Clinical Outcomes With Abemaciclib After Prior CDK4/6 Inhibitor Progression in Breast Cancer: A Multicenter Experience

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ABSTRACT

Background: Inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6i) are widely used as first-line therapy for hormone receptor–positive metastatic breast cancer (HR+ MBC). Although abemaciclib monotherapy is also FDA-approved for treatment of disease progression on endocrine therapy, there is limited insight into the clinical activity of abemaciclib after progression on prior CDK4/6i. **Patients and Methods:** We identified patients with HR+ MBC from 6 cancer centers in the United States who received abemaciclib after disease progression on prior CDK4/6i, and abstracted clinical features, outcomes, toxicity, and predictive biomarkers. **Results:** In the multicenter cohort, abemaciclib was well tolerated after a prior course of CDK4/6i (palbociclib)-based therapy; a minority of patients discontinued abemaciclib because of toxicity without progression (9.2%). After progression on palbociclib, most patients (71.3%) received nonsequential therapy with abemaciclib (with ≥ 1 intervening non-CDK4/6i regimens), with most receiving abemaciclib with an antiestrogen agent (fulvestrant, 47.1%; aromatase inhibitor, 27.6%), and the remainder receiving abemaciclib monotherapy (19.5%). Median progression-free survival for abemaciclib in this population was 5.3 months and median overall survival was 17.2 months, notably similar to results obtained in the MONARCH-1 study of abemaciclib monotherapy in heavily pretreated HR+/HER2-negative CDK4/6i-naïve patients. A total of 36.8% of patients received abemaciclib for ≥ 6 months. There was no relationship between the duration of clinical benefit while on palbociclib and the subsequent duration of treatment with abemaciclib. *RB1*, *ERBB2*, and *CCNE1* alterations were noted among patients with rapid progression on abemaciclib. **Conclusions:** A subset of patients with HR+ MBC continue to derive clinical benefit from abemaciclib after progression on prior palbociclib. These results highlight the need for future studies to confirm molecular predictors of cross-resistance to CDK4/6i therapy and to better characterize the utility of abemaciclib after disease progression on prior CDK4/6i.

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Background

The treatment landscape for patients with hormone receptor–positive (HR+), HER2-negative (HER2–) metastatic breast cancer (MBC) has evolved with the advent of targeted agents that demonstrate synergism with antiestrogens. Inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6i) have emerged as standard of care, in combination with an antiestrogen, in either the first-line setting, or after progression on endocrine therapy.¹

Multiple large, randomized studies have demonstrated improvements in progression-free survival (PFS) for three CDK 4/6i agents (palbociclib, ribociclib, abemaciclib) in combination with an antiestrogen in HR+ / HER– MBC.^{2–6} Updated analyses have also demonstrated significant improvement in overall survival (OS) with the combination of endocrine therapy and abemaciclib or ribociclib.^{7–9} A nonsignificant trend toward improved OS was also appreciated in updated analyses exploring combinations with palbociclib.^{10,11} These agents are well tolerated and common toxicities include leukopenia/neutropenia, fatigue, diarrhea (for abemaciclib), and rare instances of QTc prolongation (for ribociclib).¹ Although palbociclib and ribociclib have similar pharmacodynamic and pharmacokinetic properties (with overlapping toxicity profiles), there has been

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increasing interest in the application of abemaciclib given its unique dosing schedule (continuous vs intermittent), increased selectivity for CDK4 over CDK6, ability to cross the blood–brain barrier, and single-agent activity.^{12,13} Abemaciclib, in contrast with palbociclib and ribociclib, also appears to inhibit CDK2 and CDK1 via proteomic and transcriptional analyses.¹⁴

Abemaciclib has demonstrated efficacy as a single agent in heavily pretreated patients with HR+/HER2– MBC based on the phase II MONARCH-1 trial, a single-arm study exploring the clinical activity of abemaciclib monotherapy (200 mg, twice daily) in patients with endocrine therapy–refractory HR+/HER2– MBC.¹⁵ Median PFS was 6.0 months (95% CI, 4.2–7.5 months) in this trial, the results of which led to approval of abemaciclib as monotherapy for CDK4/6i-naïve, hormone therapy–refractory patients. However, none of the patients in the MONARCH-1 trial had received a prior CDK4/6i, and the efficacy of abemaciclib post-CDK4/6i is unclear.

Despite widespread clinical experience with these agents, we have limited insight into the role of continued CDK4/6 blockade in patients who have received a prior CDK4/6i. Emerging data suggest that clinical resistance may be mediated by inactivation of *RBI*; overexpression of *CDK6*, *CCNE1/2*, and aurora kinase A; and mutational activation of *FGFR*, *ERBB2*, *AKT1*, and *RAS* family oncogenes.^{16–28} However, the clinical utility of these putative biomarkers for routine medical decision-making has not been established. Despite the lack of data, some clinicians administer a second course of CDK4/6 blockade after progression in the first- or second-line HR+/HER2– metastatic setting, similar to the longstanding practice of continuing HER2-directed therapy after progression on trastuzumab. In particular, there is interest in the potential activity of abemaciclib after disease progression on palbociclib- or ribociclib-based treatment given its unique pharmacokinetic and pharmacodynamic properties, and many clinicians use abemaciclib in this setting without available retrospective or prospective data to support this approach. Establishing better insight into the potential utility of ongoing CDK4/6 blockade after initial progression, particularly for abemaciclib, represents a critical unmet need in the current MBC treatment landscape.

We sought to address this question by identifying patients with HR+/HER2– MBC who experienced progression on palbociclib or ribociclib and subsequently received abemaciclib-based therapy. We report on the treatment patterns of continued CDK4/6i therapy across 6 institutions, the clinical outcome data, the toxicity experience with a second course of CDK4/6i, and emerging insights into the genomic

predictors of resistance to abemaciclib in this patient population.

Patients and Methods

Patient Selection

Within each participating cancer center, patients with HR+/HER2– MBC who had received abemaciclib at any time through May 1, 2019 were identified. Within this cohort, patients were identified who had also received a prior course of palbociclib or ribociclib in the metastatic setting. Inclusion details are outlined in supplemental eAppendix 1 (available with this article at JNCCN.org).

Medical records of eligible patients were analyzed for relevant clinical metrics, including age at initial cancer diagnosis, metastatic diagnosis, and death or most recent clinic visit date (if applicable). All medical records were deidentified prior to data analysis and were collected according to the requirements of each site's Institutional Review Board. Informed consent for data collection was obtained in accordance with the Declaration of Helsinki.

For each patient, the highest grade of the specific event of interest (via the CTCAE version 4.03) was noted if multiple episodes of an adverse effect occurred during the treatment course. Subjective adverse effects, including diarrhea, fatigue, and nausea, were not graded as part of this retrospective chart review.

Statistical Analysis

OS and PFS were estimated using the Kaplan-Meier method, and survival curves were compared using log-rank test. The association of risk factors with outcome was analyzed using Cox proportional hazards method. All analyses were performed using STATA, version 16 (StataCorp LLC).

Results

We identified 87 patients with HR+ MBC from 6 medical centers in the United States who received abemaciclib after prior progression on a palbociclib- or ribociclib-containing regimen in the metastatic setting.

Median age at metastatic diagnosis was 51.8 years (Table 1). All 87 patients received palbociclib as their initial line of CDK4/6i; none of the patients who met the eligibility criteria had received ribociclib.

Abemaciclib Use After Prior CDK4/6i Therapy

Given the lack of guidance from prospective randomized trials, practice patterns differed among physicians. Most patients received palbociclib in combination with an aromatase inhibitor (AI; n=55; 63.2%), a subgroup received palbociclib + fulvestrant (n=25; 28.7%), and none received palbociclib as a single agent.

Table 1. Clinical Parameters

Parameter	n (%)
Median age (range), y	
Original diagnosis	48.6 (26.5–72.3)
Metastatic diagnosis	51.8 (29.5–74.1)
Sex	
Female	86 (98.9)
Male	1 (1.1)
Median number of prior lines, metastatic setting (range)	
Endocrine	3 (1–7)
Nonendocrine	2 (0–12)
Total	5 (1–15)
CDK4/6i sequence	
Nonsequential	62 (71.3)
Sequential	25 (28.7)
Abemaciclib status at data cutoff (May 1, 2019)	
Receiving treatment	21 (24.1)
Discontinued, progression	58 (66.7)
Discontinued, toxicity	8 (9.2)
Palbociclib treatment course	
Endocrine partner	
Aromatase inhibitor	55 (63.2)
Fulvestrant	25 (28.7)
Tamoxifen	0 (0.0)
Multiple	7 (8.1)
NA (monotherapy)	0 (0.0)
Initial dose	
125 mg	71 (81.6)
100 mg	7 (8.1)
75 mg	4 (4.6)
NA	5 (5.7)
Median duration (range), d	259 (38–1,127)
Abemaciclib treatment course	
Endocrine partner	
Aromatase inhibitor	24 (27.6)
Fulvestrant	41 (47.1)
Tamoxifen	4 (4.6)
Multiple	1 (1.2)
NA (monotherapy)	17 (19.5)
Initial dose	
200 mg	17 (19.5)
150 mg	58 (66.7)
100 mg	12 (13.8)
NA	0 (0.0)
Median duration (range), d	120 (2–510)

Abbreviations: CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitors; NA, not available or not applicable.

Most patients received just 1 endocrine agent during their initial course of palbociclib treatment (n=80; 92%) (supplemental eFigure 1A). The largest group (n=32; 36.8%) transitioned from a nonsteroidal AI and palbociclib to fulvestrant and abemaciclib (supplemental eFigure 1B). In 25.3% of the cases (n=22), the physicians opted to continue the same antiestrogen class (AI or fulvestrant) while changing the CDK4/6i. A total of 14.9% of patients (n=13) transitioned from combination endocrine + CDK4/6i therapy to abemaciclib monotherapy.

Clinical Outcomes for Patients Receiving Abemaciclib After Progression on a CDK4/6i

At the time of data cutoff (May 1, 2019), most patients had experienced disease progression on abemaciclib (n=58; 66.7%), whereas a subset remained on treatment (n=21; 24.1%). A minority of patients (n=8; 9.2%) discontinued abemaciclib because of toxicity without disease progression. Median PFS on abemaciclib-based therapy in the 87 patients was 5.3 months (95% CI, 3.5–7.8 months; Figure 1A). Median OS on abemaciclib was 17.2 months (95% CI, 13.2 months–not reached [NR]; Figure 1B). Thirty-two patients (36.8%) received abemaciclib treatment for >180 days, including 6 who received abemaciclib monotherapy and 13 who remained on treatment at the time of analysis. Conversely, 25 patients (28.7%) discontinued abemaciclib within 90 days of initiation because of disease progression, suggesting preexisting rather than acquired resistance to abemaciclib (including 5 patients on abemaciclib monotherapy).

No difference in median PFS was noted for patients who received abemaciclib in combination with an antiestrogen compared with those who received it as monotherapy (5.1 months [95% CI, 3.2–7.6] vs 5.4 months [95% CI, 1.9–NR], respectively) (supplemental eFigure 2A, B). Eight patients remained on monotherapy at the time of data cutoff, with a duration of abemaciclib treatment ranging from 2 to 460 days. To explore the relative contribution of abemaciclib to clinical benefit, patients were stratified based on the use of an antiestrogen to which they had never been exposed in the metastatic setting. Thirty patients transitioned to an antiestrogen backbone in combination with abemaciclib to which they had no prior exposure in the metastatic setting; 48 patients either received abemaciclib monotherapy or abemaciclib in combination with an antiestrogen to which they had prior exposure in the metastatic setting (and thus from which they would be expected to derive less clinical benefit). There was no meaningful difference between the PFS (5.1 vs 5.7 months) or OS (17.2 vs 15.3 months) between these groups (supplemental eFigure 3A, B).

Of note, clinical outcomes while on abemaciclib differed for patients who received the CDK4/6i sequentially

Figure 1. (A) PFS for patients receiving abemaciclib therapy after prior progression on palbociclib. (B) OS for patients receiving abemaciclib after prior progression on palbociclib therapy.

Abbreviations: NR, not reached; OS, overall survival; PFS, progression-free survival.

rather than nonsequentially. Median PFS was 8.4 months (95% CI, 4.1–NR) in patients who received sequential CDK4/6i therapies (supplemental eFigure 4A) and 3.9 months (95% CI, 2.9–5.7; $P=.0013$) in those who received nonsequential CDK4/6i therapy (supplemental eFigure 4B). This effect persisted after adjusting for the number of prior regimens the 2 groups had received, with a hazard ratio (HR) for progression of 0.42 among patients receiving sequential versus nonsequential CDK4/6i therapy (95% CI, 0.22–0.81 via univariate Cox regression analysis). Furthermore, the duration of clinical treatment on prior palbociclib-based therapy did not correlate with the subsequent duration of treatment on abemaciclib-based therapy (Figure 2, supplemental eFigure 5; correlation coefficient via Spearman method, 0.065; 95% CI, -0.197 to 0.318).

Abemaciclib Tolerability After Prior CDK4/6i Exposure

A small number of patients discontinued abemaciclib due to toxicity without disease progression ($n=8$; 9.2%). Reasons for discontinuation included transaminitis/hepatic injury ($n=4$), diarrhea ($n=2$), nausea/vomiting ($n=1$), and weakness and tremor ($n=1$).

Dose reductions occurred in 31 patients (35.6%) on abemaciclib (supplemental eTable 1). Diarrhea was the most common reason for abemaciclib dose reduction ($n=14$; 16.1%), followed by fatigue ($n=6$; 6.9%) and neutropenia ($n=6$; 6.9%).

Hematologic toxicities were common in the overall population (Table 2, supplemental eFigure 6). Anemia was the most common adverse event of interest (any grade: 72.4%; grade 3–4: 14.9%). Neutropenia (any

Figure 2. TTP on palbociclib-based therapy does not correlate with subsequent clinical outcome on abemaciclib. Butterfly plot demonstrating TTP on palbociclib (left) and subsequent abemaciclib (right). Patients who discontinued abemaciclib because of toxicity, received abemaciclib monotherapy, and remained on abemaciclib at data cutoff are indicated.

Abbreviation: TTP, time to progression.

grade: 63.2%; grade 3–4: 12.6%) and thrombocytopenia (any grade: 46.0%; grade 3–4: 9.2%) were also common. Nearly one-half of the patients experienced liver function abnormalities, including elevated aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels, although most of these events were grade 1 or 2 (Table 2). Increased serum creatinine levels were evident in more than one-third of patients; however, all but one event was either grade 1 or 2. This finding is consistent with the observation that abemaciclib inhibits renal transporters (eg, OCT2, MATE1, MATE2-K) that may result in mild, reversible elevated serum creatinine levels without affecting renal function/glomerular filtration.²⁹ Venous thromboembolism occurred in 2 patients.

Identifying Resistance Mediators via Next-Generation Sequencing

We sought to leverage available next-generation sequencing (NGS) results to identify potential genomic predictors of early progression in patients receiving abemaciclib after prior progression on palbociclib.

Alterations in *RBI* were identified via targeted sequencing of circulating tumor DNA (ctDNA; Guardant assay) in 2 patients who had rapid disease progression on abemaciclib (Figure 3A, B). Targeted sequencing of ctDNA revealed additional putative resistance drivers in patients with early progression on abemaciclib, including an alteration in *ERBB2* (Figure 3C) and an example of *CCNE1* amplification (Figure 3D). Additional exploratory analysis of available sequencing results remains ongoing and will be presented in the future.

Discussion

This study represents the first multicenter retrospective analysis of patients with HR+ MBC and abemaciclib exposure after progression on a palbociclib-containing regimen. Abemaciclib was generally well tolerated in this

CDK4/6i-pretreated population. The overall rate of select hematologic events was similar to that reported in the phase III trials of abemaciclib in combination with endocrine therapy (MONARCH-2 and -3).^{5,6}

Abemaciclib efficacy in these heavily pretreated patients was surprisingly similar to the results demonstrated in the MONARCH-1 trial.¹⁵ Although cross-trial comparisons need to be interpreted with caution, it is interesting to note that 36.8% of CDK4/6i-pretreated patients in this multicenter retrospective cohort continued abemaciclib for ≥ 6 months, while the clinical benefit rate in MONARCH-1 was 42%. Similarly, the median PFS was 5.3 months (95% CI, 3.5–7.8) in the current study compared with 6.0 months in the MONARCH-1 trial (95% CI, 4.2–7.5). Of note, although the PFS estimate in the current cohort was similar to that observed during MONARCH-1, the data presented here are limited by several factors, including sample size and the observational nature of the study. In such a retrospective analysis, the frequency of restaging studies in clinical practice can impact the estimated PFS, because scans performed less frequently outside of a clinical trial may delay the identification of progression.

Unlike MONARCH-1, in this study population, most patients received abemaciclib in combination with an antiestrogen partner. Although limited by sample size and by variations in dosing according to physician preference, there was no apparent difference in abemaciclib efficacy among patients who received abemaciclib monotherapy compared with abemaciclib in combination with hormonal therapy. Additionally, there was no clear advantage for patients who transitioned to abemaciclib in combination with a novel antiestrogen backbone compared with those who received abemaciclib monotherapy or abemaciclib in combination with an antiestrogen to which they had prior exposure in the metastatic setting. It is not likely that the endocrine therapy contributed substantially to the clinical benefit patients obtained from abemaciclib in

Table 2. AEs and Laboratory Abnormalities of Interest Associated With Abemaciclib After Prior CDK4/6i

AE	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3/4 n (%)
Anemia	27 (31.0)	23 (26.4)	13 (14.9)	0 (0.0)	63 (72.4)	13 (14.9)
Neutropenia	20 (23.0)	24 (27.6)	9 (10.3)	2 (2.3)	55 (63.2)	11 (12.6)
Thrombocytopenia	26 (29.9)	6 (6.9)	2 (2.3)	6 (6.9)	40 (46.0)	8 (9.2)
AST elevation	30 (34.5)	6 (6.9)	6 (6.9)	0 (0.0)	42 (48.3)	6 (6.9)
ALT elevation	23 (26.4)	3 (3.4)	5 (5.7)	0 (0.0)	31 (35.6)	5 (5.8)
TBIL elevation	2 (2.3)	6 (6.9)	2 (2.3)	2 (2.3)	12 (13.8)	4 (4.6)
Creatinine elevation	25 (28.7)	5 (5.7)	1 (1.2)	0 (0.0)	31 (35.6)	1 (1.2)
VTE	0 (0.0)	1 (1.2)	1 (1.2)	0 (0.0)	2 (2.3)	1 (1.2)

Evaluable AEs during abemaciclib treatment were identified through medical record review. If the patient experienced multiple grades of toxicity during the abemaciclib treatment course, then the highest grade of toxicity was documented (eg, coded as grade 3 if grade 1 and 3 AEs were experienced during the course of therapy). Highest grade of toxicity experienced for each patient if multiple occurrences of the same AE.

Abbreviations: AE, adverse effect; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; VTE, venous thromboembolism.

Figure 3. Clinical vignettes with next-generation sequencing provide insight into potential genomic predictors of rapid progression in patients receiving abemaciclib after prior progression on CDK4/6i. Treatment histories are provided along with results from targeted sequencing of circulating tumor DNA (Guardant assay) in representative patients. Patients who experienced rapid progression on abemaciclib harbored alterations in (A, B) *RB1*, (C) *ERBB2*, and (D) *CCNE1*.

Abbreviations: CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; ER, estrogen receptor; PR, progesterone receptor.

this study, because (1) no advantage was noted for patients who received a novel antiestrogen partner with abemaciclib, (2) many patients had prior disease progression on multiple hormonal agents, and (3) a subgroup of patients received abemaciclib monotherapy with durable clinical benefit. These findings suggest that abemaciclib may convey meaningful clinical benefit and disease control in a subset of patients who experienced progression on palbociclib.

There are important limitations to the current analysis, including the retrospective nature of the data collection, the heterogeneous patient population, and the concurrent use of abemaciclib with an antiestrogen agent for many patients. Unfortunately, many of the remaining clinical questions regarding the optimal use of CDK4/6i-based therapy in the metastatic setting are unlikely to be addressed in large, prospective, randomized trials. Although a variety of combinatorial strategies are being tested after initial progression on CDK4/6i, only 3 prospective trials are underway to address the relatively straightforward question of ongoing CDK4/6 blockade after initial progression on CDK4/6i. The phase II PALMIRA trial (ClinicalTrials.gov identifier: NCT03809988) is exploring the utility of palbociclib continuation with a transition in the endocrine backbone for patients who derived clinical benefit from a prior course of palbociclib-based treatment. The phase II PACE trial (NCT03147287) is designed to compare fulvestrant monotherapy with fulvestrant + palbociclib following initial progression on a CDK4/6i with an AI; a third arm on the PACE trial is exploring the utility of fulvestrant and palbociclib combined with the PD-1 inhibitor avelumab. Lastly, the phase II MAINTAIN study (NCT02632045) similarly explores the utility of ribociclib with fulvestrant following progression on an initial CDK4/6i with an AI. Neither PALMIRA, PACE, nor MAINTAIN is evaluating the potential utility of abemaciclib in a CDK4/6i-pretreated patient population. The ongoing phase Ib JBPH trial (NCT02057133) includes an arm for women with HR+ MBC whose disease had progressed on a CDK4/6i and an antiestrogen agent; the same antiestrogen is being continued while the patient transitions to abemaciclib. These results, when available, will provide insight into the utility of abemaciclib plus continued estrogen receptor inhibition after CDK4/6i progression, but will not address the efficacy of abemaciclib monotherapy nor combination therapy with an alternate antiestrogen, the 2 options that were preferred within the context of our retrospective analysis. Hence, despite these 4 studies, it is unlikely that this question—the utility of abemaciclib following progression on palbociclib or ribociclib—will be adequately answered in the context of an ongoing prospective, randomized study.

Given the widespread use of CDK4/6i agents in the large HR+ MBC population, it will be critical to identify biomarkers that help identify patients who may benefit

from a second course of CDK4/6i-based therapy. Early preclinical efforts (both in vitro and in xenografts) have suggested that HR+ breast cancer cells that develop acquired resistance to palbociclib are also cross-resistant to abemaciclib in the laboratory.^{28,30} Additional translational work to date has shed light on the heterogeneous landscape of resistance to CDK4/6i inhibitors. Acquired disruption of *RB1* function has been demonstrated in a small number of patients at the time of resistance.^{22–25} Regulation of CDK6, via the Hippo pathway or microRNA-dependent signaling, has also been implicated in the development of resistance.^{24,26} *CCNE1* overexpression was a predictor of inferior response to palbociclib, whereas loss of the *PTEN* tumor suppressor was demonstrated after progression on ribociclib-based therapy.^{27,31} The FGFR, ERBB2, AKT1, aurora kinase, and RAS pathways have also been implicated as potential CDK4/6i resistance mediators both preclinically and in patient samples.^{20,21,28,32}

Conclusions

This multicenter, retrospective analysis represents the first effort to investigate the potential for continued CDK4/6 blockade, via abemaciclib treatment, following disease progression on palbociclib in patients with HR+ MBC. Abemaciclib use after prior CDK4/6i treatment was well tolerated and, in this heavily pretreated population, clinical benefit (with at least a 6-month treatment duration) was identified in a clinically meaningful subset of patients (36.8%). Overall PFS and OS in this cohort were similar to those observed in the MONARCH-1 study, in which none of the patients had received prior CDK4/6i therapy. Furthermore, ctDNA sequencing allowed identification of multiple genomic effectors, previously implicated in CDK4/6i resistance, in patients who had rapid disease progression on abemaciclib. Overall, these findings suggest that some patients may benefit from continued CDK4/6-directed therapy and support the need for additional blood- and tissue-based studies to guide therapeutic selection for this important patient population.

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Clinical Outcomes With CDK4/6 Inhibitor Abemaciclib After Prior CDK4/6 Inhibitor Use in Breast Cancer: A Multicenter Experience

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eFigure 1: Proportion of Patients Receiving Antiestrogen

eFigure 2: Clinical Outcomes on Abemaciclib in Patients Receiving Monotherapy Versus Hormone Therapy

eFigure 3: Clinical Outcomes on Abemaciclib After Change Versus No Change in Antiestrogen Backbone

eFigure 4: Median PFS After Stratification Based on Whether Patients Received CDK4/6i Therapy Sequentially or Nonsequentially

eFigure 5: Correlation Between Time to Progression on Palbociclib-Based Therapy and on Abemaciclib

eFigure 6: Incidence of Adverse Effects of Interest During Abemaciclib Treatment

eTable 1: Abemaciclib Dose Reductions

eAppendix 1: Supplemental Methods

eFigure 1. (A) Proportion of patients receiving the indicated antiestrogen in the initial palbociclib-based regimen and subsequent abemaciclib-based regimen. (B) Proportion of patients with each pattern of antiestrogen transition (between the 2 CDK4/6i regimens) for treatment with palbociclib with an AI or with fulvestrant.

Abbreviations: AI, (nonsteroidal) aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; mono, monotherapy; SAI, steroidal aromatase inhibitor; SERD, selective estrogen receptor degrader (fulvestrant); SERM, selective estrogen receptor modulator (tamoxifen).

eFigure 2. Clinical outcomes on abemaciclib in patients receiving monotherapy versus hormone therapy. PFS results after stratification based on whether patients received abemaciclib therapy (A) in combination with an antiestrogen or (B) as monotherapy did not demonstrate any meaningful difference.

Abbreviations: mono, monotherapy; NR, not reached; PFS, progression-free survival.

eFigure 3. Clinical outcomes on abemaciclib after change versus no change in antiestrogen backbone. (A) PFS and (B) OS in patients for whom a change in the class of antiestrogen backbone was made when switching from palbociclib to abemaciclib (Group 1) and those who received abemaciclib monotherapy or abemaciclib in combination with an antiestrogen to which they had previously been exposed in the metastatic setting (Group 2).
Abbreviations: NR, not reached; OS, overall survival; PFS, progression-free survival.

eFigure 4. Median PFS after stratification based on whether patients received CDK4/6i therapy (A) sequentially or (B) nonsequentially suggested that patients receiving sequential therapy derived greater clinical benefit.
Abbreviations: CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; NR, not reached; PFS, progression-free survival.

eFigure 5. TTP on palbociclib-based therapy does not correlate with subsequent clinical outcome on abemaciclib.
Abbreviation: TTP, time to progression.

eFigure 6. Incidence of AEs of interest during abemaciclib treatment.
Abbreviations: AE, adverse effect; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; VTE, venous thromboembolism.

eTable 1. Abemaciclib Dose Reductions	
	n
Single dose reduction	31 (35.6%)
Two dose reductions	5 (5.8%)
Indication for dose reduction, per EMR review ^a	
Diarrhea	14
Neutropenia	6
Fatigue	6
Nausea/Vomiting	5
Thrombocytopenia	2
Transaminitis	2
NA	2
Cough	1
Headache	1
Weakness	1

Abbreviations: EMR, electronic medical record; NA, not available.
^aFor some patients, multiple indications for dose reductions were cited.

eAppendix 1. Supplemental Methods

Given that the primary objective was to evaluate the role of abemaciclib-based therapy in patients whose disease had progressed on prior inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6i; palbociclib or ribociclib) and to maintain homogeneity in the eligible population, we included patients who experienced progression while on the initial course of CDK4/6i but not those who discontinued the initial CDK4/6i because of toxicity or who had received abemaciclib as the initial CDK4/6i. Similarly, patients who received >1 line of CDK4/6i regimen prior to receiving abemaciclib or who received CDK4/6i in the context of a triplet regimen on a clinical trial (such as endocrine therapy with CDK4/6i and an mTOR inhibitor) were also excluded.

Patients were included if they received abemaciclib sequentially (immediately after disease progression on the initial CDK4/6i) or nonsequentially (after at least 1 intervening systemic therapy after progression on the initial CDK4/6i). Abemaciclib could have been administered in combination with an antiestrogen agent or as monotherapy. Patients with HER2-positive or triple-negative disease were excluded.

Dose, schedule, and dose reduction information for both CDK4/6i regimens were captured, along with treatment duration, whether the CDK4/6i regimens were given sequentially or nonsequentially, the number of metastatic therapy regimens given prior to the initiation of abemaciclib, the current status of the abemaciclib-based regimen (on or off treatment), reason for discontinuation (disease progression or toxicity, per medical record and radiology review), date of last follow-up, and survival status.

Medical records (progress notes, laboratory values) for each patient were reviewed to identify select adverse events and laboratory abnormalities associated with abemaciclib.