Breast cancer affects more women than any other type of cancer, and represents 15% of all new cancer cases in the United States. A total of 252,710 new breast cancer cases were estimated to be diagnosed in 2017, and more than 40,600 deaths. The prognosis worsens for patients with locally advanced breast cancer and even more so for those with metastatic disease.

Hormone receptor (HR)-positive breast cancer, which has estrogen or progesterone receptors, typically progresses more slowly than HR-negative breast cancer, but can recur years after treatment. HR-positive breast cancer is often treated with hormone therapies. Breast cancer that is human epidermal growth factor receptor (HER)2-negative has lower than normal levels of the HER2 growth-promoting protein and does not respond to therapies that target HER2.

One of the recent therapeutic targets for women with HR-positive, HER2-negative breast cancer is the inhibition of cyclin-dependent kinase (CDK)4 and CDK6—2 kinases that are part of the signaling pathway implicated in cell growth and proliferation.

**Verzenio a New Oral Option for Breast Cancer**

On September 28, 2017, the US Food and Drug Administration (FDA) approved abemaciclib (Verzenio; Eli Lilly), a new CDK4/CDK6 inhibitor, in combination with fulvestrant (Faslodex), for the treatment of adults with HR-positive, HER2-negative advanced or metastatic breast cancer that has progressed after endocrine therapy. In addition, the FDA approved abemaciclib as monotherapy for patients with HR-positive, HER2-negative advanced or metastatic breast cancer that has progressed after endocrine therapy and previous chemotherapy in the metastatic setting.

The FDA granted abemaciclib a priority review and a breakthrough therapy designation for these indications.

“Verzenio provides a new targeted treatment option for certain patients with breast cancer…and unlike other drugs in the class, it can be given as stand-alone treatment to patients who were previously treated with endocrine therapy and chemotherapy,” said Richard Pazdur, MD, Director of the FDA’s Oncology Center of Excellence.

On February 26, 2018, the FDA granted abemaciclib a new indication as initial endocrine-based treatment, in combination with an aromatase inhibitor, for postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer. This approval was based on results from the MONARCH 3 clinical trial. This indication was initially granted a priority review in October 2017.

With this approval, abemaciclib becomes the first CDK4/CDK6 inhibitor to receive FDA approval for the treatment of this patient population as a monotherapy and in combination with an aromatase inhibitor or fulvestrant.

“Verzenio provides a new targeted treatment option for certain patients with breast cancer...and unlike other drugs in the class, it can be given as stand-alone treatment to patients who were previously treated with endocrine therapy and chemotherapy.”

**Mechanism of Action**

Abemaciclib blocks CDK4 and CDK6, which are activated upon binding to D-cyclins. CDK4, CDK6, and cyclin D1 play a role in promoting cancer-cell proliferation and cell-cycle progression in estrogen receptor-positive breast cancer. Abemaciclib demonstrated antitumor activity in breast cancer xenograft models when it was dosed daily as a single agent or in combination with antiestrogen drugs.

**Dosing and Administration**

Abemaciclib is taken orally, with or without food.
When used in combination with fulvestrant, the recommended starting dose of abemaciclib is 150 mg, taken orally twice daily. When used as monotherapy, the recommended dose is 200 mg, taken orally twice daily.9

Abemaciclib dosing reductions or interruptions may be required, depending on the patient’s safety and tolerability. Abemaciclib is available as 50-mg, 100-mg, 150-mg, and 200-mg tablets.9

The MONARCH Clinical Trials
**Abemaciclib plus Fulvestrant: MONARCH 2**

The safety and efficacy of abemaciclib plus fulvestrant were evaluated in MONARCH 2, a randomized, placebo-controlled, multicenter clinical trial of 669 patients (median age, 60 years) with HR-positive, HER2-negative advanced or metastatic breast cancer that progressed during or after previous adjuvant or metastatic endocrine therapy.4,8 The median progression-free survival (PFS) was 7.1 months longer with abemaciclib plus fulvestrant versus placebo plus fulvestrant, based on investigator assessment (Table 1).4,9 The results of a blinded independent radiologic review were consistent with the investigator assessment.9

**Abemaciclib as Monotherapy: MONARCH 1**

The safety and efficacy of abemaciclib as monotherapy were evaluated in MONARCH 1, a single-arm, open-label clinical trial of 132 patients (median age, 58 years) with HR-positive, HER2-negative metastatic breast cancer that progressed during or after endocrine therapy, who received a taxane in any setting and 1 or 2 previous chemotherapy regimens in the metastatic setting.4,9 Based on investigator assessment, the objective response rate (ORR) was 19.7%, with an 8.6-month median duration of response (Table 2).4,10

**Abemaciclib as Initial Therapy plus Aromatase Inhibitor: MONARCH 3**

MONARCH 3 was a double-blind, randomized, phase 3 clinical trial that included 493 postmenopausal women (median age, 63 years) with HR-positive, HER2-negative advanced breast cancer who had not previously received systemic therapy in the advanced disease setting. Patients received abemaciclib or placebo plus a nonsteroidal aromatase inhibitor daily.7

In the interim analysis, at a median follow-up of 17.8 months, abemaciclib met the primary end point of investigator-assessed PFS; the median PFS in the abemaciclib arm was not reached versus 14.7 months in the placebo arm (Table 3).7

In addition, the ORR was 48.2% (95% confidence interval [CI], 42.8-53.6) in the abemaciclib arm versus 34.5% (95% CI, 27.3-41.8) in the placebo arm (P = .002). Furthermore, in patients with measurable disease, the ORR was 59.2% in the abemaciclib arm versus 43.8% in the placebo arm.7 Overall, 63.9% of patients in the abemaciclib arm and 59.6% in the placebo arm were still receiving treatment at the time the analysis was conducted.7

**Adverse Reactions**

The most common adverse events associated with abemaciclib in MONARCH 2 and MONARCH 1, respectively, were diarrhea (86%, 90%), neutropenia (46%, 37%), nausea (45%, 64%), abdominal pain (35%, 39%), infections (43%, 31%), fatigue (46%, 65%), ane-

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**Table 1** MONARCH 2: Abemaciclib plus Fulvestrant versus Placebo plus Fulvestrant

<table>
<thead>
<tr>
<th>Efficacy outcome</th>
<th>Abemaciclib + fulvestrant (N = 446)</th>
<th>Placebo + fulvestrant (N = 223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with an event, N (%)</td>
<td>222 (49.8)</td>
<td>157 (70.4)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>16.4 (95% CI, 14.4-19.3)</td>
<td>9.3 (95% CI, 7.4-12.7)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.553 (95% CI, 0.449-0.681)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** MONARCH 1: Abemaciclib Monotherapy

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Abemaciclib 200 mg (N = 132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator assessed</td>
<td></td>
</tr>
<tr>
<td>Objective response rate, N (%)</td>
<td>26 (19.7)</td>
</tr>
<tr>
<td>95% CI</td>
<td>13.3-27.5</td>
</tr>
<tr>
<td>Median duration of response, mo</td>
<td>8.6 (95% CI, 5.8-10.2)</td>
</tr>
</tbody>
</table>

**Table 3** MONARCH 3: Interim Analysis of Abemaciclib Therapy plus Aromatase Inhibitor as Initial Therapy

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Abemaciclib + aromatase inhibitor (N = 328)</th>
<th>Placebo + aromatase inhibitor (N = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival, mo</td>
<td>NR</td>
<td>14.7</td>
</tr>
<tr>
<td>Median duration of response, mo</td>
<td>8.6 (95% CI, 5.8-10.2)</td>
<td>7.2 (95% CI, 5.6-NR)</td>
</tr>
</tbody>
</table>
mia (29%, 25%), leukopenia (28%, 17%), decreased appetite (27%, 45%), vomiting (26%, 35%), headache (20%, 20%), and thrombocytopenia (16%, 20%).

Abemaciclib has no contraindications.9

**Drug Interactions**

Abemaciclib should not be used concomitantly with ketoconazole. Co-administration of abemaciclib with ketoconazole, a strong cytochrome (CY) P3A inhibitor, may increase the exposure of abemaciclib and may lead to increased toxicity. The abemaciclib dose should be reduced with the concomitant use of other strong CYP3A inhibitors.9

Co-administration of abemaciclib with rifampin, a strong CYP3A inducer, may reduce the activity of abemaciclib. This drug should not be used concomitantly with strong CYP3A inducers; alternative agents should be considered.9

**Use in Specific Populations**

In clinical trials, no overall differences were reported in patients aged ≥65 years and younger patients.9

For patients with mild or moderate renal impairment, no dose adjustment is required. For patients with severe renal impairment, end-stage renal disease, or those on dialysis, the effect of abemaciclib is unknown.9

For patients with mild or moderate hepatic impairment, no dose adjustment is required. For patients with severe hepatic impairment, the dosing frequency should be reduced as directed in the prescribing information.9

**Warnings and Precautions**

Patients should be instructed at the initial sign of loose stools to take anti-diarrheal therapy, increase oral fluid intake, and contact their healthcare provider.9

Patients’ complete blood counts should be monitored before starting abemaciclib treatment, every 2 weeks for the first 2 months, and monthly for the next 2 months, as clinically indicated.9

Liver function tests should be conducted before starting abemaciclib therapy, and liver function should be monitored every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated thereafter.9

Patients should be monitored for signs of thrombosis and pulmonary embolism.9

Because abemaciclib can cause fetal harm, patients should be advised to use effective contraception.9

**Conclusion**

With the FDA approval of abemaciclib, another oral CDK4/CDK6 inhibitor option became available for patients with HR-positive, HER2-negative advanced or metastatic breast cancer. Abemaciclib, in combination with fulvestrant, demonstrated a longer PFS than fulvestrant plus placebo in MONARCH 2. In the open-label MONARCH 1 study, nearly 20% of patients who received abemaciclib monotherapy had a complete or partial response that lasted approximately 9 months.

Based on interim findings from the MONARCH 3 trial, the FDA granted abemaciclib a priority review as a potential new first-line treatment, in combination with an aromatase inhibitor, for patients with HR-positive, HER2-negative advanced or metastatic breast cancer.

**References**


8. Verzenio (abemaciclib) tablets [prescribing information]. Indianapolis, IN: Eli Lilly and Company; February 2018.