

Abemaciclib becomes first CDK inhibitor to clinch single-agent approval for breast cancer

The fall 2017 approval by the US Food and Drug Administration (FDA) of abemaciclib made it the third cyclin-dependent kinase (CDK) inhibitor approved for the treatment of hormone receptor (HR)-positive breast cancer, and the first to receive an approved indication as monotherapy in that setting. Abemaciclib is a small-molecule inhibitor of the CDK4 and CDK6 proteins, which are key gatekeepers of the cell cycle and frequently dysregulated in HR-positive breast cancer. On the basis of the randomized, placebo-controlled, multicenter phase 3 MONARCH-2 trial, it was approved in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer who had progressed during endocrine therapy.¹

A total of 669 women aged 18 years and older, with any menopausal status, an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) or nonmeasurable bone-only disease, were enrolled. Patients had progressed during neoadjuvant or adjuvant endocrine therapy, within 12 months of adjuvant endocrine therapy, or during frontline endocrine treatment for metastatic disease.

Those who had received more than 1 endocrine therapy or any prior chemotherapy for metastatic breast cancer or prior treatment with everolimus or CDK4/6 inhibitors, as well as those with the presence of visceral crisis or evidence or history of central nervous system (CNS) metastases, were excluded from the study.

Patients were randomized 2:1 to receive 150 mg abemaciclib or placebo, both in combination with 500 mg fulvestrant. The initial dose of abemaciclib was 200 mg, but this was amended to 150 mg after enrollment of the first 178 patients to alleviate diarrhea-related toxicity concerns. Randomization was stratified according to metastatic site (visceral, bone only, or other) and endocrine therapy resistance (primary or secondary).

Tumors were measured by computed tomography (CT) and magnetic-resonance imaging (MRI) according to RECIST-1.1 within 28 days before random assignment, every 8 weeks for the first year, every 12 weeks thereafter, and then within 2 weeks of clinical progression. Bone scintigraphy was also performed at baseline and then every 6th cycle starting with cycle 7. Hematologic and blood chemistry laboratory tests were performed centrally on days 1 and 15 of the first cycle and day 1 of all remaining cycles.

What's new, what's important

Based on findings from the 3 MONARCH-2 trial, the CDK inhibitor abemaciclib was approved in combination with fulvestrant for HR-positive, HER2-negative advanced or metastatic breast cancer in women who had progressed during endocrine therapy. Patients were randomized to receive 150 mg abemaciclib or placebo, both in combination with 500 mg fulvestrant. The initial dose of abemaciclib was 200 mg, but this was amended to 150 mg because of diarrhea-related toxicity concerns.

The primary endpoint was PFS. Median a PFS for abemaciclib was 16.4 months and for placebo, 9.3 months (HR, 0.553; $P < .0000001$), an effective 45% reduction in risk for progression or death with the combination. ORR among patients with measurable disease was 48.1% and 21.3%, respectively, including a CRR of 3.5% with abemaciclib. The median DoR was not yet reached in the study group (25.6 months for placebo). Overall survival data were not yet mature.

The most common adverse events experienced with abemaciclib-fulvestrant were neutropenia (23.6%) and diarrhea (13.4%). Grade 4 neutropenia was higher in the study arm compared with placebo (2.9% vs 0.4%), with 3 deaths with the combination linked to treatment-related AEs. Abemaciclib carries warnings and precautions relating to diarrhea, neutropenia, hepatotoxicity, VTE, and embryofetal toxicity. Pregnant women should be advised of the potential risk to a fetus, and those of reproductive potential should be counselled on the importance of using effective contraception during treatment and for at least 3 weeks after the last dose.

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The primary endpoint was progression-free survival (PFS); median PFS was 16.4 months in the abemaciclib arm, compared with 9.3 months in the placebo arm in the intent-to-treat population (hazard ratio [HR], 0.553; $P < .0000001$), translating to a 45% reduction in the risk of disease progression or death with the combination.

Mechanism of action: abemaciclib

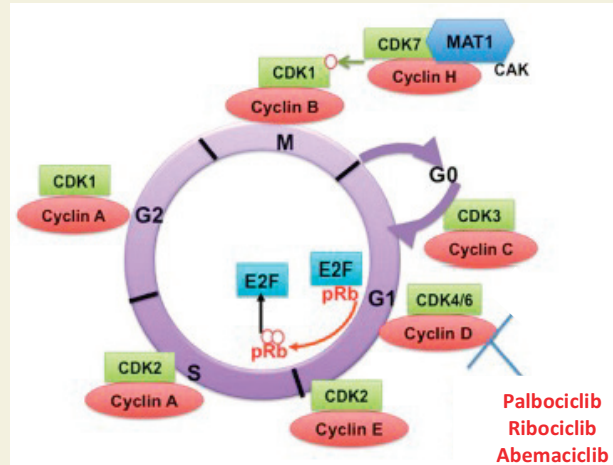
Targeting a classic hallmark of cancer. In the past several decades, characteristic alterations in cellular physiology that are essential to the transformation of a normal cell into a cancerous one, have been delineated and dubbed cancer “hallmarks.” Among them is the unrestricted growth of cancer cells that is driven in part by the dysregulation of the cell cycle.

The cell cycle, the process by which cells go from a noncycling quiescent state, through stages of growth and DNA replication, to mitotic division into 2 genetically identical daughter cells, is tightly controlled by a wealth of gatekeeper proteins that ensure that it only proceeds at the appropriate time.

One key group of gatekeepers is the cyclin-dependent kinases (CDKs) and their cyclin regulators. CDK4 and CDK6, in particular, which are dependent on cyclin D for their activity, have an important role in the cell cycle. They function at the restriction point, the transition from the first growth phase (G1) to the DNA synthesis (S) phase, beyond which the cell commits to entering the cell cycle.

One of the best characterized signaling pathways downstream of CDK4/6 activation involves the retinoblastoma protein (pRb). The pRb protein forms multiprotein complexes with a number of other signaling proteins, including the E2F transcription factors, which it maintains in an inactive state. CDK4/6 phosphorylate pRb, deactivating it, removing its repression of the E2F transcription factors and therefore activating their target genes, many of which are involved in the G1-S transition.

A significant proportion of breast cancers exhibit dysregulation of the cell cycle, through the CDK4/6-cyclin D-pRb pathway, driving sustained activation of the cell cycle and, as a result, unchecked cell proliferation. This is especially true of hormone receptor (HR)-positive breast cancers, which seem to have a particular dependence on this pathway, in large part because CDK4/6 are downstream targets of estrogen receptor activation. Therefore,



Cyclin-dependent kinases (CDKs) and their cyclin regulators play key roles as ‘gatekeepers’ of the cell cycle and their dysregulation contributes to the characteristic unrestricted growth of cancer cells. Using small-molecule inhibitors of CDKs to reestablish cell cycle control is an attractive approach to anti-cancer therapy. Reproduced under a creative commons license: Aleem E, Arceci RJ. Targeting cell cycle regulators in hematologic malignancies. *Front Cell Dev Biol.* 2015;3:16.

using small molecule inhibitors of CDK4/6 to interrupt this signaling pathway has emerged as a promising potential means of regaining control of the cell cycle and defeating breast cancer.

Furthermore, dysregulation of the CDK4/6 pathway has been shown to be associated with resistance to endocrine therapy, the standard of care for patients with HR-positive breast cancer. Preclinical studies demonstrated significant synergy between endocrine therapies and CDK inhibitors and this also seems to have been borne out in clinical trials. Indeed, abemaciclib is the third CDK inhibitor now on the market, which is approved in combination with fulvestrant.

Objective response rate in the 2 groups among patients with measurable disease was 48.1% and 21.3%, respectively, which included a complete response rate of 3.5% in the abemaciclib arm. The median duration of response was not yet reached in the study group, compared with 25.6 months for placebo. Overall survival data were not yet mature.

The agency also approved abemaciclib as monotherapy for women and men with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. That approval was based on data from the single-arm MONARCH-1 trial of 132 patients who received 200 mg abemaciclib twice daily on a continuous schedule.²

Patients had adequate organ function, measurable disease per RECIST-1.1, and an ECOG performance status of 0 or 1. Patients must have progressed on or after previous

endocrine therapy and have received prior treatment with at least 2 chemotherapy regimens, at least 1 of them, but no more than 2, having been administered in the metastatic setting. Exclusion criteria included prior receipt of a CDK inhibitor, major surgery within 14 days of the start of the study, and CNS metastases.

Tumor assessments were performed by CT or MRI according to RECIST-1.1 within the 4 weeks prior to the first dose of study drug and then subsequently at every other cycle. Responses were confirmed at least 4 weeks after the initial observation. The overall response rate was 19.7%, made up completely of partial responses. Median duration of response was 8.6 months, median PFS was 6 months and median OS was 17.7 months.

Adverse events

The most common adverse events experienced with the

combination of abemaciclib and fulvestrant were neutropenia (23.6%) and diarrhea (13.4%). The rate of grade 4 neutropenia was higher in the combination arm (2.9% vs 0.4%) and there were 3 deaths with the combination that were linked to treatment-related AEs. In the monotherapy trial, abemaciclib treatment most commonly caused diarrhea (90.2%), fatigue (65.2%), nausea (64.4%), decreased appetite (45.5%), and abdominal pain (38.6%). Grade 3 diarrhea and fatigue occurred in 19.7% and 12.9% of patients, respectively. Serious AEs occurred in 24.2% of patients and AEs led to treatment discontinuation in 7.6% of patients.

Warnings and precautions

Abemaciclib is marketed as Verzenio by Eli Lilly and Company. Warnings and precautions relating to diarrhea, neutropenia, hepatotoxicity, venous thromboembolism (VTE), and embryofetal toxicity are detailed in the prescribing information. In the event of diarrhea, patients should be treated with antidiarrheal therapy and should increase oral fluids and notify their health care provider. Treatment should be interrupted for grade 3 or 4 diarrhea

and then resumed at a lower dose upon return to grade 1.

To guard against neutropenia, complete blood counts should be performed prior to starting therapy, every 2 weeks for the first 2 months, monthly for the subsequent 2 months, and then as clinically indicated. Treatment should be interrupted or delayed or the dose reduced for grade 3 or 4 neutropenia and patients should report episodes of fever.

Liver function tests should be performed before starting abemaciclib, every 2 weeks for the first 2 months, monthly for the next 2 months, and then as clinically indicated. For patients who develop persistent or recurrent grade 2, 3 or 4 hepatic transaminase elevation, dose interruption, reduction, discontinuation, or delay should be considered.

Patients should be monitored for signs and symptoms of VTE and pulmonary embolism, and treated appropriately. Pregnant women should be advised of the potential risk to a fetus, and those of reproductive potential should be counselled on the importance of using effective contraception during treatment and for at least 3 weeks after the last dose.³

References

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2. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase 2 study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. *Clin Cancer Res*. <http://clincancerres.aacrjournals.org/content/early/2017/05/20/1078-0432.CCR-17-0754>. Published online first on May 22, 2017. Accessed January 19, 2018.
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