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ORIGINAL ARTICLE

Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: safety and patient-reported outcomes from the monarchE study

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Available online 23 March 2022

Background: In monarchE, abemaciclib plus endocrine therapy (ET) as adjuvant treatment of hormone receptor-positive, human epidermal growth factor 2-negative, high-risk, early breast cancer (EBC) demonstrated a clinically meaningful improvement in invasive disease-free survival versus ET alone. Detailed safety analyses conducted at a median follow-up of 27 months and key patient-reported outcomes (PROs) are presented.

Patients and methods: The safety population included all patients who received at least one dose of study treatment ($n = 5591$). Safety analyses included incidence, management, and outcomes of common and clinically relevant adverse events (AEs). Patient-reported health-related quality of life, ET symptoms, fatigue, and side-effect burden were assessed.

Results: The addition of abemaciclib to ET resulted in higher incidence of grade $\geq$3 AEs (49.7% versus 16.3% with ET alone), predominantly laboratory cytopenias [e.g. neutropenia (19.6%)] without clinical complications. Abemaciclib-treated patients experienced more serious AEs (15.2% versus 8.8%). Discontinuation of abemaciclib and/or ET due to AEs occurred in 18.5% of patients, mainly due to grade 1/2 AEs (66.8%). AEs were managed with comedications (e.g. antidiarrheals), abemaciclib dose holds (61.7%), and/or dose reductions (43.4%). Diarrhea was generally low grade (grade 1/2: 76%); grade 2/3 events were highest in the first month (20.5%), most were short-lived ($\leq$7 days) and did not recur. Venous thromboembolic events (VTEs) were higher with abemaciclib + ET (2.5%) versus ET (0.6%); in the abemaciclib arm, increased VTE risk was observed with tamoxifen versus aromatase inhibitors (4.3% versus 1.8%). PROs were similar between arms, including being 'bothered by side-effects of treatment', except for diarrhea. At $\geq$3 months, most patients reporting diarrhea reported 'a little bit' or 'somewhat'.

Conclusions: In patients with high-risk EBC, adjuvant abemaciclib + ET has an acceptable safety profile and tolerability is supported by PRO findings. Most AEs were reversible and manageable with comedications and/or dose modifications, consistent with the known abemaciclib toxicity profile.

Key words: abemaciclib, early breast cancer, HER2 negative, HR positive, monarchE, safety

INTRODUCTION

After the monarchE study demonstrated a clinically meaningful and significant improvement in invasive disease-free survival, abemaciclib became the first cyclin-dependent kinase 4 and 6 (CDK4 and 6) inhibitor to be approved by the Food and Drug Administration (FDA) for use in the adjuvant

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setting for treatment of patients with hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2−), node-positive, early breast cancer (EBC) at high risk of recurrence and a Ki67 index ≥20%.[1-3] Efficacy and safety data supporting this approval were previously published.[1] Herein, we report monarchE safety analyses and key patient-reported outcomes (PROs), representing the first detailed safety report and PRO data from a CDK4 and 6 adjuvant trial.

PATIENTS AND METHODS

Study design and participants

The monarchE study (NCT03155997) is an open-label, global, randomized, phase III trial which investigated the addition of abemaciclib to standard-of-care (SOC) ET in patients with HR+, HER2−, node-positive, high-risk EBC.[2] The study protocol and all amendments were approved by ethical/institutional review boards before implementation and all patients gave written informed consent. The study was carried out in compliance with the Declaration of Helsinki.

The detailed study design was previously published[2] and enrolled patients with HR+, HER2−, high-risk EBC, defined as having ≥4 positive pathologic axillary lymph nodes (ALNs) or 1-3 positive ALNs and one of the following: tumor size ≥5 cm, histologic grade 3 disease, or centrally assessed Ki-67 ≥20%. Randomized patients received SOC adjuvant ET of physician's choice for a total of 5-10 years ±abemaciclib for the first 2 years (treatment period) or until meeting criteria for discontinuation. Switching ET agents was permissible as per physician's choice at any time during the study and patients who discontinued abemaciclib were encouraged to remain on ET.

Safety measures

In monarchE, the type, severity, seriousness, timing, and duration of adverse events (AEs), as well as their potential relationship to study treatment, were reported by investigators. Regardless of causality, investigator-reported terms were mapped to MedDRA (medical dictionary) terms and AEs were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Clinic visits, including central laboratory assessments, were conducted before randomization, on day 1, every 2 weeks during the first 2 months on treatment, monthly to month 6, then 3-monthly through the treatment period, and 30 days after discontinuation. Serious adverse events (SAEs) included AEs with an outcome of death, initial/prolonged hospitalization, or life-threatening events. By protocol design, all SAEs in both arms, regardless of causality, will be collected from randomization through year 5.

Venous thromboembolic events (VTEs), hepatic events (increased transaminases), and interstitial lung disease (ILD) were analyzed as composite terms (Table 1 footnote). Those composite terms resulted from a comprehensive search of all investigator-reported AEs under the appropriate MedDRA queries to fully characterize those AEs in the EBC population. For any patient experiencing a VTE, additional details about symptoms, diagnosis, and prior risks factors were collected in the study database.

The study protocol included mandated abemaciclib dose modification (holds and reductions) instructions to manage AEs, with a maximum of 2 dose reductions. Patients requiring >2 dose reductions were required to discontinue abemaciclib. Management guidelines for diarrhea and neutropenia have been previously described[4] (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.03.006). Patients with a history of VTE were excluded from the study. Guidance for confirmed VTE management included holding abemaciclib for 1-2 weeks, starting anticoagulation therapy as per standard clinical practice, and recommending patients treated with tamoxifen switch ET. Anticoagulation treatment was to be continued for the duration of abemaciclib treatment. At randomization, patients were required to have had alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3× upper limit of normal (ULN). Patients with grade 3 increased transaminases required an abemaciclib dose hold until toxicity resolved to grade 1; patients with grade 4 increased transaminases were required to discontinue abemaciclib. Patients with serious preexisting ILD were excluded. Grade ≥2 ILD required abemaciclib dose modifications.

Patient-reported outcome data

The PRO assessments focused on capturing the implications of treatment on patient-reported health-related quality of life (HRQoL) (FACT-B) and treatment-related symptoms/AEs: ET symptoms (FACT-ES; two cognitive/three bladder FACIT items), fatigue (FACIT-Fatigue), and side-effect burden (FACT-B GP5). Within the FACT-B, scores are presented over time for item GP5 'I am bothered by side-effects of treatment' and for FACT-ES item C5 'I have diarrhea'. PROs were administered manually and assessed at baseline (randomization), 3, 6, 12, 18, and 24 months on treatment and during follow-up (1, 6, and 12 months after discontinuation). All PRO items used a five-point scale. Summary scores were calculated as per the FACIT guidance.[5] A positive change in summary scale scores represented an improvement in HRQoL and vice versa.

Statistical analyses

The safety population included patients who received ≥1 dose of study treatment. AEs were summarized by maximum toxicity regardless of causality. Clinically synonymous terms were grouped together under a consolidated preferred term. Descriptive statistics were used to summarize safety information including incidence, dose modifications, comedications, and outcomes of common and clinically relevant AEs.

Analysis of PROs was conducted using a mixed-effects repeated-measures (MMRM) model to compare mean summary scores and item scores, and change from baseline by

Table 1. Clinically relevant adverse events observed in the abemaciclib + ET arm regardless of causality

	Abemaciclib + ET (N = 2791)				ET alone (N = 2800)			
	Any grade	G1	G2	G ≥ 3	Any grade	G1	G2	G ≥ 3
≥10% in the abemaciclib + ET arm								
Patients with ≥1 AE,[a] n (%)	2745 (98.4)	165 (5.9)	1192 (42.7)	1388 (49.7)	2486 (88.8)	634 (22.6)	1396 (49.9)	456 (16.3)
Diarrhea	2331 (83.5)	1255 (45.0)	857 (30.7)	219 (7.8)[b]	242 (8.6)	184 (6.6)	52 (1.9)	6 (0.2)
Infections[c]	1429 (51.2)	245 (8.8)	1029 (36.9)	155 (5.6)	1102 (39.4)	229 (8.2)	790 (28.2)	83 (3.0)[d]
Neutropenia	1278 (45.8)	178 (6.4)	554 (19.8)	546 (19.6)	157 (5.6)	66 (2.4)	68 (2.4)	23 (0.8)
Fatigue	1133 (40.6)	632 (22.6)	421 (15.1)	80 (2.9)	499 (17.8)	378 (13.5)	117 (4.2)	4 (0.1)
Nausea	824 (29.5)	623 (22.3)	187 (6.7)	14 (0.5)	252 (9.0)	198 (7.1)	52 (1.9)	2 (0.1)
Anemia	681 (24.4)	383 (13.7)	241 (8.6)	57 (2.0)	104 (3.7)	75 (2.7)	19 (0.7)	10 (0.4)
Headache	546 (19.6)	415 (14.9)	123 (4.4)	8 (0.3)	421 (15.0)	321 (11.5)	95 (3.4)	5 (0.2)
Vomiting	491 (17.6)	375 (13.4)	101 (3.6)	15 (0.5)	130 (4.6)	98 (3.5)	29 (1.0)	3 (0.1)
Stomatitis[e]	385 (13.8)	309 (11.1)	72 (2.6)	4 (0.1)	151 (5.4)	133 (4.8)	18 (0.6)	0 (0.0)
Thrombocytopenia	373 (13.4)	276 (9.9)	61 (2.2)	36 (1.3)	52 (1.9)	40 (1.4)	8 (0.3)	4 (0.1)
Decreased appetite	329 (11.8)	243 (8.7)	70 (2.5)	16 (0.6)	68 (2.4)	53 (1.9)	13 (0.5)	2 (0.1)
Alopecia	313 (11.2)	283 (10.1)	30 (1.1)	N/A	75 (2.7)	68 (2.4)	7 (0.3)	0 (0.0)
Alanine aminotransferase increase (ALT)	343 (12.3)	184 (6.6)	82 (2.9)	77 (2.8)	157 (5.6)	113 (4.0)	25 (0.9)	19 (0.7)
Aspartate aminotransferase increase (AST)	330 (11.8)	220 (7.9)	58 (2.1)	52 (1.9)	137 (4.9)	103 (3.7)	19 (0.7)	15 (0.5)
Rash	312 (11.2)	239 (8.6)	61 (2.2)	11 (0.4)	127 (4.5)	104 (3.7)	23 (0.8)	0 (0.0)
Other AEs of interest—composite terms								
VTE[f]	71 (2.5)	2 (0.1)	31 (1.1)	38 (1.4)[h]	17 (0.6)	0 (0.0)	9 (0.3)	8 (0.3)
PE[g]	28 (1.0)	N/A	N/A	28 (1.0)[i]	4 (0.1)	N/A	N/A	4 (0.1)
ILD[j]	89 (3.2)	44 (1.6)	34 (1.2)	11 (0.4)	37 (1.3)	26 (0.9)	10 (0.4)	1 (0.0)
Pneumonitis	49 (1.8)	21 (0.8)	21 (0.8)	7 (0.3)	10 (0.4)	7 (0.3)	3 (0.1)	0 (0.0)
Radiation pneumonitis	25 (0.9)	13 (0.5)	10 (0.4)	2 (0.1)	15 (0.5)	9 (0.3)	5 (0.2)	1 (0.0)
Increased transaminases[k]	433 (15.5)	241 (8.6)	94 (3.4)	98 (3.5)	209 (7.5)	143 (5.1)	38 (1.4)	28 (1.0)

AE, adverse event; ET, endocrine therapy; G, grade; ILD, interstitial lung disease; N, number of patients in the safety population; n, number of patients within category; N/A, not applicable; PE, pulmonary embolism; VTE, venous thromboembolic events.
Max grade 2 event (according to CTCAE v.4).
[a]The severity of AEs was recorded by investigators and graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.
[b]No G4 events, one G5 event.
[c]Infection is a composite term that includes all reported preferred terms that are part of the infections and infestations system organ class.
[d]Four G5 events.
[e]Stomatitis is a consolidated term that includes mouth ulceration, mucosal inflammation, oropharyngeal pain, and stomatitis.
[f]VTE is a composite term including the following preferred terms: abemaciclib arm (any grade—n)—catheter site thrombosis (1), cerebral vein thrombosis (2), cerebral venous thrombosis (0), deep vein thrombosis (36), device-related thrombosis (3), embolism (1), hepatic vein thrombosis (0), jugular vein occlusion (0), jugular vein thrombosis (3), ovarian vein thrombosis (0), portal vein thrombosis (1), pulmonary embolism (27), subclavian vein thrombosis (2), and venous thrombosis limb (1); ET arm (any grade—n)—catheter site thrombosis (0), cerebral vein thrombosis (1), cerebral venous thrombosis (0), deep vein thrombosis (7), device-related thrombosis (1), embolism (0), hepatic vein thrombosis (1), jugular vein occlusion (1), jugular vein thrombosis (0), ovarian vein thrombosis (1), portal vein thrombosis (0), pulmonary embolism (4), subclavian vein thrombosis (0), and venous thrombosis limb (0).
[g]PE is a composite term: embolism (n = 1 in the abemaciclib arm not confirmed by imaging) and pulmonary embolism (n = 27); minimum severity grade as per CTCAE for PE is gG3 for uncomplicated events.
[h]Six (0.2%) grade 3 VTEs occurred in the abemaciclib arm.
[i]Three PE (%) grade 4 occurred in the abemaciclib arm.
[j]ILD is a composite term including the following preferred terms: abemaciclib arm (any grade—n)—interstitial lung disease (6), lung opacity (3), pneumonitis (49), pulmonary fibrosis (4), radiation fibrosis—lung (2), radiation pneumonitis (25), sarcoidosis (0), organizing pneumonia (2), pulmonary granuloma (0); and ET arm (any grade—n): pneumonitis (10), radiation pneumonitis (15), interstitial lung disease (1), pulmonary fibrosis (3), lung opacity (2), radiation fibrosis—lung (2), organizing pneumonia (3), pulmonary granuloma (1), and sarcoidosis (1). There was one fatality due to ILD (pneumonitis) in the abemaciclib arm and none in the control arm.
[k]Increased transaminases is a composite term including the following preferred terms: abemaciclib arm (n)—ALT increased (343), AST increased (330), transaminases increased (16), hepatic function abnormal (10), hepatic enzyme abnormal (0), hepatic enzyme increased (2), drug-induced injury (3), liver function test increased (5), hepatotoxicity (1), hypertransaminasemia (2), and liver function test abnormal (4); ET arm (n)—ALT increased (157), AST increased (137), transaminases increased (7), hepatic function abnormal (9), hepatic enzyme increased (5), drug-induced injury (1), liver function test increased (1), hepatotoxicity (2), hypertransaminasemia (1), liver function test abnormal (0), and hepatic enzyme abnormal (2).

treatment arm, excluding 24-month or follow-up data, as <25% of randomized patients were assessed. Frequency of scores over time for FACT-ES C5 'I have diarrhea' and FACT-B GP5 'I am bothered by side-effects of treatment' were summarized graphically. Exploratory analyses were conducted on patient-reported items reflecting common AEs such as diarrhea, fatigue, arthralgia (compound pain items), and hot flushes. Given the large trial size, comparisons of PRO data are overpowered and numerical differences are likely to reach statistical significance at the 5% level regardless of clinical significance. Therefore, for the summary scores, an effect size of ½ standard deviation (SD) at baseline was used to represent a minimally important difference (MID).[6] For the item scores, a change of 1 (i.e. moving from one level of response to the next) was deemed meaningful.

PRO data were analyzed at the prespecified primary outcome analysis (cut-off date: 8 July 2020, median follow-up 19 months). Safety data are reported utilizing the additional follow-up 1 analysis (cut-off date: 1 April 2021, median follow-up 27 months).

RESULTS

Patients

A total of 5637 patients were randomized 1 : 1 to receive abemaciclib + ET (n = 2808) or ET alone (n = 2829)

(Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2022.03.006); 5591 received at least one dose of ET ± abemaciclib and comprise the safety population. Baseline characteristics were balanced as previously reported.[2] At the most recent data cut-off date, 89.6% of patients were off the study treatment period, including 72.2% who completed the 2-year treatment period and 17.4% discontinued prematurely (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2022.03.006).

Exposure, median duration, and compliance

The median duration of abemaciclib treatment was 24 months. Exposure to ET was balanced across arms with a median duration of 24 months in both arms. The median compliance with abemaciclib treatment, calculated by counting the dispensed and returned tablets, was 98.4%.

Overview of adverse events and serious adverse events

Safety was assessed in 2791 patients in the abemaciclib + ET arm and 2800 in the ET-alone arm (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2022.03.006). Most patients reported ≥1 AE (98.4% abemaciclib + ET; 88.8% ET; Table 1). Grade ≥3 AEs occurred more frequently in the abemaciclib + ET arm (49.7% versus 16.3%); these were predominantly laboratory cytopenias (Table 1), including neutropenia (19.6% versus 0.8%) and leukopenia (11.3% versus 0.4%). A higher incidence of SAEs was observed in abemaciclib-treated patients (15.2% versus 8.8%) (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.03.006). The most frequently reported SAEs in both arms were infections (5.2% versus 2.9%) and gastrointestinal disorders (2.1% versus 0.6%; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.03.006). There were 15 (0.5%) and 10 (0.4%) deaths due to AEs on study treatment or ≤30 days from discontinuation in the abemaciclib arm and control arm, respectively (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.03.006).

Discontinuations of abemaciclib

Overall, 25.8% of patients discontinued abemaciclib for reasons other than recurrence, including 18.5% due to AEs (Figure 1A); most patients continued receiving background ET after stopping abemaciclib, either as part of the treatment period or in the follow-up period (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2022.03.006). The most common AEs leading to discontinuation were diarrhea (5.3%), fatigue (2.0%), and neutropenia (0.9%) (Figure 1B). In total, 181 patients (6.5%) discontinued both abemaciclib and ET due to AEs; for comparison, 30 patients (1.1%) in the control arm discontinued ET due to AEs (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2022.03.006).

Abemaciclib discontinuations were highest in the first month, including 76 patients (2.7%) stopping treatment due to AEs (Figure 1B); the higher rate of discontinuations during the first few months stabilized beyond 6 months (Figure 1A). In total, 66.8% of abemaciclib discontinuations due to AEs were due to grade 1/2 events and were not protocol mandated.

Dose modifications due to adverse events

Abemaciclib dose holds and reductions due to AEs occurred in 61.7% and 43.4% of patients, respectively, generally related to diarrhea, neutropenia, or fatigue (Figure 2). Most patients continued on abemaciclib and only a small proportion of patients with dose reductions discontinued abemaciclib due to AEs [8.9% ($n = 249$)]. In contrast, over half of the patients (52%) who discontinued abemaciclib did not have a prior dose reduction, particularly those who discontinued during the first month of therapy (88%; Figure 1 footnote).

Most abemaciclib dose modifications occurred ≤6 months of therapy initiation and diminished over time (Figure 2). Less than half of dose modifications were carried out due to grade ≥3 events.

Clinically relevant adverse events observed in patients receiving abemaciclib

Table1 summarizes clinically relevant AEs occurring in ≥10% of the abemaciclib arm and other important AEs. The most clinically relevant AEs are further characterized (Table 2).

Diarrhea. Most patients treated with abemaciclib (83.5%) reported diarrhea, typically low grade; 7.8% of patients experienced grade ≥3 events (Table 1). Diarrhea occurred early on treatment (median 8 days to onset) and incidence decreased over time (Table 2, Figure 3). Grade 2/3 events primarily occurred in the first 3 months (first: 20.5%; second: 12.1%; third: 7.3%), and most were short-lived (median duration ≤7 days) and did not recur (Table 2). Diarrhea was mainly managed with antidiarrheal medication (79%) and <25% of patients required dose modifications. Although ∼30% of patients reported grade 1 diarrhea in the second year of treatment, abemaciclib dose modifications were rare (≤0.6%) (Figure 3). Abemaciclib discontinuations due to diarrhea occurred in 5.3% of patients, with the vast majority (84%) due to grade 1/2 events. Discontinuations occurred mainly in the first 3 months, and mostly (74%) without a prior dose reduction.

VTE. Within the abemaciclib arm, 71 (2.5%) reported a VTE compared to 17 (0.6%) receiving ET alone; most were grade ≥3 and primarily pulmonary embolism (PE) events (1.0%; Table 1). Only 0.7% of patients who experienced PEs required hospitalizations; the remaining cases were uncomplicated PEs (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.03.006). There were no fatal VTEs in patients treated with abemaciclib (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.03.006). Approximately half of VTEs (33 out of 71) occurred within the first 180 days. Most VTEs (96%) did not recur (Table 2), with only one recurrence after resuming abemaciclib treatment. VTEs were mainly

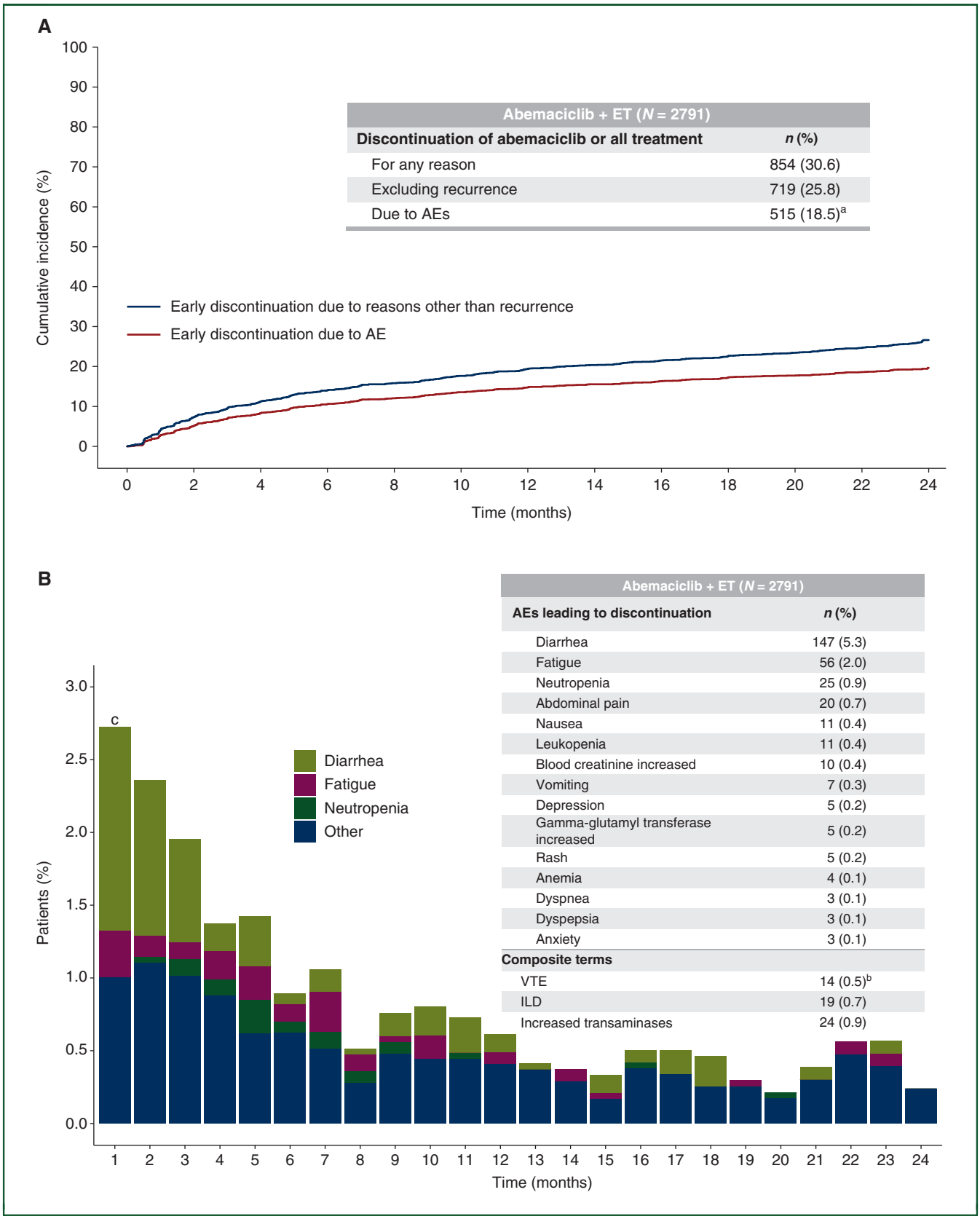
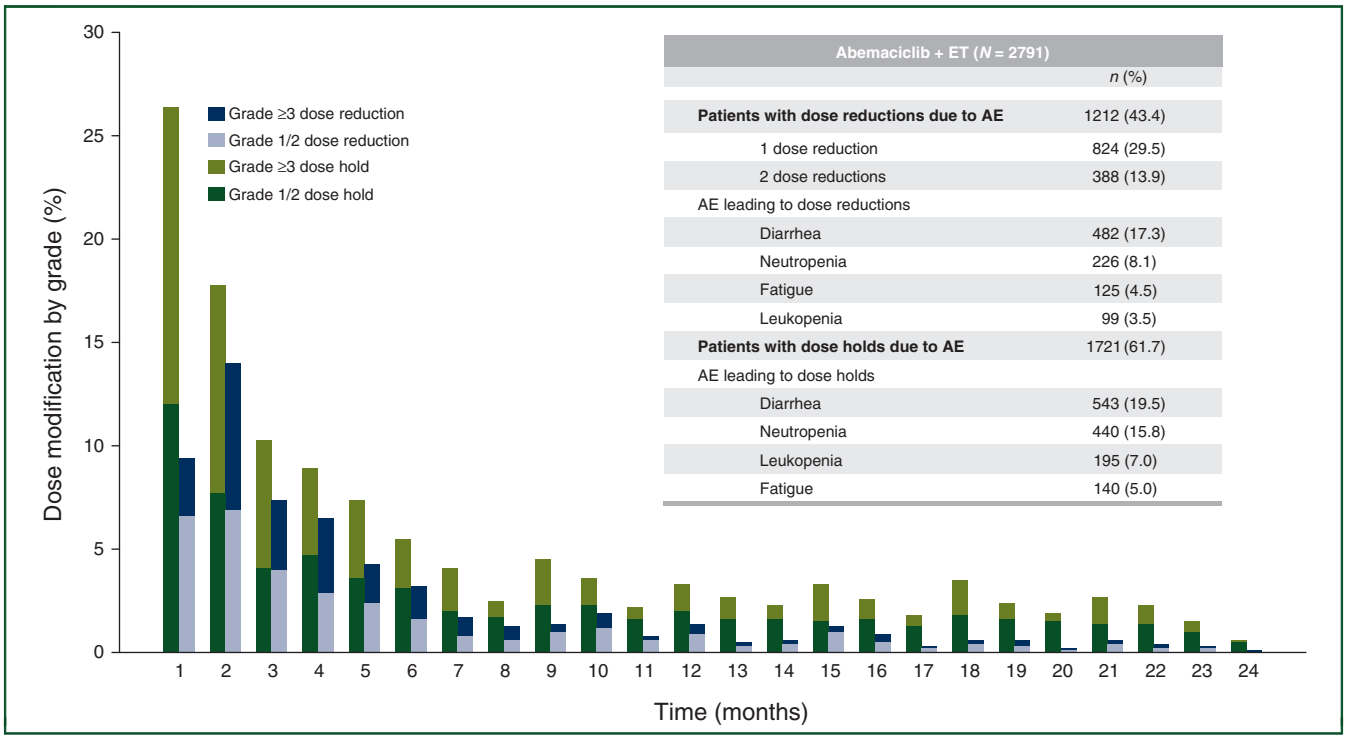


Figure 1. Discontinuations in the abemaciclib arm. (A) Due to reasons other than recurrences. (B) Due to AEs.
ET, endocrine therapy; ILD, interstitial lung disease; *N*, number of patients in the safety population; *n*, number of patients within category; VTE, venous thromboembolic events.
[a]Three hundred and forty-four of the 515 (66.8%) abemaciclib discontinuations were due to grade1/2 AEs, and 266 out of the 515 (52%) discontinued without a prior dose reduction.
[b]Six of 14 patients who discontinued abemaciclib also discontinued ET.
[c]Sixty-seven out of 76 (88%) discontinued treatment during the first month without a prior dose reduction.



Abemaciclib + ET (*N* = 2791)	*n* (%)
Patients with dose reductions due to AE	1212 (43.4)
1 dose reduction	824 (29.5)
2 dose reductions	388 (13.9)
AE leading to dose reductions	
Diarrhea	482 (17.3)
Neutropenia	226 (8.1)
Fatigue	125 (4.5)
Leukopenia	99 (3.5)
Patients with dose holds due to AE	1721 (61.7)
AE leading to dose holds	
Diarrhea	543 (19.5)
Neutropenia	440 (15.8)
Leukopenia	195 (7.0)
Fatigue	140 (5.0)

Figure 2. Abemaciclib dose modifications.
AE, adverse events; ET, endocrine therapy; *N*, number of patients in the safety population; *n*, number of patients within category.

managed with anticoagulation (93%), and 56% led to dose holds. Abemaciclib discontinuations due to VTEs were low (0.5%; Figure 1).

Further analyses were done to characterize the risks factors of VTEs, including those associated to the ET partner (Supplementary Table S3A and B, available at https://doi.org/10.1016/j.annonc.2022.03.006). Tamoxifen administered as initial ET was associated with numerically higher VTEs compared to aromatase inhibitors (4.3% versus 1.8% in abemaciclib + ET; 0.7% versus 0.6% in ET alone). Risk factors for VTE (Khorana risk score) were generally well balanced across arms. The most frequent risk factors observed in patients experiencing VTEs were recent flights or periods of immobility [22/88 (25%)] and having had an indwelling port catheter [24/88 (27%); Supplementary Table S3B, available at https://doi.org/10.1016/j.annonc.2022.03.006]. Additional analyses in abemaciclib-treated patients showed that patients with high body mass index (BMI) had a higher risk of developing a severe (grade ≥3) VTE (BMI ≥25 kg/m^2, 1.9%; BMI <25 kg/m^2, 0.7%). There was no association observed between the incidence of VTE and age.

ILD. A total of 89 (3.2%) patients treated with abemaciclib reported ILD, compared to 37 (1.3%) in the ET-alone arm (Table 1). Half of ILD events in the abemaciclib-treated patients were asymptomatic (grade 1) and grade 3 events occurred in 0.4%, with one fatal event. Most patients (98%) experiencing an ILD event did not have recurrent ILD events (Table 2). Grade ≥2 (symptomatic) events occurred mainly during the first year (80%) and were treated with steroids and/or antibiotics, with rare dose modifications. Abemaciclib discontinuation due to ILD was uncommon (0.7%; Figure 1). In both arms, 95% of patients had prior adjuvant radiotherapy, a known risk factor for ILD. In the abemaciclib arm, the incidence of any grade ILD was higher in the Asian population (5.4%); however, the overall incidence of grade ≥3 or SAE was <1.0% and similar across region subgroups.

Neutropenia. Neutropenia was the most frequently reported grade ≥3 AE (19.6%; Table 1), with a median time to onset of 1 month (Table 2). Febrile neutropenia was rare ($n = 8$; 0.3%). Importantly, grade ≥3 neutropenia was not associated with severe infections (no cases of neutropenic sepsis) and was managed with dose modifications, mainly occurring within the first 6 months. This allowed most patients who experienced neutropenia to remain on abemaciclib (discontinuation rate: 0.9%; Figure 1).

Increased transaminases. Of patients treated with abemaciclib, 15.5% had increased transaminases (ET alone: 7.5%; Table 1). The incidence of grade ≥3 increased transaminases was 3.5% with a median time to onset of ∼3 months (Table 2). Grade ≥3 increased transaminases were managed with a dose hold/reduction and most events (86%) did not recur. Discontinuation of abemaciclib ± ET due to any grade increased transaminases was low (0.9%; Figure 1).

ALT increases, as an indicator of liver function effects, were further characterized. All laboratory grade ≥3 ALT

Table 2. Characterization and management of clinically relevant adverse events in monarchE

n (%)	Abemaciclib + ET	ET alone
Adverse events		
Diarrhea, *n*	2331	242
Patients with single occurrence[a]	889 (38.1)	179 (74.0)
Time to onset, median (range), days	8.0 (1.0–711.0)	133.5 (1.0–754.0)
Dose reduction	479 (20.5)	N/A
Dose hold[b]	541 (23.2)	N/A
Antidiarrheal medication[c]	1829 (78.5)	75 (31.0)
VTE, *n*[d]	71	17
Patients with single occurrence[e]	68 (96%)	14 (82.4)
Time to onset, median (range), days	204.0 (8.0–714.0)	202.0 (9.0–716.0)
Dose reduction	4 (5.6)	N/A
Dose hold	40 (56.3)	N/A
Anticoagulation treatment	66 (93.0)	15 (88.2)
ILD, *n*[d]	89	37
Patients with single occurrence	87 (97.8)	36 (97.3)
Time to onset, median (range), days	211.0 (23.0–736.0)	176.0 (29.0–655.0)
Dose reduction	5 (5.6)	N/A
Dose hold	13 (14.6)	N/A
Antibiotic and/or corticosteroid treatment	47 (52.8)	12 (32.4)
Neutropenia grade ≥3, *n*	546	23
Patients with single occurrence	372 (68.1)	20 (87.0)
Time to onset, median (range), days	30.0 (1.0–694.0)	58.0 (14.0–755.0)
Dose reduction	203 (37.2)	N/A
Dose hold	406 (74.4)	N/A
Increased transaminases grade ≥3, *n*[d]	98	28
Patients with single occurrence[f]	84 (85.7)	22 (78.6)
Time to onset, median (range), days	117.5 (1.0–764.0)	153.0 (16.0–719.0)
Dose reduction	45 (45.9)	N/A
Dose hold	61 (62.2)	N/A
Laboratory abnormalities		
ALT/AST ≥3× ULN and TBILI ≥2× ULN, *n*	11	2

ET, endocrine therapy; G, grade; ILD, interstitial lung disease; *n*, number of patients within category; N/A, not applicable; PE, pulmonary embolism; VTE, venous thromboembolic events.

[a]In the abemaciclib arm, of patients experiencing grade 2 diarrhea, 687 out of 1076 (63.8%) patients experienced single occurrences and of patients experiencing grade ≥3 190 out of 219 (86.7%) patients experienced single occurrences.

[b]Three hundred and eight out of 857 (36%) patients had a dose hold for grade 2 diarrhea and 136 out of 218 (62%) for grade 3 diarrhea.

[c]Eight hundred and ninety-eight out of 1255 (71.5%) patients received antidiarrheal medication for grade 1 diarrhea; 737 out of 857 (86.0%) patients received antidiarrheal medication for grade 2; and 193 out of 218 (88.5%) patients for grade 3 diarrhea.

[d]Composite terms, see Table 1—footnote for definitions.

[e]Including six patients in abemaciclib + ET and one patient in ET alone who reported simultaneous PE/deep vein thrombosis (DVT).

[f]Recurrent event defined as a new grade ≥3 event after resolution of the initial occurrence.

were reversible with dose modifications or abemaciclib discontinuation. The study sponsor conducted an in-depth analysis in 11 patients with laboratory abnormalities of AST/ALT >3× ULN with total bilirubin >2× ULN, and in 3 additional patients with reported AEs which could indicate potential liver injury (Table 2). This analysis showed that no patients developed drug-induced liver injury and identified other reasons to explain the abnormal laboratory findings (i.e. metastatic disease, preexisting or acute liver disease, other comedication).

Adverse events by age

An analysis to characterize AEs in the older population was conducted (840 patients aged ≥65 years, 15% of the safety population) (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.03.006). The incidence of any grade AEs was similar in both arms across age subgroups. However, older patients (≥65 years) had ∼5% higher incidence of grade ≥3 AEs compared to younger patients (<65 years); in the abemaciclib arm, clinically relevant AEs driving this difference were diarrhea (11.9% versus 7.1%) and fatigue (5.6% versus 2.4%). Other events reported more frequently in older patients included nausea, anemia, thrombocytopenia, and decreased appetite and were mainly low grade.

Patient-reported outcome data

The overall patient compliance was >90% of the expected patients at each study visit across the PRO instruments. The MMRM mean summary scores for HRQoL, ET symptoms, and fatigue were numerically similar between treatment arms (<0.5 baseline SD MID) (Supplementary Figures S4-S6, available at https://doi.org/10.1016/j.annonc.2022.03.006). The MMRM mean scores for items reflecting symptoms of arthralgia, fatigue, and hot flushes were also numerically similar (<1 MID) between arms in the post-randomization assessments (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.03.006).

There were observed differences between arms in the MMRM analysis for the item 'I have diarrhea' (FACT-ES C5). In the abemaciclib arm, changes from baseline in the MMRM item score at 3 months [mean = 1.19; standard error (SE) = 0.02] and 6 months (mean = 1.03; SE = 0.02) were greater than the MID; from ≥12 months, the change from baseline was <1 MID (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.03.006). From ≥3 months, most patients who experienced diarrhea in the abemaciclib arm reported having diarrhea 'a little bit' or 'somewhat' (Figure 4A); diarrhea was more frequently reported in the earlier PRO assessments (months 3 and 6). The frequency of patient-reported diarrhea reduced after treatment discontinuation (first follow-up visit).

The MMRM mean scores for the FACT-B GP5 item 'I am bothered by side-effects of treatment' were, however, numerically similar, reflected in similar changes from baseline between treatment arms (<1 MID) (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.03.006). Most patients in both arms reported being bothered 'a little' or 'not at all' by treatment side-effects (Figure 4B).

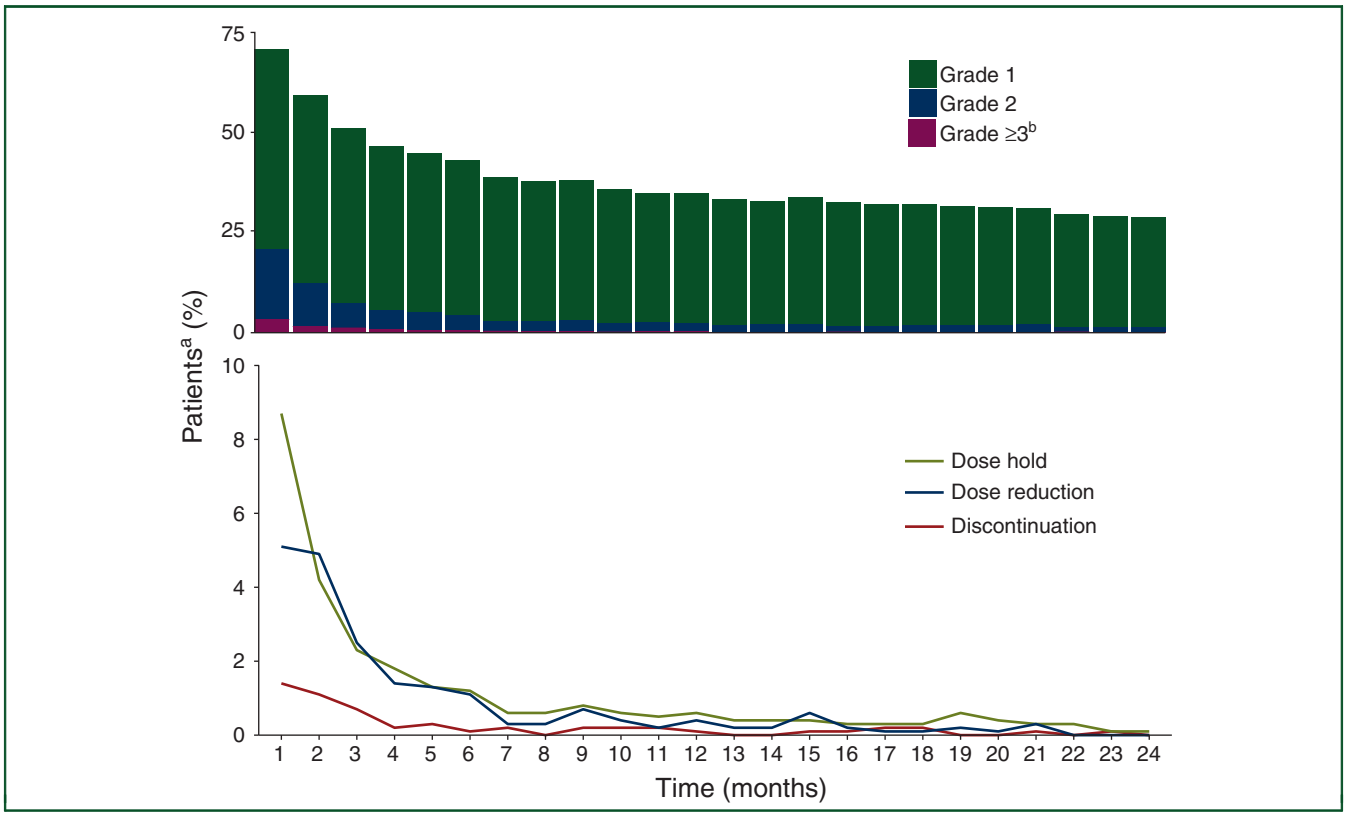


Figure 3. Diarrhea management over time.
G, grade.
[a]In the by-month analyses, number of patients at risk each month is used as the denominator to calculate % of events.
[b]There were no G4 events and one G5 event.

DISCUSSION

The safety profile of abemaciclib + ET is well established and clinically manageable in ABC.[4] The safety profile of adjuvant abemaciclib has now also been established and is considered predictable, manageable, and acceptable in a high-risk EBC population based on a comprehensive assessment of safety in 2791 patients treated with abemaciclib + ET in monarchE. With 90% of patients off the study treatment period and a follow-up duration in excess of 2 years, the safety data are considered mature.

Although grade ≥3 AEs were higher in the abemaciclib arm, they were predominantly laboratory events without clinical symptoms, such as neutropenia, which were effectively managed with dose adjustments as per protocol and rarely caused serious complications, like febrile neutropenia or infections. Similarly, grade ≥3 increased transaminases were more frequent in the abemaciclib arm, were easily managed with dose adjustments, and did not result in drug-related liver injury.[7] There was a 6% higher incidence of SAE in the abemaciclib arm compared to the ET-alone arm; however, discontinuation rates due to SAEs were similar (abemaciclib + ET: 0.9%; ET: 0.6%), with the most common SAEs in both arms being non-neutropenic infections. In the follow-up period, the incidence of SAEs was similar in both arms, and no serious safety concerns were identified.

Medical review of individual fatal AEs during treatment or ≤30 days from discontinuation did not reveal any common pathophysiological cause for deaths, or a common mechanistic reason attributed to a drug effect in either treatment arm. Except for a death due to pneumonia (suspected coronavirus disease-19), all deaths in the abemaciclib arm were in patients with predisposing risk factors, including clinically important comorbidities. Half of the fatal events in the control arm were infections with no common pathogen.

The most frequently reported AEs, including the clinically important AEs, occurred early during treatment. Events were mainly low grade, reversible, and manageable, and most patients continued abemaciclib treatment. Of note, ET-associated AEs were lower in abemaciclib-treated patients (arthralgia, 26.6% versus 37.9%; hot flush, 15.3% versus 23.0%) (see Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.03.006 in Harbeck et al.[1]). Overall, PRO data showed that the addition of abemaciclib to ET did not result in a clinically meaningful difference in patients being bothered by treatment side-effects after the first 3 months of treatment.

Abemaciclib dose modifications occurred early during treatment and were used to effectively manage both high- and low-grade AEs, thus helping to improve tolerability and retain patients on treatment, as demonstrated by the small proportion of patients discontinuing abemaciclib after a dose reduction. Two-thirds of the abemaciclib discontinuations due to AEs were triggered by low-grade events, mainly occurring early on treatment. Notably, in over half of total

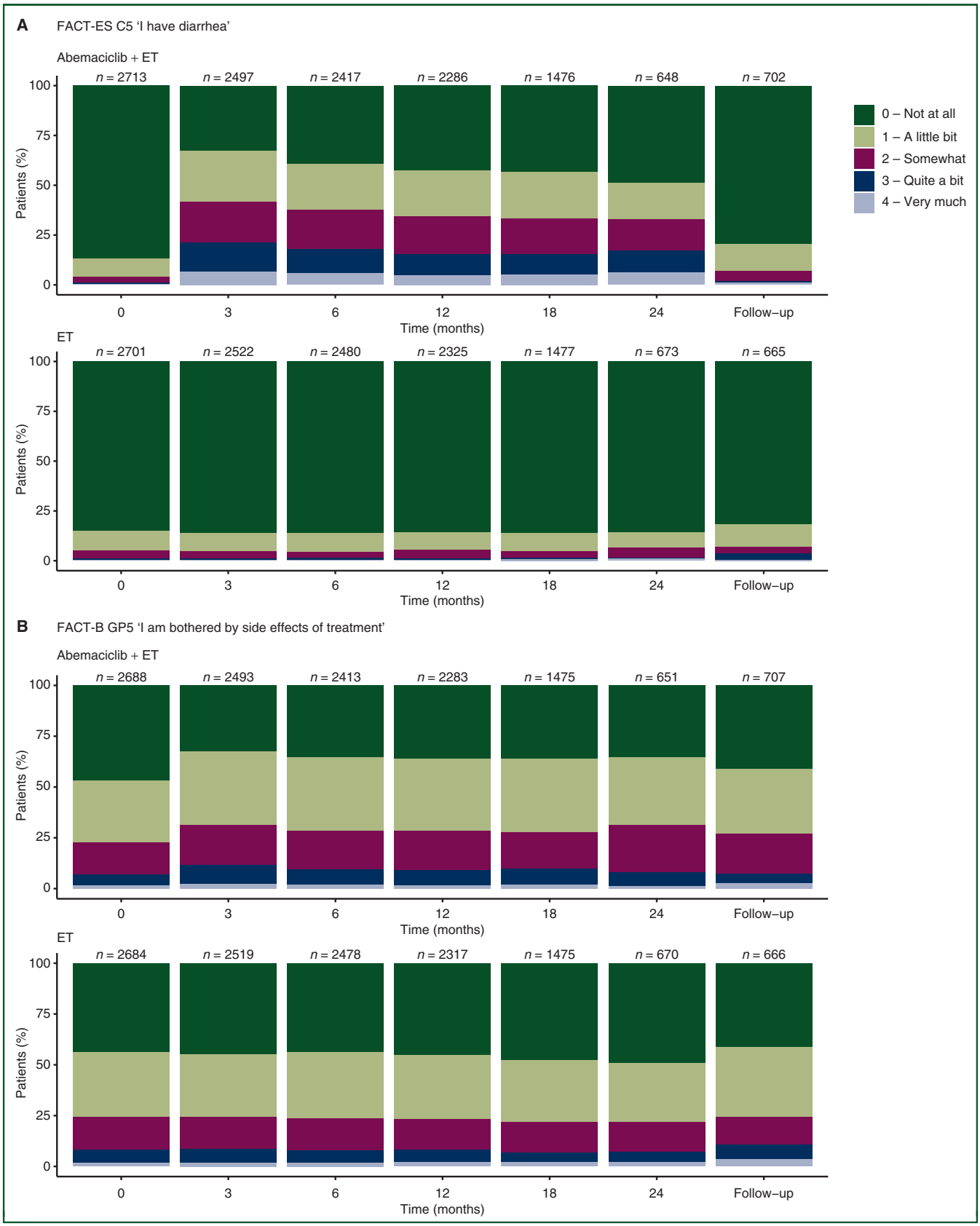


Figure 4. Percent stacked bar plot of patient-reported outcomes (PROs) as per study visit.
(A) PRO on FACT-ES C5 'I have diarrhea' in patients in the abemaciclib arm and (B) PRO on FACT-B GP5 'I am bothered by side-effects of treatment' in patients in the abemaciclib arm and the control arm. The observed differences between the trial arms in patient-reported diarrhea were not, however, reflected in patients' responses to 'I am bothered by side-effects of treatment' (FACT-B GP5).
ET, endocrine therapy; *n*, number of patients having answered the questionnaires at each study visit.

discontinuations, there was no prior dose reduction, highlighting the importance of patient counseling for symptom management before starting therapy and management of symptomatic patients with early use of concomitant medications and/or dose modifications to achieve tolerable individualized dosing. Several factors may have contributed to early discontinuations without dose modifications, including early appearance of nuisance AEs like diarrhea, 'treatment fatigue' due to prolonged symptom-inducing adjuvant therapy (~95% of patients had prior chemo/radiotherapy), potential lack of knowledge about management of toxicities, and the unknown benefit of the novel combination during study participation.

Most patients treated with abemaciclib experienced mild or moderate diarrhea, and most patients experiencing >4 stools over baseline (grade ≥2) reported only one episode, with events concentrated in the first months of treatment. Patients should be counseled regarding the early onset of diarrhea and begin antidiarrheal medication at the first sign of loose stools (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.03.006). In clinical practice, a personalized approach to diarrhea management should be considered, including dietary changes or institution of prophylaxis with antidiarrheal medication for recurrent events, balanced against the risk of constipation. If symptoms do not resolve after initiation of antidiarrheal medication, dose adjustments can improve tolerability by decreasing the severity and duration of the episodes. In monarchE, most patients managed their diarrhea with over-the-counter medication, some (<25%) required a dose modification, and few patients discontinued due to diarrhea (5%). Education is needed to optimize diarrhea management in patients with EBC to further reduce early discontinuations associated with low-grade diarrhea; ~1/3 of patients experiencing <4 stools over baseline (grade 1) did not take antidiarrheal medication (footnote, Table 2), and over 60% of patients with grade 2 diarrhea did not hold the abemaciclib dose, most discontinuations occurring in patients with no dose reductions. After the first 6 months, diarrhea was generally grade 1 and most likely intermittent since it rarely required dose modifications, consistent with most of the patients reporting diarrhea were 'a little bit' or 'somewhat' bothered by symptoms at 3 months onward. Altogether, these data demonstrate that early, proactive management of diarrhea is an effective strategy.

VTEs and ILDs have been reported with other CDK4 and 6 inhibitors in combination with ET,[8] and confirmed as a class effect by the United States FDA.[9] Oncologists are familiar with recognizing and treating those events in clinical practice. Although VTEs and ILDs were higher in the abemaciclib arm, serious VTE and ILD events were uncommon.[8] PE was reported in 1% of abemaciclib-treated patients; however, one-third were uncomplicated grade 3 events (which is a minimum CTCAE grading for PE) not requiring hospitalization.

Most patients experiencing VTE continued abemaciclib after starting anticoagulation, and only one event recurred after resuming treatment. Half of the events occurred within the first 6 months; no cumulative effect or increased risk with longer treatment duration of abemaciclib was observed. Risk factors for VTEs were further investigated. In particular, tamoxifen is known to increase the risk of VTE[10] and was associated with a numerically higher proportion of VTE versus aromatase inhibitors in the abemaciclib arm. Although the low incidence of VTEs precludes definitive conclusions, all risks associated with VTE [including prior history of VTE (exclusion criterion in monarchE study), high BMI, central venous catheter, or immobility] must be considered when deciding the appropriate ET for each patient. Patients should receive counseling on lifestyle modifications to prevent VTE, as well as symptoms concerning for VTE to allow early detection and management.

To fully characterize the risk of ILD in the adjuvant population, a comprehensive analysis was conducted, including broad terms such as 'radiation pneumonitis'. Half of the ILD events were asymptomatic. Most patients with symptomatic ILDs (grade ≥2) could continue abemaciclib after being treated with steroids and/or antibiotics, as per standard practice. The higher rate of ILD in Asia was attributed to reporting asymptomatic findings.

Fatigue was higher in the abemaciclib arm and was mainly low grade, but the difference in AE incidence between the two arms was not reflected in PRO data, suggesting an overall minimal impact on patients. Adequate monitoring and timely management with dose adjustments are recommended to reduce discontinuations due to fatigue.

The safety profile of abemaciclib was generally consistent across age subgroups, as previously described in ABC.[11] The higher rates of certain AEs, mainly low grade, reported in older patients, are expected in this generally more fragile subgroup.

As treatment in the adjuvant setting is with curative intent, it does not provide the opportunity seen in the metastatic palliative care setting to improve disease-related symptoms and HRQoL. The PRO findings in monarchE support the tolerability of abemaciclib + ET in EBC, with similar patient-reported HRQoL and patients reporting being 'bothered by side-effects of treatment' compared to ET alone. Safety and PRO data collection continue to further evaluate long-term safety and tolerability. Some limitations should be considered; the frequency of PRO assessments was insufficient to capture patient-reported side-effects and HRQoL within the first 3 months. Moreover, the MMRM analysis reports mean values and does not provide granularity into the effects of abemaciclib for patients experiencing AEs. The PRO data were administered manually within the monarchE trial as, at the time of the implementation, broad access to electronic systems and devices or internet was not uniform across all 37 countries. In routine clinical practice, more frequent monitoring of patient-reported symptoms captured electronically, plus offering alternative modes of administration to assure vulnerable patients report their symptoms, may improve side-effect management and patient outcomes.[12,13]

In conclusion, the overall safety profile of abemaciclib in monarchE is consistent with the well-established safety profile of abemaciclib. The combination of abemaciclib + ET

has a manageable and acceptable safety profile as adjuvant therapy and supports a positive benefit–risk balance for patients with HR+, HER2−, node-positive, high-risk EBC. Given the risk of VTE, which may be impacted by the choice of endocrine partner, and the time course of diarrhea, education of health care providers and patients as well as early intervention and risk monitoring are important to improve tolerability.

ACKNOWLEDGEMENTS

The authors generously thank the patients who participated in the trial, as well as their families, and all those who provided support to the participants. The authors thank the investigators and their support staff who participated in this work. The authors are very grateful for the time and efforts of the monarchE Executive and Steering Committees. The authors thank Sarah C. Nabinger and Eglantine Julle-Daniere for their writing and editorial assistance.

FUNDING

This study was sponsored by Eli Lilly and Company (no grant number).

DISCLOSURE

HSR reports grants from Pfizer, Novartis, Eli Lilly and Company, Genentech/Roche, Macrogenics, Merck, Boehringer Ingelheim, Polyphor, OBI, Odonate, Daiichi, Astra Zeneca, Seattle Genetics, Immunomedics, Sermonix; personal fees from Mylan, Puma, Samsung outside the submitted work. JO reports personal fees from AbbVie Inc., Agendia, Amgen Biotechnology, Aptitude Health, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene Corporation, Clovis Oncology, Daiichi Sankyo, Eisai, G1 Therapeutics, Gilead Sciences, GRAIL, Halozyme Therapeutics, Heron Therapeutics, Immunomedics, Ipsen Biopharmaceuticals, Eli Lilly and Company, Merck, Myriad, Nektar Therapeutics, Novartis, Pfizer, Pharmacyclics, Pierre Fabre Pharmaceuticals, Puma Biotechnology, Prime Oncology, Roche/Genentech, Samsung Bioepis, Sanofi, Seagen, Seattle Genentech, Syndax Pharmaceuticals, Taiho Oncology, Takeda, Synthon outside the submitted work. FB reports personal fees for honoraria and advisory role for Roche, Pfizer, Eli Lilly and Company, and Novartis outside the submitted work. MT reports research grants from JBCRG association, Astellas, AFI technologies, Shionogi, and GL Science; research grants and personal fees from Chugai, Takeda, Pfizer, Kyowa-Kirin, Taiho, Eisai, Daiichi-Sankyo, AstraZeneca, Shimadzu, Yakult, and Nippon Kyaku; other fees from Kyowa-Kirin and Daiichi-Sankyo; personal and other fees from Eli Lilly and Company, Konica Minolta, Bristol Myers Squibb, Athenex Oncology, Bertis Terumo, and Kansai Medical Net; personal fees for honoraria from MSD, Exact Science, and Novartis; and serves as a board of director for JBCRG association, Organisation for Oncology and Translational Research, and Kyoto Breast Cancer Research Network, outside the submitted work. IB reports grants and research support to institution: AstraZeneca, Roche and Eli Lilly and Company; personal fees for honoraria and advisory role from AstraZeneca, Roche, Novartis, Eisai, Celgene, Pfizer, Eli Lilly and Company, Pierre Fabre and Bristol-Myers Squibb, Veracyte outside the submitted work. MG reports personal fees from MSD, Novartis, GenDrug, and Amgen, outside the submitted work. TY reports grant and other fees from Chugai, Taiho, Nippon Kayaku, Kyowa Kirin; other fees from Eisai, Novartis Pharma, Astra Zeneca, Eli Lilly and Company, Daiichi Sankyo, and Pfizer Japan outside the submitted work. FZ reports personal fees for honoraria, fees for lectures and advisory role for Astra Zeneca, Daiichi, Eli Lilly and Company, Merck, Novartis, Pfizer, and Roche outside the submitted work. MC reports personal fees from Eli Lilly and Company, Novartis, and GT1; other fees from AstraZeneca, Sanofi, Servier, AbbVie, Accord, Pfizer, Seagen, and Daichii Sankyo, outside of the submitted work. BSA, AS, MH, JB, AZ, RW are full-time employees of Eli Lilly and Company and/or Eli Lilly and Company shareholders. SRDJ reports personal fees from AstraZeneca, Eli Lilly and Company, Novartis, Pfizer, Puma Biotechnology, Eisai, and Roche/Genentech; personal fees and other from AstraZeneca, Eli Lilly and Company, Novartis, Pfizer, Puma Biotechnology, and Roche/Genentech, outside the submitted work. MR reports personal fees from Pfizer, Novartis, Eli Lilly and Company, Roche Pharma AG, AstraZeneca, Daiichi Sankyo, Hexal, Novartis, SOMATEX, Seagen, and Pfizer; other fees from Pfizer, Celgene, and Novartis, outside the submitted work. SMT reports grants and personal fees from Eli Lilly and Company during the conduct of the study; grants and personal fees from AstraZeneca, Eli Lilly and Company, Merck, Nektar, Novartis, Pfizer, Genentech/Roche, Exelixis, Bristol-Myers Squibb, Eisai, Nanostring, Sanofi, Odonate, Immunomedics/Gilead; grants from Cyclacel; personal fees from Puma, Celldex, Seattle Genetics, Silverback Therapeutics, G1 Therapeutics, Athenex, OncoPep, Kyowa Kirin Pharmaceuticals, Daiichi Sankyo, CytomX, Samsung Bioepsis Inc., Certara, Mersana Therapeutics, OncoSec, Ellipses Pharma, 4D Pharma, Chugai Pharma, Infinity Therapeutics, BeyondSpring Pharmaceuticals outside the submitted work. All other authors have declared no conflicts of interest.

DATA SHARING

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 United States and European Union or after primary publication acceptance, whichever is later. No expiration date for data requests is set once the 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 online instructions.

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