

Metastatic Breast Cancer

CDK 4/6 INHIBITORS:

What's New and What's Left to Learn

BY ERIC FITZSIMMONS

Becky Oliver, 64, of Hattiesburg, Mississippi, went for her annual mammogram in February 2016. Soon after, though she never had early-stage disease, she was diagnosed with metastatic breast cancer to the liver. Her oncologist suggested hormonal therapy in combination with palbociclib (Ibrance), a cyclin-dependent kinase inhibitor.

Kinases are a type of protein everyone has in their bodies. Certain ones, the cyclin-dependent kinases (CDKs) 4 and 6, can cause breast cancer cells to multiply. Palbociclib and other CDK 4/6 inhibitors work by interrupting that process, killing the cancer cells or stopping them from growing. In February 2015, palbociclib became the first CDK 4/6 inhibitor approved by the FDA to be given, with letrozole (Femara), as a first-line treatment for postmenopausal women with metastatic hormone receptor-positive, HER2-negative breast cancer.

For Becky, taking a medicine that was so new on the market worried her.

"It was only about a year out from when [palbociclib] was approved," Becky says. "It took a little bit of courage to try something that was so different ... but on the other hand, if it works, which it did, then I didn't have to go through [other treatments]."

Palbociclib went on to be approved in 2016 to be given with the hormonal therapy fulvestrant (Faslodex) to people with cancer that grew while taking other hormonal therapy. Then, in 2017, two new CDK 4/6 inhibitors were approved by the FDA: ribociclib (Kisqali) in March and abemaciclib (Verzenio) in September.



Becky Oliver

Choosing a CDK 4/6 Inhibitor

The three CDK 4/6 inhibitors available — palbociclib, ribociclib and abemaciclib — are only available to people with metastatic hormone receptor-positive, HER2-negative breast cancer. But their approvals are slightly different. (See "CDK 4/6 Inhibitors" section at end of article.)

Where the approvals are the same, it is up to doctors and the person being treated to decide what will be best for their situation. **Heather McArthur, MD, MPH**, medical director of breast oncology at Cedars-Sinai Medical Center, in Los Angeles, says that decision usually comes down to each medicine's side effects. For example, diarrhea is very common with abemaciclib but not palbociclib or ribociclib. Low white blood cell counts, a condition called neutropenia, is most associated with palbociclib. Fatigue is more common in abemaciclib and palbociclib than ribociclib.

Ribociclib and palbociclib have similar approvals as a first treatment for metastatic breast cancer, but ribociclib requires extra tests to monitor heart health. In rare cases, it can disrupt electrical signals in the heart, causing a longer cycle in the heart beat, called the QT interval. Although serious, this problem can usually be reversed by stopping treatment with ribociclib or lowering the dose. Your doctor may test your heart rate before you start treatment and over time to monitor it.



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Mary Lynn Wekenmann

Some people may take hormonal therapy alone to start, and if the disease grows, their doctors may recommend changing to a different hormonal therapy with a CDK 4/6 inhibitor, Dr.

McArthur says. But CDK 4/6 inhibitors are becoming more common as the first treatment for people like Becky, who never had breast cancer before. Studies of CDK 4/6 inhibitors with hormonal therapy show a near doubling of progression-free survival — how long a cancer goes without growing — as a first treatment for metastatic breast cancer over hormonal therapy alone. And Dr. McArthur says CDK 4/6 inhibitors with hormonal therapy work particularly well in certain people, such as those whose first breast cancer diagnosis is metastatic disease.

The CDK 4/6 inhibitors are similar to each other in structure but work in your body slightly differently. Abemaciclib, for example, is the only CDK 4/6 inhibitor FDA approved to be given alone and taken continuously. Ribociclib and palbociclib have been approved with hormonal therapy and are taken in 4-week cycles that include a week-long break.

Abemaciclib affects CDK 4 more than CDK 6, which may account for some ways it differs from the other two medicines, says **Sarah Mougalian, MD**, an assistant professor of medicine at Yale Cancer Center, in New Haven, Connecticut.

Researchers don't know yet if another CDK 4/6 inhibitor can be given after one has stopped working but the possibility is being explored in trials.

Why They Are Important

CDK 4/6 inhibitors have not been around long enough for researchers to know if they extend people's lives. But Dr. McArthur says the medicines have shown important gains in progression-free survival. The phase III PALOMA-2 trial found people were able to stay on palbociclib in combination with letrozole for a median 24.8 months without the cancer progressing, compared to 14.5 months with letrozole alone.

"It represents a major innovation in the treatment of hormone receptor-positive metastatic breast cancer," Dr. McArthur says.

Palbociclib with letrozole is the only treatment Becky has known. She has taken that combination for the last 2 years, and has had no evidence of disease since spring 2016.

"I'm thinking [my experience] is as good as it can get under the circumstances. I certainly wish I didn't have this diagnosis, but considering that I do, I think that my quality of life is very good," she says.

Progression-free survival can be important because it may allow you to live better for a longer time without growth of the disease, says Dr. Mougalian.

"We have an arsenal of medications [for metastatic breast cancer] and once you use up something in the arsenal you can't really go back to it. So the longer you can stay on one combination, the better you can do," Dr. Mougalian says.

Side Effects

An exciting thing about CDK 4/6 inhibitors is that side effects tend to be less severe compared to chemotherapy. Becky has faced minor side effects. Others may experience more challenging ones. Fatigue and neutropenia, which can increase risk of infection, are common. Abemaciclib often causes diarrhea, but it is rarely severe and can be treated, Dr. McArthur says. Doctors may recommend an antidiarrheal such as loperamide (Imodium) at the first sign of diarrhea.

Mary Lynn Wekenmann, 70, of Elma, New York, was diagnosed with metastatic breast cancer in 2016. She has taken palbociclib since September of that year, alongside an aromatase inhibitor.

Mary Lynn is happy the treatment has worked for over a year, and she doesn't mind the few side effects she feels. Still, blood tests showed her white blood cell counts were low. Mary Lynn's doctors worked around the problem by changing her dose. After a couple adjustments, they settled on a reduced schedule: She takes palbociclib every other week instead of the recommended 3 weeks on and 1 week off. This has brought her counts to an acceptable, though still low, level.

Dr. McArthur says such changes in dose are common to deal with side effects. In at least one study, more than 40 percent of people on abemaciclib had their dose changed.

Cost

One barrier to treatment is cost. One cycle, or 28 days, of treatment with palbociclib or ribociclib can cost over \$10,000. Abemaciclib is about \$5,000. Even with insurance, the co-pay can be hundreds of dollars every month.

Some people, like Becky, are able to get help from the company that makes the medicines. The makers of palbociclib, ribociclib and abemaciclib each have co-pay assistance programs on their websites for each medicine.

Not everyone is eligible for these programs. Mary Lynn's family's income is too high to qualify, but the monthly co-pays of between \$300 and \$700 she's paid during her treatment with palbociclib remain a strain on her family's finances.

The Future of CDK 4/6 Inhibitors

No new CDK 4/6 inhibitors are expected to be approved in the near future. But trials of approved medicines continue to look at who may benefit and from what combinations.

Results from the MONALEESA-7 trial showed ribociclib could help women who haven't been through menopause or who may not have finished menopause go longer without metastatic cancer growing. This could open this treatment to younger women who have not been included in many FDA approvals for CDK 4/6 inhibitors so far. In the study ribociclib was given with hormonal therapy and ovarian suppression, medicine to stop periods and prevent the ovaries from working.

Meanwhile, the PALLAS trial and the monarchE trial are testing if the addition of CDK 4/6 inhibitors to hormonal therapy works in early-stage breast cancer. Researchers are also

studying whether CDK 4/6 inhibitors help immunotherapy medicines work better. If you are interested in joining a clinical trial visit clinicaltrials.gov or lbcc.org/metastatic-trial-search.

“They are complicated medications, and I think that we are on the cusp of understanding broader combinations,” says Dr. McArthur. 🐾

CDK 4/6 INHIBITORS

These medicines treat metastatic hormone receptor-positive, HER2-negative breast cancer:

ABEMACICLIB (VERZENIO)

- For all women. Taken with fulvestrant if cancer has grown despite hormonal therapy given for early-stage or metastatic breast cancer.
 - One 150mg tablet, taken twice every day with no cycle breaks.
- For all women and men. Taken alone if the cancer has grown after treatment with hormonal therapy and chemotherapy.
 - One 200mg tablet, taken twice every day with no breaks.
- For postmenopausal women. Taken with an aromatase inhibitor as first-line treatment.
 - One 150mg tablet, taken twice every day with no cycle breaks.

PALBOCICLIB (IBRANCE)

- For postmenopausal women. Taken with an aromatase inhibitor as first-line treatment.
- For all women. Taken with fulvestrant if breast cancer has grown during treatment with hormonal therapy (either during treatment for early-stage or metastatic breast cancer).
- One 125mg tablet taken once daily for 3 weeks, followed by a 1-week break.

RIBOCICLIB (KISQALI)

- For postmenopausal women. Taken with an aromatase inhibitor as first-line treatment.
- Three 200mg tablets, taken once daily for 3 weeks, followed by a 1-week break.

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BEING ACTIVE TOGETHER:

A Q&A With Matt Hines

BY ERIC FITZSIMMONS



Matt and April Hines

Matt and April Hines, of Chattanooga, Tennessee, went on their first date in December 2011, and just a month later April was diagnosed with early-stage breast cancer. They dated through her treatments and, in the years that followed, got engaged, and then married. But just a few months into their marriage, in January 2016, doctors found that April had stage IV breast cancer.

Matt, 36, and April, 37, had always been active people, and as April turned her energy toward breast cancer advocacy, Matt was there with her. In 2016 April was trained as a volunteer with Living Beyond Breast Cancer’s Hear My Voice program, educating people in her community about metastatic breast cancer. In 2018 she returned to continue that service as a Hear My Voice Alumni volunteer. Together, Matt and April have attended seven breast cancer conferences since 2016, including LBBC conferences in Memphis and Philadelphia.

LBBC's copy editor and content coordinator, **Eric Fitzsimmons**, met up with Matt at the 2017 San Antonio Breast Cancer Symposium, in December. There, Matt talked to Eric about supporting April in their personal adventures and in breast cancer advocacy.

Eric

You guys continue to be very active, in personal activities and advocacy. How do you go about trying to be a caregiver, helping April stay comfortable and safe, without getting in her way?

Matt

We were both very outdoors-oriented people, and then we just started doing everything together. We try to stay as active as our bodies will allow.

We've changed. We don't hike out in the woods, because we're afraid of what could happen if we do get too far out. We're still outdoors and active, it's just we're more on the pavement, less out in the mud.

We still spend a lot of time [kayaking] on the rivers though. Paddling is something she's still able to do and something we're both avid about doing.

Eric

You join April for many of these conferences. What do you get out of attending as a caregiver?

Matt

The people and the knowledge. That's what I tell everybody that I know or encounter: [These are] some of the most real people you will ever meet in your life. There's no games, there's no walls put up, no not-being-themselves. The women here are real. That's the way I've always been, you know, if people don't like me, then you don't have to be around me, this is who I am, either you like it or you don't. And that's how everybody is here.

Eric

Do you find the conferences helpful?

Matt

Yeah, very much. I never really had many conversations with the caregivers. I mean there's a couple of husbands that I've clicked with [and] we hang out, but I learn more from the women and men with the disease than I do anybody else. You know, I learn more from them what I need to do to help her.

Luckily, I work for myself and I can take off and be active in most everything we got going on in life. If I didn't, then I'd be like most of the other husbands. I'd be tied to work hours and a Monday-through-Friday job. But luckily, I can take off most of the time that I need to and can do these things.

Eric

The San Antonio Breast Cancer Symposium is just winding down now. Do you get to enjoy the travel aspect beyond the educational part of the conferences?

Matt

Yeah, definitely. Even though a lot of the times we're going back to the same city for the same conference, year after year, we get to go experience more while we're there.

This last trip to [Washington,] D.C., we took April's parents, and they've never been there so we spent a day out with them, showing them what we've already seen, but it was fun taking the family out. And this year to [LBBC's 2018 Conference on Metastatic Breast Cancer in] Philly, I think we're going to take my parents along. That's more of a bonding thing, where we can get family involved, and all spend time together.

April's parents had no idea the work that goes into the advocacy part of that, especially for the D.C. trip. They were amazed at everything we do and how active we were in everything: No time to slow down when you're there.

Eric

Do you have any insights or advice you would share with other caregivers?

Matt

I would recommend that anyone, even early-stage, get involved and do as much as you can with your partner. ... I mean, if April hadn't pulled me into the first [conference], I don't think I would be as involved as I am, getting in and going to all of them and meeting everyone. From doctors to researchers to patients and caregivers, it's a great network of people. 🍌

On March 24, as we went to press, April died of metastatic breast cancer. We send our deepest condolences to Matt and to their family and loved ones.