MONARCH 2: Subgroup Analysis of Patients Receiving Abemaciclib Plus Fulvestrant as First-Line and Second-Line Therapy for HR$^+$, HER2$^-$-Advanced Breast Cancer

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ABSTRACT

Purpose: In MONARCH 2, abemaciclib plus fulvestrant significantly prolonged progression-free survival (PFS) and overall survival (OS) versus placebo plus fulvestrant in patients with hormone receptor positive (HR$^+$), HER2$^-$ advanced breast cancer. This exploratory analysis assessed the efficacy of abemaciclib plus fulvestrant across subgroups of patients receiving study therapy as first- or second-line treatment for metastatic disease.

Patients and Methods: Improvements were estimated using Cox models, and a test of interactions of subgroups with treatment was performed.

Results: The benefit in PFS [first-line, HR, 0.57; 95% confidence interval (CI), 0.45–0.73; second-line, HR, 0.48; 95% CI, 0.36–0.64] and OS (first-line, HR, 0.85; 95% CI, 0.64–1.14; second-line, HR, 0.66; 95% CI, 0.46–0.94) was observed across both subgroups, consistent with the intent-to-treat (ITT) population. In first-line patients (abemaciclib arm, $n = 265$; placebo arm, $n = 133$), the numerically largest effect on PFS and OS was observed in patients with primary resistance to endocrine therapy (ET; PFS, HR, 0.40; 95% CI, 0.26–0.63; OS, HR, 0.58; 95% CI, 0.35–0.97) and visceral disease (PFS, HR, 0.54; 95% CI, 0.39–0.73; OS, HR, 0.82; 95% CI, 0.58–1.20). In second-line patients (abemaciclib arm, $n = 170$; placebo arm, $n = 86$), a numerical benefit in PFS and OS was observed across primary and secondary ET resistance, with numerically more pronounced effects observed in patients with visceral disease (PFS, HR, 0.39; 95% CI, 0.27–0.57; OS, HR, 0.51; 95% CI, 0.33–0.81). Prolongation of time to second disease progression, time to chemotherapy, and chemotherapy-free survival was observed in both subgroups.

Conclusions: Consistent with the ITT population, a benefit in PFS and OS was observed across the first- and second-line subgroups in MONARCH 2.

Introduction

Abemaciclib in combination with endocrine therapy (ET) is approved for management of hormone receptor positive (HR$^+$), HER2$^-$ advanced breast cancer (ABC) as initial therapy with an aromatase inhibitor (MONARCH 3; ref. 1), or after disease progression on prior ET in combination with fulvestrant (MONARCH 2; ref. 2). In addition, abemaciclib is approved by the FDA as monotherapy treatment for endocrine refractory disease in patients with HR$^+$, HER2$^-$ ABC (MONARCH 1; ref. 3).

In MONARCH 2 (NCT02107703), abemaciclib plus fulvestrant demonstrated a statistically significant improvement in progression-free survival (PFS) and overall survival (OS) compared with placebo plus fulvestrant in patients with ET-resistant HR$^+$, HER2$^-$ ABC, regardless of menopausal status (2, 4). PFS and OS benefits in the abemaciclib arm versus the placebo arm were consistent across stratification factors. More pronounced PFS and OS benefits in the abemaciclib arm were observed in patients with primary resistance to prior ET [PFS, HR, 0.45; 95% confidence interval (CI), 0.31–0.67; OS, HR, 0.69; 95% CI, 0.45–1.04] and in patients with visceral disease (PFS, HR, 0.48; 95% CI, 0.37–0.63; OS, HR, 0.68; 95% CI, 0.51–0.89). The addition of abemaciclib to fulvestrant demonstrated a statistically significant improvement in exploratory endpoints such as time to second disease progression (PFS2; median, 23.1 months vs. 20.6 months; HR, 0.68; 95% CI, 0.56–0.82), time to chemotherapy (TTC; median, 50.2 months vs. 22.1 months; HR, 0.63; 95% CI, 0.50–0.78), and chemotherapy-free survival (CFS; median, 25.5 months vs. 18.2 months; HR, 0.64; 95% CI, 0.53–0.77; ref. 4).

Here, we present the efficacy and safety results from an exploratory analysis of MONARCH 2 in patients receiving first-line study treatment and patients receiving second-line study treatment for metastatic

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Line of treatment in the metastatic setting is often discussed in clinical practice. This exploratory analysis of the MONARCH 2 study assessed the efficacy of abemaciclib across first- and second-line subgroups of patients with HR^+, $HER2^-$ advanced breast cancer. Consistent with progression-free survival (PFS) and overall survival (OS) results in the intent-to-treat population, benefit was seen in both subgroups of this exploratory analysis. In first-line patients, the numerically largest effect on PFS and OS was observed in patients with primary resistance to endocrine therapy (ET) and visceral disease. In second-line patients, a numerical benefit in PFS and OS was observed across primary and secondary ET resistance, with a numerically more pronounced effect in patients with visceral disease. Prolongation of time to second disease progression, time to chemotherapy, and chemotherapy-free survival was observed in both subgroups. Abemaciclib plus fulvestrant was well tolerated with a manageable safety profile.

disease. In addition, we explored the impact of the stratification factors as well as duration of prior endocrine treatment on the efficacy, separately within first- and second-line patients.

Patients and Methods

Study design and treatment

MONARCH 2 was a global, randomized (2:1), double-blind, placebo-controlled phase III study of abemaciclib plus fulvestrant versus placebo plus fulvestrant in ET-resistant HR^+, $HER2^-$ patients with ABC, regardless of menopausal status, and with no prior chemotherapy for metastatic disease. The study details, including randomization, stratification, and inclusion/exclusion criteria, have been previously published (2). Patients received abemaciclib (150 mg) or placebo orally twice daily each 28-day cycle on a continuous schedule plus fulvestrant (500 mg) by intramuscular injection on days 1 and 15 of the first cycle and on day 1 of each cycle thereafter (2). Treatment continued until progressive disease (PD), death, or withdrawal from the study for any other reason. The study was conducted in compliance with the Declaration of Helsinki. The conduct of the trial was overseen by a steering committee, and an independent data monitoring committee reviewed the safety data up to the primary analysis. The ethics committees of all participating centers approved the protocol, and all patients included in the study signed an informed consent before joining the study.

Patients

Patients included in the first-line subgroup were those receiving study therapy as first-line treatment for metastatic disease, and their most recent line of ET was in the (neo)adjuvant setting. Patients included in the second-line subgroup were those receiving study therapy as second-line therapy for metastatic disease, and their most recent line of ET was in the metastatic setting. Within each subgroup, outcomes were also analyzed by stratification factors [site of metastasis (visceral, bone only, or other) and resistance to prior ET (primary vs. secondary)] and by prior ET duration. Primary ET resistance included patients whose disease relapsed during the first 2 years of neoadjuvant or adjuvant ET, or progressed within the first 6 months of first-line ET for ABC. Secondary resistance included patients who did not meet the criteria for primary ET resistance (2).

Efficacy and safety measures

Efficacy and safety assessments were performed on all enrolled patients. CT or MRI (according to RECIST version 1.1) was used to measure tumors within 28 days before random assignment (baseline) and then every 8 weeks for the first year, every 12 weeks thereafter, and within 2 weeks of clinical progression. Bone scintigraphy was performed at baseline, and then every sixth cycle starting with Cycle 7.

Endpoints

Investigator-assessed PFS (MONARCH 2 primary endpoint) and OS (key secondary endpoint) are reported across all exploratory subgroups. PFS is defined as the time from randomization until objective PD or death for any reason. OS is defined as the time from randomization to death due to any cause. Exploratory endpoints PFS2, TTC, and CFS, as well as safety and tolerability are reported across subgroups as previously described (2). Briefly, PFS2 is the time from randomization to the discontinuation of first subsequent postdiscontinuation therapy or death, whichever occurs first; TTC is the time from randomization to initiation of first postdiscontinuation chemotherapy, censoring patients who died before initiation of chemotherapy; and CFS is the time from randomization to the initiation of first postdiscontinuation chemotherapy or death, whichever occurs first.

Statistical analyses

Exploratory efficacy subgroup analyses were conducted by first- or second-line treatment. For time-to-event endpoints (PFS, OS, PFS2, TTC, and CFS), treatment effect HRs with 95% CIs were estimated using Cox models, and a test of interactions of subgroups with treatment was performed. In addition, separately within first- or second-line patients, the similar Cox models were performed on PFS and OS by stratification factors (ET resistance and site of metastases), as well as by prior ET duration. Two-sided P values were used to compare efficacy between treatment groups and for interaction tests associated with the subgroup factors. All hypotheses were tested at the two-sided 0.05 level, and all CIs used a 95% confidence level. Safety was assessed in all patients who received at least 1 dose of any study treatment (i.e., the safety population), separately by first- versus second-line patients. SAS (version 9.2 or later; SAS Institute) was used for statistical analyses.

Results

About 59.5% of patients in MONARCH 2 received study treatment as first-line therapy [abemaciclib arm, $n = 265$ (59.4%); placebo arm, $n = 133$ (59.6%)], and 38.3% as second-line therapy [abemaciclib arm, $n = 170$ (38.1%); placebo arm, $n = 86$ (38.6%)] for metastatic disease (2). Baseline characteristics were balanced within each subgroup (**Table 1**). Similar to the intent-to-treat (ITT) population, the majority of patients within each subgroup entered the study with secondary ET resistance (72.4% in first-line and 77.7% in second-line) and/or visceral disease (56.5% in first-line and 56.3% in second-line).

PFS and OS

At data cutoff (June 20th, 2019), the benefit in PFS (**Fig. 1A**) and OS (**Fig. 1B**) observed across first- and second-line therapies was consistent with the ITT population, with no statistically significant interaction between the first- and second-line for PFS ($P = 0.341$) or OS ($P = 0.265$). The Kaplan–Meier curves of PFS (**Fig. 1A**) showed early and sustained separation between treatment arms starting at 3 months in both first-line (HR, 0.57; 95% CI, 0.45–0.73) and second-line (HR, 0.48; 95% CI, 0.36–0.64) subgroups. With regards to OS in

Table 1. Baseline characteristics by subgroup.

	First-line subgroup		Second-line subgroup	
	Abemaciclib + fulvestrant *N* = 265	**Placebo + fulvestrant *N* = 133**	**Abemaciclib + fulvestrant *N* = 170**	**Placebo + fulvestrant *N* = 86**
Metastatic site, *n* (%)				
Visceral	147 (55.5)	78 (58.6)	95 (55.9)	49 (57.0)
Bone only	77 (29.1)	36 (27.1)	44 (25.9)	20 (23.3)
Other[a]	41 (15.5)	19 (14.3)	31 (18.2)	17 (19.8)
Endocrine therapy resistance, *n* (%)				
Primary[b]	71 (26.8)	39 (29.3)	39 (22.9)	18 (20.9)
Secondary[c]	194 (73.2)	94 (70.7)	131 (77.1)	68 (79.1)

Abbreviations: ET, endocrine therapy; *N*, number of patients in trial; *n*, number of patients in subgroups.
[a]*Other* refers to sites not involving visceral and not bone, such as lymph nodes, soft tissue, skin, etc., with or without bone metastases, additionally.
[b]Primary ET resistance: In the adjuvant setting, recurrence within the first 2 years of adjuvant ET while on ET; in the locally advanced or metastatic setting, progression within first 6 months of initiating first-line ET while on ET.
[c]Patients receiving prior ET who do not meet the definition of primary endocrine resistance.

the first-line subgroup (**Fig. 1B**), an initial trend for separation of the 2 arms was observed around the median (36–42 months) followed by heavy censoring along the tails of the curves (42–54 months; HR, 0.85; 95% CI, 0.64–1.14). In the second-line subgroup, a separation of the OS Kaplan–Meier curves was observed starting at 30 months and was maintained over time (HR, 0.66; 95% CI, 0.46-0.94). Additional OS follow-up is warranted to further characterize these results.

Within first- and second-line subgroups, the treatment effects on PFS and OS were consistent across stratification factors, without statistically significant interactions. Among first-line patients, the numerically largest effect on PFS (**Fig. 2A**) and OS (**Fig. 2B**) was observed in patients with primary endocrine resistance (PFS, HR, 0.40; 95% CI, 0.26–0.63; OS, HR, 0.58; 95% CI, 0.35–0.97) and visceral disease (PFS, HR, 0.54; 95% CI, 0.39–0.73; OS, HR, 0.82; 95% CI, 0.57–1.17). In second-line patients, numerical benefit in PFS (**Fig. 2C**) and OS (**Fig. 2D**) was observed across primary (PFS, HR, 0.59; 95% CI, 0.33–1.08; OS, HR, 0.95; 95% CI, 0.43–2.11) and secondary (PFS, HR, 0.43; 95% CI, 0.31–0.60; OS, HR, 0.61; 95% CI, 0.41–0.91) endocrine resistance, with numerically more pronounced effects observed in patients with visceral disease (PFS, HR, 0.39; 95% CI, 0.27–0.57; OS, HR, 0.51; 95% CI, 0.33–0.81).

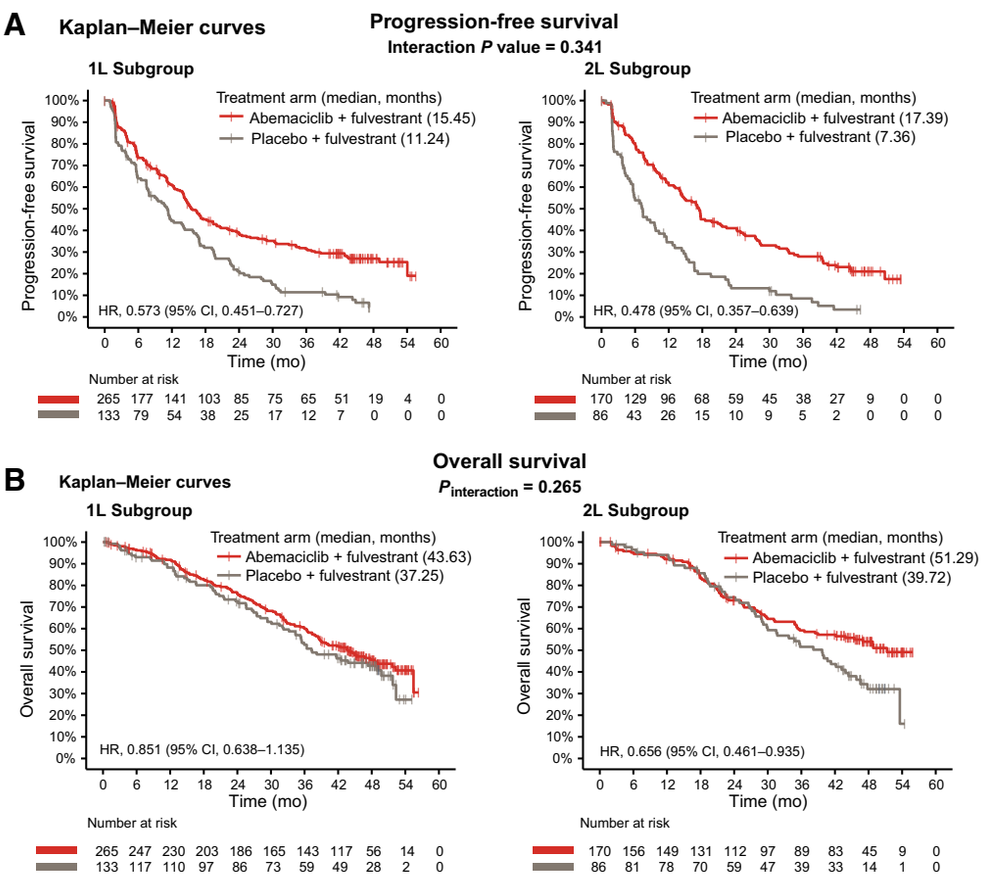

Figure 1.
Kaplan–Meier curves for first- and second-line subgroups. **A,** Progression-free survival by exploratory subgroup; **B,** overall survival by exploratory subgroup. $P_{interaction}$ values were calculated for values between the first-line and second-line subgroups. HR, hazard ratio.

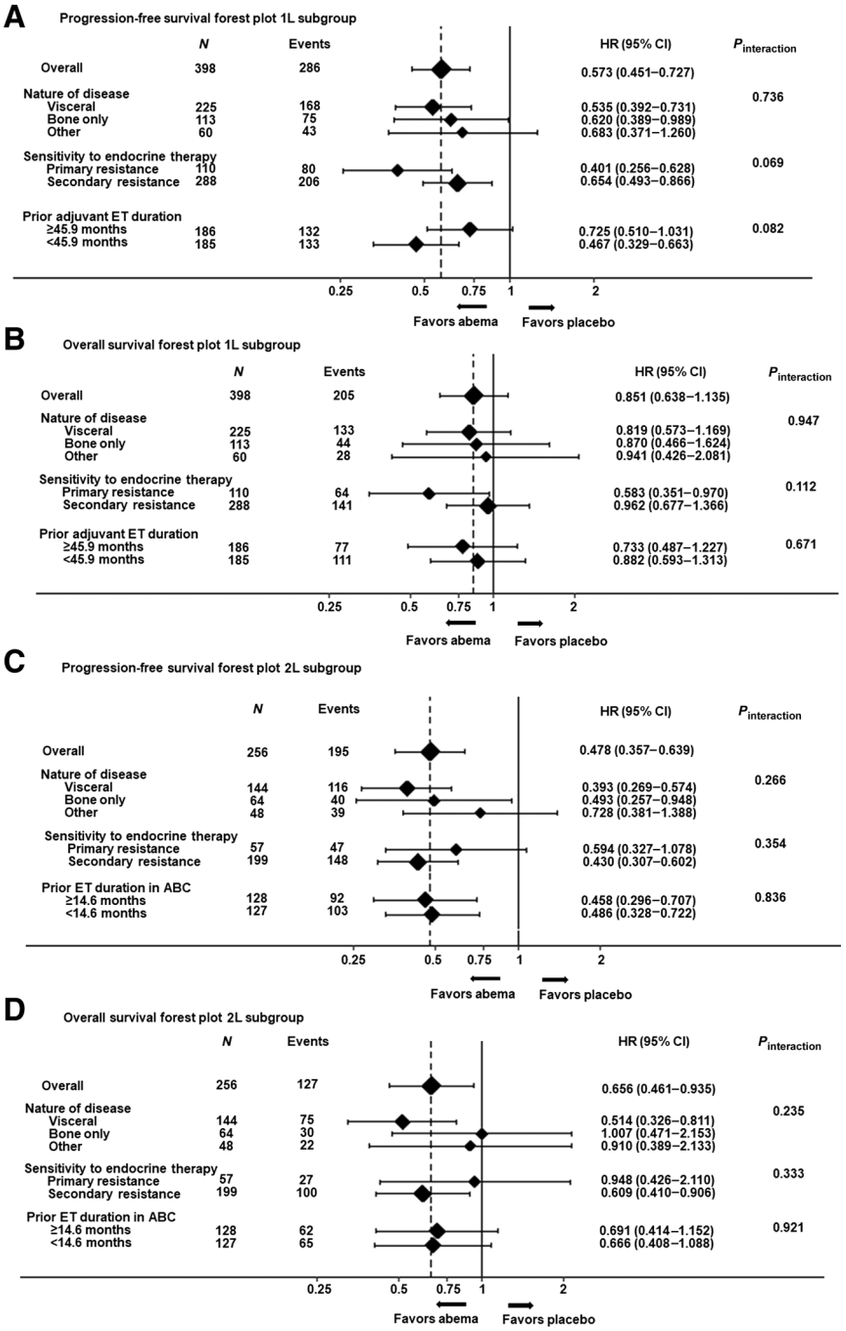

Figure 2.

Forest plot by first- and second-line subgroups. **A,** Progression-free survival (PFS) in first-line patients; **B,** overall survival (OS) in first-line patients; **C,** PFS in second-line patients; and **D,** OS in second-line patients. $P_{interaction}$ values were calculated for values between the categories for each stratification factor. The median duration of prior adjuvant ET was 45.9 months for first-line patients, and the median prior ET duration in ABC setting was 14.6 months for second-line patients. *N*, number of patients in population; *n*, number of patients in specified category. Note: *Other* refers to sites not involving visceral and not bone, such as lymph nodes, soft tissue, skin, etc., with or without bone metastases, additionally.

In addition, duration of ET is considered a potential prognostic variable in metastatic breast cancer. Of note, the stratification factor of primary versus secondary resistance used a 2-year cutoff for prior adjuvant ET duration, and 6 months for duration of prior first-line ET in the metastatic setting. Efficacy by prior ET duration was further explored within subgroups defined by median prior ET duration cutoff values, separately in first- and second-line patients. For first-line patients, the median duration of prior adjuvant ET was 45.9 months. In the placebo arm, median PFS and OS were both shorter in patients with primary versus secondary resistance (PFS, 7.9 months vs. 11.9 months; OS, 29.4 months vs. 47.3 months), and were also shorter in patients with prior adjuvant ET duration below versus above median (PFS, 8.9 months vs. 17.1 months; OS, 34.4 months vs. 47.3 months). As shown in **Fig. 2A**, similar to results by ET resistance, abemaciclib benefit in PFS was consistent across first-line patients above or below the median prior adjuvant ET duration ($P_{interaction} = 0.082$), with a more pronounced effect on those with ET duration below the median (HR, 0.47; 95% CI, 0.33–0.66). For OS (**Fig. 2B**), more pronounced effects were observed in those patients who had ET duration above the median unlike the results by ET resistance, although the benefit was consistent with prior ET duration below the median ($P_{interaction} = 0.671$).

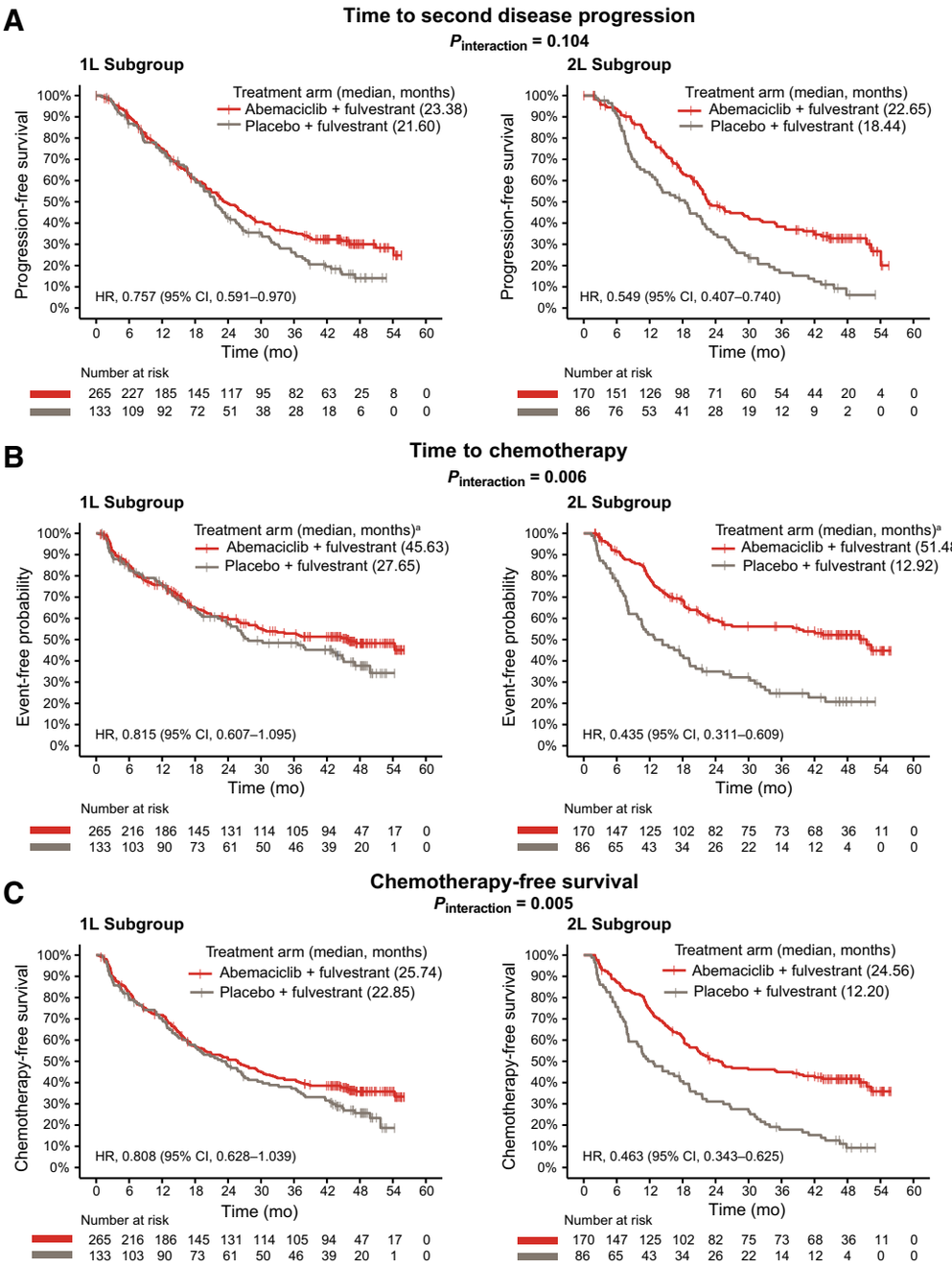

Figure 3.

Exploratory endpoints. Kaplan–Meier plots of time to second disease progression (**A**), time to chemotherapy (**B**), and chemotherapy-free survival (**C**) in first-line and second-line subgroups. $P_{interaction}$ values were calculated for values between the first-line and second-line. [a]The absolute median of TTC in each arm cannot be properly interpreted, as the concept of TTC is hampered by a lack of adjustment for patient death (i.e., patients who died before receiving chemotherapy were censored). *N*, number of patients in population; *n*, number of patients in specified category.

A similar dichotomized (below and above the median) analysis of prior ET duration in the ABC setting was performed for second-line patients. The median prior ET duration in second-line patients with ABC was 14.6 months. In the placebo arm, the lack of a clear pattern on median PFS and OS by primary versus secondary ET resistance (PFS, 7.4 months vs. 7.2 months; OS, 44.4 months vs. 35.8 months) and by prior ET duration in patients with ABC below versus above the median (PFS, 7.1 months vs. 9.5 months; OS, 31.5 months vs. 40.7 months) did not support prior ET duration as a prognostic variable for second-line patients. As a result, benefits in PFS (**Fig. 2C**) and OS (**Fig. 2D**) were both consistent across second-line patients with numerically comparable effects above or below

the median prior ET duration in patients with ABC (PFS, $P_{interaction}$ = 0.836; OS, $P_{interaction}$ = 0.921).

Other exploratory endpoints

In both first-and second-line subgroups, prolongation of PFS2 (**Fig. 3A**), TTC (**Fig. 3B**), and CFS (**Fig. 3C**) was observed for patients in the abemaciclib arm compared with the placebo arm. Delay in subsequent chemotherapy was statistically significantly larger (**Fig. 3B** and **C**; TTC, $P_{interaction}$ = 0.006; CFS, $P_{interaction}$ = 0.005) in the second-line subgroup (TTC, HR, 0.44; 95% CI, 0.31-0.61; CFS, HR, 0.46; 95% CI, 0.34–0.63) compared with the first-line subgroup (TTC, HR, 0.82; 95% CI, 0.61–1.10; CFS, HR, 0.81; 95% CI, 0.63–1.04). However, this result may have been driven by the large differences observed in the medians in the placebo arm. In addition, improvement in PFS2 (**Fig. 3A**) was consistent ($P_{interaction}$ = 0.104) across the first-line (HR, 0.76; 95% CI, 0.59–0.97) and second-line subgroups (HR, 0.55; 95% CI, 0.41–0.74).

Table 2. Treatment-emergent adverse events (≥10% in either arm) in first- and second-line subgroups.

	CTCAE Grade, *n* (%)							
	First-line				Second-line			
	Abemaciclib + fulvestrant (*N* = 264)		Placebo + fulvestrant (*N* = 133)		Abemaciclib + fulvestrant (*N* = 169)		Placebo + fulvestrant (*N* = 86)	
Adverse event (≥10% in either arm)	All Grade	≥Grade 3	All Grade	≥Grade 3	All Grade	≥Grade 3	All Grade	≥Grade 3
At least 1 TEAE	262 (99.2)	178 (67.4)	121 (91.0)	35 (26.3)	165 (97.6)	118 (69.8)	78 (90.7)	25 (29.1)
Diarrhea	229 (86.7)	37 (14.0)	36 (27.1)	1 (0.8)	150 (88.8)	27 (16.0)	23 (26.7)	0 (0.0)
Neutropenia	129 (48.9)	74 (28.0)	4 (3.0)	3 (2.3)	88 (52.1)	56 (33.1)	5 (5.8)	1 (1.2)
Nausea	126 (47.7)	5 (1.9)	33 (24.8)	4 (3.0)	87 (51.5)	6 (3.6)	21 (24.4)	1 (1.2)
Fatigue	109 (41.3)	9 (3.4)	40 (30.1)	1 (0.8)	75 (44.4)	9 (5.3)	23 (26.7)	1 (1.2)
Abdominal pain	95 (36.0)	6 (2.3)	23 (17.3)	1 (0.8)	66 (39.1)	8 (4.7)	13 (15.1)	0 (0.0)
Anemia	89 (33.7)	25 (9.5)	6 (4.5)	2 (1.5)	63 (37.3)	14 (8.3)	4 (4.7)	1 (1.2)
Leukopenia	84 (31.8)	28 (10.6)	2 (1.5)	0 (0.0)	61 (36.1)	21 (12.4)	2 (2.3)	0 (0.0)
Vomiting	76 (28.8)	1 (0.4)	16 (12.0)	4 (3.0)	47 (27.8)	3 (1.8)	9 (10.5)	1 (1.2)
Decreased appetite	72 (27.3)	1 (0.4)	18 (13.5)	1 (0.8)	53 (31.4)	3 (1.8)	11 (12.8)	0 (0.0)
Headache	66 (25.0)	2 (0.8)	21 (15.8)	1 (0.8)	39 (23.1)	1 (0.6)	14 (16.3)	0 (0.0)
Aspartate aminotransferase increased	49 (18.6)	9 (3.4)	10 (7.5)	3 (2.3)	20 (11.8)	3 (1.8)	6 (7.0)	4 (4.7)
Stomatitis	49 (18.6)	0 (0.0)	16 (12.0)	0 (0.0)	27 (16.0)	2 (1.2)	7 (8.1)	0 (0.0)
Alanine aminotransferase increased	48 (18.2)	15 (5.7)	6 (4.5)	2 (1.5)	22 (13.0)	5 (3.0)	6 (7.0)	2 (2.3)
Dysgeusia	45 (17.0)	0 (0.0)	3 (2.3)	0 (0.0)	36 (21.3)	0 (0.0)	3 (3.5)	0 (0.0)
Alopecia	43 (16.3)	0 (0.0)	3 (2.3)	0 (0.0)	31 (18.3)	0 (0.0)	1 (1.2)	0 (0.0)
Cough	43 (16.3)	2 (0.8)	17 (12.8)	0 (0.0)	28 (16.6)	0 (0.0)	12 (14.0)	0 (0.0)
Arthralgia	42 (15.9)	1 (0.4)	18 (13.5)	1 (0.8)	25 (14.8)	0 (0.0)	15 (17.4)	0 (0.0)
Upper respiratory tract infection	42 (15.9)	0 (0.0)	10 (7.5)	0 (0.0)	39 (23.1)	0 (0.0)	7 (8.1)	2 (2.3)
Edema peripheral	41 (15.5)	0 (0.0)	9 (6.8)	0 (0.0)	20 (11.8)	0 (0.0)	7 (8.1)	0 (0.0)
Thrombocytopenia	41 (15.5)	11 (4.2)	3 (2.3)	0 (0.0)	34 (20.1)	3 (1.8)	3 (3.5)	1 (1.2)
Constipation	40 (15.2)	1 (0.4)	23 (17.3)	1 (0.8)	28 (16.6)	2 (1.2)	12 (14.0)	0 (0.0)
Dizziness	39 (14.8)	3 (1.1)	11 (8.3)	0 (0.0)	26 (15.4)	0 (0.0)	5 (5.8)	0 (0.0)
Rash	38 (14.4)	4 (1.5)	8 (6.0)	0 (0.0)	[a]	[a]	[a]	[a]
Pruritus	37 (14.0)	0 (0.0)	9 (6.8)	0 (0.0)	27 (16.0)	0 (0.0)	5 (5.8)	0 (0.0)
Pyrexia	37 (14.0)	3 (1.1)	12 (9.0)	1 (0.8)	20 (11.8)	2 (1.2)	4 (4.7)	0 (0.0)
Weight decreased	36 (13.6)	1 (0.4)	5 (3.8)	2 (1.5)	[a]	[a]	[a]	[a]
Muscular weakness	33 (12.5)	2 (0.8)	9 (6.8)	0 (0.0)	18 (10.7)	4 (2.4)	4 (4.7)	0 (0.0)
Blood creatinine increased	32 (12.1)	1 (0.4)	1 (0.8)	0 (0.0)	32 (18.9)	3 (1.8)	0 (0.0)	0 (0.0)
Back pain	31 (11.7)	1 (0.4)	20 (15.0)	0 (0.0)	26 (15.4)	2 (1.2)	12 (14.0)	3 (3.5)
Hot flush	31 (11.7)	0 (0.0)	13 (9.8)	0 (0.0)	19 (11.2)	0 (0.0)	10 (11.6)	0 (0.0)
Pain in extremity	31 (11.7)	0 (0.0)	8 (6.0)	1 (0.8)	21 (12.4)	2 (1.2)	1 (1.2)	0 (0.0)
Dyspnea	27 (10.2)	9 (3.4)	16 (12.0)	1 (0.8)	26 (15.4)	3 (1.8)	9 (10.5)	1 (1.2)
Myalgia	27 (10.2)	0 (0.0)	8 (6.0)	0 (0.0)	[a]	[a]	[a]	[a]
Insomnia	[a]	[a]	[a]	[a]	21 (12.4)	0 (0.0)	5 (5.8)	0 (0.0)
Injection site reaction	[a]	[a]	[a]	[a]	20 (11.8)	2 (1.2)	11 (12.8)	0 (0.0)
Lymphopenia	[a]	[a]	[a]	[a]	20 (11.8)	7 (4.1)	1 (1.2)	0 (0.0)
Dry skin	[a]	[a]	[a]	[a]	19 (11.2)	0 (0.0)	1 (1.2)	0 (0.0)
Urinary tract infection	[a]	[a]	[a]	[a]	19 (11.2)	2 (1.2)	6 (7.0)	1 (1.2)
Influenza like illness	[a]	[a]	[a]	[a]	17 (10.1)	0 (0.0)	8 (9.3)	0 (0.0)
TEAEs of special interest[b]								
Venous thromboembolic events	17 (6.4)	7 (2.7)	0	0	12 (7.1)	6 (3.6)	2 (2.3)	1 (1.2)
Interstitial lung disease	8 (3.0)	1 (0.4)	1 (0.8)	0	3 (1.8)	1 (0.6)	0	0

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; *n*, number of patients in subgroup; TEAE, treatment-emergent adverse event.
[a]TEAEs less than 10% in both treatment arms are not presented.
[b]TEAEs <10% but of special interest.

Exposure and safety

Overall, no new safety signals were noted for the abemaciclib arm for patients receiving first- and second-line treatment. Any grade and grade ≥3 adverse events are shown in **Table 2**. Other treatment-emergent adverse events of special interest, including venous thromboembolic events (VTE) and interstitial lung disease (ILD), occurred in less than 10% of the patients each (**Table 2**). For patients receiving abemaciclib plus fulvestrant, VTEs occurred in 6.4% and 7.1% of first-line and second-line patients, respectively. Of these, 2.7% and 3.0% were reported as pulmonary embolism. ILD was reported in 3.0% and 1.8% of first-line and second-line patients receiving abemaciclib plus fulvestrant, respectively. The incidence of ≥grade 3 VTE and ILD was infrequent. Treatment discontinuation, drug exposure, and dose adjustment are presented in Supplementary Table S1. At the data cutoff date, a higher percentage of patients continued study treatment in the abemaciclib arm compared with the placebo arm in both first-line (20.0% vs. 4.5%) and second-line (13.5% vs. 2.3%) subgroups.

Discussion

This exploratory analysis evaluated efficacy and safety to determine the outcome of patients receiving study treatment (abemaciclib arm vs. placebo arm) as first- or second-line treatment for metastatic disease. In previous reports of the MONARCH 2 study, the abemaciclib arm showed a statistically significant improvement in OS, PFS, ORR, PFS2, TTC, and CFS compared with the control arm in patients with ET-resistant HR^+, $HER2^-$ ABC regardless of menopausal status (2, 4). In addition, the largest PFS and OS benefit from the abemaciclib arm was observed in patients with visceral disease and primary ET resistance (2).

The current exploratory analysis of patients demonstrated a benefit in PFS and OS across patients receiving abemaciclib plus fulvestrant as first- or second-line treatment for metastatic disease. This benefit was consistent with the ITT population. Although the results for first-line patients in the placebo arm indicated that prior adjuvant ET duration was a relevant prognostic variable, the abemaciclib effects on PFS and OS within first- and second-line subgroups were consistent across stratification factors and regardless of prior ET duration without statistically significant interactions, indicating the benefit of abemaciclib independent of ET duration.

ET is the backbone of HR^+ breast cancer treatment (5, 6). Although ET is effective in disease control, a substantial number of patients will develop endocrine resistance (7), which represents a clinical challenge. In the first-line subgroup, a numerically more pronounced effect on PFS and OS was noted in patients with primary ET resistance compared with those with secondary ET resistance, consistent with the previous observations in the ITT population (2, 4). This observation was not seen in the second-line subgroup. These results should be interpreted with caution because these exploratory analyses looked at subgroups (by ET resistance) within a subgroup (first- or second-line), resulting in small sample size for this comparison. Furthermore, the patient population composition was different between first- and second-line subgroups in terms of ET history before study treatment. The first-line subgroup includes patients whose most recent line of ET was in the (neo)adjuvant setting, either relapsed while receiving (neo) adjuvant ET or with a disease-free interval (DFI: defined as the time between the completion of adjuvant ET and disease recurrence) within 1 year. The second-line subgroup includes a mixture of patients: (i) those with *de novo* metastatic disease and who received 1 line of ET in the metastatic setting; (ii) those who received adjuvant ET with a DFI more than 1 year before they relapsed, then received 1 line of ET for metastatic disease. The heterogeneity of prior ET history for second-line patients may have confounded the results. Also, unlike in first-line patients where shorter median PFS and OS in the placebo arm appeared to be associated with primary ET resistance and shorter prior ET duration, the lack of a pattern on median PFS and OS in the placebo arm for second-line patients does not support ET resistance or prior ET duration as a prognostic variable in the second-line setting for ABC. As a result, subgroup analysis by prior ET duration only confirmed a more pronounced benefit in PFS in first-line patients with shorter prior adjuvant ET duration, consistent with the related observation of prior ET resistance; yet no clear and consistent pattern on PFS or OS could be interpreted in second-line patients by prior ET duration or resistance.

The site of metastases is a prognostic factor in breast cancer (8). Several studies have shown that patients with breast cancer with visceral metastases have a less favorable prognosis compared with patients with bone only metastases (8–12). Previous analysis of MONARCH 2 showed numerically more pronounced effects on PFS and OS among patients with visceral disease compared with patients with non-visceral disease in the ITT population (2, 4). The current exploratory analysis demonstrated patients with visceral disease had the numerically largest benefit in PFS and OS when treated with abemaciclib versus placebo, in both first- and second-line subgroups. These findings are important, as patients with visceral disease are less responsive to most cancer treatments (8–12).

In general, an important consideration in the treatment of ABC is to postpone chemotherapy as long as possible to maintain quality of life. The delay in chemotherapy initiation after abemaciclib was comparable between first- and second-line subgroups as indicated by the medians for TTC in the treatment arms. In contrast, large differences in median TTC/CFS in the placebo arms were observed between the 2 subgroups. This may indicate potential unmeasured confounding effects in specific types of postdiscontinuation therapy by subsequent lines between the two arms. In contrast with TTC/CFS, PFS2 was anchored to discontinuation of first subsequent line of postdiscontinuation therapy regardless of therapy type, and thus was more robust in assessing the benefit of abemaciclib carried over after discontinuation by the first- and second-line subgroups.

A potential limitation of the current analysis is the limited sample size within subgroups. Given the study was not powered to test treatment effect within any subgroups or interactions between subgroups and treatment, the focus of the current analysis was to estimate the key efficacy parameters and to describe the safety profile by the first- and second-line subgroups, as well as to explore the consistency of findings with the ITT population. The results (PFS and OS) thus need to be interpreted with caveats in general, especially for further breakdown by stratification factors (ET resistance and site of metastases) or by prior ET duration within the first- and second-line subgroups. Furthermore, the OS data were not fully mature at the time of the current analysis, resulting in even smaller sample sizes in certain subgroups; therefore, additional follow-up is warranted.

The PALOMA 3 and MONALEESA 3 studies evaluated efficacy of palbociclib and ribociclib, respectively, in combination with fulvestrant (13–17). PALOMA 3, MONALEESA 3, and MONARCH 2 had different eligibility criteria leading to differences in trial populations; therefore, cross-trial comparisons should be interpreted with caution. PALOMA 3 included patients who had received previous

chemotherapy or more than 1 line of prior ET for metastatic disease (15). Twenty-two percent of patients in PALOMA 3 received study therapy as first-line treatment for metastatic disease (15). PFS and OS outcomes for these patients were reported as part of broader subgroup analyses and were consistent with the ITT population with a statistically significant benefit in PFS (but not OS) for patients treated with palbociclib plus fulvestrant compared with placebo plus fulvestrant (15). MONALEESA 3 inclusion criteria were broader than MONARCH 2 in terms of prior ET history. In addition to the type of patients enrolled in MONARCH 2 ITT population, MONALEESA 3 also included patients who were "treatment naïve in advanced setting hereafter" (that is, with *de novo* advanced disease or relapsed greater than 12 months from completion of (neo)adjuvant ET, with no treatment for advanced disease; ref. 17). In MONALEESA 3, PFS and OS results were reported within the subgroup of patients who received up to 1 line of ET for advanced disease (i.e., early relapse or second-line; approximately 50% of the MONALEESA 3 population, and corresponding to MONARCH 2 ITT population); OS results were further reported by sensitivity to ET (16, 17). However, neither endpoint in MONALEESA 3 was reported by first- versus second-line patients as was done in this exploratory analysis of MONARCH 2.

In conclusion, abemaciclib plus fulvestrant demonstrated PFS and OS benefit across first- and second-line subgroups consistent with the ITT population. Among first-line patients treated with abemaciclib plus fulvestrant, the numerically largest effect on PFS and OS was observed in patients with visceral disease and primary ET resistance; benefit in PFS was also more pronounced in those with shorter prior adjuvant ET duration (below median). In second-line patients, numerical benefits in PFS and OS were observed across patients with primary and secondary ET resistance, with a numerically more pronounced effect in patients with visceral disease. Prolongation of TTC and CFS was observed in first- and second-line subgroups, and was statistically greater in the second-line subgroup, although this may have resulted from the larger difference in the medians for the placebo arm. Treatment with abemaciclib plus fulvestrant also improved PFS2 consistently across first- and second-line subgroups. Overall, this exploratory analysis indicated that the addition of abemaciclib to fulvestrant benefited both first-line and second-line ET-resistant HR^+, HER2− patients with ABC, including those patients with visceral metastases and primary ET resistance.

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