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ORIGINAL ARTICLE

Overall survival with abemaciclib in early breast cancer☆

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Background: Adjuvant abemaciclib combined with endocrine therapy (ET) significantly improved invasive disease-free survival (IDFS) in patients with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative, node-positive, high-risk early breast cancer (EBC). The impact on overall survival (OS) remained unknown.

Patients and methods: In the phase III monarchE trial (NCT03155997), patients received ET for at least 5 years with or without abemaciclib for 2 years. In this article, we report the primary OS results, a key secondary endpoint, and updated estimates of IDFS and distant relapse-free survival (DRFS).

Results: Overall, 5637 patients underwent randomization, with 2808 assigned to abemaciclib—ET, and 2829 to ET. In the intent-to-treat population, with a median follow-up of 76.2 months, abemaciclib—ET resulted in a 15.8% lower risk of death than ET [661 deaths; hazard ratio 0.842, 95% confidence interval (CI) 0.722-0.981, $P = 0.027$], meeting the prespecified boundary for significance. The 7-year OS was 86.8% with abemaciclib—ET and 85.0% with ET (absolute difference, 1.8%). OS benefit was consistent across prespecified subgroups. In addition to patients who had already died of metastatic disease, fewer patients in the abemaciclib—ET arm were living with metastatic disease compared with the ET arm (6.4% versus 9.4%). Sustained improvement was demonstrated in IDFS and DRFS (hazard ratio 0.734, 95% CI 0.657-0.820 and hazard ratio 0.746, 95% CI 0.662-0.840, respectively). Seven-year IDFS was 77.4% with abemaciclib—ET and 70.9% with ET (absolute difference, 6.5%) and 7-year DRFS were 80.0% and 74.9% (absolute difference, 5.1%). The long-term safety data compiled did not support any concerns of delayed toxicities.

Conclusions: Adjuvant abemaciclib—ET resulted in a statistically significant and clinically meaningful improvement in OS compared with ET in patients with HR-positive, HER2-negative, node-positive, high-risk EBC. At 7 years, abemaciclib—ET continued to demonstrate a sustained IDFS and DRFS benefit.

Key words: abemaciclib, adjuvant therapy, high-risk early breast cancer, monarchE, overall survival

INTRODUCTION

Abemaciclib is globally approved for high-risk early breast cancer (EBC) as well as for advanced breast cancer in both first- and second-line settings.[1,2] Two years of adjuvant cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) therapy with abemaciclib in combination with endocrine therapy (ET) is considered the standard of care for eligible patients with hormone receptor (HR)-positive, human epidermal

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growth factor receptor 2 (HER2)-negative, node-positive, EBC at high risk of recurrence, with National Comprehensive Cancer Network category 1 recommendation and European Society for Medical Oncology-Magnitude of Clinical Benefit Scale score A based on outcomes from the monarchE trial.[3,4] At a median follow-up of 54 months, abemaciclib—ET demonstrated a sustained and clinically meaningful improvement in invasive disease-free survival (IDFS) [hazard ratio of 0.680; 5-year rates: 83.6% versus 76.0%] and distant relapse-free survival (DRFS) (hazard ratio 0.675, 86.0% versus 79.2% at 5 years).[5] The increasing absolute improvement seen at 5 years is consistent with a carryover effect of the 2 years of abemaciclib treatment.

Overall survival (OS) is a clinically meaningful measure of both efficacy and safety and is considered the gold standard for establishing the clinical benefit of cancer treatments. Improving OS in HR-positive EBC has remained a challenge over recent decades. In 2011, a meta-analysis of 20 trials in >21 000 patients showed that 5 years of tamoxifen substantially reduced recurrence rates during the first 10 years and reduced mortality by about one-third over 15 years (absolute difference: 9.2%), compared with no therapy.[6] A 2015 meta-analysis of 31 920 patients treated with aromatase inhibitors (AIs) versus tamoxifen showed a 15% reduction in 10-year mortality and a 2.1% absolute difference in OS, favoring AIs.[7] In the TEXT and SOFT studies, the addition of 5 years of ovarian function suppression (OFS) to tamoxifen improved 12-year OS rates by 2.2% in premenopausal women compared with tamoxifen alone, while exemestane + OFS reduced 12-year OS rates by 2.0% compared with tamoxifen + OFS, but these absolute differences did not reach statistical significance.[8,9] More recently, a 2025 meta-analysis of 22 031 patients showed that extending AI treatment beyond the initial 5 years further reduced the rate of ongoing recurrence. However, no significant improvement in 10-year OS was noted, with a modest 0.6% absolute difference at a median of 8-years of follow-up.[10]

As expected, given the disease course of HR-positive breast cancer, OS events have accrued slowly in this adjuvant study. At a 5-year data interim analysis in the monarchE study, a favorable OS trend emerged (442 deaths; hazard ratio 0.903, 95% CI 0.749-1.088) with nearly twice as many patients in the ET arm living with metastatic disease compared with those receiving abemaciclib—ET, suggesting that the OS effect could emerge with longer follow-up.[5]

In this article, we present the primary OS analysis and the updated estimates of IDFS and DRFS from the monarchE trial at a median follow-up of 6.3 years.

PATIENTS AND METHODS

Trial oversight

The trial was designed by the sponsor, Eli Lilly and Company, in collaboration with a global steering committee. The protocol was approved by the ethical review board at each participating site. The trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines, and applicable laws and regulations. All participants provided written informed consent.

The investigators gathered the data, while the sponsor monitored the conduct of the trial, received the data, and carried out all the analyses. The authors affirm the accuracy and completeness of the data and confirm that the trial was conducted in strict adherence to the approved protocol.

The first draft of the manuscript was written by the authors employed by the sponsor, together with the first author, with assistance from a sponsor-funded medical writer. Subsequently, all authors reviewed and contributed to the manuscript.

The investigators and steering committee worked under confidentiality agreements with the sponsor.

Trial design and patients

MonarchE is a global, randomized, open-label, phase III study evaluating the efficacy and safety of abemaciclib—ET versus standard ET in adult patients with HR-positive, HER2-negative, node-positive, high-risk EBC. The detailed study design and eligibility criteria have been previously reported.[5,11,12] In brief, a total of 5637 patients were randomly assigned in a 1 : 1 ratio to receive at least 5 years of ET with or without abemaciclib for a 2-year treatment period. Patients were assigned to one of two cohorts. Cohort 1 included patients with either four or more positive pathological axillary lymph nodes or one to three pathological axillary lymph nodes with additional high-risk features of grade 3 disease and/or tumor ≥5 cm. Inclusion of patients with micrometastatic (N1mi) disease and multifocal or multicentric disease was allowed. Cohort 2 included patients with one to three positive pathological axillary lymph nodes, tumor grade <3, tumor size <5 cm, and central Ki-67 ≥20% as the only additional high-risk factor. The intent-to-treat (ITT) population included all patients from both cohorts.

Endpoints

The primary efficacy endpoint was IDFS, as defined by the Standardized Definitions for Efficacy End Points (STEEP) system.[13] IDFS was defined as the time from randomization until the first occurrence of one of the following events: ipsilateral invasive disease, ipsilateral locoregional invasive disease, contralateral invasive breast cancer, distant recurrence, second primary non-breast invasive cancer, or death from any cause. Key secondary efficacy endpoints were DRFS and OS. DRFS was defined as the time from randomization until the first occurrence of metastatic disease or death from breast cancer. OS was defined as the time from randomization until the date of death from any cause. Safety endpoints included treatment-emergent adverse events, all serious adverse events (SAEs) up to 5 years from randomization, hospitalizations, and clinical laboratory abnormalities.

Statistical analysis

Statistical analysis methods have been described in detail.[14] OS was a key secondary endpoint with type-1 error

control, according to a gated testing strategy. At each analysis time point of OS, the critical *P* value boundary was calculated based on the observed number of events using the Lan—Demets method with an O'Brien—Fleming type stopping boundary.[15] The target number of events for this primary OS analysis was increased from 390 to 650 after the primary outcome analysis in consultation with health authorities, to ensure a minimum follow-up of at least 5 years in the adjuvant setting. At this updated analysis, descriptive assessments were planned for IDFS and DRFS. For each efficacy endpoint in the ITT and subpopulations, hazard ratios and corresponding 95% confidence intervals (CIs) were estimated with a Cox proportional hazards model stratified according to the randomization factors, and landmark analyses were carried out each year up to 7 years using the Kaplan—Meier method. For subgroups, landmark yearly rates were estimated up to 6 years to ensure sufficient numbers of events within subgroups.

RESULTS

Patients

From July 2017 through August 2019, 5637 patients were randomly assigned 1 : 1 to receive abemaciclib—ET ($n = 2808$) or ET ($n = 2829$) (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.10.005). The ITT population included all patients, with cohort 1 comprising 5120 patients (91%) and cohort 2 comprising 517 patients (9%). Updated baseline demographics and clinical characteristics were well balanced between arms and are previously published.[5]

At the time of the primary OS analysis (data cut-off date: 15 July 2025), the median follow-up was 6.3 years in both arms. Approximately 78% of patients had been in follow-up for recurrence and survival for at least 6 years (4 years after completion of the abemaciclib treatment period). The majority of patients were alive in the study follow-up (73.3% in the abemaciclib—ET arm and 70.7% in the ET arm) and a similar proportion of patients between arms withdrew or were lost from the study follow-up (8.4% versus 8.7%).

Efficacy

Efficacy in the ITT population. At data cut-off for this analysis, a total of 661 patients had died, 301/2808 patients (10.7%) in the abemaciclib—ET arm and 360/2829 (12.7%) in the ET arm. The addition of abemaciclib to ET resulted in a 15.8% reduction in the risk of death versus ET (stratified hazard ratio 0.842, 95% CI 0.722-0.981, two-sided $P = 0.027$), meeting the prespecified boundary of 0.0434 for statistical significance. The estimated 7-year OS rate was 86.8% in the abemaciclib—ET arm and 85.0% in the ET arm (absolute difference of 1.8%) (Figure 1A). The majority of deaths in both arms were associated with breast cancer recurrence (Figure 2; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.10.005). Most frequent adverse events (AEs) leading to death were infections [16 (0.6%) versus 10 (0.4%)], including coronavirus disease 2019 (COVID-19) infections [9 (0.3%) versus 3 (0.1%)], second primary neoplasm [13 (0.5%) versus 8 (0.3%)], and cardiac disorders [11 (0.4%) versus 9 (0.3%)]. There was no underlying pattern of pathophysiological cause of the deaths in either treatment arm. No relevant differences in causes of death related to AEs were observed (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.10.005). In addition to patients who had already died of metastatic disease, fewer patients in the abemaciclib—ET arm were living with metastatic disease compared with the ET arm [180 (6.4%) versus 266 (9.4%) patients, respectively] (Figure 2).

There was a sustained benefit of adjuvant abemaciclib in reducing the risk of developing an IDFS event (hazard ratio 0.734, 95% CI 0.657-0.820, nominal $P < 0.0001$). At 5 years, ~4000 patients across arms were at risk (compared with only ~950 at prior analysis), enabling robust estimation of 5-year IDFS rates of 83.1% in the abemaciclib—ET arm and 76.5% in the ET arm (absolute benefit of 6.6%). The estimated IDFS rate at 7 years was 77.4% and 70.9% in each arm, respectively (absolute benefit, 6.5%) (Figure 1B). Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.10.005, shows the Kaplan—Meier curves with yearly rates of OS, IDFS, and DRFS. Most IDFS events involved distant metastatic disease (Table 1). A similar number of second primary neoplasms were reported in both arms [48 (1.7%) in abemaciclib—ET and 52 (1.8%) in ET, with the most frequent neoplasm being colon cancer with 4 and 6 cases, respectively].

The addition of abemaciclib to ET also resulted in a 25.4% reduction in the risk of developing a DRFS event, compared with ET (hazard ratio 0.746, 95% CI 0.662-0.840, nominal $P < 0.0001$). At 7 years, the absolute benefit in DRFS rates was 5.1% (Figure 1C), an absolute difference that has remained consistent over landmark estimates for several years. Distant metastatic disease was documented as the first recurrence event in 381 patients (13.6%) in the abemaciclib—ET arm and 523 (18.5%) in the ET arm with common sites of distant recurrence being bone, liver, and lung/pleura. Notably, abemaciclib treatment reduced the number of patients with metastatic disease in most common locations (Table 1).

The OS benefits were consistent across all subgroups (Figure 3). With additional events observed at this longer follow-up, the IDFS and DRFS continue to demonstrate consistent benefit with better precision across subgroups (Supplementary Figures S3 and S4, available at https://doi.org/10.1016/j.annonc.2025.10.005).

Efficacy in subpopulations. In cohort 1, OS, IDFS, and DRFS were consistent with the ITT population (Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2025.10.005). A total of 630 patients had died, 286/2555 patients (11.2%) in the abemaciclib—ET arm and 344/2565 (13.4%) in the ET arm. Abemaciclib—ET resulted in a clinically meaningful reduction of 16.5% in the risk of death compared with ET (hazard ratio 0.835, 95% CI 0.713-0.977, nominal $P = 0.0239$). Sustained IDFS and DRFS benefit was observed with abemaciclib—ET versus ET (IDFS: hazard ratio

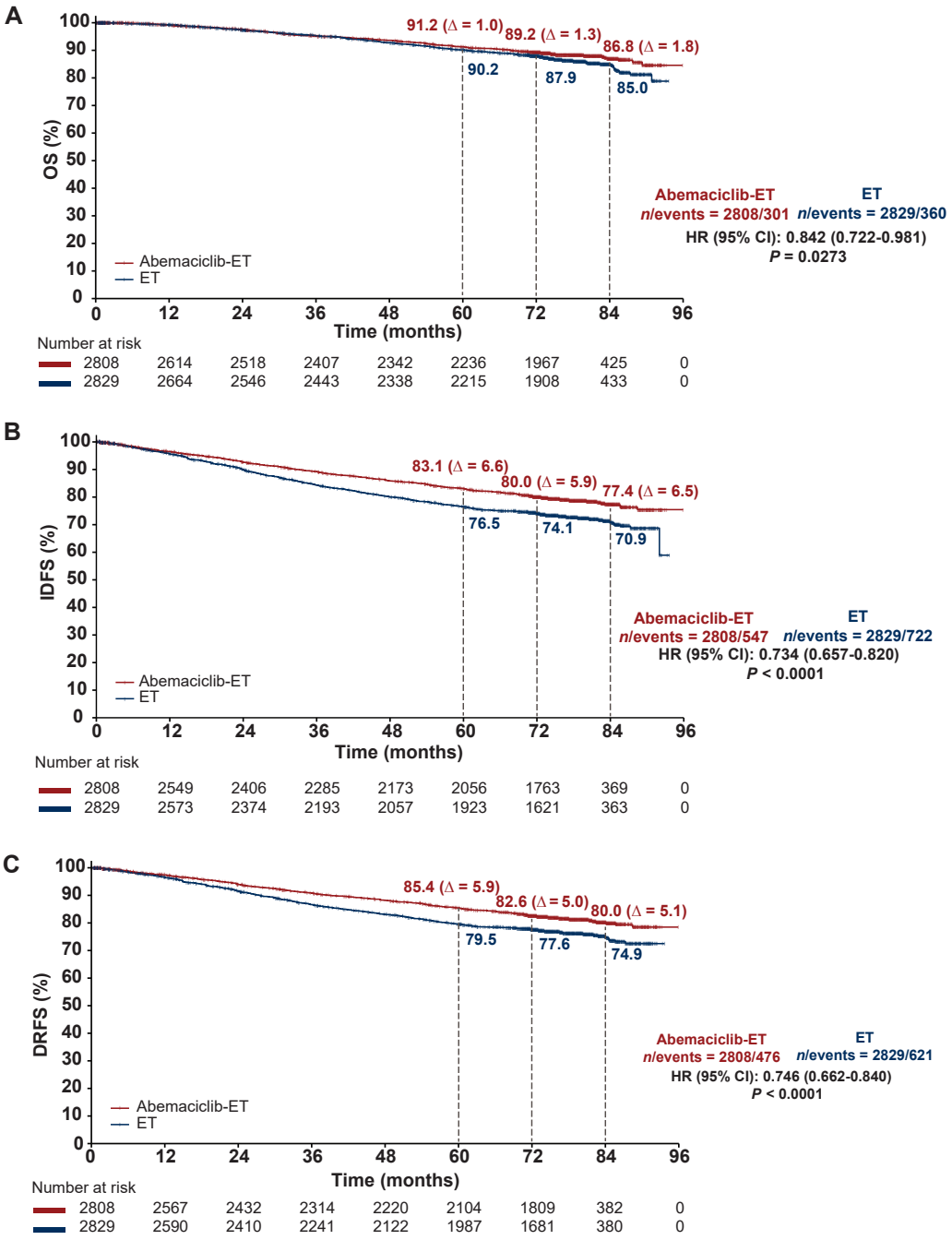

Figure 1. Efficacy in the ITT population. Kaplan—Meier survival curves of (A) overall survival, (B) invasive disease-free survival, and (C) distant relapse-free survival in the ITT population; n, number of events in the specified category.
CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; ITT, intent-to-treat.

0.726, 95% CI 0.648-0.815, $P < 0.0001$; DRFS: hazard ratio 0.736, 95% CI 0.651-0.832, $P < 0.0001$). The 7-year IDFS rate was 77.0% with abemaciclib—ET and 70.1% with ET (absolute difference, 6.9%) and the 7-year DRFS rate was 79.5% with abemaciclib—ET and 74.0% with ET (absolute difference, 5.5%). Distribution of the first recurrence event in cohort 1 is shown in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.10.005.

In cohort 1, abemaciclib—ET showed consistent benefit across subgroups, as well as by Ki-67 index (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.10.005). The subgroup analyses for OS, IDFS, and DRFS within cohort 1 are shown in Supplementary Figures S6-S8, available at https://doi.org/10.1016/j.annonc.2025.10.005, respectively. Similar to the ITT population, the majority of deaths in cohort 1 population across both arms were associated with breast cancer recurrence (Supplementary Figure S9, available at https://doi.org/10.1016/j.annonc.2025.10.005).

In cohort 2, a similar number of OS events were reported in each arm, 15/253 (5.9%) and 16/264 (6.1%) of abemaciclib—ET and ET arm patients (hazard ratio 0.966,

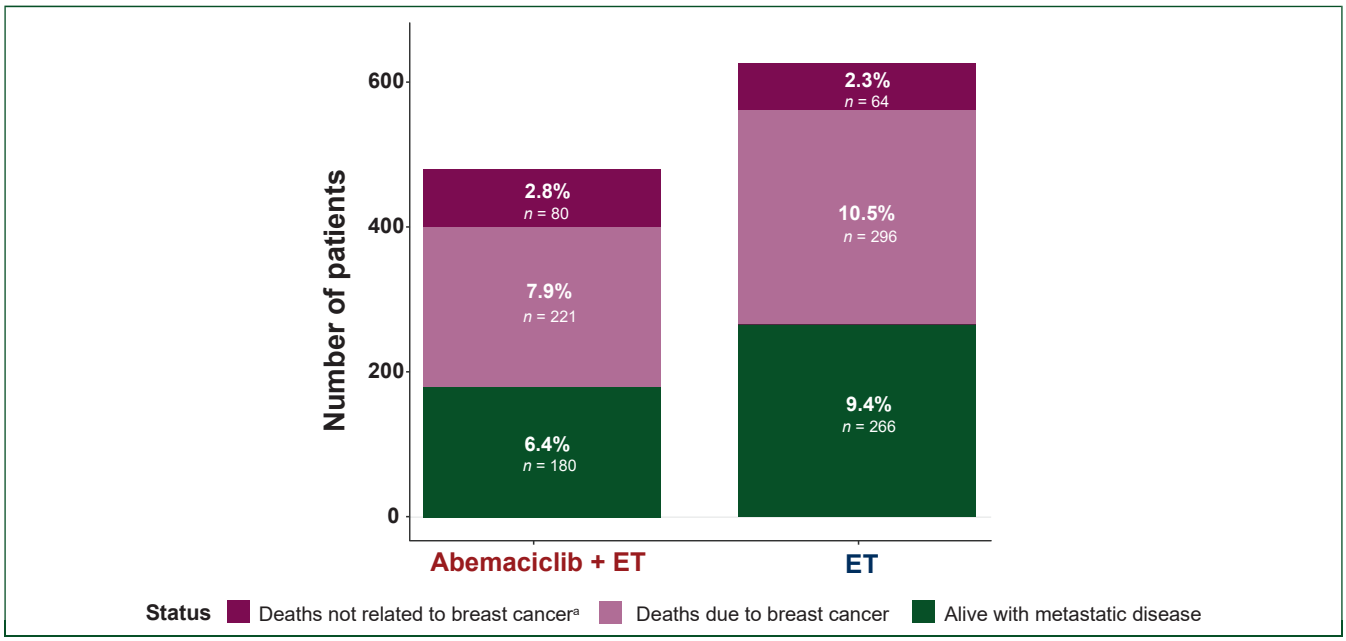

Figure 2. Bar plot of survival status in the ITT population who had distant metastatic disease or died. Percentages were calculated using the respective ITT populations as the denominators for each treatment arm (abemaciclib—ET, $n = 2808$; ET, $n = 2829$).
[a] Deaths due to AEs and due to unknown cause.
ET, endocrine therapy; ITT, intent-to-treat.

95% CI 0.468-1.992). Despite the small sample size of this cohort, abemaciclib—ET illustrated numerically favorable trends in IDFS and DRFS compared with ET (hazard ratio 0.797, 95% CI 0.508-1.252 for IDFS; hazard ratio 0.902, 95% CI 0.541-1.505 for DRFS) (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.10.005).

Safety

At the time of this analysis, all patients had discontinued from the 2-year study treatment period ~4 years ago; consequently, there were no changes in discontinuations or dose adjustments from prior analyses and the overall safety data are unchanged and consistent with prior reports.[11,12] During long-term follow-up (30 days after study treatment discontinuation) the only safety data collected were non-serious AEs related to study treatment and SAEs regardless of causality.[11] The incidence of SAEs in long-term follow-up was higher in the ET arm (8.1%) than in the abemaciclib—ET arm (7.5%), with infections being the most frequent SAEs in both arms (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.10.005).

Table 1. Distribution of first recurrence in ITT population

	Abemaciclib—ET $n = 2808$	ET $n = 2829$
Patients with any recurrence event, *n* (%)	505 (18.0)	693 (24.5)
Type of recurrence event, *n* (%)		
Distant recurrence	381 (13.6)	523 (18.5)
Local/regional recurrence	70 (2.5)	109 (3.9)
Second primary neoplasm	48 (1.7)	52 (1.8)
Contralateral breast cancer	14 (0.5)	22 (0.8)
Site of initial distant recurrence, *n* (%)		
Bone	166 (5.9)	265 (9.4)
Liver	99 (3.5)	133 (4.7)
Lung	69 (2.5)	76 (2.7)
Lymph node	29 (1.0)	46 (1.6)
Brain/central nervous system	32 (1.1)	31 (1.1)
Pleura	8 (0.3)	28 (1.0)

ET, endocrine therapy; ITT, intent-to-treat.

Post-discontinuation anticancer therapies

Anticancer treatments received after completion or discontinuation from study treatment are being collected.

The majority of patients without documented distant recurrence continued receiving ET (97.0% in the abemaciclib—ET arm versus 96.7% in the ET arm), including 85.4% versus 82.4% patients receiving ≥5 years of ET.

Among patients who experienced distant recurrence, 78.9% in the abemaciclib—ET arm and 83.4% in the ET arm received systemic anticancer therapy at any time in the metastatic setting (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.10.005). For the remaining patients, the lack of reported treatments is mainly due to either rapid deterioration to death, recent progression with ongoing evaluation of subsequent therapies, pending information from another treating institution, or patients lost to follow-up.

In addition to endocrine therapies, the most frequently reported first-line treatments in both abemaciclib—ET and ET arms were CDK4/6is (30.0% versus 47.3%) and chemotherapy (32.7% versus 23.7%) (Table 2). An additional *post hoc* analysis of first-line therapies was conducted by time of distant recurrences relative to study treatment completion/discontinuation. Earlier recurrences were defined as those occurring on treatment or within 12 months of 2-year treatment completion/discontinuation and later recurrences as those

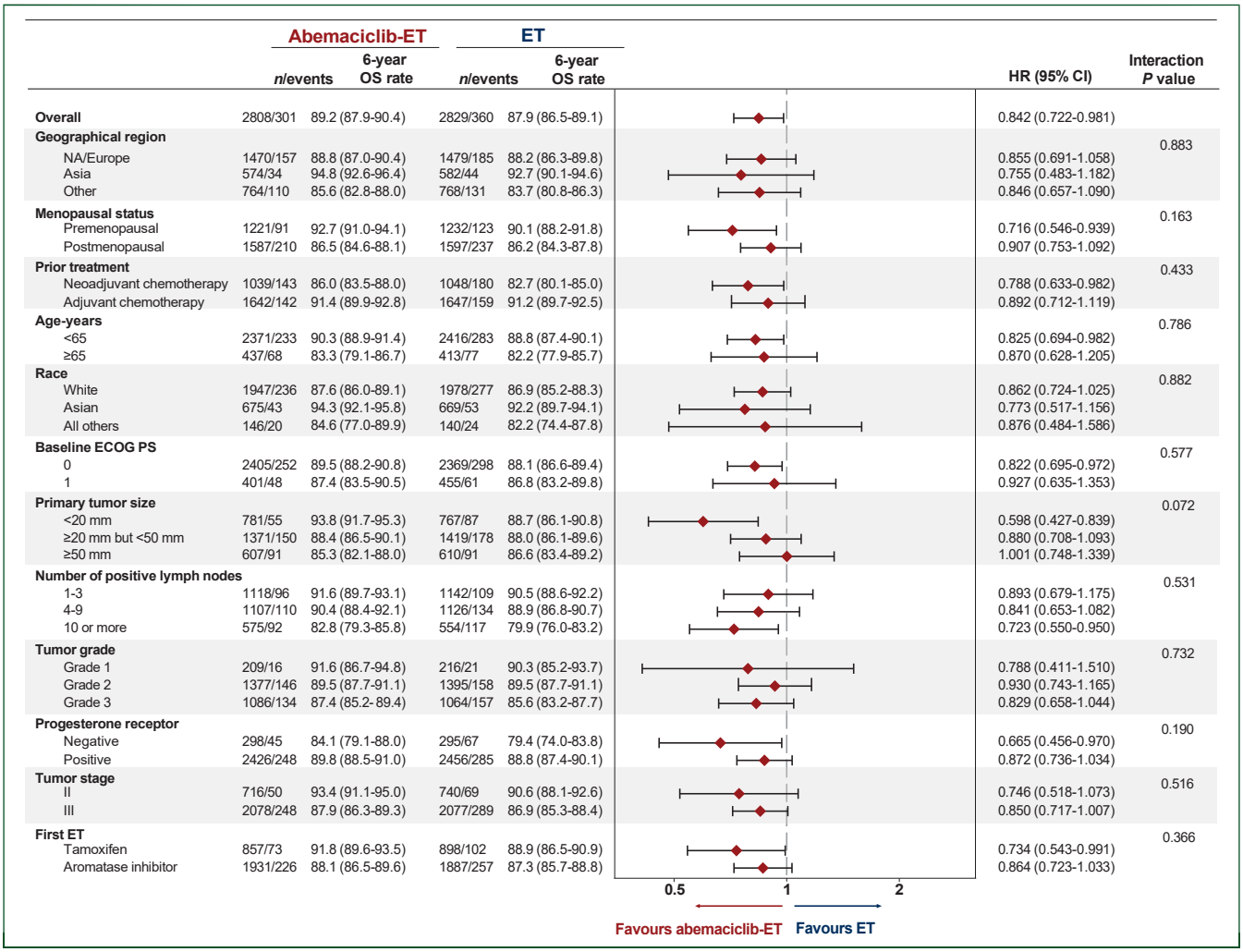

Figure 3. Overall survival in the ITT population and according to prespecified subgroups. Confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing; all subgroup analyses were prespecified.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HR, hazard ratio; ; ITT, intent-to-treat; NA, North America; OS, overall survival.

occurring >12 months from treatment completion/discontinuation. The difference in CDK4/6i was primarily observed among patients who developed earlier recurrences (15.2% in abemaciclib—ET versus 44.7% in the ET arm) while the difference was less pronounced among patients with later recurrences (43.1% versus 50.4%). The higher use of chemotherapy in the abemaciclib—ET arm was observed primarily in patients with earlier recurrences (43.5% versus 26.8%), with similar use in patients with later recurrences (23.1% versus 19.8%) across both arms (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2025.10.005).

Distribution of post-discontinuation anticancer treatments in cohort 1 is similar to the ITT population. The majority of cohort 1 patients without documented distant recurrence continued receiving ET (97.1% in the abemaciclib—ET arm versus 96.6% in the ET arm), including 85.1% versus 81.9% patients receiving ≥5 years of ET. Detailed information about treatments in the metastatic setting is shown in Supplementary Tables S7-S9, available at https://doi.org/10.1016/j.annonc.2025.10.005.

DISCUSSION

In the monarchE trial, with a median follow-up of 6.3 years, 2 years of adjuvant abemaciclib demonstrated a statistically significant and clinically meaningful 15.8% reduction in the risk of death, with an absolute improvement of 1.8% in the 7-year OS rate, and a sustained treatment benefit in IDFS and DRFS. Additionally, fewer patients in the abemaciclib arm developed and were living with metastatic disease compared with those in the ET arm. This substantial improvement in DRFS is expected to continue driving the OS benefit with longer follow-up. Abemaciclib, therefore, represents the first novel therapy since the introduction of AIs over two decades ago to confer a statistically significant OS benefit in the adjuvant setting, reinforcing its role as the standard of care for the adjuvant treatment of patients with HR-positive, HER2-negative, node-positive, high-risk EBC.

monarchE was prospectively designed to alpha control and statistically test for the OS endpoint. To allow adequate follow-up time more commensurate with the long natural history of HR-positive, HER2-negative breast cancer, following consultation with regulators, the target number of OS events

Table 2. Systemic anticancer therapies received as first-line treatment in the metastatic setting

Patients with distant recurrence who entered post-discontinuation follow-up	Abemaciclib—ET $N = 407$	ET $N = 565$
Any systemic therapy, *n* (%)	321 (78.9)	471 (83.4)
Endocrine therapy,[a] *n* (%)	190 (46.7)	330 (58.4)
Fulvestrant	117 (28.7)	188 (33.3)
Letrozole	40 (9.8)	95 (16.8)
Exemestane	20 (4.9)	18 (3.2)
Anastrozole	12 (2.9)	23 (4.1)
Tamoxifen	7 (1.7)	20 (3.5)
Targeted therapy, *n* (%)	135 (33.2)	276 (48.8)
CDK4/6i	122 (30.0)	267 (47.3)
Palbociclib	44 (10.8)	100 (17.7)
Ribociclib	54 (13.3)	90 (15.9)
Abemaciclib	23 (5.7)	83 (14.7)
PI3K/AKT/mTOR pathway inhibitors	13 (3.2)	4 (0.7)
Chemotherapy, *n* (%)	133 (32.7)	134 (23.7)
Other[b], *n* (%)	21 (5.2)	27 (4.8)
Bevacizumab	8 (2.0)	11 (1.9)

Includes systemic therapies which were started after distant recurrence as first-line in the metastatic setting. Percentages may not add up to the total in each group as patients may have received more than one drug in each group and table includes only individual drugs received by at least 2% of patients.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy.
[a]Includes monotherapy and in combination with other therapies.
[b]Antibody—drug conjugates not included as did not meet 2% threshold.

was increased from 390 to 650 after the primary outcome analysis to ensure a minimum of 5 years of follow-up.[16] As a result, by the data cut-off of this analysis, the magnitude of OS effect size was robustly characterized.

Demonstrating OS benefit in EBC is particularly challenging due to the relatively long life expectancy in HR-positive, HER2-negative breast cancer and the availability of effective therapies in the metastatic setting. Some of these therapies have substantially improved survival outcomes, including the use of CDK4/6is as the standard of care in first-line treatment of metastatic disease.[17-21] We analyzed the use of anticancer treatments in the metastatic setting, given those that can prolong survival could potentially confound the impact of adjuvant therapy on OS outcomes. As expected, more patients in the ET arm received CDK4/6i (mostly as first-line treatment), especially among patients with early distant recurrences. The proportion of patients receiving these therapies and the distribution of these therapies must be interpreted in the context of a global trial, with different standards of care and access to novel therapies across countries during follow-up, also acknowledging that this analysis reflects the data available at the time of this cut-off and efforts are ongoing to complete data collection for all patients. The observed OS advantage, despite differences in post-recurrence treatments (including higher use of CDK4/6is in the ET arm), reinforces the justification for adjuvant abemaciclib early in the management of HR-positive breast cancer.

Further follow-up from the monarchE trial has demonstrated a sustained and persistent improvement in both IDFS and DRFS. The early separation of the Kaplan—Meier curves, which remained evident beyond the completion of 2 years of abemaciclib treatment, suggests a durable carryover effect, implying that the natural history of the disease may have been altered in a subset of patients. Substantially more patients have been followed up for at least 5 years at this time compared with prior analyses.[5] The extent of follow-up enables robust estimation around IDFS rates at 5 years, generating an absolute improvement of 6.5% with improved precision. These data confirm the deepening of effect size through 5 years in the adjuvant setting. From 5 to 7 years, the IDFS and DRFS curves remain separated and run parallel, with an absolute difference of 6.5% at 7 years. Overall, the updated hazard ratio estimates across the entire follow-up period comprehensively reflect the cumulative relative risk reduction that continuously evolved with greater magnitude up to 5 years, together with a maintained and stabilized effect size from 5 to 7 years.

The substantial improvements in long-term IDFS and DRFS were consistent across subgroups. The effect size in individual subgroup analyses by baseline characteristics should be interpreted with caution, as there is no formal statistical significance testing within subgroup and the effect of individual factors might be confounded by other risk features [e.g. patients with tumor size <2 cm or grade 1 were eligible only if they had concurrent high-risk feature(s)]. Of note, abemaciclib benefit was observed regardless of the number of positive lymph nodes. While patients with one to three positive lymph nodes are generally considered to have lower risk, in a real-world study, 24% of patients with HR-positive, HER2-negative EBC with one to three positive lymph nodes and additional monarchE risk features (i.e. G3, tumor size of $\geq$5 cm) experienced an IDFS event at 5 years, compared with only 10% of those patients with one to three positive lymph nodes who do not meet monarchE criteria. These data are consistent with the current monarchE analysis where 20.4% of the N1 patients treated with ET experienced IDFS events at 6 years, and confirm that all patients enrolled in monarchE, including those with N1 disease and additional high-risk features, were at high risk of recurrence and therefore warranted intensified adjuvant therapy.[22] Subgroup analyses from monarchE strengthen the benefit of 2 years of adjuvant abemaciclib across the entire study population.

IDFS and DRFS benefit were observed regardless of menopausal status at the time of breast cancer diagnosis[23] or the first ET partner administered (tamoxifen or AI). Of note, ET switch was allowed any time during treatment period and in follow-up and has been previously discussed.[24] Abemaciclib is the only CDK4/6i approved in combination with either tamoxifen or AI and provides consistent treatment effect in IDFS, DRFS, and now OS, regardless of ET partner. Based on the estimated 6-year OS rates in the ET-alone arm, patients receiving tamoxifen as their first ET had comparable risk of death than those receiving an AI, suggesting that both ET options are appropriate in this setting at the discretion of the treating physician. Tamoxifen and AIs have different safety profiles; while tamoxifen is known to increase the risk of venous thromboembolism, AIs produce more arthralgias, a common reason for non-adherence to adjuvant AIs. The benefit—risk balance must be considered when deciding the appropriate ET partner for each patient.[12] The ability to use abemaciclib allows clinicians to optimize ET for their patients to improve tolerability and persistence, without compromising efficacy.

At the time of this 7-year analysis, patients in the trial had completed their adjuvant abemaciclib ≥4 years ago. No new safety signals have emerged. Of note, the incidence of second primary neoplasm (including those leading to death like colon and pancreatic cancer) was similar across both arms. The minor numerical imbalance in deaths due to AEs disfavoring the abemaciclib—ET arm cannot be attributed to any particular underlying pathology, apart from a minor imbalance in COVID-19-related fatalities in the context of the global pandemic with no other reported confounding lung comorbidities in these cases. The safety profile of abemaciclib + ET has been previously characterized and is considered manageable with dose adjustments and supportive medications. Patient-reported outcomes findings confirm a tolerable and reversible toxicity profile. The long-term safety data compiled did not support any concerns of delayed toxicities, consistent with prior abemaciclib experience in the metastatic setting.[21] This reassurance is particularly important in the adjuvant setting, where patients have longer life expectancy and a potential for cure.

For patients with HR-positive breast cancer, there remains a constant ongoing risk of recurrence, which is greater for those with high-risk clinicopathological features such as nodal involvement, higher tumor grade, and larger tumor size. The recurrence risk is in excess of 25% at 5 years despite standard-of-care adjuvant cytotoxic and endocrine-based therapies and is similar to triple-negative disease, highlighting the medical need for optimized treatments to improve outcomes.[22,25] The monarchE study is ongoing, with continued follow-up to further characterize the long-term benefits of adding 2 years of abemaciclib to adjuvant ET, including impact on late recurrences and survival. Continued follow-up will help define if the reduction in breast cancer mortality with abemaciclib deepens over time, particularly in light of the increasing numerical separation in the OS curves observed at years 5, 6, and 7, with absolute differences of 1.0%, 1.3%, and 1.8%, respectively. There is a substantial difference in the numbers of patients who have experienced distant recurrence and are still being treated for their metastatic disease, with 33% fewer patients (180 versus 266) in the group treated with abemaciclib. Given that metastatic disease is incurable, over time this difference in the monarchE trial may lead to a further reduction in breast cancer mortality.

Furthermore, event rates occur more slowly in patients with lower-risk estrogen receptor (ER)-positive EBC making it more challenging to demonstrate any impact of an adjuvant therapy intervention in OS. In monarchE, we have previously demonstrated that in subgroups with lower risk of recurrence, the full effect of abemaciclib took longer to be observed. For example, in contrast to the cohort 1 Ki-67-high subgroup, a group with a notablye high risk of recurrence, the cohort 1 Ki-67-low subgroup required longer follow-up to reveal a similar magnitude of effect.[11] As such, higher-risk subgroups (e.g. patients with ≥10 lymph nodes) are more likely to show OS benefit earlier, with OS evolving over time in lower-risk subgroups. Similar evolution over time has been observed even in subgroups with apparently less differences in the risk rates (e.g. premenopausal versus postmenopausal). These observations also point to a potential further improvement in OS once the signs observed in higher-risk subgroups fully manifest in other lower-risk subgroups. Cohort 2 is an exploratory cohort accounting for 9% of the ITT and characterized by intermediate-risk features, whereas cohort 1 enrolled a higher-risk population based on clinical pathological features. While analyses have shown encouraging trends in cohort 2, longer follow-up may be needed to more accurately assess the potential benefit of abemaciclib + ET in this intermediate-risk population.

The robustness of efficacy outcomes was not compromised by the censoring observed in the monarchE study. Patients who were in the follow-up period without disease recurrence were censored at their most recent disease assessment and defined as administrative censoring. Since these patients were still in the follow-up period, they did not contribute to any informative censoring and therefore should not be accounted for in any sensitivity analyses of assessing censoring impact. Permanent censorings that could potentially impact the efficacy outcomes were limited to being lost to follow-up or subject withdrawal. However, given the low incidence of those cases and their well-balanced distribution between treatment arms (8.4% versus 8.7%) in the monarchE study, they are not expected to introduce bias or impact the efficacy results. This interpretation is further supported by a recently published sensitivity analysis that applied a 24- or 48-month timeframe to differentiate the potential cases of permanent censoring from administrative censoring and led to the conclusion that informative censoring had minimal impact on efficacy results in monarchE.[26]

Outcomes in ER-positive EBC have notably improved in the last 20 years and the monarchE results pose a significant advancement for patients with high risk of recurrence. However, continued outcome improvements are still warranted in the curative setting, and current efforts are ongoing that may impact later recurrences and survival in this patient population, including a delayed switch after a few years from AIs/tamoxifen to next-generation oral selective estrogen receptor degrader (SERDs) such as imlunestrant (EMBER4-NCT05514054), elacestrant (ELEGANT-NCT06492616; TREAT ctDNA-NCT05512364), and camizestrant (CAMBRIA1-NCT05774951) or the combination of abemaciclib with a SERD after primary adjuvant treatment (CAMBRIA-2, NCT05952557).

In conclusion, the addition of 2 years of abemaciclib to adjuvant ET resulted in a statistically significant and clinically meaningful improvement in OS compared with ET alone in patients with HR-positive, HER2-negative, node-positive, high-risk EBC. At 7 years, abemaciclib—ET continued to demonstrate a sustained IDFS and DRFS benefit. The survival benefit, together with the substantial reduction in the risk of metastatic disease, represents a favorable efficacy outcome that should be weighed against the short-term known safety profile of 2 years of abemaciclib therapy. Abemaciclib is the first CDK4/6i to demonstrate the translation of the reduction in the risk of recurrence into a significantly improved OS. This marks a major milestone in the development of effective therapies that have the potential to cure more patients with this common form of breast cancer.

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DATA SHARING

Eli 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, and 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.

REFERENCES

1. FDA. FDA approves abemaciclib for HR-positive. *HER2-negative breast cancer.* Available at https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/scorecard-371-1; 2017. Accessed October 16, 2025.
2. FDA. FDA expands early breast cancer indication for abemaciclib with endocrine therapy. 2023. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-early-breast-cancer-indication-abemaciclib-endocrine-therapy. Accessed October 16, 2025.
3. ESMO-MCBS. ESMO-MCBS Scorecard. 2025. Available at https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/scorecard-371-1. Accessed October 16, 2025.
4. Gradishar WJ, Moran MS, Abraham J, et al. Breast cancer, version 3. 2024, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2024;22(5):331-357.
5. Rastogi P, O'Shaughnessy J, Martin M, et al. Adjuvant abemaciclib plus endocrine therapy for hormone receptor—positive, human epidermal growth factor receptor 2—negative, high-risk early breast cancer: results from a preplanned monarchE overall survival interim analysis, including 5-year efficacy outcomes. *J Clin Oncol*. 2024;42(9):987-993.
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG)Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;378(9793):771-784.
7. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386(10001):1341-1352.
8. Francis PA, Fleming GF, Láng I, et al. Adjuvant endocrine therapy in premenopausal breast cancer: 12-year results from SOFT. *J Clin Oncol*. 2023;41(7):1370-1375.
9. Pagani O, Walley BA, Fleming GF, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer: long-term follow-up of the combined TEXT and SOFT trials. *J Clin Oncol*. 2023;41(7):1376-1382.
10. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Extending the duration of endocrine treatment for early breast cancer: patient-level meta-analysis of 12 randomised trials of aromatase inhibitors in 22031 postmenopausal women already treated with at least 5 years of endocrine therapy. *Lancet*. 2025;406(10503):603-614.
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. Rugo HS, O'Shaughnessy J, Boyle F, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: safety and patient-reported outcomes from the monarchE study. *Ann Oncol*. 2022;33(6):616-627.
13. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol*. 2007;25(15):2127-2132.
14. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE). *J Clin Oncol*. 2020;38(34):3987-3998.
15. DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. *Stat Med*. 1994;13(13-14):1341-1352. ; discussion 1353-1346.
16. Harbeck N, Rastogi P, Martin M, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. *Ann Oncol*. 2021;32(12):1571-1581.
17. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379(20):1926-1936.
18. Sledge GW Jr, 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.
19. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med*. 2020;382(6):514-524.
20. 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.
21. Goetz MP, Toi M, Huober J, et al. Abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy for HR+, HER2− advanced breast cancer: final overall survival results of MONARCH 3. *Ann Oncol*. 2024;35(8):718-727.
22. Rugo HS, Johnston SRD, Cortés J, et al. 215P Real-world survival outcomes by risk features in patients with HR+, HER2− early breast cancer (EBC) in the US. *ESMO Open*. 2025;10:104769.
23. Paluch-Shimon S, Neven P, Huober J, et al. Efficacy and safety results by menopausal status in monarchE: adjuvant abemaciclib combined with endocrine therapy in patients with HR+, HER2−, node-positive, high-risk early breast cancer. *Ther Adv Med Oncol*. 2023;15:17588359231151840.
24. Harbeck N, Karapanagiotou EM, Le Du F, et al. 194P Efficacy and safety of abemaciclib in younger patients with early breast cancer in the monarchE trial. *ESMO Open*. 2025;10:104748.
25. Martín M, Carrasco E, Rodríguez-Lescure Á, et al. Long-term outcomes of high-risk HR-positive and HER2-negative early breast cancer patients from GEICAM adjuvant studies and El Álamo IV registry. *Breast Cancer Res Treat*. 2023;201(2):151-159.
26. Conforti F, Merlo F, Pala L, et al. Why adjuvant treatment with a CDK4/6 inhibitor should be recommended for women with high-risk breast cancer: methodologic considerations on available evidence. *J Clin Oncol*. 2025:JCO2501148.