were observed, corresponding to > 80% of the total planned number of events (390). Overall type I error was robustly controlled using an O'Brien-Fleming spending function, ensuring highly statistically significant and definitive results. Although the median follow-up of 15 months at this time is short for an EBC adjuvant study, the positive outcome demonstrated the effectiveness of abemaciclib in reducing the risk of invasive disease within 2 years—a critical outcome for this high-risk population. Additional follow-up in monarchE will determine the persistence of this benefit on later recurrences and overall survival in node-positive, high-risk HR+ HER2− EBC, which is unknown at present.

Understanding the subgroups of patients with HR+, HER2− breast cancer for whom the addition of a targeted therapy is most beneficial is an important goal. In monarchE, a population with increased risk of recurrence on the basis of disease characteristics such as axillary lymph node involvement, tumor size, and biology was selected, and a clear efficacy benefit for the addition of abemaciclib was demonstrated. Whether benefit of a CDK4/6 inhibitor can be demonstrated in patients at lower risk is unclear, especially given that many of these patients experience recurrence late (> 10 years after diagnosis), and extended adjuvant ET is increasingly used and may benefit these patients. There are additional ongoing clinical trials evaluating CDK4/6 inhibitors in EBC (ClinicalTrials.gov identifiers: NCT03701334 and NCT02513394). Results from these trials using different compounds in different populations will further determine the role of CDK4/6 inhibitors in EBC. The definitive results from monarchE have identified a specific high-risk patient population for whom the addition of abemaciclib prevents early disease recurrences and reduces the risk of distant metastases. In addition, understanding the tumor biology of patients who benefit most from adjuvant abemaciclib is important, and parallel translational research to investigate tissue and plasma samples from patients in monarchE is underway.

Adherence to therapy is a challenge in the adjuvant setting, and a manageable toxicity profile for any novel therapy is crucial. The safety profile of abemaciclib in this adjuvant study was consistent with the known adverse effect profile of abemaciclib previously reported in the ABC setting. Of interest, arthralgia and hot flush are known frequent and often
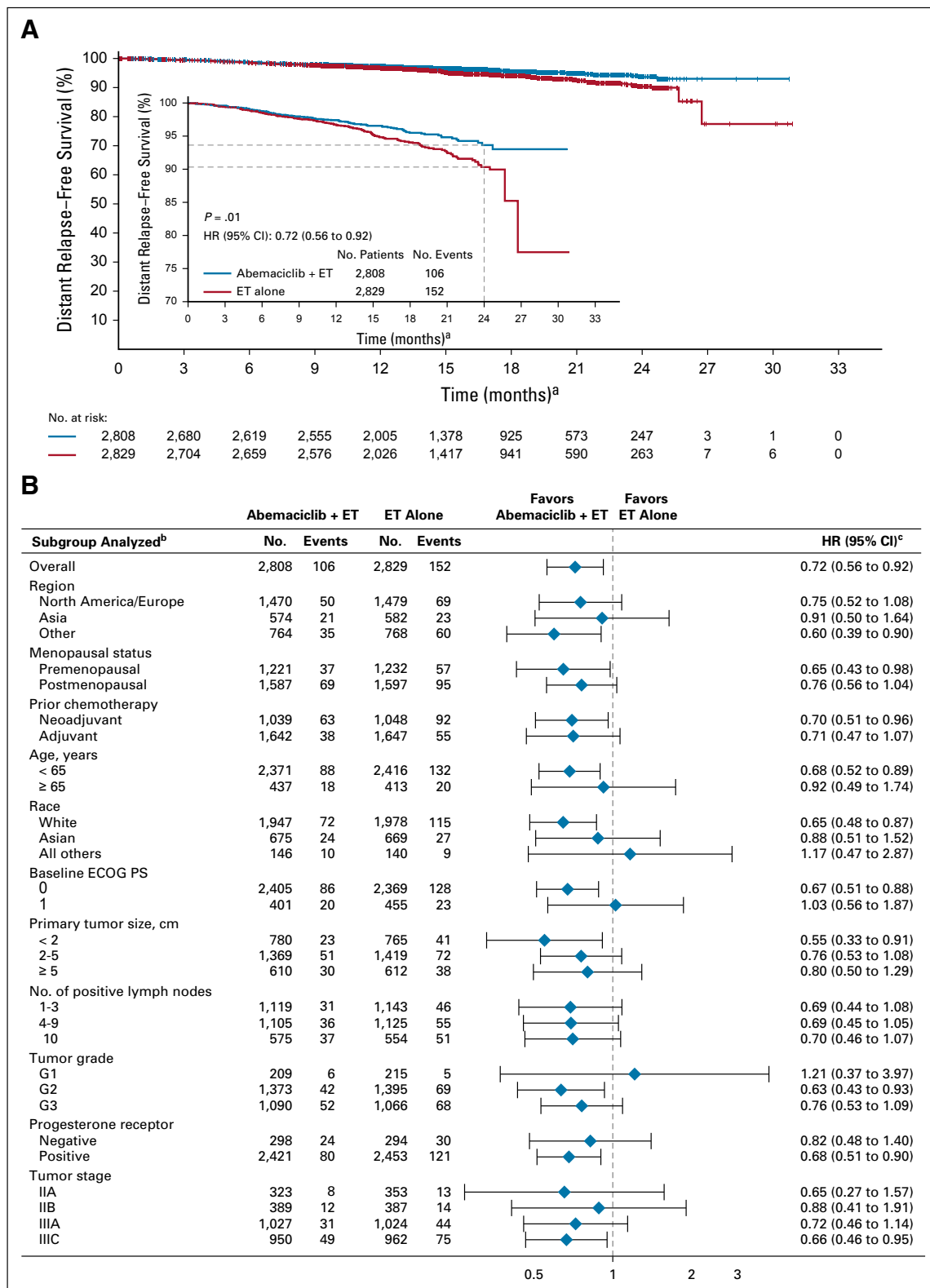
A

P = .01
HR (95% CI): 0.72 (0.56 to 0.92)

	No. Patients	No. Events
Abemaciclib + ET	2,808	106
ET alone	2,829	152

No. at risk:

2,808	2,680	2,619	2,555	2,005	1,378	925	573	247	3	1	0
2,829	2,704	2,659	2,576	2,026	1,417	941	590	263	7	6	0

B

Subgroup Analyzed[b]	Abemaciclib + ET		ET Alone		Favors Abemaciclib + ET	Favors ET Alone	HR (95% CI)[c]
	No.	Events	No.	Events			
Overall	2,808	106	2,829	152			0.72 (0.56 to 0.92)
Region							
North America/Europe	1,470	50	1,479	69			0.75 (0.52 to 1.08)
Asia	574	21	582	23			0.91 (0.50 to 1.64)
Other	764	35	768	60			0.60 (0.39 to 0.90)
Menopausal status							
Premenopausal	1,221	37	1,232	57			0.65 (0.43 to 0.98)
Postmenopausal	1,587	69	1,597	95			0.76 (0.56 to 1.04)
Prior chemotherapy							
Neoadjuvant	1,039	63	1,048	92			0.70 (0.51 to 0.96)
Adjuvant	1,642	38	1,647	55			0.71 (0.47 to 1.07)
Age, years							
< 65	2,371	88	2,416	132			0.68 (0.52 to 0.89)
≥ 65	437	18	413	20			0.92 (0.49 to 1.74)
Race							
White	1,947	72	1,978	115			0.65 (0.48 to 0.87)
Asian	675	24	669	27			0.88 (0.51 to 1.52)
All others	146	10	140	9			1.17 (0.47 to 2.87)
Baseline ECOG PS							
0	2,405	86	2,369	128			0.67 (0.51 to 0.88)
1	401	20	455	23			1.03 (0.56 to 1.87)
Primary tumor size, cm							
< 2	780	23	765	41			0.55 (0.33 to 0.91)
2-5	1,369	51	1,419	72			0.76 (0.53 to 1.08)
≥ 5	610	30	612	38			0.80 (0.50 to 1.29)
No. of positive lymph nodes							
1-3	1,119	31	1,143	46			0.69 (0.44 to 1.08)
4-9	1,105	36	1,125	55			0.69 (0.45 to 1.05)
10	575	37	554	51			0.70 (0.46 to 1.07)
Tumor grade							
G1	209	6	215	5			1.21 (0.37 to 3.97)
G2	1,373	42	1,395	69			0.63 (0.43 to 0.93)
G3	1,090	52	1,066	68			0.76 (0.53 to 1.09)
Progesterone receptor							
Negative	298	24	294	30			0.82 (0.48 to 1.40)
Positive	2,421	80	2,453	121			0.68 (0.51 to 0.90)
Tumor stage							
IIA	323	8	353	13			0.65 (0.27 to 1.57)
IIB	389	12	387	14			0.88 (0.41 to 1.91)
IIIA	1,027	31	1,024	44			0.72 (0.46 to 1.14)
IIIC	950	49	962	75			0.66 (0.46 to 0.95)

0.5   1   2   3

FIG 3. Distant relapse–free survival (DRFS). (A) Kaplan-Meier curves of DRFS and DRFS zoomed in to better visualize separation of the curves in the intent-to-treat population. (B) DRFS of patient subgroups. Hazard ratios (HRs) are stratified in overall population and unstratified in subgroups for abemaciclib plus endocrine therapy (ET) versus ET alone. HR estimates for DRFS are indicated by diamonds, and 95% CIs are indicated by the crossing horizontal lines. ([a]) Curves should not be interpreted beyond 24 months because of the limited follow-up. ([b]) If a subgroup consists of < 5% of randomly assigned patients, analysis within that subgroup was omitted. ([c]) The width of CIs in subgroups has not been adjusted for multiplicity; thus, the subgroup results are exploratory in nature. ECOG PS, Eastern Cooperative Oncology Group performance status.

TABLE 3. Safety Table

≥ 10% in Either Arm	Abemaciclib + ET (n = 2,791)			ET Alone (n = 2,800)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any adverse event	2,731 (97.9)	1,200 (43.0)	70 (2.5)	2,410 (86.1)	335 (12.0)	19 (0.7)
Diarrhea	2,294 (82.2)	212 (7.6)	0	199 (7.1)	3 (0.1)	0
Neutropenia	1,246 (44.6)	501 (18.0)	18 (0.6)	141 (5.0)	16 (0.6)	3 (0.1)
Fatigue	1,073 (38.4)	78 (2.8)	0	433 (15.5)	4 (0.1)	0
Leukopenia	1,027 (36.8)	301 (10.8)	4 (0.1)	171 (6.1)	10 (0.4)	0
Abdominal pain	948 (34.0)	37 (1.3)	0	227 (8.1)	9 (0.3)	0
Nausea	779 (27.9)	13 (0.5)	0	223 (8.0)	1 (0.0)	0
Anemia	638 (22.9)	47 (1.7)	1 (0.0)	90 (3.2)	9 (0.3)	1 (0.0)
Arthralgia	571 (20.5)	6 (0.2)	0	876 (31.3)	18 (0.6)	0
Hot flush	393 (14.1)	3 (0.1)	0	587 (21.0)	8 (0.3)	0
Lymphopenia	372 (13.3)	140 (5.0)	2 (0.1)	94 (3.4)	13 (0.5)	0
Thrombocytopenia	341 (12.2)	25 (0.9)	6 (0.2)	40 (1.4)	1 (0.0)	2 (0.1)
Vomiting	455 (16.3)	13 (0.5)	0	117 (4.2)	2 (0.1)	0
Constipation	288 (10.3)	1 (0.0)	0	142 (5.1)	0	0
Upper respiratory tract infection	285 (10.2)	6 (0.2)	0	214 (7.6)	0	0
Urinary tract infection	284 (10.2)	13 (0.5)	0	170 (6.1)	6 (0.2)	0
Decreased appetite	312 (11.2)	15 (0.5)	0	54 (1.9)	1 (0.0)	0
Headache	482 (17.3)	6 (0.2)	0	359 (12.8)	3 (0.1)	0
Cough	337 (12.1)	1 (0.0)	0	193 (6.9)	0	0
Lymphedema	285 (10.2)	2 (0.1)	0	208 (7.4)	0	0
Additional adverse events of interest[a]						
Aspartate aminotransferase increase	257 (9.2)	43 (1.5)	3 (0.1)	106 (3.8)	13 (0.5)	0
Alanine aminotransferase increase	265 (9.5)	59 (2.1)	5 (0.2)	119 (4.3)	16 (0.6)	0
Alopecia	254 (9.1)	0	0	53 (1.9)	0	0
Venous thromboembolic event	63 (2.3)	27 (1.0)	6 (0.2)	14 (0.5)	4 (0.1)	0
Interstitial lung disease[b]	75 (2.7)	9 (0.3)	0	33 (1.2)	1 (0.0)	0

NOTE. Data are presented as No. (%).

[a]Includes events of clinical significance and/or observed in earlier clinical studies of abemaciclib.

[b]Term is based on the Standard MedDRA Query.

troublesome AEs related to ET. Both were significantly reduced in those treated with abemaciclib plus ET compared with ET alone (arthralgia, 20.5% v 31.3%; hot flush, 14.1% v 21.0%). This intriguing observation has been reported previously in a randomized study of a CDK4/6 inhibitor plus ET.[20]

The most frequently reported AE in the abemaciclib arm was diarrhea. Diarrhea occurred early (median time to onset for any grade of 8 days), was short-lived (median duration for grades 2 and 3 of 5 to 6 days), and was managed with antidiarrheal medication and dose adjustments per protocol. The frequency of diarrhea grade ≥ 3 was 7.6%; however,

a very low number of patients (4.8%) discontinued abemaciclib because of diarrhea. Neutropenia grade ≥ 3 occurred in < 20% of abemaciclib-treated patients (0.3% febrile neutropenia, any grade). VTE and ILD were reported more often in the abemaciclib arm, and although SAEs were uncommon, signs and symptoms should be closely monitored for patients on abemaciclib.

In conclusion, monarchE has demonstrated that abemaciclib added to standard adjuvant ET significantly improves IDFS in women and men with HR+, HER2−, node-positive EBC at high risk of early recurrence.

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

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Research Funding: Genentech/Roche (Inst), Merck (Inst), Exelixis (Inst), Pfizer (Inst), Eli Lilly (Inst), Novartis (Inst), Bristol Myers Squibb (Inst), Eisai (Inst), AstraZeneca (Inst), NanoString Technologies (Inst), Cyclacel (Inst), Nektar (Inst), Immunomedics (Inst), Odonate Therapeutics (Inst), Sanofi (Inst), Seattle Genetics (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Eli Lilly, Merck, Nektar, Novartis, Pfizer, Genentech/Roche, Immunomedics, Eisai, NanoString Technologies, Puma Biotechnology, Celldex

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Maarten Hulstijn
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Travel, Accommodations, Expenses: Celgene, Eli Lilly, Novartis, Pfizer, AbbVie, Agendia, Amgen, Eisai, Genomic Health, GRAIL, Ipsen, Jounce Therapeutics, Myriad Pharmaceuticals, Puma Biotechnology, Seattle Genetics, AstraZeneca, Sanofi, Roche

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No other potential conflicts of interest were reported.