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Clinical Significance of *PIK3CA* and *ESR1* Mutations in Circulating Tumor DNA: Analysis from the MONARCH 2 Study of Abemaciclib plus Fulvestrant

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Abstract

Purpose: *PIK3CA* and *ESR1* mutations have been implicated in resistance to endocrine therapy (ET) in HR+, HER2− advanced breast cancer (ABC). Inhibition of CDK4 and 6 has been hypothesized as a therapeutic strategy to overcome endocrine resistance in patients with *PIK3CA*- or *ESR1*-mutant breast cancers. The objective of this exploratory analysis was to assess efficacy of abemaciclib plus fulvestrant in patients with or without *PIK3CA* or *ESR1* mutations in MONARCH 2.

Patients and Methods: MONARCH 2 was a global, randomized, double-blind phase III trial of abemaciclib plus fulvestrant in 669 women with HR+, HER2− ABC, which had progressed on ET. Patients were randomized 2:1 to receive abemaciclib plus fulvestrant or placebo plus fulvestrant. Exploratory analyses assessed progression-free survival (PFS) and overall survival (OS), and other endpoints, in patients with or without *PIK3CA* or *ESR1* mutations detectable in baseline ctDNA.

Results: From the MONARCH 2 population, 219 and 248 patient samples were successfully analyzed for either *PIK3CA* or *ESR1* mutations, respectively. Abemaciclib plus fulvestrant improved PFS compared with placebo plus fulvestrant in both *PIK3CA*-wild-type (median 16.9 months vs. 12.3 months; HR, 0.51; 95% CI, 0.33–0.78) and *PIK3CA*-mutant subgroups (median 17.1 months vs. 5.7 months; HR, 0.53; 95% CI, 0.33–0.84), as well as both *ESR1*-wild-type (median 15.3 months vs. 11.2 months; HR, 0.44; 95% CI, 0.27–0.71) and *ESR1*-mutant subgroups (median 20.7 months vs. 13.1 months; HR, 0.54; 95% CI, 5.7–16.9). Additional endpoints, including OS, were also improved following treatment with abemaciclib plus fulvestrant regardless of *PIK3CA* or *ESR1* mutation status.

Conclusions: Abemaciclib plus fulvestrant was effective regardless of *PIK3CA* or *ESR1* mutation status, with benefit in both PFS and OS, with a numerically greater improvement in median PFS relative to placebo plus fulvestrant for *PIK3CA*- or *ESR1*-mutant tumors compared with the respective wild-type subgroups, in women with HR+, HER2− ABC that had progressed on ET.

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Introduction

Breast cancer is the most common cancer among women worldwide and the leading cause of cancer death in women (1). Of those diagnosed with breast cancer, hormone receptor–positive (HR+), HER2-negative (HER2−) is the most common subtype, accounting for nearly 70% of all metastatic breast cancer (2). Within this population, resistance to endocrine therapy (ET) is common, and most patients ultimately succumb to disease, leading to interest in development of more precise therapeutic approaches (3, 4).

Endocrine resistance evolves from many mechanisms, including genetic dysregulation, posttranslational modifications, and altered cell signaling promoting ligand-independent activation of the estrogen receptor (ER) and decreased sensitivity to antiestrogens (5–7). A major mechanism of resistance is mutation of the ERα gene, *ESR1*, frequently observed after treatment with aromatase inhibitors (8, 9). Most somatic *ESR1* mutations occur at either D538 or Y537, within the *ESR1* ligand-binding domain. The clinical implications of these frequently observed mutations, with regard to fulvestrant response, remain unclear (6, 9, 10).

In addition to *ESR1*-mediated endocrine resistance, studies have also identified a prominent role for PI3K pathway dysregulation in metastatic breast cancer progression and endocrine resistance (4, 11). *PIK3CA*, which encodes phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit α, is mutated in approximately 40% of HR+, HER2− advanced breast cancers (ABC), resulting in a gain-of-function phenotype and increased downstream signaling and oncogenesis (4, 12). Most mutations occur at E542K or E545K of exon 9 (helical domain of p110α), and H1047R/L of exon 20 (activation loop in the kinase domain), representing “hotspot” mutations (4). Prior clinical studies have demonstrated HR+ breast cancers with mutations in either exon 9 or exon 20 exhibited decreased response to ET (4). To address this clinically, several targeted therapies have been developed to inhibit the PI3K pathway (4). Efficacy of the PI3Kα inhibitor alpelisib in an endocrine-resistant population with HR+, HER2− ABC was demonstrated in the phase III SOLAR-1 study, demonstrating improved median PFS in combination with fulvestrant in patients with *PIK3CA*-mutant tumors, although no statistical benefit in OS was observed (13).

CDK4 and 6 have also been identified as actionable therapeutic targets in the setting of endocrine resistance (4, 14). Abemaciclib is an oral, potent, and selective CDK4 and 6 inhibitor, dosed on a continuous schedule and approved as monotherapy and in combination with either fulvestrant or an aromatase inhibitor for HR+, HER2− ABC (3). MONARCH 2 was a phase III randomized, double-blind, placebo-controlled study that evaluated the efficacy of abemaciclib in combination with fulvestrant in patients with HR+, HER2− ABC whose disease had progressed on ET. This trial demonstrated improved PFS (median 16.4 months vs. 9.3 months; HR, 0.553; 95% CI, 0.449–0.681; $P < 0.001$) and overall survival (OS; median 46.7 months vs. 37.3 months; HR, 0.757; 95% CI, 0.606–0.945; $P = 0.01$) with a tolerable safety profile (3, 15).

Here we report the results of an exploratory analysis to assess the PFS, OS, time to chemotherapy (TTC), chemotherapy-free survival (CFS), and time to second disease

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progression (PFS2) in patients with *PIK3CA*- or *ESR1*-wild-type or -mutant tumors who received abemaciclib plus fulvestrant or placebo plus fulvestrant in the MONARCH 2 study.

Patients and Methods

Study design and patients

MONARCH 2 was a randomized, double-blind, placebo-controlled, phase III study of abemaciclib plus fulvestrant or placebo plus fulvestrant in women with HR+, HER2− ABC who had disease progression on ET.

Eligible patients were adult females (≥18 years) with any menopausal status (pre- or perimenopausal women received a gonadotropin-releasing hormone agonist), diagnosed with HR+, HER2− ABC and disease progression while receiving neoadjuvant or adjuvant ET, within 12 months after adjuvant ET, or while receiving first-line ET for ABC. Patient performance status must have been ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale and patients must have had measurable disease defined according to the RECIST (version 1.1) or nonmeasurable bone-only disease (i.e., blastic, lytic, or mixed lytic). Patients must not have had prior treatment with more than one line of ET or any prior chemotherapy for ABC. Exclusion criteria also included prior treatment with fulvestrant, everolimus, or any CDK4 and CDK6 inhibitors, presence of visceral crisis, or evidence or history of central nervous system metastasis.

The protocol was approved by ethical and institutional review boards and the study was conducted in compliance with the Declaration of Helsinki. All patients provided written informed consent prior to joining the study.

Randomization and treatment

Dosing was as previously described (3, 15). Briefly, 669 patients [intent-to-treat (ITT) population] were randomized 2:1 to receive either abemaciclib (150 mg) or placebo twice daily on days 1 to 28 of a 28-day cycle plus fulvestrant (500 mg intramuscularly) on days 1 and 15 of cycle 1, and on day 1 of each subsequent cycle. Treatment continued until disease progression, death, or patient withdrawal (15). Randomization was stratified by metastatic site (visceral, bone-only, or other) and sensitivity to ET (primary or secondary resistance).

Assessments

Efficacy and safety assessments were conducted as described previously (3, 15). Droplet digital PCR (ddPCR) was used to evaluate four mutations each in *PIK3CA* (E542K, E545K, H1047L, and H1047R) and *ESR1* (D538G and Y537C/S/N) via the Bio-Rad QX200 Droplet Digital PCR system (Asuragen) in baseline plasma samples. Samples were considered positive if at least one mutation tested positive and defined the translational research (TR) population. End-of-treatment samples were not collected.

Endpoints

PFS, the primary endpoint, was measured from the time of randomization to the date of objective progression or death. Additional endpoints included OS (time from randomization

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until death), TTC (time from randomization to first postdiscontinuation chemotherapy, death prior to initiation was treated as censored), CFS (time from randomization to initiation of first postdiscontinuation chemotherapy or death), and PFS2 (time from randomization to the discontinuation of first subsequent postdiscontinuation therapy or death).

Statistical analysis

Analyses were conducted on those patients with valid baseline samples. PFS, OS, TTC, CFS, and PFS2 were analyzed with a data cut-off of June 20, 2019. The median PFS, OS, TTC, CFS, and PFS2 estimated using the Kaplan–Meier method are reported along with their 95% confidence intervals (CI). HR and 95% CI were derived from the unstratified Cox regression model.

Data availability

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 and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

Results

Patients

From August 2014 to December 2015, 669 patients were randomized 2:1 to abemaciclib plus fulvestrant ($N = 446$) or placebo plus fulvestrant ($N = 223$; Supplementary Fig. S1; ref. 3). Baseline plasma from 334 patients was analyzed for *PIK3CA* mutations in ctDNA by ddPCR, with 219 of 334 (65.6%) samples successfully analyzed and defined as the *PIK3CA* translational research (TR) population. In this population, *PIK3CA* mutations were detected in 96 (43.8%) of 219 patients (26.5% abemaciclib arm, 17.4% placebo arm). The most frequently observed mutation was H1047R (33.3%), followed by E545K (6.1%), E542K (4.3%), and H1047 L (1.4%; Supplementary Table S1). Eight of 219 patients (3.7%) had both H1047R/L and E545K/E542K mutations. At baseline, 248 of 334 (74.3%) samples were successfully analyzed and defined as the *ESR1* TR population. *ESR1* mutations were detected in 147 (59.3%) of 248 patients (36.7% abemaciclib arm, 22.6% placebo arm). The most frequently observed mutation was D538G (45.1%), followed by Y537C (15.8%), Y537S (7.8%), and Y537N (7.5%; Supplementary Table S1). Forty-four of 248 patients (17.7%) had both D538G and Y537C/S/N mutations. Seventy-one patients had both *PIK3CA* and *ESR1* mutations. Baseline characteristics were generally similar between the TR population and the rest of the ITT population, as well as between *PIK3CA*- and *ESR1*-mutant and wild-type subgroups (Table 1). A slight increase in the percentage of patients with visceral disease was observed in the *PIK3CA*-mutant compared with

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PIK3CA-wild-type subgroup, whereas a slightly higher percentage of bone-only disease was observed in the wild-type subgroup, although differences in metastatic sites were not statistically significant. A higher prevalence of patients with secondary endocrine resistance was observed in the *ESR1*-mutant subgroup, whereas primary endocrine resistance was more prevalent in the *ESR1*-wild-type subgroup. Progesterone receptor–positive tumors were more common in the *ESR1*-mutant subgroup compared with *ESR1*-wild-type.

PFS

Median PFS in the ITT population was 16.9 months compared with 17.1 months in the *PIK3CA* TR population and 17.2 months in the *ESR1* TR population in patients treated with abemaciclib plus fulvestrant (Supplementary Fig. S2). Overall, PFS was improved in the abemaciclib arm compared with placebo, regardless of *PIK3CA* or *ESR1* mutation status, consistent with results in the ITT population.

Patients with and without *PIK3CA* mutations in the abemaciclib arm demonstrated improved PFS compared with the placebo arm (wild-type: median 16.9 months vs. 12.3 months; HR, 0.51; 95% CI 0.33–0.78; mutant: median 17.1 months vs. 5.7 months; HR, 0.53; 95% CI, 0.33–0.84; Fig. 1). In addition, irrespective of the specific *PIK3CA* mutation (E545K/E542K or H1047R/H1047L), patients in the abemaciclib arm demonstrated numerically improved PFS compared with the placebo arm (E545K/E542K: median 17.1 months vs. 13.9 months; HR, 0.60; 95% CI, 0.24–1.52; H1047R/H1047L: median 17.2 months vs. 4.8 months; HR, 0.50; 95% CI, 0.29–0.83; Supplementary Fig. S3). For patients who received placebo plus fulvestrant, median PFS was shorter in the *PIK3CA*-mutant population (5.7 months) compared with patients without *PIK3CA* mutations (12.3 months). The numerical improvement in median PFS with abemaciclib plus fulvestrant was greater in patients with *PIK3CA*-mutant tumors (17.1 months vs. 5.7 months), compared with wild-type (16.9 months vs. 12.3 months).

Similarly, regardless of *ESR1* mutation status, patients in the abemaciclib arm showed improved PFS compared with the placebo arm (wild-type: median 15.3 months vs. 11.2 months; HR, 0.44; 95% CI, 0.27–0.71; mutant: median 20.7 months vs. 13.1 months; HR, 0.54, 95% CI, 5.7–16.9; Fig. 2) and PFS was extended regardless of which *ESR1* mutation (D538G or Y537C/S/N) was present (D538G: median 26.0 months vs. 13.1 months; HR, 0.45; 95% CI, 0.29–0.69; Y537: median 16.6 months vs. 4.8 months; HR, 0.48; 95% CI, 0.28–0.83; Supplementary Fig. S4). For patients harboring D538G-mutant tumors who received placebo + fulvestrant, median PFS was similar to wild-type tumors (13.1 months vs. 11.2 months). In contrast, median PFS was shorter in patients harboring Y537-mutant tumors compared with wild-type who were treated with placebo + fulvestrant (4.8 months vs. 11.2 months; Supplementary Fig. S4). In addition, the numerical improvement in median PFS with abemaciclib plus fulvestrant was greater in patients with *ESR1*-mutant tumors (20.7 months vs. 13.1 months) compared with wild-type (15.3 months vs. 11.2 months).

Overall survival

Median OS in the ITT population was 46.7 months compared with 47.7 months in the *PIK3CA* TR population in patients treated with abemaciclib plus fulvestrant and was

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not reached in the *ESR1* TR population. Overall, abemaciclib plus fulvestrant prolonged median OS compared with the placebo arm regardless of *PIK3CA* or *ESR1* mutation status (Supplementary Fig. S5). Median OS was numerically extended in the abemaciclib arm versus the placebo arm in patients with *PIK3CA*-mutant tumors (44.5 months vs. 33.8 months) and in the *PIK3CA*-wild-type subgroup (55.5 months vs. 39.7 months) tumors (Fig. 3). Likewise, in patients harboring either the E545K/E542K or H1047R/L mutations median OS was numerically prolonged in the abemaciclib arm compared with the placebo arm (E545K/E542K: 48.8 months vs. 34.8 months; H1047R/H1047L: 44.5 months vs. 33.8 months; Supplementary Fig. S6).

Median OS was also numerically extended in the abemaciclib arm versus the placebo arm in patients with either *ESR1*-mutant (not reached vs. 42.2 months) or *ESR1*-wild-type tumors (52.2 months vs. 29.4 months; Fig. 4). Interestingly, in this analysis, median OS was longer in patients with *ESR1*-mutant versus *ESR1*-wild-type tumors receiving placebo plus fulvestrant (42.2 months vs. 29.4 months; Fig. 4). This was particularly pronounced for the D538G-mutant subgroup compared with wild-type *ESR1* (Supplementary Fig. S7).

Postdiscontinuation therapy

At the time of the data cut-off, all patients in the abemaciclib arm and the placebo arm of the TR population had received a first subsequent postdiscontinuation therapy. Therapies were generally well balanced across *PIK3CA*- and *ESR1*-mutant vs. wild-type subgroups and across treatment arms. Use of chemotherapy as first subsequent postdiscontinuation therapy was higher in the placebo arm (*PIK3CA*: 37.2%; *ESR1*: 38.5%) compared with the abemaciclib arm (*PIK3CA*: 25.6%; *ESR1*: 28.0%). ET was more common in both the *PIK3CA*- and *ESR1*-wild-type subgroups of the placebo arm compared with the mutant subgroups (Supplementary Tables S2 and S3).

Other endpoints

TTC was extended in patients treated with abemaciclib plus fulvestrant compared with placebo plus fulvestrant regardless of *PIK3CA* mutation status (wild-type: median not reached vs. 18.6 months; HR, 0.47; 95% CI, 0.29–0.78; mutant: median 39.2 months vs. 19.2 months; HR, 0.64; 95% CI, 0.36–1.15; Supplementary Fig. S8A). It should be noted that in the TTC analysis, patient death was not counted as an event.

TTC was also extended in patients treated with abemaciclib plus fulvestrant compared with placebo plus fulvestrant regardless of *ESR1* mutation status (wild-type: median 50.2 months vs. 12.8 months; HR, 0.45; 95% CI, 0.26–0.78; mutant: median 51.5 months vs. 26.8 months; HR, 0.65; 95% CI, 0.41–1.03; Supplementary Fig. S8B). CFS was likewise improved in patients treated with abemaciclib plus fulvestrant compared with placebo plus fulvestrant, regardless of *PIK3CA* or *ESR1* mutation status (Supplementary Fig. S9). Interestingly, TTC and CFS were prolonged in the placebo arm for patients with *ESR1*-mutant tumors compared with wild-type.

PFS2 was extended in patients receiving abemaciclib compared with placebo regardless of *PIK3CA* or *ESR1* mutation status. PFS2 in *PIK3CA*-wild-type patients was prolonged in the abemaciclib arm compared with the placebo arm (median 31.7 months vs. 19.7 months; HR,

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0.52; 95% CI, 0.34–0.80). In the *PIK3CA*-mutant population, PFS2 was also numerically extended in the abemaciclib arm versus the placebo arm (median 23.1 months vs. 17.8 months; HR, 0.72; 95% CI, 0.45–1.16; Supplementary Fig. S10A). PFS2 was extended in patients with wild-type *ESR1* treated with abemaciclib plus fulvestrant compared with placebo plus fulvestrant, (median: 25.5 months vs. 16.6 months; HR, 0.44; 95% CI, 0.27–0.70), as well as in patients with mutant *ESR1*, with a late separation of the curves after 30 months (26.6 months vs. 26.5 months; HR, 0.66; 95% CI, 0.44–0.97; Supplementary Fig. S10B).

Discussion

This exploratory analysis from MONARCH 2 demonstrated that abemaciclib extended PFS and OS when added to fulvestrant in women with HR+, HER2− ABC that had progressed on ET, regardless of *PIK3CA* or *ESR1* mutation status in ctDNA. In addition, other exploratory endpoints, TTC, CFS, and PFS2, were also improved with abemaciclib plus fulvestrant.

The MONARCH 2 patient population, HR+, HER2− ABC, represents a large component of ABC clinically, and, importantly, included patients with disease progression on ET (3). The MONARCH 2 study demonstrated that patients treated with abemaciclib plus fulvestrant consistently derived benefit with regards to PFS and OS compared with placebo plus fulvestrant across both the ITT population and clinically relevant subgroups, including patients with primary ET resistance (3).

Previous studies have highlighted a role for mutations in *PIK3CA* as a mediator of endocrine resistance and association with worse clinical outcome (4, 12, 13). Consistent with this hypothesis, we report shorter median PFS (5.7 months vs. 12.3 months) and OS (33.8 months vs. 39.7 months) in patients with mutant *PIK3CA* compared with wild-type when treated with placebo plus fulvestrant.

Somatic mutations in the PI3K pathway occur in more than 70% of breast cancers, with the majority occurring in *PIK3CA* (nearly 40% of HR+, HER2− MBC; refs. 4, 12). Specifically targeting *PIK3CA* has resulted in improved patient benefit with manageable safety profile, as demonstrated in the SOLAR-1 clinical study of alpelisib plus fulvestrant in patients with HR+, HER2− ABC that had progressed on previous ET. SOLAR-1 reported statistically improved PFS in patients harboring *PIK3CA*-mutant tumors when treated with alpelisib plus fulvestrant compared with placebo plus fulvestrant (median 11.0 months vs. 5.7 months; ref. 13), although statistically improved OS was not observed (16). Here we report median PFS of 5.7 months in patients harboring *PIK3CA*-mutant tumors treated with placebo plus fulvestrant, whereas the addition of abemaciclib to fulvestrant improved median PFS to 17.1 months. Similarly, median OS was 33.8 months in patients harboring *PIK3CA*-mutant tumors treated in the placebo arm, and treatment with abemaciclib plus fulvestrant improved median OS to 44.5 months.

Interestingly, although we observed little change in PFS in tumors harboring *ESR1* mutations when treated with placebo plus fulvestrant, compared with wild-type, OS was unexpectedly prolonged in the *ESR1*-mutant subgroup compared with wild-type. Previous

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studies have demonstrated minimal effect of *ESR1* mutation status on the PFS of patients receiving fulvestrant (17, 18), whereas OS tended to be shorter in *ESR1*-mutant subgroups (19, 20). The reason for this difference, as well as the increased prevalence of *ESR1* mutations observed in this analysis, is not clear, but may be due to the sample size, patient population (inclusion criteria and endocrine-resistant population evaluated in this study), or methodology used (including differences in assay used and sensitivity).

Prior preclinical studies characterizing *ESR1* mutants demonstrated that D538G continued to respond to single-agent fulvestrant therapy, with only modest differences compared to wildtype (6, 8–10). In contrast, cells harboring the Y537S mutation were less responsive to single-agent fulvestrant therapy (6). In our study, analysis of specific *ESR1* mutations following fulvestrant treatment (placebo arm) demonstrated that the median PFS was similar between the *ESR1*-wild-type and D538G mutant subgroups, and shorter for the Y537 subgroup, consistent with these prior studies indicating relative resistance to fulvestrant (6, 9). Importantly, regardless of *ESR1* mutation status or which *ESR1* mutation was present, tumors treated with abemaciclib plus fulvestrant demonstrated improved PFS and OS compared with placebo plus fulvestrant. In agreement with our observations, the PALOMA-3 clinical trial reported improved OS in patients treated with palbociclib plus fulvestrant compared with placebo plus fulvestrant, regardless of *ESR1* (mutant: 27.7 months vs. 20.2 months; wild-type: 32.8 months vs. 28.0 months) and *PIK3CA* (mutant: 27.7 months vs. 18.3 months; wild-type: 32.8 months vs. 26.6 months) mutation status (21).

In conclusion, abemaciclib plus fulvestrant improved both PFS and OS, regardless of *PIK3CA* or *ESR1* mutation status. The numerical improvement in median PFS relative to placebo plus fulvestrant was greater in patients with either *PIK3CA*-mutant tumors (17.1 months vs. 5.7 months), compared with wild-type (16.9 months vs. 12.3 months) or *ESR1*-mutant tumors (20.7 months vs. 13.1 months) compared with wild-type (15.3 months vs. 11.2 months). Similarly, median OS was prolonged in the abemaciclib arm compared with placebo arm in patients harboring either *PIK3CA*-mutant tumors (44.5 months vs. 33.8 months) compared with wild-type (55.5 months vs. 39.7 months), or *ESR1*-mutant tumors (not reached vs. 42.2 months) compared with wild-type (52.2 months vs. 29.4 months). Although benefit was observed in the abemaciclib plus fulvestrant arm regardless of mutation status, this study is limited by the small sample size, as a subgroup of the MONARCH 2 study population. These exploratory data are hypothesis-generating and provide insight on abemaciclib treatment for tumors with and without *PIK3CA* or *ESR1* mutations. While acknowledging the limitations of cross study comparisons, the similarity of outcomes for the single-agent fulvestrant control arms in *PIK3CA*-mutant cancers between MONARCH 2 and SOLAR-1 and the magnitude of improvement in PFS and OS demonstrated in MONARCH 2 also highlights a potential therapeutic strategy for treatment of HR+, *PIK3CA*-mutant metastatic breast cancer and support further evaluation in prospective, and suitably powered, clinical trials.

Supplementary Material

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Acknowledgments

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Translational Relevance

Abemaciclib is an oral, potent, and selective CDK4 and 6 inhibitor, dosed on a continuous schedule and approved as monotherapy and in combination with either fulvestrant or an aromatase inhibitor for HR+, HER2− advanced breast cancer (ABC). *ESR1* mutation and PI3K pathway dysregulation are associated with resistance to endocrine therapy, and treatment with CDK4 and 6 inhibitors has been hypothesized as a therapeutic strategy to overcome endocrine resistance. In this exploratory analysis, we show in HR+, HER2− ABC, abemaciclib plus fulvestrant improved both PFS and OS, regardless of *PIK3CA* or *ESR1* mutation status. In addition, abemaciclib plus fulvestrant improved other endpoints, including TTC, CFS, and PFS2, regardless of *PIK3CA* or *ESR1* mutation status. This analysis was limited by sample size; findings support further evaluation in suitably powered trials.

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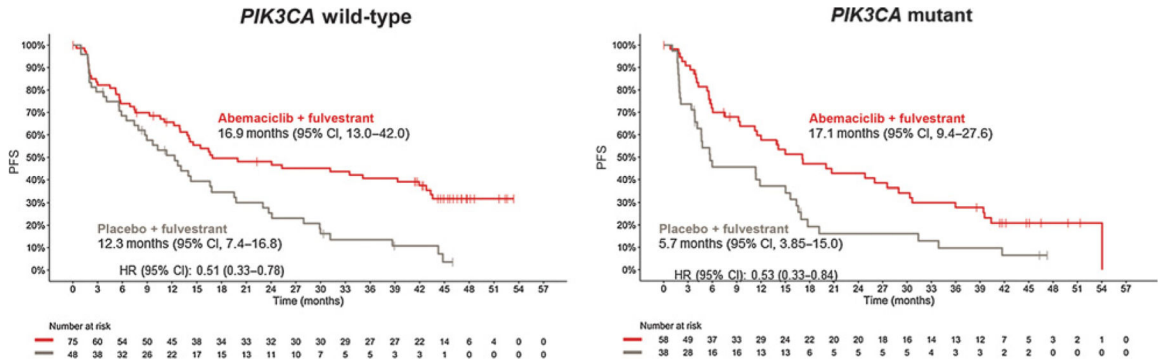

Figure 1.

Kaplan–Meier plots of PFS for patients with *PIK3CA*-wild-type or -mutant tumors.

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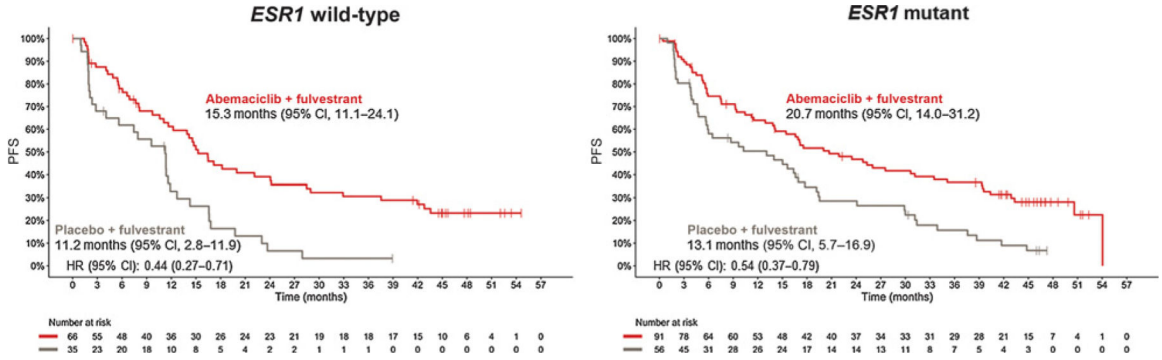

Figure 2.

Kaplan–Meier plots of PFS for patients with *ESR1*-wild-type or -mutant tumors.

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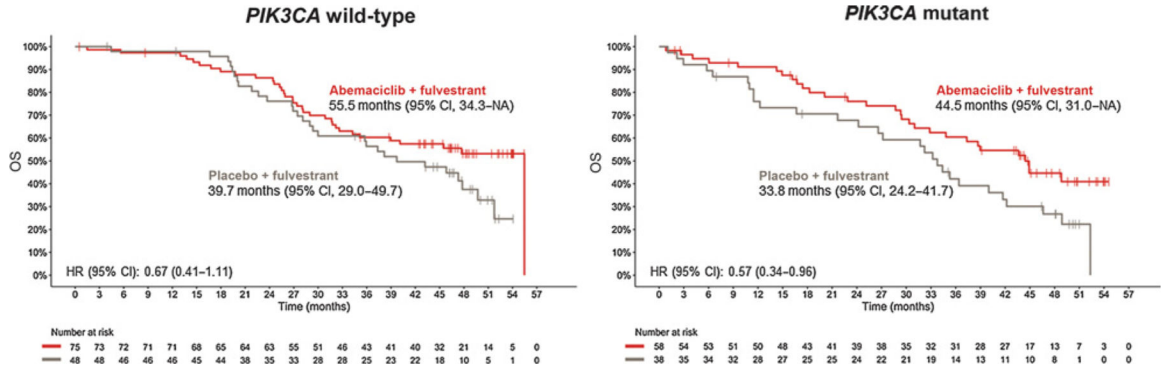

Figure 3.

Kaplan–Meier plots of OS for patients with *PIK3CA*-wild-type or -mutant tumors.

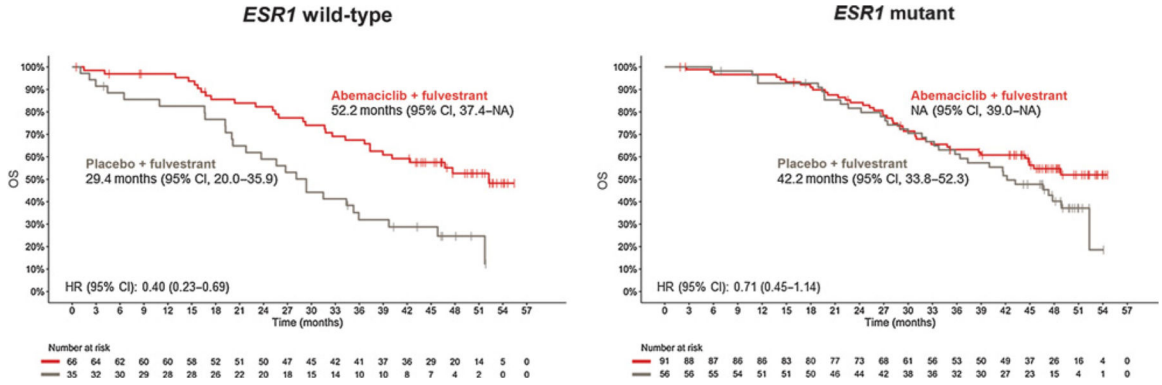

Figure 4.

Kaplan–Meier plots of OS for patients with *ESR1*-wild-type or -mutant tumors.

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Table 1.

Baseline demographics and disease characteristics, ITT and TR.

Characteristic	ITT population (*N* = 669)	*PIK3CA* mutant (*N* = 96)	*PIK3CA* wild-type (*N* = 123)	*ESR1* mutant (*N* = 147)	*ESR1* wild-type (*N* = 101)
Age (years), median (range)	60 (32–91)	60 (32–85)	60 (32–80)	60 (32–85)	58 (35–82)
Race, *n* (%)					
Asian	214 (32.0)	35 (36.5)	51 (41.5)	65 (44.2)	46 (45.5)
Caucasian	373 (55.8)	49 (51.0)	69 (56.1)	71 (48.3)	50 (49.5)
Other	42 (6.3)	8 (8.3)	0	5 (3.4)	3 (3.0)
ET resistance, *n* (%)					
Naive	6 (0.9)	0	2 (1.6)	1 (0.7)	1 (1.0)
Primary[a]	172 (25.7)	21 (21.9)	34 (27.6)	28 (19.0)	34 (33.7)
Secondary[b]	488 (72.9)	75 (78.1)	87 (70.7)	118 (80.3)	66 (65.3)
Progesterone receptor status, *n* (%)					
Negative	141 (21.1)	17 (17.7)	25 (20.3)	20 (13.6)	28 (27.7)
Positive	509 (76.1)	76 (79.2)	98 (79.7)	123 (85.0)	72 (71.3)
Metastatic sites, *n* (%)					
Bone only	180 (26.9)	20 (20.8)	37 (30.1)	33 (22.4)	31 (30.7)
Visceral[c]	373 (55.8)	59 (61.5)	62 (50.4)	87 (59.2)	51 (50.5)
Other	113 (16.9)	17 (17.7)	24 (19.5)	27 (18.4)	19 (18.8)
Liver metastases, *n* (%)					
Yes	176 (26.3)	33 (34.4)	28 (22.8)	42 (28.6)	31 (30.7)
No	490 (73.2)	63 (65.6)	95 (77.2)	105 (71.4)	70 (69.3)
Tumor grade, *n* (%)					
High	169 (25.3)	23 (24.0)	31 (25.2)	37 (25.2)	18 (17.8)
Low/intermediate	345 (51.6)	58 (60.4)	65 (52.8)	78 (53.1)	59 (58.4)
Unknown	155 (23.2)	15 (15.6)	27 (22.0)	32 (21.8)	24 (23.8)

Note: Data missing for remaining patients.

Abbreviations: AI, aromatase inhibitor; ITT, intent-to-treat; *N*, number of patients; *n*, number of patients per category; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; TR, translation research.

[a]Primary ET resistance includes patients whose disease relapsed while receiving the first 2 years of neoadjuvant or adjuvant ET or progressed while receiving the first 6 months of ET for ABC.

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[b] Secondary ET resistance includes patients who were not considered to have primary resistance.

[c] Refers to lung, liver, pleural, or peritoneal involvement at the time of randomization.