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ORIGINAL REPORT

MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer

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ABSTRACT

Purpose

Abemaciclib, a cyclin-dependent kinase 4 and 6 inhibitor, demonstrated efficacy as monotherapy and in combination with fulvestrant in women with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer previously treated with endocrine therapy.

Methods

MONARCH 3 is a double-blind, randomized phase III study of abemaciclib or placebo plus a nonsteroidal aromatase inhibitor in 493 postmenopausal women with HR-positive, HER2-negative advanced breast cancer who had no prior systemic therapy in the advanced setting. Patients received abemaciclib or placebo (150 mg twice daily continuous schedule) plus either 1 mg anastrozole or 2.5 mg letrozole, daily. The primary objective was investigator-assessed progression-free survival. Secondary objectives included response evaluation and safety. A planned interim analysis occurred after 189 events.

Results

Median progression-free survival was significantly prolonged in the abemaciclib arm (hazard ratio, 0.54; 95% CI, 0.41 to 0.72; $P = .000021$; median: not reached in the abemaciclib arm, 14.7 months in the placebo arm). In patients with measurable disease, the objective response rate was 59% in the abemaciclib arm and 44% in the placebo arm ($P = .004$). In the abemaciclib arm, diarrhea was the most frequent adverse effect (81.3%) but was mainly grade 1 (44.6%). Comparing abemaciclib and placebo, the most frequent grade 3 or 4 adverse events were neutropenia (21.1% *v* 1.2%), diarrhea (9.5% *v* 1.2%), and leukopenia (7.6% *v* 0.6%).

Conclusion

Abemaciclib plus a nonsteroidal aromatase inhibitor was effective as initial therapy, significantly improving progression-free survival and objective response rate and demonstrating a tolerable safety profile in women with HR-positive, HER2-negative advanced breast cancer.

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INTRODUCTION

Approximately 70% of patients with metastatic breast cancer have hormone receptor (HR)–positive disease and are commonly treated with endocrine-based therapies that include an aromatase inhibitor (AI).[1-4] Because resistance occurs in nearly all patients, attention has focused on identifying novel approaches to address endocrine resistance.[4-10]

Cyclin-dependent kinases 4 and 6 (CDK 4 and CDK 6) in complex with D-type cyclin catalysts are critical regulators of cell cycle progression and have important implications in breast carcinogenesis and endocrine therapy resistance.[11,12] Cyclin D1 is a major transcriptional target of the estrogen receptor. Following ligand binding of estrogen with its receptor, cyclin D1 is critically necessary for the transition from G1 to S phase in a CDK 4/cyclin D–dependent manner.[13-16] Targeting CDK 4 and CDK 6 has been an effective means to attenuate the growth of HR-positive breast cancer.[5-10,17]

Abemaciclib, an oral, selective small-molecule inhibitor of CDK 4 and CDK 6, is dosed twice daily on a continuous schedule and is 14 times more potent against CDK 4/cyclin D1 than CDK 6/cyclin D3 in enzymatic assays.[5-7,17,18] Preclinical evidence

ASSOCIATED CONTENT

Appendix
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demonstrated the importance of continuous inhibition of CDK 4 and CDK 6 to promote sustained growth arrest resulting in apoptosis or senescence, whereas short-term inhibition caused a temporary G1 arrest.[17,18]

In patients with HR-positive, HER2-negative advanced breast cancer refractory to endocrine therapy, abemaciclib demonstrated clinical activity as monotherapy (MONARCH 1).[6] In the phase III MONARCH 2 study, which evaluated patients with HR-positive, HER2-negative breast cancer whose disease progressed while receiving endocrine therapy, abemaciclib plus fulvestrant resulted in a 7.2-month extension in median progression-free survival compared with the placebo arm (hazard ratio, 0.553; 95% CI, 0.449 to 0.681; $P < .001$).[7] Patients in the abemaciclib arm with measurable disease achieved an objective response rate of 48.1% compared with 21.3% in the placebo arm.[7] Here, we report the results of MONARCH 3, a phase III placebo-controlled trial evaluating abemaciclib in combination with a nonsteroidal AI as initial treatment in women with HR-positive, HER2-negative advanced breast cancer.

METHODS

Study Design and Patients

MONARCH 3 is a phase III, randomized, double-blind trial of abemaciclib or placebo plus a nonsteroidal AI (anastrozole or letrozole per physician's choice) in women with HR-positive, HER2-negative advanced breast cancer. MONARCH 3 was conducted in 158 sites in 22 countries.

Eligible postmenopausal women were 18 years or older with locally tested HR-positive, HER2-negative locoregionally recurrent breast cancer not amenable to surgical resection or radiotherapy with curative intent or metastatic disease. Patients must have had measurable disease or nonmeasurable bone-only disease (blastic, lytic, or mixed) as defined by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[19] and must not have received systemic therapy for advanced disease. Endocrine therapy in the neoadjuvant or adjuvant setting was permitted if the patient had a disease-free interval > 12 months from the completion of endocrine therapy.

Patients must have had adequate organ function and an Eastern Cooperative Oncology Group performance status of ≤ 1. Exclusion criteria included presence of visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis; inflammatory breast cancer; evidence or history of CNS metastases; or prior treatment with everolimus or a CDK 4 and CDK 6 inhibitor.

MONARCH 3 received ethical/institutional review board approval. Patients were required to provide informed consent before enrollment. The trial was conducted in accordance with the Declaration of Helsinki and was overseen by a steering committee. An independent data monitoring committee evaluated safety data quarterly.

Random Assignment and Treatment

An interactive Web response system was used to randomly assign patients 2:1 to receive abemaciclib (150 mg twice daily, with or without food) or matching placebo plus a nonsteroidal AI (either 1 mg anastrozole or 2.5 mg letrozole). All drugs were orally administered and taken daily during each 28-day cycle. Randomly assigned patients were stratified by metastatic site (visceral, bone only, or other) and prior neoadjuvant or adjuvant endocrine therapy (AI, no endocrine therapy, or other).

Treatment continued until disease progression, unacceptable toxicity, death, or patient withdrawal for any reason. Dose interruptions were allowed; dose reductions were allowed for abemaciclib/placebo as defined by prespecified guidelines in the protocol but were not applicable for nonsteroidal AI per label. Crossover of treatment arms was not permitted. Patients were permitted to discontinue either abemaciclib/placebo or nonsteroidal AI and continue the other drug.

Efficacy and Safety Measures

Tumors were assessed by computed tomography or magnetic resonance imaging according to RECIST version 1.1 at baseline, every second cycle during cycles two to 18, every third cycle thereafter, and within 14 days of clinical progression. All patients underwent bone scintigraphy at baseline and every sixth cycle starting with cycle six. Central hematologic and chemistry analyses were performed up to 3 days before day 1 of each cycle. Adverse events were graded for severity according to the National Cancer Institute Common Terminology Criteria version 4.0.

End Points

The primary end point, investigator-assessed progression-free survival, was evaluated from random assignment until the time of objective disease progression or death. Secondary end points reported here include objective response rate (percentage of patients with best response of complete or partial response), duration of response (time from complete or partial response until disease progression or death), clinical benefit rate (percentage of patients with best response of complete response, partial response, or stable disease ≥ 6 months), and safety and tolerability. Other end points not included in this analysis include overall survival, quality of life, pharmacokinetics, and biomarker analyses.

Statistical Analysis

MONARCH 3 compared the investigator-assessed progression-free survival of patients treated with abemaciclib with that of those treated with placebo. The primary statistical analysis included all patients in the intent-to-treat population. An additional sensitivity analysis was planned to assess progression-free survival by a full, blinded independent central review. Progression-free survival was analyzed using a log-rank test stratified by metastatic site and prior neoadjuvant or adjuvant endocrine therapy. The study was powered to 80% at one-sided $\alpha = 0.025$ assuming a hazard ratio of 0.67 in favor of the abemaciclib arm, with a final analysis at 240 progression-free survival events. A prespecified interim analysis was planned after 189 events. A positive study at the interim required a hazard ratio < 0.56 and a two-sided $P < .0005$.

Stratified tests using the Cochran-Mantel-Haenszel test were performed to compare response rates between treatment arms. Unless noted, hypothesis tests were performed at the two-sided 0.05 level and used 95% CIs. Exploratory subgroup analyses were performed on subgroups prespecified in the protocol and on subgroups identified in the literature as associated with prognosis and/or sensitivity to endocrine therapy. Analysis of adverse events was performed in the safety population (defined as all patients who received at least one dose of study drug). Statistical analyses were performed using SAS (version 9.2 or later).

RESULTS

Patients

Between November 18, 2014 and November 11, 2015, 493 patients were randomly assigned 2:1 to receive abemaciclib plus a nonsteroidal AI (n = 328) or placebo plus a nonsteroidal AI (n = 165; Fig 1). Patient baseline characteristics were well balanced between arms (Table 1). At baseline, 261 (52.9%) patients had visceral disease, 196 (39.8%) presented with de novo metastatic breast cancer, and 230 (46.7%) had previously received neoadjuvant or adjuvant endocrine therapy, including 135 (27.4%) who had received prior AI therapy.

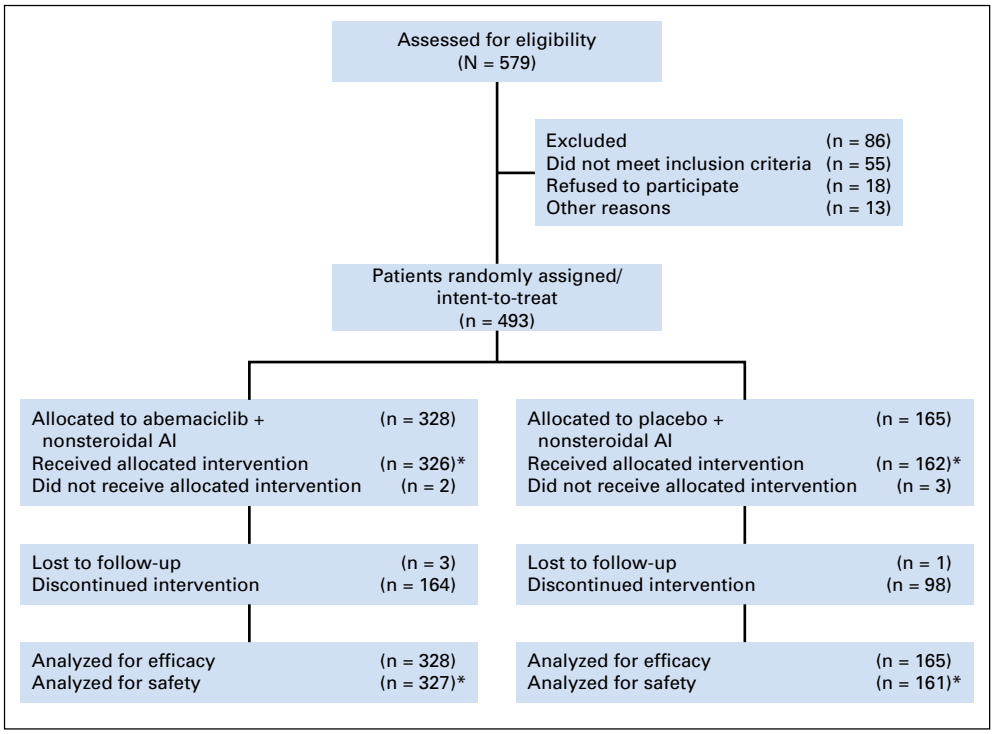

Fig 1. CONSORT diagram. (*) One patient who was randomly assinged to placebo actually received abemaciclib during cycle one. This patient is counted in the abemaciclib safety population. AI, aromatase inhibitor.

Treatment

The majority (79.1%) of patients received letrozole. At the interim analysis cutoff, 162 (49.4%) patients in the abemaciclib arm and 64 (38.8%) in the placebo arm continued treatment. Patients in the abemaciclib arm received a median of 16 cycles of therapy versus 15 cycles in the placebo arm. The median relative dose intensity was 86% for abemaciclib and 98% for placebo.

Abemaciclib dose reductions as the result of adverse events occurred in 142 (43.4%) patients versus 10 (6.2%) receiving placebo. Interruption of abemaciclib as the result of an adverse event occurred in 184 (56.3%) patients versus 31 (19.3%) receiving placebo. A total of 64 (19.6%) patients in the abemaciclib arm versus four (2.5%) in the placebo arm discontinued abemaciclib or placebo, respectively, as the result of adverse events. The most frequent cause of treatment discontinuation was progressive disease (91 [27.7%] patients in the abemaciclib arm and 86 [52.1%] in the placebo arm).

Efficacy

The interim analysis occurred after 194 progression-free survival events (108 [32.9%] in the abemaciclib arm and 86 [52.1%] in the placebo arm). The median follow-up was 17.8 months. MONARCH 3 met its primary end point with an observed investigator-assessed progression-free survival hazard ratio of 0.54 (95% CI, 0.41 to 0.72; $P = .000021$; Fig 2A). The median was not reached in the abemaciclib arm and was 14.7 months in the placebo arm. Consistent progression-free survival results (hazard ratio, 0.51; 95% CI, 0.36 to 0.72) were observed by independent central review (Fig 2B).

The objective response rate achieved by patients was 48.2% (95% CI, 42.8% to 53.6%) in the abemaciclib arm and 34.5% (95% CI, 27.3% to 41.8%) in the placebo arm ($P = .002$; Table 2). Of these responders, 101 (63.9%) in the abemaciclib arm and 34 (59.6%) in the placebo arm were continuing on treatment at time of the analysis. In patients with measurable disease, the objective response rate was 59.2% (95% CI, 53.3% to 65.1%) in the abemaciclib arm and 43.8% (95% CI, 35.3% to 52.4%) in the placebo arm ($P = .004$). In the intent-to-treat population, clinical benefit was achieved by 78.0% (95% CI, 73.6% to 82.5%) in the abemaciclib arm versus 71.5% (95% CI, 64.6% to 78.4%) in the placebo arm. Median duration of response was not reached in the abemaciclib arm and was 14.1 months in the placebo arm (Appendix Fig A1, online only).

Subgroup Analysis

A progression-free survival benefit was demonstrated across all prespecified subgroups (Fig 3). A greater progression-free survival hazard ratio was observed in the Asian population than in the white population; however, an interaction between race and treatment effect was not observed in the MONARCH 2 study.[7] In exploratory subgroup analyses, the hazard ratios for the abemaciclib arm versus the placebo arm were consistent across subgroups relating to prognosis and endocrine sensitivity (treatment-free interval, metastatic site). For patients in the control arm, it was notable that patients with adverse prognostic factors such as treatment-free interval $<$ 36 months (median progression-free survival, 9.0 months) or liver metastases (median progression-free survival, 7.2 months) exhibited relatively rapid progression (Fig 4). Conversely, patients with good prognostic factors such as treatment-free interval $>$ 36 months or bone-only disease had longer progression-free survival on placebo plus nonsteroidal AI (median not reached for both groups).

Table 1. Patient and Disease Baseline Characteristics

Variable	Abemaciclib Plus Nonsteroidal AI	Placebo Plus Nonsteroidal AI
No. of patients	328	165
Median age, years (range)	63 (38-87)	63 (32-88)
Race, No. (%)*†		
White	186 (56.7)	102 (61.8)
Asian	103 (31.4)	45 (27.3)
Other	11 (3.4)	7 (4.2)
ECOG performance status, No. (%)		
0	192 (58.5)	104 (63.0)
1	136 (41.5)	61 (37.0)
Disease setting, No. (%)‡		
De novo metastatic	135 (41.2)	61 (37.0)
Metastatic recurrent	182 (55.5)	99 (60.0)
Locoregionally recurrent	11 (3.4)	5 (3.0)
Progesterone receptor status, No. (%)§		
Positive	255 (77.7)	127 (77.0)
Negative	70 (21.3)	36 (21.8)
Metastatic site, No. (%)‡		
Visceral	172 (52.4)	89 (53.9)
Bone only	70 (21.3)	39 (23.6)
Other	86 (26.2)	37 (22.4)
Prior neoadjuvant or adjuvant chemotherapy, No. (%)		
Yes	125 (38.1)	66 (40.0)
No	203 (61.9)	99 (60.0)
Prior endocrine therapy, No. (%)		
None	178 (54.3)	85 (51.5)
AI	85 (25.9)	50 (30.3)
Other endocrine therapy	65 (19.8)	30 (18.2)
Treatment-free interval, No. (%)‖		
< 36 months	42/150 (28.0)	32/80 (40.0)
≥ 36 months	94/150 (62.7)	40/80 (50.0)
Unknown	14/150 (9.3)	8/80 (10.0)
Measurable disease, No. (%)		
Yes	267 (81.4)	130 (78.8)
No	61 (18.6)	35 (21.2)
No. of organ sites, No. (%)†		
1	96 (29.3)	47 (28.5)
2	76 (23.2)	42 (25.5)
≥ 3	154 (47.0)	75 (45.5)

Abbreviations: AI, aromatase inhibitor; ECOG, Eastern Cooperative Oncology Group.
*Race was self-reported.
†Data missing for remaining patients.
‡Percentage does not equal 100% as the result of rounding.
§Progesterone receptor status was unknown in remaining patients.
‖Treatment-free interval calculated only for patients with prior endocrine therapy.

Of note, patients with a short treatment-free interval or liver metastases benefited substantially from the addition of abemaciclib (Fig 4A and 4E).

Safety

In the safety population (n = 327 in the abemaciclib arm; n = 161 in the placebo arm), the most frequent adverse events reported by the investigator in the abemaciclib arm were diarrhea, neutropenia, fatigue, and nausea (Table 3). On the basis of central laboratory analysis, the most common abnormalities were increased serum creatinine, decreased white blood cell and neutrophil counts, and anemia (Appendix Table A1, online only). Serious adverse events were reported in 27.5% of patients in the abemaciclib arm and 14.9% in the placebo arm, with lung infection being the most frequent (2.8% *v* 0%, respectively).

Diarrhea was predominantly low grade (abemaciclib arm *v* placebo arm, grade 1: 44.6% *v* 21.7%; grade 2: 27.2% *v* 6.8%; Table 3). In the abemaciclib arm, the median onset was 8.0 days and the median duration was 10.5 days (grade 2) and 8.0 days (grade 3). In the abemaciclib arm, most patients (76.3%) who experienced diarrhea did not undergo any treatment modifications. Among patients who experienced diarrhea, 73.3% reported use of antidiarrheal therapy. Discontinuation of study drug as the result of diarrhea was 2.3% in the abemaciclib arm.

A total of 41.3% of patients in the abemaciclib arm experienced neutropenia. Overall, once decreased, the neutrophil count typically remained stable during abemaciclib treatment and was reversible following discontinuation (Appendix Fig A2, online only). On the basis of central laboratory analysis, all grades of neutropenia were generally observed by cycle two, and grade 3 and 4 neutropenia was uncommonly observed during later cycles (typically < 5% in any given cycle). One patient in the abemaciclib arm experienced nonserious febrile neutropenia (associated with a grade 2 urinary tract infection).

Infections occurred in 39.1% of patients in the abemaciclib arm and 28.6% in the placebo arm, with most being grade 1 and 2 (33.3% in the abemaciclib arm *v* 25.5% in the placebo arm).

Venous thromboembolic events occurred in 16 (4.9%) of patients in the abemaciclib arm versus one (0.6%) in the placebo arm. The majority of the patients (11 of 16) in the abemaciclib arm did not discontinue treatment (four had dose interruptions at the time of the event).

Laboratory-based abnormalities of increased ALT were observed in 47.6% of patients (grade 3: 6.4%, grade 4: 0.6%) in the abemaciclib arm versus 25.2% (grade 3: 1.9%, no grade 4) in the placebo arm (Appendix Table A1, online only). Increased AST was observed in 36.7% of patients (grade 3: 3.8%, no grade 4) in the abemaciclib arm versus 23.2% (grade 3: 0.6%, no grade 4) in the placebo arm.

Survival

Although data are not mature at this time, overall survival was similar between the arms, with 32 (9.8%) deaths in the abemaciclib arm and 17 (10.3%) in the placebo arm (hazard ratio, 0.97). Regarding deaths occurring either while receiving treatment or within 30 days of discontinuation, 11 (3.4%) deaths occurred in the abemaciclib arm (eight as the result of adverse events) versus three (1.9%) in the placebo arm (two as the result of adverse events; Appendix Table A2, online only). A final overall survival analysis will occur after 315 events.

DISCUSSION

Interim results of the MONARCH 3 trial demonstrated significant improvements in progression-free survival and objective response rate when combining abemaciclib with a nonsteroidal AI as initial therapy for patients with HR-positive, HER2-negative advanced breast cancer. These efficacy results in the intent-to-treat population were consistent with other reported first-line combination studies of CDK 4 and CDK 6 inhibitors and AIs.[8,10]

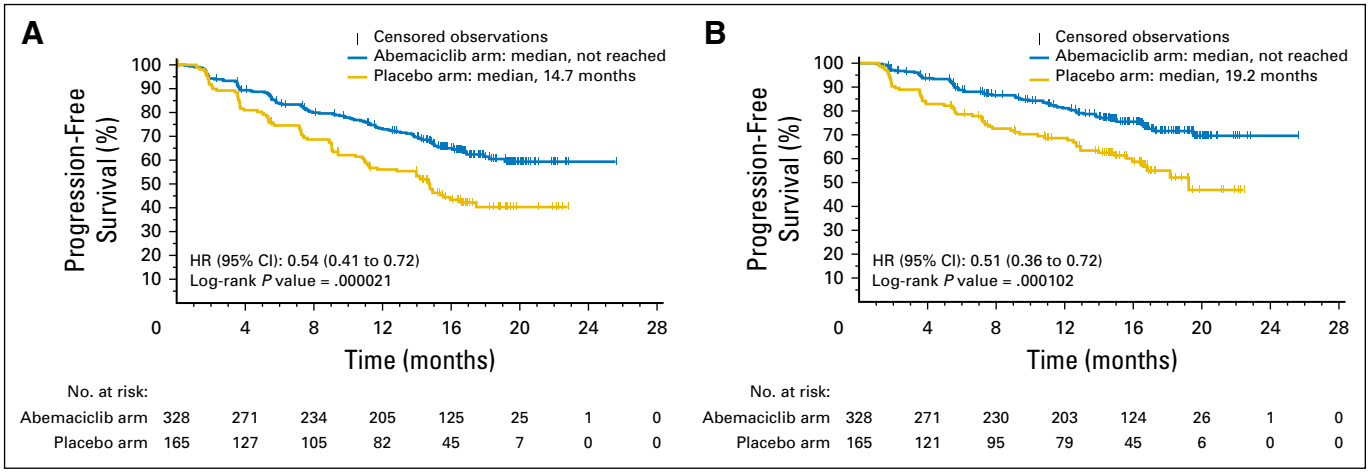

Fig 2. Progression-free survival. (A) Investigator-assessed progression-free survival in the intent-to-treat population. (B) Progression-free survival in the intent-to-treat population as evaluated by a blinded, independent central review. Abbreviations: HR, hazard ratio.

Abemaciclib has demonstrated substantial antitumor activity as initial therapy for patients with metastatic disease (MONARCH 3) and in patients who have progressed on endocrine therapy (MONARCH 2).[7] In each of these studies, the addition of abemaciclib to endocrine therapy provided benefit across all subgroups. However, not all patients benefited equally from endocrine monotherapy. Exploratory subgroup analyses of this study indicate that some subpopulations (prolonged treatment-free interval, bone-only disease, no liver metastases) exhibited a comparatively better prognosis with endocrine monotherapy. Conversely, subpopulations without these characteristics exhibited early progression on endocrine monotherapy and may derive greater advantage from the addition of abemaciclib (Fig 4). MONARCH 3 data suggest the potential of using clinical factors to determine patient subgroups who may derive benefit from the addition of abemaciclib in this setting. Identifying which patients may benefit the most from the addition of abemaciclib as initial treatment and those who may be treated with abemaciclib after progression on endocrine therapy remains a topic of considerable interest to better support more personalized treatment strategies.

At this time, there are no biomarkers predictive of treatment benefit of CDK 4 and CDK 6 inhibitors. Biomarkers that track cellular proliferation, including those which evaluate retinoblastoma protein and estrogen receptor activity, are logical candidates.[20,21]

Table 2. Best Overall Response

	Abemaciclib Plus Nonsteroidal AI		Placebo Plus Nonsteroidal AI			
Best Overall Response*	No. (%)	95% CI†	No. (%)	95% CI†	Odds Ratio	*P*
All patients	328 (100.0)		165 (100.0)			
Complete response	5 (1.5)	0.2 to 2.9	0 (0.0)	NA		
Partial response	153 (46.6)	41.2 to 52.0	57 (34.5)	27.3 to 41.8		
Stable disease	133 (40.5)	35.2 to 45.9	86 (52.1)	44.5 to 59.7		
≥ 6 months	98 (29.9)	24.9 to 34.8	61 (37.0)	29.6 to 44.3		
Progressive disease	14 (4.3)	2.1 to 6.5	12 (7.3)	3.3 to 11.2		
Not evaluable	23 (7.0)	4.2 to 9.8	10 (6.1)	2.4 to 9.7		
Objective response rate‡	158 (48.2)	42.8 to 53.6	57 (34.5)	27.3 to 41.8	1.8 (1.3-2.3)	.002
Clinical benefit rate§	256 (78.0)	73.6 to 82.5	118 (71.5)	64.6 to 78.4	1.4 (1.0-2.0)	.101
Measurable disease, no. of patients	267 (100.0)		130 (100.0)			
Complete response	5 (1.9)	0.2 to 3.5	0 (0.0)	NA		
Partial response	153 (57.3)	51.4 to 63.2	57 (43.8)	35.3 to 52.4		
Stable disease	82 (30.7)	25.2 to 36.2	55 (42.3)	33.8 to 50.8		
≥ 6 months	54 (20.2)	15.4 to 25.0	33 (25.4)	17.9 to 32.9		
Progressive disease	11 (4.1)	1.7 to 6.5	12 (9.2)	4.3 to 14.2		
Not evaluable	16 (6.0)	3.1 to 8.8	6 (4.6)	1.0 to 8.2		
Objective response rate‡	158 (59.2)	53.3 to 65.1	57 (43.8)	35.3 to 52.4	1.9 (1.4-2.5)	.004
Clinical benefit rate§	212 (79.4)	74.5 to 84.3	90 (69.2)	61.3 to 77.2	1.7 (1.2-2.5)	.024

Abbreviation: AI, aromatase inhibitor; NA, not applicable.
*According to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.
†CIs were on the basis of normal approximation.
‡Objective response rate consisted of patients with a complete or partial response.
§Clinical benefit rate consisted of patients with a complete response, partial response, or stable disease ≥ 6 months.

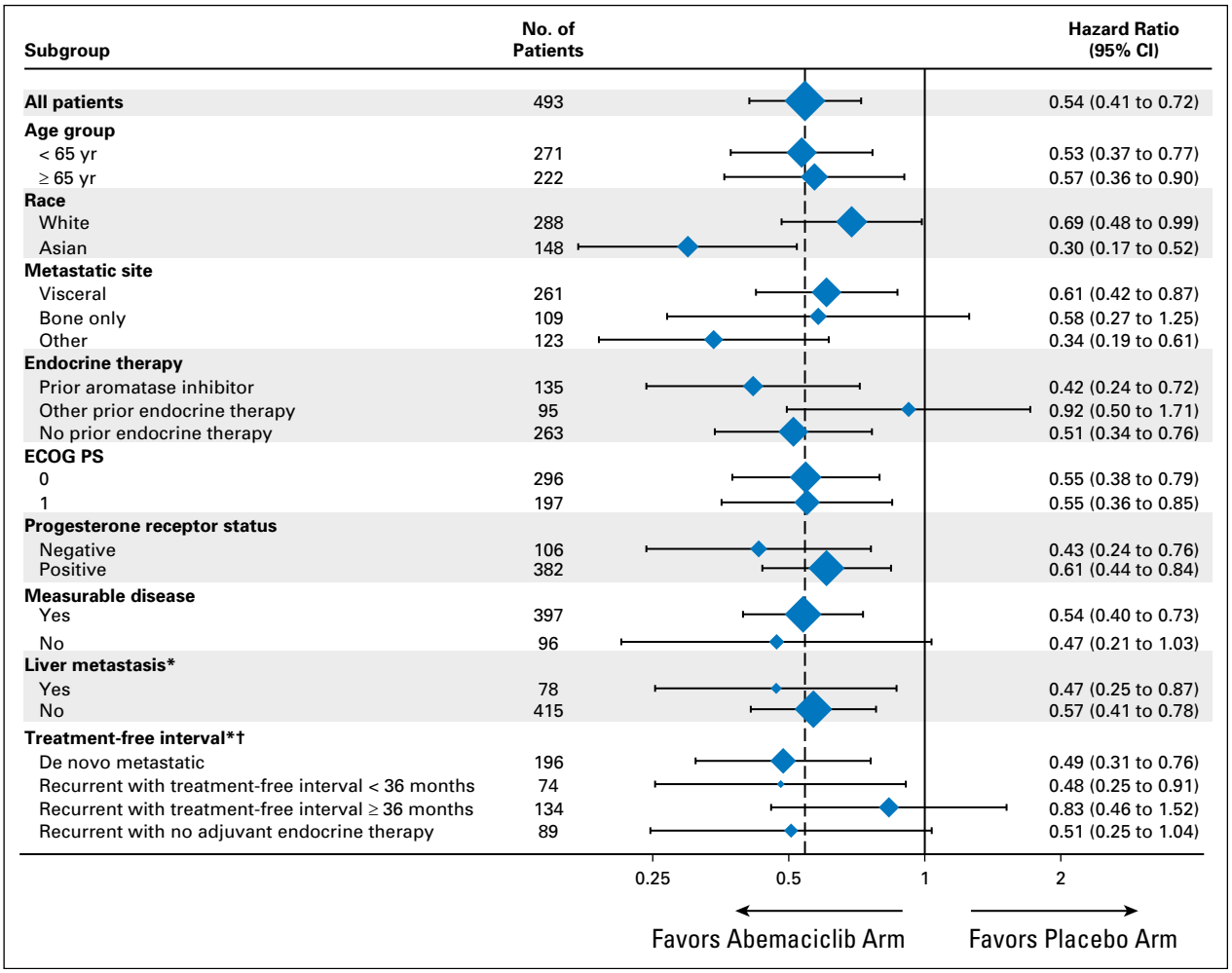

Fig 3. Subgroup analysis of progression-free survival. Progression-free survival hazard ratios with 95% CIs are shown. Diamond size is proportional to the number of patients in each subgroup. Subgroup hazard ratios are unstratified and estimated with the adjustment of arm X subgroup interaction. Overall progression-free survival is stratified by metastatic site and prior endocrine therapy. Factor levels with < 10% of patients were omitted from the analysis. ECOG PS, Eastern Cooperative Oncology Group performance status; yr, years. (*) Not a prespecified subgroup. (†) Treatment-free interval is defined as the time from the end of adjuvant endocrine therapy until informed consent.

Furthermore, CDK 4 and CDK 6 may modify epithelial-mesenchymal transition and metastases independent of retinoblastoma protein.[22] Future studies and biomarker analyses are warranted to help identify patients most likely to benefit from this class of medicines.

The adverse event profile of abemaciclib plus a nonsteroidal AI was consistent with the profile in MONARCH 2.[7] In contrast to other CDK 4 and CDK 6 inhibitors,[8,10] the most common adverse event in MONARCH 3 was low-grade diarrhea, which was readily managed in most instances with conventional antidiarrheal medications and dose adjustments. The MONARCH 3 antidiarrheal management plan recommended suspension of abemaciclib until diarrhea resolved to at least grade 1. Antidiarrheal medication (eg, loperamide) was advised at the first onset of diarrhea. Recurrent or high-grade diarrhea required dose reductions. This management seemed to be effective, with the majority (83.8%) of patients with initial grade 2 or 3 diarrhea not experiencing a subsequent event of the same or greater severity.

Similar to MONARCH 1 and 2, the majority of patients did not experience severe neutropenia.[6,7] In this study, a higher incidence of venous thromboembolic events was observed in the abemaciclib arm. However, the majority of patients who experienced these events did not discontinue abemaciclib. There was also a higher rate of elevated hepatic transaminases in the abemaciclib arm, which were generally managed by dose reduction or dose omission and were resolved with drug discontinuation. Creatinine increases were more common in the abemaciclib arm. It is known that abemaciclib increases serum creatinine levels as the result of inhibition of renal tubular secretion of creatinine without affecting glomerular function.[23]

In conclusion, abemaciclib dosed in combination with a nonsteroidal AI significantly improved progression-free survival and objective response rate compared with a nonsteroidal AI alone; thus, abemaciclib plus a nonsteroidal AI was an effective initial treatment with a tolerable safety profile for postmenopausal patients with HR-positive, HER2-negative advanced breast cancer.

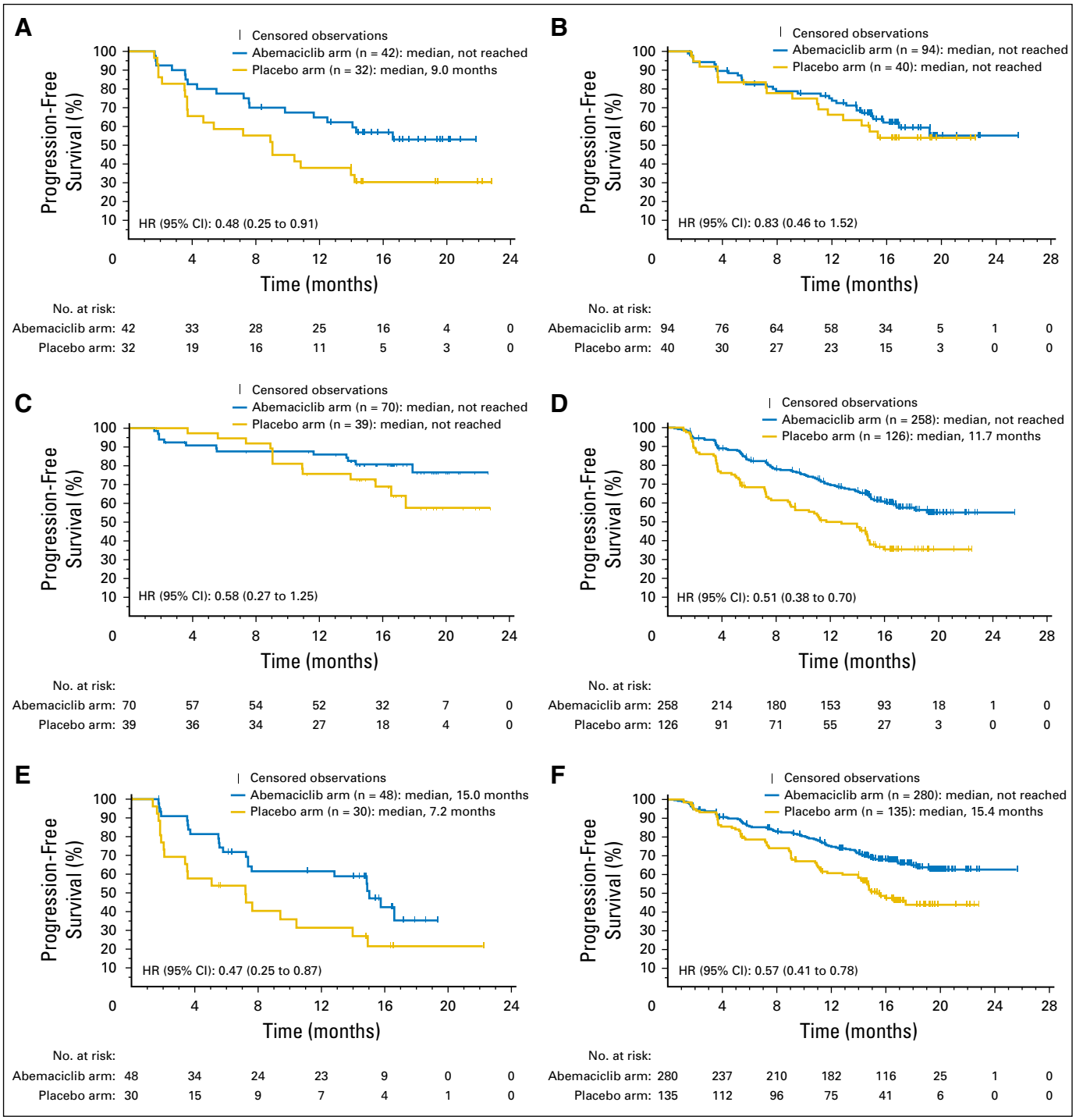

Fig 4. Investigator-assessed progression-free survival of patient subgroups. (A and B) Progression-free survival for patients with a treatment-free interval of < 36 months and of ≥ 36 months, respectively. (C and D) Progression-free survival for patients with or without bone-only disease at baseline, respectively. (E and F) Progression-free survival for patients with or without sites of liver metastases at baseline, respectively. NOTES: Treatment-free interval is defined as the time from the end of adjuvant endocrine therapy until informed consent. Twenty-two patients who reported prior endocrine therapy were not included in the treatment-free interval analysis as the result of incomplete data entry or neoadjuvant endocrine therapy only. HR, hazard ratio.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Matthew P. Goetz, Masakazu Toi, Mario Campone, Tammy Forrester, Martin Frenzel, Ian C. Smith, Nawel Bourayou, Angelo Di Leo

Table 3. Treatment-Emergent Adverse Events

At Least 15% in Either Arm	Abemaciclib Plus Nonsteroidal AI, n = 327				Placebo Plus Nonsteroidal AI, n = 161			
	All CTCAE Grades, No. (%)	CTCAE Grade 2, No. (%)	CTCAE Grade 3, No. (%)	CTCAE Grade 4, No. (%)	All CTCAE Grades, No. (%)	CTCAE Grade 2, No. (%)	CTCAE Grade 3, No. (%)	CTCAE Grade 4, No. (%)
Any adverse event	322 (98.5)	111 (33.9)	159 (48.6)	21 (6.4)	145 (90.1)	61 (37.9)	32 (19.9)	3 (1.9)
Diarrhea	266 (81.3)	89 (27.2)	31 (9.5)	0	48 (29.8)	11 (6.8)	2 (1.2)	0
Neutropenia	135 (41.3)	53 (16.2)	64 (19.6)	5 (1.5)	3 (1.9)	1 (0.6)	1 (0.6)	1 (0.6)
Fatigue	131 (40.1)	55 (16.8)	6 (1.8)	—	51 (31.7)	20 (12.4)	0	—
Infections and infestations*	128 (39.1)	92 (28.1)	13 (4.0)	3 (0.9)	46 (28.6)	34 (21.1)	4 (2.5)	1 (0.6)
Nausea	126 (38.5)	36 (11.0)	3 (0.9)	—	32 (19.9)	1 (0.6)	2 (1.2)	—
Abdominal pain	95 (29.1)	21 (6.4)	4 (1.2)	—	19 (11.8)	4 (2.5)	2 (1.2)	—
Anemia	93 (28.4)	45 (13.8)	19 (5.8)	0	8 (5.0)	2 (1.2)	2 (1.2)	0
Vomiting	93 (28.4)	26 (8.0)	4 (1.2)	0	19 (11.8)	3 (1.9)	3 (1.9)	0
Alopecia	87 (26.6)	5 (1.5)	—	—	17 (10.6)	0	—	—
Decreased appetite	80 (24.5)	26 (8.0)	4 (1.2)	0	15 (9.3)	2 (1.2)	1 (0.6)	0
Leukopenia	68 (20.8)	31 (9.5)	24 (7.3)	1 (0.3)	4 (2.5)	1 (0.6)	0	1 (0.6)
Increased blood creatinine	62 (19.0)	22 (6.7)	7 (2.1)	0	6 (3.7)	1 (0.6)	0	0
Constipation	52 (15.9)	12 (3.7)	2 (0.6)	0	20 (12.4)	5 (3.1)	0	0
Increased ALT	51 (15.6)	12 (3.7)	19 (5.8)	1 (0.3)	11 (6.8)	2 (1.2)	3 (1.9)	0
Headache	51 (15.6)	6 (1.8)	2 (0.6)	—	24 (14.9)	4 (2.5)	0	—

Abbreviations: AI, aromatase inhibitor; CTCAE, Common Terminology Criteria for Adverse Events.
*Includes any adverse event in the infections and infestations system organ class.
— No grade exists for this adverse event.

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MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer

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Appendix

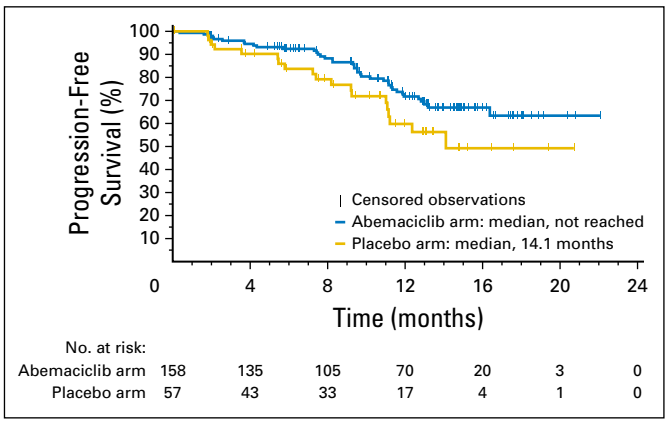

Fig A1. Duration of response.

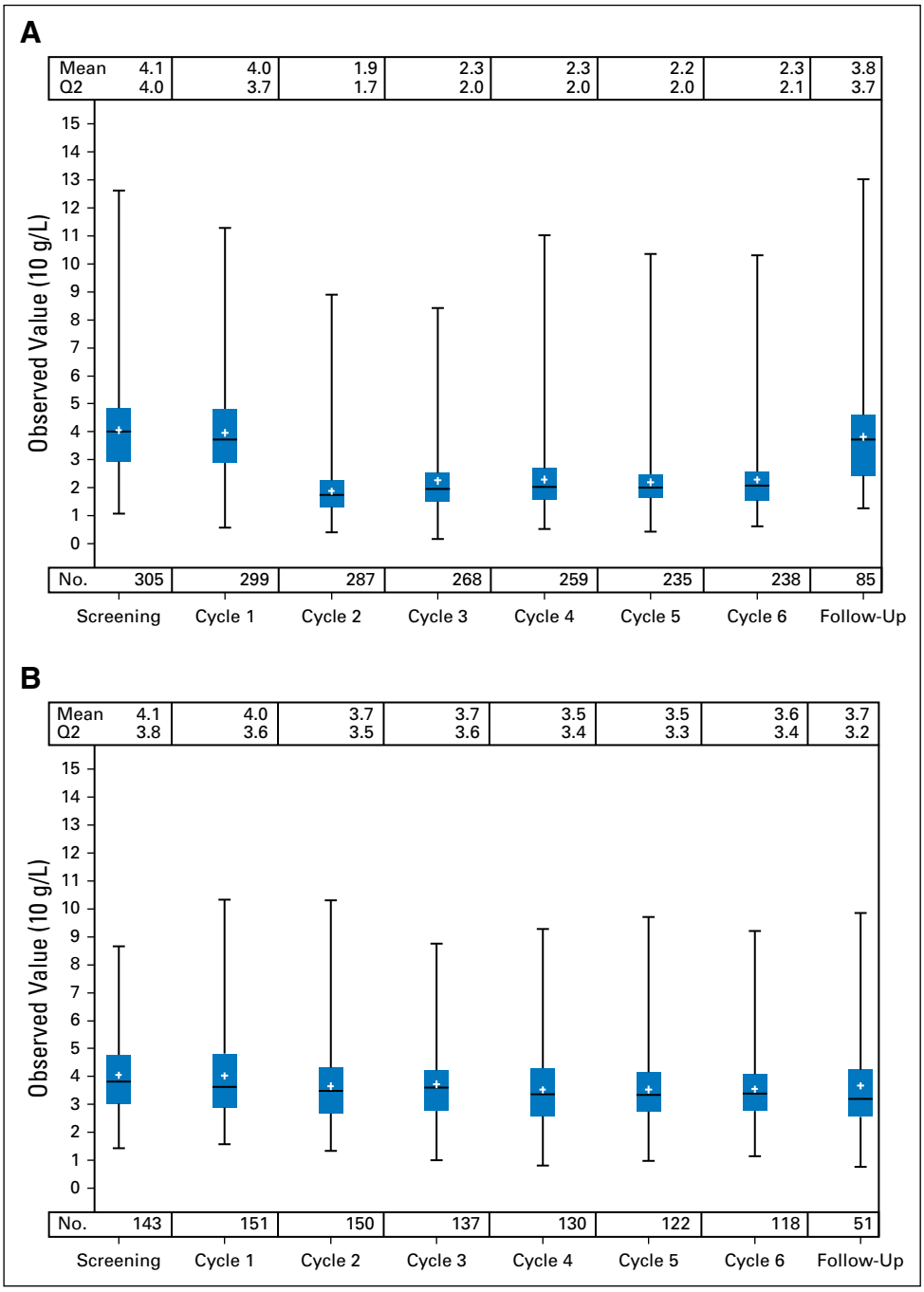

Fig A2. Neutrophil counts per cycle. (A) Abemaciclib arm; (B) placebo arm. Abbreviation: Q2, median.

Table A1. Central Laboratory-Based Abnormalities

At Least 10% in Either Arm	Abemaciclib Plus Nonsteroidal AI, n = 327				Placebo Plus Nonsteroidal AI, n = 161			
	All CTCAE Grades, No. (%)	CTCAE Grade 2, No. (%)	CTCAE Grade 3, No. (%)	CTCAE Grade 4, No. (%)	All CTCAE Grades, No. (%)	CTCAE Grade 2, No. (%)	CTCAE Grade 3, No. (%)	CTCAE Grade 4, No. (%)
Any laboratory abnormality	315 (99.7)	146 (46.2)	121 (38.3)	21 (6.6)	150 (94.9)	38 (24.1)	14 (8.9)	1 (0.6)
Creatinine increased*	308 (98.1)	166 (52.9)	7 (2.2)	0	131 (84.0)	7 (4.5)	0	0
White blood cell decreased	258 (82.4)	134 (42.8)	40 (12.8)	0	42 (26.9)	11 (7.1)	1 (0.6)	0
Anemia	256 (81.8)	122 (39.0)	5 (1.6)	0	43 (27.6)	14 (9.0)	0	0
Neutrophil count decreased	251 (80.2)	120 (38.3)	60 (19.2)	9 (2.9)	32 (20.5)	4 (2.6)	4 (2.6)	0
Lymphocyte count decreased	165 (52.7)	63 (20.1)	23 (7.3)	2 (0.6)	40 (25.6)	15 (9.6)	3 (1.9)	0
ALT increased	149 (47.6)	29 (9.3)	20 (6.4)	2 (0.6)	39 (25.2)	3 (1.9)	3 (1.9)	0
AST increased	115 (36.7)	12 (3.8)	12 (3.8)	0	36 (23.2)	6 (3.9)	1 (0.6)	0
Platelet count decreased	113 (36.2)	10 (3.2)	4 (1.3)	2 (0.6)	18 (11.6)	0	1 (0.6)	0
Hypercalcemia	96 (30.6)	0	0	2 (0.6)	50 (32.1)	1 (0.6)	0	0
Hypokalemia	92 (29.3)	0	22 (7.0)	1 (0.3)	18 (11.6)	0	0	0
Hyponatremia	90 (28.7)	0	15 (4.8)	1 (0.3)	37 (23.7)	0	0	0
Hypocalcemia	72 (22.9)	10 (3.2)	1 (0.3)	1 (0.3)	28 (17.9)	3 (1.9)	0	1 (0.6)
Alkaline phosphatase increased	54 (17.2)	8 (2.5)	1 (0.3)	0	21 (13.5)	3 (1.9)	1 (0.6)	0

Abbreviations: AI, aromatase inhibitor; CTCAE, Common Terminology Criteria for Adverse Events.
*CTCAE version 4.0 defines grade 1 creatinine increased as > 1 to 1.5× baseline or greater than the upper limit of normal to 1.5× the upper limit of normal.

Table A2. Deaths During Therapy or Within 30 Days of Discontinuation

Variable	Abemaciclib Plus Nonsteroidal AI, No. (%)	Placebo Plus Nonsteroidal AI, No. (%)
No. of patients	327	161
Deaths as the result of study disease	3 (0.9)	1 (0.6)
Deaths as the result of adverse events	8 (2.4)	2 (1.2)
Lung infection	3 (0.9)	0
Embolism*	2 (0.6)	0
Cerebral ischemia	1 (0.3)	0
Pneumonitis	1 (0.3)	0
Respiratory failure†	1 (0.3)	0
General physical health deterioration	0	1 (0.6)
Sudden death	0	1 (0.6)

Abbreviation: AI, aromatase inhibitor.
*Reported terms for embolism were thromboembolism no further information (one patient) and pulmonary embolism (one patient).
†Investigator also reported pulmonary embolism as possible cause of death.