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ORIGINAL ARTICLE

Abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy for HR+, HER2− advanced breast cancer: final overall survival results of MONARCH 3☆

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Background: In MONARCH 2, the addition of abemaciclib to fulvestrant significantly improved both progression-free survival (PFS) and overall survival (OS) in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC) with disease progression on prior endocrine therapy. In MONARCH 3, the addition of abemaciclib to a nonsteroidal aromatase inhibitor (NSAI) as initial therapy for HR+, HER2− ABC significantly improved PFS. Here, we present the prespecified final OS results for MONARCH 3.

Patients and methods: MONARCH 3 is a randomized, double-blind, phase III study of abemaciclib plus NSAI (anastrozole or letrozole) versus placebo plus NSAI in postmenopausal women with HR+, HER2− ABC without prior systemic therapy in the advanced setting. The primary objective was investigator-assessed PFS; OS was a gated secondary endpoint, and chemotherapy-free survival was an exploratory endpoint.

Results: A total of 493 women were randomized 2 : 1 to receive abemaciclib plus NSAI ($n = 328$) or placebo plus NSAI ($n = 165$). After a median follow-up of 8.1 years, there were 198 OS events (60.4%) in the abemaciclib arm and 116 (70.3%) in the placebo arm (hazard ratio, 0.804; 95% confidence interval 0.637-1.015; $P = 0.0664$, non-significant). Median OS was 66.8 versus 53.7 months for abemaciclib versus placebo. In the subgroup with visceral disease, there were 113 OS events (65.3%) in the abemaciclib arm and 65 (72.2%) in the placebo arm (hazard ratio, 0.758; 95% confidence interval 0.558-1.030; $P = 0.0757$, non-significant). Median OS was 63.7 months versus 48.8 months for abemaciclib versus placebo. The previously demonstrated PFS benefit was sustained, and chemotherapy-free survival numerically improved with the addition of abemaciclib. No new safety signals were observed.

Conclusions: Abemaciclib combined with an NSAI resulted in clinically meaningful improvement in median OS (intent-to-treat population: 13.1 months; subgroup with visceral disease: 14.9 months) in patients with HR+ HER2− ABC; however, statistical significance was not reached.

Key words: overall survival, abemaciclib, CDK4/6 inhibitor, first-line therapy, HR-positive/HER2-negative, advanced breast cancer

INTRODUCTION

Hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) breast cancer is the most prevalent breast cancer subtype (∼70% of all breast cancers),[1] and metastatic disease remains incurable. The majority of patients with HR+ HER2− advanced breast cancer (ABC) treated with aromatase inhibitors (AIs) in the

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first-line setting will experience disease progression/recurrence within ∼15 months.[2-4] Thus, alternative therapies that synergize with endocrine therapy (ET) are needed to improve patient survival.

Cyclin-dependent kinase (CDK) 4/6 inhibitors in combination with ET have improved outcomes for patients with HR+, HER2− ABC and have become a standard treatment option on the basis of prolonged progression-free survival (PFS).[5,6] Abemaciclib is an oral, selective CDK4/6 inhibitor with greater selectivity for CDK4 than CDK6, which, unlike other currently approved CDK4/6 inhibitors, allows continuous dosing due to less myelosuppression.[7] Abemaciclib has demonstrated efficacy as monotherapy and in combination with AIs/fulvestrant in ABC in the MONARCH trials[2,8-10] and also in combination with ET in node-positive, high-risk early breast cancer (EBC) in the monarchE trial,[11] which has led to regulatory approvals in both the metastatic and adjuvant settings.

In the absence of cure, improvement in overall survival (OS) remains an important goal for patients with ABC. In MONARCH 2, the addition of abemaciclib to fulvestrant significantly improved both PFS and OS in patients with HR+, HER2− ABC with disease progression on prior ET.[8,12] MONARCH 3 is a phase III trial evaluating abemaciclib in combination with a nonsteroidal aromatase inhibitor (NSAI) in postmenopausal women with HR+, HER2− ABC who have not received prior systemic therapy in the advanced setting. The primary objective was previously met with the results showing significantly prolonged PFS with the addition of abemaciclib versus placebo to NSAI [median, 28.2 months versus 14.8 months; hazard ratio, 0.540; 95% confidence interval (CI) 0.418-0.698; $P = 0.000002$].[2] At the last interim OS analysis (5.8-year follow-up), a numerically favorable median OS difference of 12.6 months was observed (hazard ratio, 0.754; 95% CI 0.584-0.974; $P = 0.0301$, non-significant).[13] Here, we report the results of the prespecified final OS analysis of MONARCH 3.

METHODS

Procedures

MONARCH 3 is a global, randomized, double-blind, placebo-controlled, phase III study evaluating abemaciclib with an NSAI versus placebo with an NSAI in postmenopausal women with HR+, HER2− ABC who have not received prior systemic therapy in the advanced setting. The NSAI selected was anastrozole or letrozole per physician's choice. Prior ET in the neoadjuvant or adjuvant setting was permitted if the patient had a disease-free interval >12 months from the completion of ET. This study was conducted in 158 centers in 22 countries.

Eligible patients were randomized in a 2 : 1 ratio to receive abemaciclib or placebo (150 mg twice daily continuous schedule) plus either 1 mg anastrozole or 2.5 mg letrozole daily. Cycles were 28 days. Stratification factors included metastatic site (visceral, bone only, other) and prior (neo)adjuvant ET (AI, other, none). The presence of visceral disease refers to lung, liver, pleural, peritoneal, or adrenal gland involvement at the time of randomization. Additional study details were previously reported.[10]

This study was funded by the sponsor, Eli Lilly and Company, and designed together with the steering committee. The study was carried out in compliance with the Declaration of Helsinki. The study protocol and amendments were approved by the relevant ethical and institutional review boards and all patients gave written informed consent.

Patients

Women ≥18 years of age with locally tested HR+, HER2− breast cancer, postmenopausal status, locoregionally recurrent disease not amenable to resection or radiation therapy with curative intent, or metastatic disease were eligible. Patients must have had measurable disease or non-measurable bone-only disease, as defined by RECIST v1.1, in addition to adequate organ function and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of ≤1.

Patients with visceral crisis, lymphangitic spread, leptomeningeal carcinomatosis, inflammatory breast cancer, or evidence or history of central nervous system metastasis were excluded. Prior CDK4/6 inhibitor or systemic therapy for advanced disease was not permitted.

Endpoints

The primary endpoint was investigator-assessed PFS, defined as the time from randomization until progressive disease or death. OS, a key secondary endpoint, was assessed from time of randomization until death. Chemotherapy-free survival (CFS), an exploratory endpoint, was defined as time from randomization to initiation of first post-discontinuation chemotherapy or death. Efficacy and safety measures have been previously described.[10] Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria, version 4.0, and coded by MedDRA.

Statistical analysis

All efficacy analyses were carried out on the intent-to-treat (ITT) population, which included all randomized patients, and all safety analyses were carried out in patients who received at least one dose of abemaciclib, placebo, or NSAI.

With 240 PFS events, the study was powered to 80% with a two-sided alpha of 5% assuming a hazard ratio of 0.67 in favor of the abemaciclib arm. No power assumptions were made for the secondary endpoint of OS. A gate-keeping hierarchical strategy between the primary PFS and secondary OS endpoints was used to control the overall familywise two-sided type I error rate at 5%, such that OS was to be tested only if PFS was statistically significant. The alpha of 0.05 was split between the ITT population and the subgroup with visceral disease (sVD) using a graphical approach, with an initial allocation of 0.04 for the ITT population and 0.01 for sVD. The cumulative type I error rate within each population was maintained using the Lan—DeMets spending function with O'Brien—Fleming boundary

used to control multiplicity for all the interim and final analyses. The final OS analysis was to be carried out after observing ∼315 events. For this final OS analysis, based on the actual number of events observed, the two-sided *P* value boundary was 0.034 for the ITT population and 0.009 for sVD.

The Kaplan—Meier method was used to estimate survival curves. OS of the treatment groups was compared in the ITT population using a stratified log-rank test and in sVD using an unstratified log-rank test. Cox proportional hazards (PH) model was used to estimate the treatment effect hazard ratio between the abemaciclib plus NSAI arm and the placebo plus NSAI arm. The inverse probability of censoring weights (IPCW) method was prespecified as a sensitivity analysis and used to evaluate the impact of follow-up systemic therapy with other CDK4/6 inhibitors on OS.[14] The IPCW method involved (i) censoring patients in both arms at the time of initiation of additional post-progression CDK4/6 inhibitor treatment and (ii) determining appropriate weights for each subject at risk at each censoring timepoint using a Cox PH model. The variables to be used as weights for the model were selected from a set of prespecified covariates including demographics and baseline disease characteristics: race, age group, geographical region, baseline ECOG PS, disease extent at study entry, prior (neo)adjuvant ET, nature of disease, progesterone receptor status, and number of organs involved. The final IPCW-adjusted treatment effect was estimated using a weighted Cox PH model. SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses.

RESULTS

Patients

Between 18 November 2014 and 11 November 2015, 493 patients were randomly assigned 2 : 1 to receive abemaciclib plus an NSAI ($n = 328$) or placebo plus an NSAI ($n = 165$) (Figure 1). At the final OS cut-off (29 September 2023), a total of 23 (7.0%) patients in the abemaciclib arm and 5 (3.0%) patients in the placebo arm continued to receive study treatment. The majority (79.1%) of patients received letrozole. Baseline patient and disease characteristics were well balanced between treatment arms (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.04.013). A total of 263 (53.3%) patients had visceral disease. Overall, 196 (39.8%) patients had *de novo* metastatic breast cancer and 297 (60.2%) patients had locoregional or metastatic recurrent breast cancer. A total of 231 (46.9%) patients had received prior (neo)adjuvant ET [including 135 (27.4%) who had received prior AI therapy] and 191 (38.7%) patients had received prior (neo)adjuvant chemotherapy.

Overall survival

At the cut-off for this final OS analysis with a median follow-up of 8.1 years, 314 OS events had occurred among 493 patients in the ITT population [abemaciclib arm, $n = 198$ (60.4%); placebo arm, $n = 116$ (70.3%)]. The hazard ratio for death was 0.804 (95% CI 0.637-1.015; $P = 0.0664$). The threshold for statistical significance was not reached.

Median OS was 66.8 months in the abemaciclib arm and 53.7 months in the placebo arm, an absolute difference of 13.1 months in the ITT population (Figure 2). The 5- and 6-year OS rates were 54.5% versus 42.1% and 45.7% versus 35.2%, respectively, for abemaciclib versus placebo.

Consistent OS effect sizes were observed across prespecified subgroups, including patients who had *de novo* and recurrent metastatic disease (Figure 3). In subgroup analyses, the hazard ratios for the abemaciclib arm versus the placebo arm were consistent across subgroups with respect to prognosis and endocrine sensitivity, with a numerically greater effect observed in patients with bone-only disease, progesterone receptor—negative tumors, or prior AI therapy.

In sVD, 178 OS events had occurred among 263 patients [abemaciclib arm, $n = 113$ (65.3%); placebo arm, $n = 65$ (72.2%)]. The hazard ratio for death was 0.758 (95% CI 0.558-1.030; $P = 0.0757$). The threshold for statistical significance was not reached. Median OS was 63.7 months in the abemaciclib arm and 48.8 months in the placebo arm, an absolute difference of 14.9 months in sVD (Figure 2). The 5- and 6-year OS rates were 50.1% versus 37.0% and 41.5% versus 28.0%, respectively, for abemaciclib versus placebo.

Post-discontinuation therapy

Most patients who entered the post-treatment discontinuation follow-up received additional therapies after progression (Table 1). Across all lines of therapies after progression, ETs were most frequently reported (abemaciclib arm, 59.8%; placebo arm, 73.3%).

A total of 41.5% of patients in the abemaciclib arm and 61.8% in the placebo arm received subsequent chemotherapy. CFS was prolonged with the addition of abemaciclib to NSAI (hazard ratio, 0.693; 95% CI 0.557-0.863; nominal $P = 0.0010$). Median CFS (including both chemotherapy and death as events) was 46.7 months in the abemaciclib arm versus 30.6 months in the placebo arm (absolute difference 16.1 months; Figure 4).

Subsequent targeted agents were received by 28.7% of patients in the abemaciclib arm and 48.5% in the placebo arm. Of note, a lower proportion of patients in the abemaciclib arm versus the placebo arm received additional CDK4/6 inhibitor treatment in any subsequent line after study treatment completion (abemaciclib arm, 11.6%; placebo arm, 31.5%). Among these patients, the median time from randomization until initiation of the additional CDK4/6 inhibitor treatment was 49.0 months in the abemaciclib arm and 33.0 months in the placebo arm. For IPCW analysis, the censoring weights used to calculate the adjusted treatment effect were derived based on the progesterone receptor status covariate, which was selected using a stepwise variable selection procedure. The resulting hazard ratio for death for this sensitivity analysis was 0.772 (95% CI

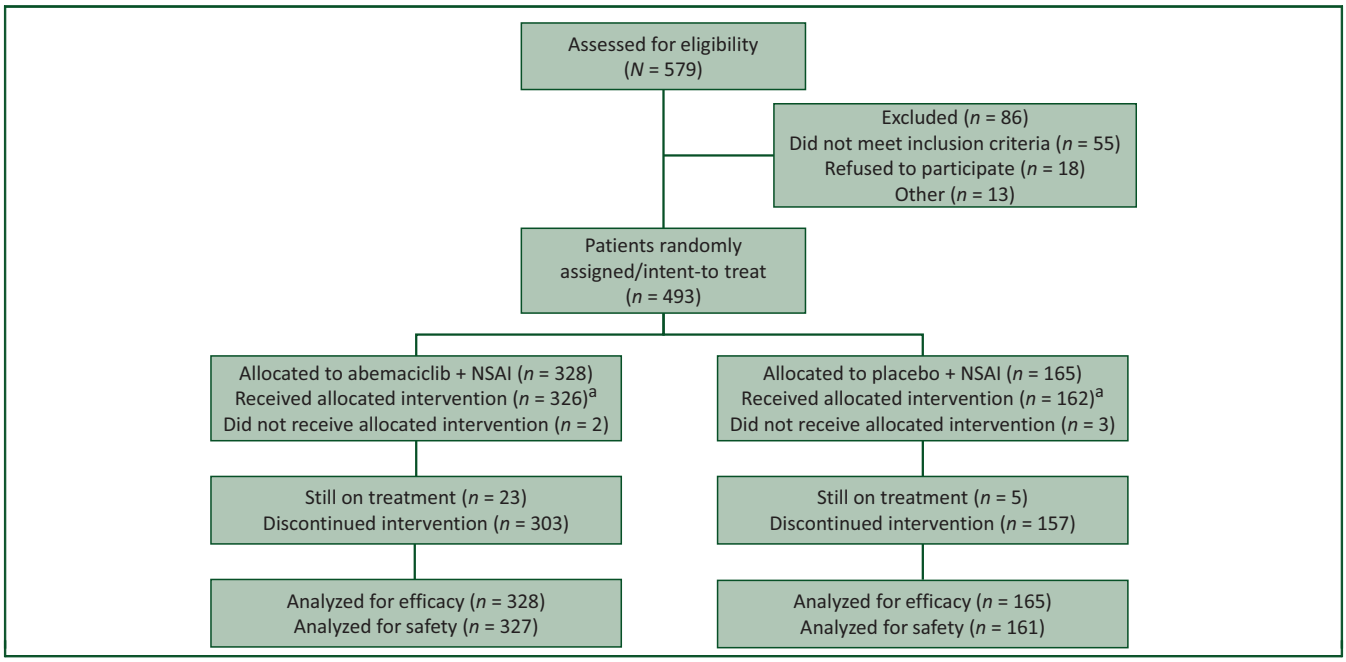

Figure 1. CONSORT Diagram.
[a]One patient who was randomized to placebo actually received abemaciclib during cycle one. This patient is counted in the abemaciclib safety population.
NSAI, nonsteroidal aromatase inhibitor.

0.593-1.003; nominal $P = 0.0531$) in favor of the abemaciclib arm.

Updated investigator-assessed progression-free survival

With a median follow-up of 8.1 years (additional 5.9 years from the final PFS analysis), the PFS treatment effect is persistent. Consistent with results of the primary analysis, the updated PFS at this final OS analysis was significantly improved by the addition of abemaciclib to NSAI (hazard ratio, 0.535; 95% CI 0.429-0.668; nominal $P < 0.0001$) with a continued separation of the curves. Median PFS was 29.0 months in the abemaciclib arm and 14.8 months in the placebo arm (absolute difference 14.3 months; Figure 5).

Safety

The type, relative frequency, and severity of AEs remained consistent with those in previous analyses (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.04.013). The most common hematologic AEs graded 3 or higher in the abemaciclib arm were neutropenia [$n = 90$ (27.5%)], anemia [$n = 31$ (9.5%)], and leukopenia [$n = 35$ (10.7%)]. Diarrhea was the most frequent nonhematologic AE reported in the abemaciclib arm but was predominantly low grade [$n = 273$ (83.5%) any grade; $n = 32$ (9.8%) grade ≥ 3]. Diarrhea cases were managed using medication or dose adjustments; treatment discontinuation due to diarrhea remained infrequent (1.2%).

Interstitial lung disease/pneumonitis and venous thromboembolic events, including pulmonary embolism and deep vein thrombosis, are clinically important AEs for abemaciclib and have previously been described.[15] Overall, there were 23 (7.0%) interstitial lung disease events in the abemaciclib arm [$n = 5$ (1.5%) grade ≥ 3] versus 1 (0.6%) in the placebo arm (grade 2). A total of 25 (7.6%) venous thromboembolic events occurred in the abemaciclib arm [$n = 13$ (4.0%) grade ≥ 3] versus 2 (1.2%) in the placebo arm [$n = 1$ (0.6%) grade ≥ 3].

DISCUSSION

In the MONARCH 3 trial, a clinically and statistically significant prolongation of PFS was seen in postmenopausal women with HR+, HER2− ABC receiving initial therapy of abemaciclib and NSAI.[2,10] Endpoints based on tumor assessments, such as PFS, enable faster drug approvals and access to patients, but it is important to confirm that the initially demonstrated PFS benefit translates into a clinically meaningful improvement in OS. At this final OS analysis from MONARCH 3 with a median follow-up of 8.1 years, although the results did not meet the prespecified threshold for statistical significance in the ITT population (hazard ratio, 0.804; $P = 0.0664$) or sVD (hazard ratio, 0.758; $P = 0.0757$), clinically meaningful improvements in median OS were observed with the addition of abemaciclib to NSAI (ITT: 13.1 months; sVD: 14.9 months).

No new safety concerns were observed after this longer follow-up period and with prolonged use of abemaciclib. Consistent with the findings of previous analyses, the most common AE observed was low-grade diarrhea, which was effectively managed with antidiarrheal medications and dose adjustments without risk of compromising efficacy. The combination of abemaciclib plus NSAI continues to demonstrate an acceptable AE profile. The numerical OS improvement combined with the sustained separation of

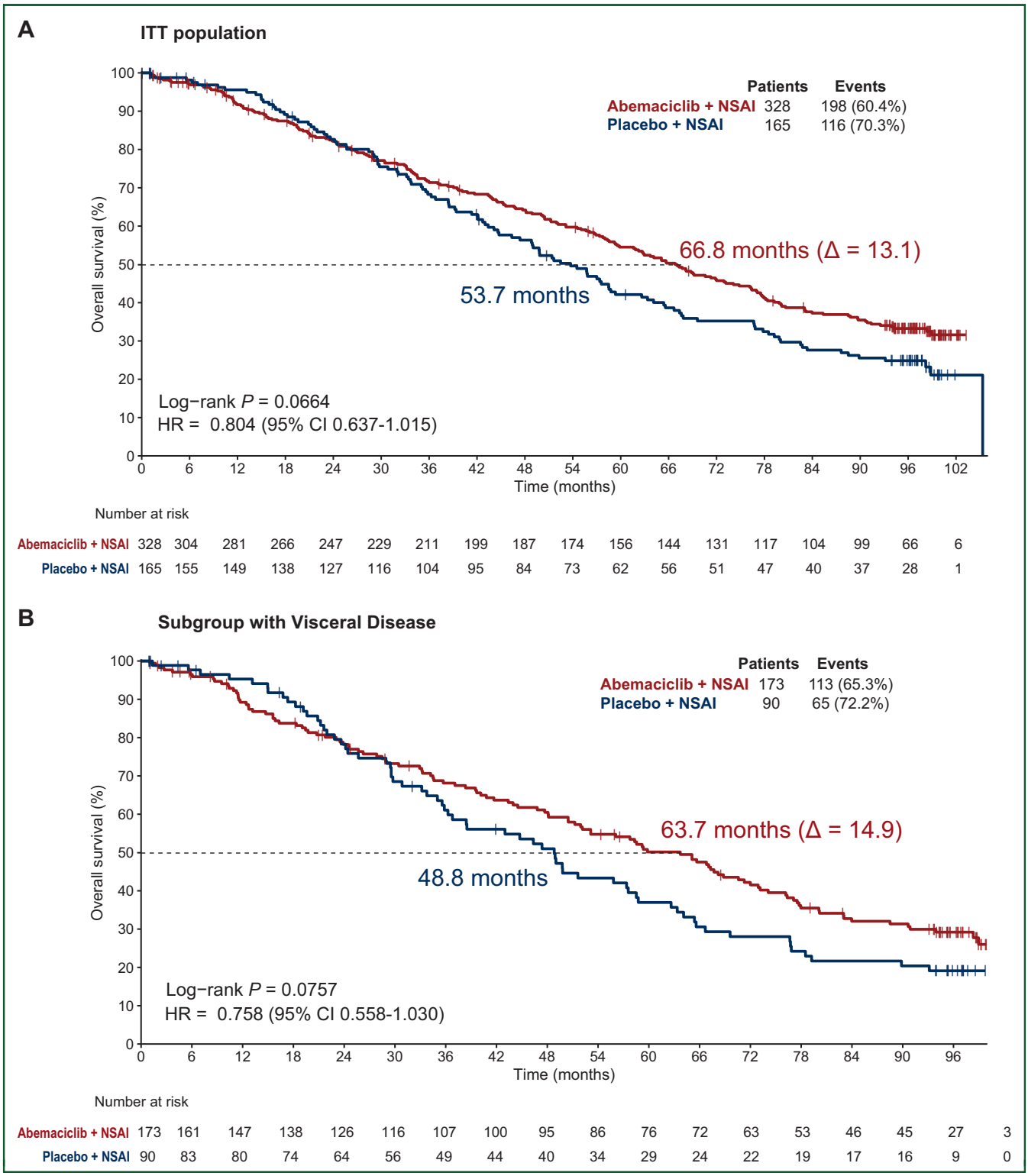

Figure 2. Kaplan–Meier curves of overall survival in the (A) ITT population and (B) subgroup with visceral disease.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NSAI, nonsteroidal aromatase inhibitor.

the PFS curves and favorable safety profile reinforces the use of this combination as first-line treatment of HR+, HER2− ABC.

In HR+ HER2− metastatic disease, the post-progression survival after first-line therapy is relatively long, and patients often receive multiple lines of therapy during the metastatic disease course.[16] In this context, the OS assessment of first-line therapy can take years and potentially be confounded by additional systemic therapies after progression. In MONARCH 3, we hypothesize that additional post-progression therapies, including CDK4/6 inhibitors, may have contributed to the slight

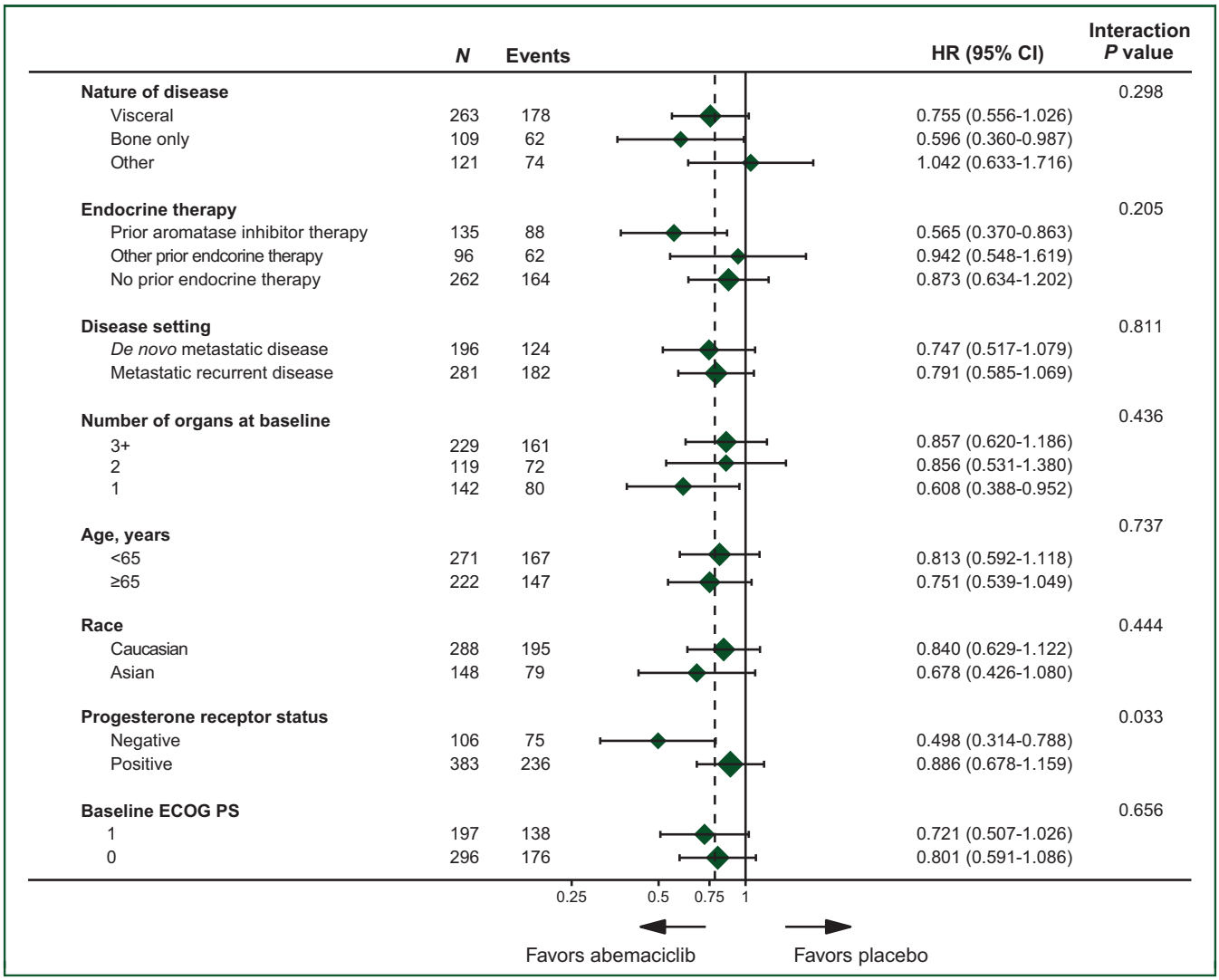

Figure 3. Subgroup analysis of overall survival.
CI, confidence interval; HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance status.

dilution of the OS effect observed beyond 6 years, consistent with the increased effect size (hazard ratio, 0.772; $P = 0.0531$) from the prespecified sensitivity analysis adjusting for CDK4/6 inhibitor use. Additionally, the greatest degree of separation between the OS curves is observed before 6 years, as reflected by the hazard ratio of 0.754 observed at the MONARCH 3 second OS interim analysis with a median follow-up of 5.8 years.[13] This numerically greater effect size (compared with that observed at the final analysis at 8.1 years) corresponds to the hazard ratio, which would have been obtained with a shorter follow-up of ∼6 years, and confirms the important impact of the timing of final analysis.

Table 1. Post-discontinuation therapy. CDK, cyclin-dependent kinase; ITT, intent-to-treat; NSAI, nonsteroidal aromatase inhibitor.

Parameter, *n* (%)[a]	Abemaciclib + NSAI (*N* = 328)	Placebo + NSAI (*N* = 165)
Patients who received subsequent systemic therapy	234 (71.3)	142 (86.1)
Endocrine therapy	196 (59.8)	121 (73.3)
Chemotherapy	136 (41.5)	102 (61.8)
Targeted agent therapy	94 (28.7)	80 (48.5)
Other	39 (11.9)	29 (17.6)
Patients who received a CDK4/6 inhibitor in any subsequent line	38 (11.6)	52 (31.5)
Palbociclib	25 (7.6)	41 (24.8)
Abemaciclib	10 (3.0)	7 (4.2)
Palbociclib + abemaciclib	2 (0.6)	2 (1.2)
Ribociclib	1 (0.3)	2 (1.2)

[a]Denominator used to calculate % corresponds to ITT population. A total of 284 (86.6%) in the abemaciclib arm and 154 (93.3%) in the placebo arm entered the post-treatment discontinuation follow-up.

CDK4/6 inhibitors have transformed the treatment landscape of HR+, HER2− ABC in both the first- and second-line setting and also the EBC setting and are included in clinical guidelines such as NCCN and ABC5 with an ET partner as the preferred regimens in these settings.[5,6] Inconsistencies have been observed, however, between CDK4/6 inhibitors with respect to their impact on OS. In the PALOMA-2 trial ($n = 666$; 2 : 1 randomization; 7.5 years median follow-up), the addition of palbociclib versus placebo to letrozole did not lead to a statistically significant improvement in OS, and the observed increase in median OS was 2.7 months (median

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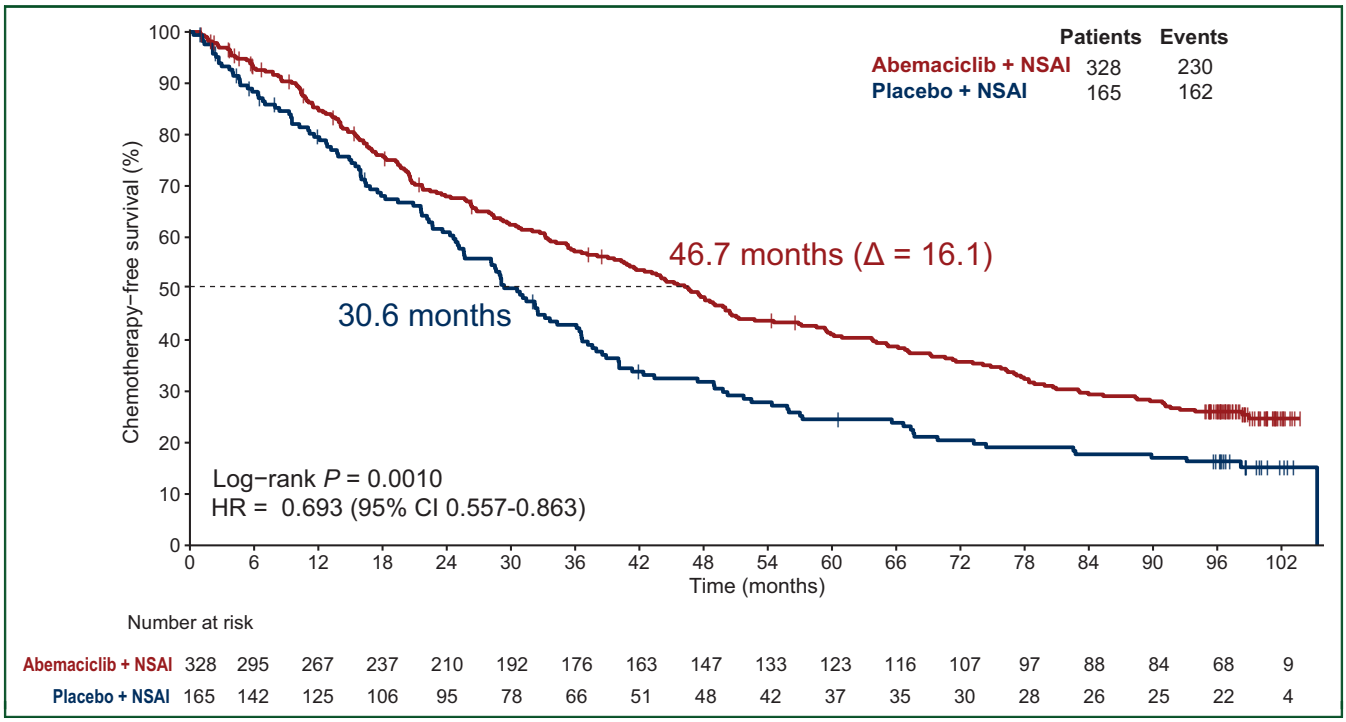

Figure 4. Kaplan−Meier curve of chemotherapy-free survival in the ITT population.
CI, confidence interval; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor.

OS 53.9 versus 51.2 months).[17,18] In the MONALEESA-2 trial ($n = 668$; 1 : 1 randomization; 6.6 years median follow-up), the addition of ribociclib versus placebo to letrozole demonstrated a significant improvement in OS, with a median OS increase of 12.5 months (median OS 63.9 versus 51.4 months).[19] In MONARCH 3, the addition of abemaciclib versus placebo to an NSAI did not reach formal statistical significance, but the 13.1-month increase in median OS (median OS 66.8 versus 53.7 months) was comparable with the 12.5-month improvement in median OS observed in the MONALEESA-2 trial. These results show that ribociclib and abemaciclib both led to a clinically meaningful median OS

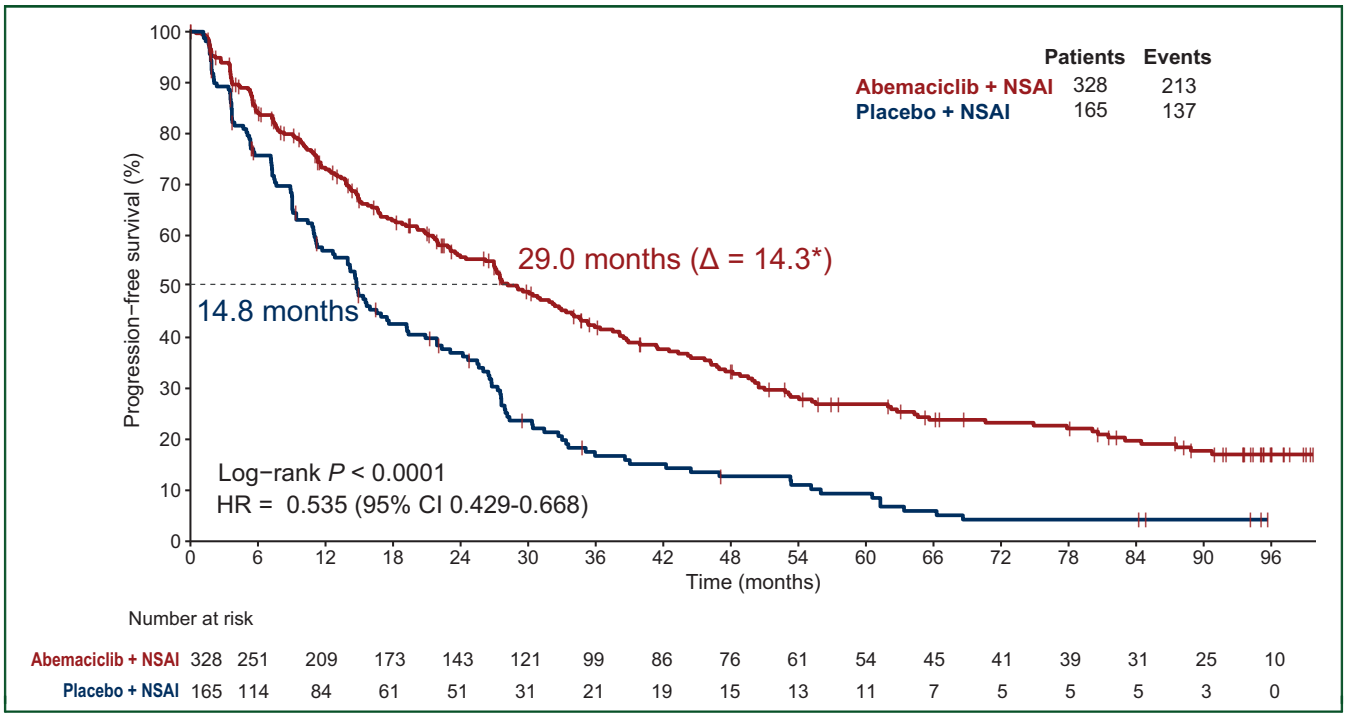

Figure 5. Kaplan-Meier Curve of Updated Progression-Free Survival in the ITT Population.
[a]The difference in median progression-free survival may differ due to rounding.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NSAI, nonsteroidal aromatase inhibitor.

improvement, while the clinical relevance of the observed median OS improvement for palbociclib is less clear. While recognizing the limitations of cross-trial comparisons, it must be considered that there are important differences between these studies with respect to design, size, and resulting statistical power. MONARCH 3 was the smallest of the phase III CDK4/6 inhibitor studies in the first-line ABC setting, with a sample size of 493 patients and a 2 : 1 randomization design.

The use of CDK4/6 inhibitors in the first-line setting for ABC was recently challenged by findings from the SONIA trial, which showed no survival advantage of introducing CDK4/6 inhibitors in first-line treatment compared with second-line treatment.[20] Of note, 91% of the patients enrolled in SONIA received palbociclib, which in contrast to abemaciclib and ribociclib, has not shown a clinically meaningful or statistically significant difference in OS in the first- or second-line ABC setting or an invasive disease-free survival (IDFS) benefit in the EBC setting.[17,18,21,22] While head-to-head comparisons of these three CDK4/6 inhibitors have not been conducted, consistent differences in outcomes (OS and IDFS) have emerged across phase III studies of these therapies such that the results of the SONIA trial should not be extrapolated to assume similar outcomes across this class of therapies. Furthermore, patients in the SONIA trial received fulvestrant following a CDK4/6 inhibitor, the use of which as a single-agent is now suboptimal in the second line, with newer, more effective alternatives available that target *ESR1* mutations (e.g. elacestrant) or PIK3CA/AKT signaling pathway alterations (either alpelisib or capivasertib in combination with fulvestrant).[23-25]

Consistent OS effect size was seen across all subgroups in MONARCH 3, notably in patients with the potential to have more comorbidities such as the elderly and those with an ECOG PS score of 1, and also in those with bone-only and visceral disease. The latter is an interesting finding considering no numerical effect was observed in patients with liver metastases with the addition of ribociclib to letrozole in MONALEESA-2.[19] Importantly, the effect size was consistent in *de novo* and recurrent metastatic disease. It was previously reported that the benefit of adding abemaciclib to either AI or fulvestrant appeared largest in patients with concerning tumor characteristics, including progesterone receptor-negative tumors, and those with visceral disease.[26] In this MONARCH 3 final OS analysis, the effect of abemaciclib was largest in patients with prior AI therapy as well as those with progesterone receptor-negative disease. These OS data are consistent with the findings in MONARCH 2, where the addition of abemaciclib to fulvestrant resulted in a larger OS effect in patients with primary endocrine resistance.[12]

Although the lack of statistical significance in this final OS analysis may be viewed as a limitation of these data, it is important to consider the clinical relevance of the absolute effect size in the context of the limitations of the study design, including the smaller sample size than that in the PALOMA-2 and MONALEESA-2 studies, along with the body of consistent evidence generated with abemaciclib across the first- and second-line ABC and EBC settings. MONARCH 3 is the third contemporary clinical trial investigating CDK4/6 inhibitors as first-line therapy in postmenopausal patients to report final OS data. In addition to extent of follow-up and the natural history of the disease during which patients receive multiple additional therapies, both study size and randomization ratio impact the ability to prove statistical significance for OS.

CONCLUSIONS

Abemaciclib in combination with an NSAI resulted in numerically longer OS compared with NSAI alone not only in the ITT population (median improvement 13.1 months), but also in patients with visceral disease (median improvement 14.9 months) in postmenopausal women with HR+, HER2− ABC in this pivotal phase III trial; however, statistical significance was not reached at this final analysis. After a median follow-up of 8.1 years, the previously demonstrated PFS benefit was sustained, median CFS was substantially improved, and no new safety signals were observed. These data continue to support the consistent and meaningful clinical benefit abemaciclib has demonstrated across the MONARCH program, including as adjuvant therapy in node-positive, high-risk EBC, as initial therapy with AI for metastatic disease, in combination with fulvestrant following disease progression, and as monotherapy in later lines of therapy.

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DISCLOSURE

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REFERENCES

1. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer stat facts: female breast cancer subtypes. Available at https://seer.cancer.gov/statfacts/html/breast-subtypes.html. Accessed February 23, 2024.
2. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer*. 2019;5:5.
3. Rugo HS, Finn RS, Dieras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast Cancer Res Treat*. 2019;174(3):719-729.
4. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol*. 2018;29(7):1541-1547.
5. Gradishar WJ, Moran MS, Abraham J, et al. NCCN guidelines® insights: breast cancer, version 4.2023. *J Natl Compr Canc Netw*. 2023;21(6):594-608.
6. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. 2020;31(12):1623-1649.
7. Torres-Guzmán R, Ganado MP, Mur Perez C, et al. Abemaciclib, a CDK4 and 6 inhibitor with unique pharmacological properties for breast cancer therapy. *J Clin Oncol*. 2021;39(suppl 15):e12506.
8. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2− advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35(25):2875-2884.
9. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR(+)/HER2(−) metastatic breast cancer. *Clin Cancer Res*. 2017;23(17):5218-5224.
10. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35(32):3638-3646.
11. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2023;24(1):77-90.
12. Sledge GW, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor−positive, ERBB2-negative breast cancer that progressed on endocrine therapy—MONARCH 2: a randomized clinical trial. *JAMA Oncol*. 2020;6(1):116-124.
13. Goetz MP, Toi M, Huober J, et al. MONARCH 3: interim overall survival (OS) results of abemaciclib plus a nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+, HER2− advanced breast cancer (ABC). *Ann Oncol*. 2022;33(suppl 7):S1384.
14. Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) log-rank tests. *Biometrics*. 2000;56(3):779-788.

15. Rugo HS, Huober J, García-Sáenz JA, et al. Management of abemaciclib-associated adverse events in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: safety analysis of MONARCH 2 and MONARCH 3. *Oncologist*. 2021;26(1):e53-e65.
16. Seidman AD, Maues J, Tomlin T, Bhatnagar V, Beaver JA. The evolution of clinical trials in metastatic breast cancer: design features and endpoints that matter. *Am Soc Clin Oncol Educ Book*. 2020;40:1-11.
17. Finn RS, Rugo HS, Dieras VC, et al. Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor−positive/human epidermal growth factor receptor 2−negative advanced breast cancer (ER+/HER2− ABC): analyses from PALOMA-2. *J Clin Oncol*. 2022;40(suppl 17):LBA1003.
18. Slamon DJ, Diéras V, Rugo HS, et al. Overall survival with palbociclib plus letrozole in advanced breast cancer. *J Clin Oncol*. 2024;42:994-1000.
19. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med*. 2022;386(10):942-950.
20. Sonke GS, Van Ommen-Nijhof A, Wortelboer N, et al. Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2−) advanced breast cancer (ABC). *J Clin Oncol*. 2023;41(suppl 17):LBA1000.
21. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379:1926-1936.
22. Gnant M, Dueck AC, Frantal S, et al. Adjuvant palbociclib for early breast cancer: the PALLAS trial results (ABCSG-42/AFT-05/BIG-14-03). *J Clin Oncol*. 2022;40(3):282-293.
23. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized phase III EMERALD trial. *J Clin Oncol*. 2022;40(28):3246-3256.
24. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-1940.
25. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2023;388(22):2058-2070.
26. Di Leo A, O'Shaughnessy J, Sledge GW Jr, et al. Prognostic characteristics in hormone receptor-positive advanced breast cancer and characterization of abemaciclib efficacy. *NPJ Breast Cancer*. 2018;4:41.