

THE COLLABORATIVE MANAGEMENT OF PATIENTS WITH ESTROGEN RECEPTOR-POSITIVE BREAST CANCER

WENDY H. VOGEL, MSN, FNP, AOCNP

Our last

presentation is one that we've been looking forward to since the schedule was set. This is truly a dream team brought back by popular demand speaking on a topic, The Collaborative Management of Patients With Estrogen Receptor-Positive Breast Cancer, and I am delighted to introduce our wonderful lecturers, Dr. Lee Schwartzberg and Ms. Heather Greene, of the West Cancer Center.

MS. GREENE I have to make a disclaimer. There will be no immunotherapy in this lecture, which I know has been a common theme. It's a very important theme, but the good part about that is you won't have to hear me try and pronounce all of those names.

Today we are going to focus on CDK4/6 inhibitors and their mechanism of action and how that differs from how we're used to treating our breast cancer patients. How, when we combine those with endocrine therapy, that may benefit some breast cancer subpopulations. I'm going to talk to you specifically about the side effect profile of these medications, especially neutropenia, and how to manage those toxicities and other hematologic toxicities.

Dr. Schwartzberg has served on Speakers Bureau for Novartis and is a consultant for Pfizer. I am a consultant and Speakers Bureau for Pfizer.

Dr. Schwartzberg and I have had the privilege of presenting a couple of times, and we like to use this kind of layout. We weave patients from our clinic through the presentation, and it works really well because it mimics the

collaborative practice that we do every day in our clinic. We are going to start with one of his patients.

She was diagnosed with breast cancer in 2003. At the time, she was 65 years old. She had a 7.5-cm infiltrating ductal carcinoma, with 3 of 17 nodes positive for disease. Her tumor was ER/PR-positive and HER2-negative. She had a left mastectomy for a pathologic T3N2N0 tumor. At the time, her adjuvant chemotherapy consisted of EC x4 followed by docetaxel x4 and then radiation to the chest wall.

She was started on adjuvant tamoxifen and she was ER-positive for 2 years, then changed to an aromatase inhibitor in the form of anastrozole, which she stopped after a year due to toxicities but was changed to exemestane., tolerated that for another 4 years, and then was followed with surveillance. She got a total of 7.5 years of adjuvant endocrine therapy.

We'll jump ahead to November of last year. She developed lower pelvic pain. She was first evaluated by her orthopedist, who ordered some plain films and an MRI of her pelvis, showing lesions suspicious for metastatic disease. She had a biopsy of one of these lesions -- the right posterior iliac sclerotic lesion -- and pathology was consistent with metastatic adenocarcinoma of a breast primary.

It is important to note here that we did check again for ER/PR and HER2, which I think you all know is important to do to make sure that those indicators haven't changed, as they can.

She was ER/PR-positive and HER2-negative consistent with her original pathology. She had a staging PET CT scan showing mediastinal adenopathy, one noncalcified right lower lobe nodule, and some subcutaneous metastatic lesions in the gluteal area and back. She had blastic metastases at T11, T6, right and left iliac crest, and also her left femur.

You all can see, because if I can see it, anybody can see it. You've got this mediastinal activity here. You can see these right and left lesions on the iliac crest femur. And then on this axial view, you've got this gluteal subcutaneous implant here, and also in the abdominal wall. In January of this year, she's now 79 years old, she brings with her a history of diabetes type 2, vertigo, hypertension, CHF, hypothyroidism, GERD, and depression.

She's now been diagnosed with metastatic ER/PR-positive HER2-negative breast cancer with bone, nodal, and cutaneous metastases. Her treatment plan was decided upon based on these factors and started fulvestrant, palbociclib, and then denosumab for her bone metastases in February of this year.

DR. SCHWARTZBERG Good morning everyone, and thank you all for staying. We really appreciate it, and it's really a pleasure to be back here again at JADPRO Live and particularly to present with Heather, and it's really a real privilege to have her in our clinic. She is such a wonderful source and authority in taking care of our patients.

We are going to talk about metastatic breast cancer. You heard the case, which is a real case, as it unfolded. And we've been a little jealous in breast

cancer, those of us who do breast cancer the last few years as you've heard about all those new drugs and the targeted therapies that have occurred in other diseases and the immunotherapy. And we are not quite there yet in breast cancer, which, for the last couple of decades, has led the way in terms of the development of new treatments for cancer. But we are going to talk today about one very exciting area where breast cancer is leading the way. And that's in endocrine ER-positive or hormone receptor-positive metastatic breast cancer.

What are our goals of therapy when we take care of metastatic breast cancer? We want to reduce the symptoms that the patients have. We want to increase the time until the next treatment, or what we call progression-free survival. We want to increase the time to chemotherapy if we can because, in general, endocrine therapy has less toxicity than chemotherapy. And importantly, what we are trying to do is improve the quality of life for these women and improve overall survival, if we can, at the same time.

Metastatic breast cancer is still a very common problem. This year, 40,000 women will die of metastatic breast cancer and that's the number two cause of death in women from cancer. Number one remains lung cancer. And despite the fact that breast cancer is the most commonly diagnosed cancer in women. Three to 6% of women present to your office with metastatic disease. That number varies from locale to locale and, to some extent, by socioeconomic strata, but there are definitely some patients who will always present with metastatic disease.

And although we've made remarkable progress in terms of treating early-stage breast cancer and improving the outcome, there will still be about 20% of women who relapse from an original diagnosis of stage I to stage III breast cancer and then develop metastatic breast cancer. That accounts for the women we see in the clinic today.

Today we break down breast cancer into three major subgroups, and that's far from all the subgroups that we know about. But for the purposes of our discussion, we talk about hormone receptor-positive breast cancer, which is typically ER-positive plus or minus PR-positive. We talk about HER2-positive breast cancer, and HER2-positive breast cancer is about half also endocrine-positive and half ER-negative. And then triple-negative breast cancer, which is defined by what it isn't rather than what it is. And I firmly believe that that will change in years to come, and we'll actually be defining specific subgroups based on what they are, like we are starting to in non-small cell lung cancer -- sort of the similar analogy.

But ER-positive breast cancer represents about 75% of breast cancers. So it's the most important group when you're dealing with metastatic breast cancer patients.

What are the clinical predictors that we use for outcome for these patients? And one of the important ones is disease-free interval. We've known for a long time now that the natural history of metastatic ER-positive breast cancer can be very slow. And it's not surprising to see women relapse 10 years, 15 years later. I've seen a patient relapse 25 to 30 years after their original

diagnosis, and we couldn't find another tumor. And it really seemed to be a very dormant metastasis that, for whatever reason, became clinically apparent later.

Prior endocrine therapy is very important. And it's more important now than it ever was. And if you look through the literature about endocrine therapy for hormone receptor-positive breast cancer, you must take into account what the endocrine therapy was that was used in prior lines of therapy. In particular today, in the adjuvant setting, as we moved in the adjuvant setting from tamoxifen as a 5-year agent to 10 years of endocrine therapy with either tamoxifen or aromatase inhibitors, which are the standard now for postmenopausal women. And now, 10 years to 15 years of adjuvant endocrine therapy, what happens after those women relapse is very different than a woman who has never had adjuvant endocrine therapy like in the '70s. We have to keep that in mind.

The quantitative ER expression is a good predictive factor for response in hormone receptor-positive patients to endocrine therapy. [With] low levels of ER expression, you're less likely to get a response. High levels, more likely.

We also know that clinical parameters are important. We've seen in the past, the typical phenotype of hormone receptor-positive metastatic breast cancer tends to be bone and soft tissue. And then later, as in initial presentation, later on you see visceral metastases or brain metastases. Those are uncommon in hormone receptor-positive breast cancer and that may influence the way we treat these patients; although, to be honest, now that we have effective therapies as you'll see the data, that distinction is starting to go away.

HER2 expressions are important. We usually treat HER2-positive patients with chemotherapy and anti-HER2 agents, and continue the anti-HER2 agents. There is an appropriate area for some selected patients who are ER-positive and HER2-positive to get endocrine therapy plus anti-HER2 therapy.

And then PR negativity is more of a prognostic factor, not a predictive factor, for response to a particular endocrine agent. But if you're ER-positive and PR-negative, that's probably a different subgroup of patients often called luminal B, if you look at genomic expression profiling. And those patients tend to be a little bit more aggressive than those that are ER-positive, PR-positive.

The NCCN Guidelines recommend serial endocrine therapy for hormone receptor-positive, HER2-negative advanced breast cancer not in visceral crisis. It's hard to define visceral crisis, but I think you'll all know it when you see it. It's basically, if a patient has big burden disease in the liver or the lung, particularly, and they're symptomatic from that and you need an early response. Those may be the small group of patients in this particular setting, because that's not a typical way that they present. But those patients may need the rapid response rate that you do get with chemotherapy.

In the 90% of patients who don't have visceral crisis, you should start with serial endocrine therapy. And those patients can actually proceed through several lines of endocrine therapy with much less toxicity. And I would argue now, as good a response, if not better, than chemotherapy itself.

Only when you get to the progression or unacceptable toxicity through several lines of endocrine therapy should you then switch to chemo. If you think

about it this way, you then have many lines of therapy for the women who present with hormone receptor–positive breast cancer. And it's not uncommon to see women get through the course of their disease, five, seven, 10 lines of therapy if they are getting two lines of endocrine therapy, or three lines, and then get multiple lines of chemotherapy.

Metastatic breast cancer -- now I would say all three subsets, particularly ER-positive and HER2-positive, where we have targeted therapies, those have become chronic diseases. And these patients now are living years to decades even. And that's really a wonderful progress.

We are going to talk today about one particular mechanism of action where inhibition can enhance the response to endocrine therapy and that's the cell cycle pathway and one of the important regulators of the cell cycle pathway, which are two proteins called CKD4 and 6. We know that resistance to endocrine therapy -- although endocrine therapy is great -- resistance invariably develops. If you put a patient on a single endocrine therapy, whether it's an AI or fulvestrant or tamoxifen in the metastatic setting, you may get good responses, but those patients will all eventually relapse.

Why is that? It's complicated actually. We don't know that answer in many cases. But we do know that inhibition of the ER pathway, the cancer cell can use other pathways of stimulation and that can be resistance. One way is to enhance cell cycling -- in other words, the division of cells. And the growth of hormone receptor–positive breast cancer is dependent on cell cycling and a particular target, cyclin D1, which is a direct transcriptional target of ER. And cyclin D1

inhibits a complicated pathway, where cyclin D1 activates CDK4/6. And then, CDK4/6 activates retinoblastoma protein, RB, and allows RB -- which is truly the traffic cop in the cell cycle -- to allow G1 to S phase transition. At each part in the cell cycle, there are control points, which allows change from G1 to S, or S to M, or M to G2. And the very important one is RB. And CDK4/6 work on RB.

In endocrine resistance pathways, the cycling remains important. In fact, it may be amplified if there's endocrine resistance. So this is potentially a good target. And, in fact, in preclinical experiments done a few years ago, there was synergy of a CDK4/6 inhibitor, palbociclib, one of several we'll talk about, with tamoxifen as an endocrine agent in ER-positive cancer cell lines. And this just shows several cell lines, which are ER positive. MCF7 is the grandmother of all of them that's been used for 30 years as sort of the standard ER-positive cell line. And you can see that there's good inhibition when you add palbociclib. Actually, synergistic inhibition with tamoxifen in these cell lines.

That led to clinical experiments, and the first phase II study was a study called PALOMA-1, which was a study in ER-positive HER2-negative metastatic breast cancer for women to receive letrozole, nonsteroidal aromatase inhibitor, with or without what's now called palbociclib. And palbociclib was given 3 weeks out of 4 in this study. And letrozole was given daily. Both of these drugs are oral drugs.

There were two parts in this study. One part was an unselected population. Part 2 were patients that were selected on putative biomarkers, which were CCND1 or cyclin D1 gene amplification, or a loss of p16, which is one of the

regulators of the CDK4/6 interaction. This was about 160 patients in this clinical trial. And these were the results that were published last year in *The Lancet*, and you can see the blue line on top is the combination arm. These are patients who had first-line treatment in this phase II study. They had not received treatment in the metastatic setting with endocrine therapy and they did much better, as you can see. In fact, there was about a 50% improvement in progression-free survival. And as you can see from these curves, you don't need the statistics to show that this is an effective therapy. The curves separate very early and they remain separated out through 3+ years of follow-up for these patients.

There was a lot of excitement about adding this drug and this class of drugs to endocrine therapy.

Based on these phase II data, palbociclib received the first designation as a breakthrough therapy by the FDA and was granted accelerated approval in February 2015 for patients with metastatic ER-positive breast cancer, not based on this data, but based on the data from this trial, which was the PALOMA-3 study, which was published in June of 2015 and also presented at ASCO a year and a half ago.

In this particular trial, palbociclib was combined with fulvestrant. Fulvestrant is a selective estrogen receptor down regulator, so it basically destroys the estrogen receptor as opposed to AIs, which inhibit estrogen in the body, and tamoxifen, which is a selective estrogen receptor modulator or inhibitor of the receptor.

In this particular study, large phase III trial, patients were randomized to receive palbociclib at this same schedule, 3 weeks on/1 week off, 125 mg a day, and fulvestrant, which was given in what we now know is the best standard therapy, which is 500 mg given intramuscularly on days 1, 15, and 29, and then monthly thereafter. And this was a placebo-controlled study.

In contrast to PALOMA-1, these were patients that had previously received treatment with endocrine therapy in the metastatic setting, and they could also have received up to one chemotherapy. Most of these patients were ER/PR-positive, some were ER/PR-negative. Visceral metastases, I will point out, were seen in 60% of patients, and over half the patients had two or more disease sites.

In addition, patients were allowed on this trial who were premenopausal who could get prior aromatase inhibitor and a GnRH antagonist as well.

And these were the results of this study. A pretty striking result with a 60% improvement or a hazard ratio of 0.42, favoring the palbociclib fulvestrant arm with a median progression-free survival of 9 months. This is in the advanced metastatic ER-positive setting, compared to 3.8 months with fulvestrant alone. And this is still fairly early follow-up for these patients.

The subgroup analysis forest plot is shown here, and as you can see, and I want to point out the visceral metastases, which is halfway down there, you can see that there's no difference in patients' response if they had visceral metastases or did not have visceral metastases. In addition, about 20% of the patients on this study were premenopausal, who received a drug like leuprolide

to cause ovarian function suppression and were then able to receive fulvestrant plus or minus the palbociclib, and they also responded.

This is the first study that shows that you can actually treat patients in the metastatic setting with ovarian function suppression and appropriate therapy, which you cannot use in pre-menopausal women and see that benefit. And that is shown here.

In terms of the secondary endpoints, the response rate was numerically better. But the clinical benefit rate, which is the number of patients that stay stable or responding at 6 months, was 34% compared to 19% in the patients who did not receive palbociclib here. And the overall survival data is immature at this time.

What's the downside of giving palbociclib? The predominant downside is hematologic and particularly neutropenia. And you can see here that patients who receive palbociclib and fulvestrant had a high incidence of neutropenia, about 50% of them developed grade 3 neutropenia. In other words, a neutrophil count of 500 to 1000, and 9% developed grade 4 neutropenia, which was a neutrophil count less than 500 at some point.

Anemia was modestly increased, and thrombocytopenia modestly increased, but very little grade 3 and essentially no grade 4 for each of those blood elements. There is slightly more fatigue, and otherwise the event profile in terms of toxicity is fairly similar across both arms of the study.

Interestingly, despite the fact that grade 3 neutropenia develops frequently, very, very few patients develop febrile neutropenia here. And infectious complications were relatively rare.

The overall incidence of serious adverse events was similar in these. The incidence of febrile neutropenia was identical in both arms and less than 1%. There were more infections of any grade, and no deaths due to AE.

So palbociclib compared with fulvestrant improved the progression-free survival by approximately 60%, and the benefit was seen across all prespecified subgroups and the drug was well tolerated. And this became an effective treatment option for women whose cancer progressed on prior endocrine therapy and was approved about a year and a half ago by the FDA.

And then we waited for the PALMOA-2 trial, which was the phase III study with an identical design to what I showed you for PALOMA-1. These are patients who had not received therapy in the metastatic setting yet. It was a 2:1 randomization, 666 patients, same schedule of drug. Again, using letrozole with placebo or letrozole in the 3 out of 4 week palbociclib schedule.

And here are the results that were presented at ASCO and published simultaneously in the *New England Journal of Medicine* a few months ago. And the curves, I think we could argue, look very similar to what I showed you for the other two. There is an early separation of the curves. The overall hazard ratio is 0.58, so a 42% improvement in progression-free survival with the addition of palbociclib to letrozole.

And it is hard to read, but the basic concept from the forest plot here is all subgroups benefited from the addition of palbociclib, and if they had measurable disease, if they had visceral disease, if they had prior hormonal therapy, they did well.

In terms of the secondary endpoints in PALOMA-2, the response rates were actually statistically improved. The clinical benefit rate was improved in the intent-to-treat population. And I point out that number -- the clinical benefit rate in this study was 85%. That means five out of six women who got the combination had benefit from the combination. Only one out of six women did not benefit from that combination. Those are pretty staggering numbers when you are treating metastatic disease with any type of therapy. The median duration of response was 23 months if you did respond to therapy.

The studies were consistent across PALOMA-1 and PALOMA-2, so the results were gratifying but not unexpected. There wasn't a variation, which sometimes you see when the phase II results are really good and the phase III results aren't so good as the numbers go up. That was the not case here. They looked very consistent across both studies.

In terms of the adverse events, we saw the same thing that we have seen in other studies regardless of what palbociclib is paired with. Neutropenia is the common grade 3 toxicity and a little bit more fatigue, but modest amount, and very little more grade 2 fatigue. And very little in terms of febrile neutropenia or infection here.

I'll turn it back over to Heather.

MS. GREENE Back to our case study. Our patient has been started on palbociclib with fulvestrant, CDK4/6 inhibitor. She fits the criteria: postmenopausal, hormone receptor–positive -- and, if you remember, her bone metastasis was 100% ER/PR-positive. That gives us an indication that this is one of her factors that would indicate that she would benefit from this. We know that she is not in visceral crises. With our patient, it is used in the second indication that's listed up there that Dr. Schwartzberg went through, with fulvestrant in disease progression following endocrine therapy. And that does include adjuvant therapy. So, let's see here, 4 years later, she developed metastatic disease.

The recommended starting dose of palbociclib is 125 mg/day for 21 days of a 28-day cycle. It's important to educate our patients to take palbociclib with food, and we will talk about some of the reasons for that a little bit later. As Dr. Schwartzberg mentioned, there are some side effects associated with this combination although it is very well tolerated. But some of those side effects may require dose interruptions, dose delays, or modifications. But should your patients require dose reductions, the first recommended dose reduction is down to 100 mg/day, and the second dose reduction, should your patients need it, goes down to 75 mg/day.

I do want to make one point here. Even though the case study that we're doing is not with letrozole, it's been my experience and probably your experience too that if you have patients on two oral therapies, the letrozole and the palbociclib, these are generally elderly little ladies. They may be a little shell-shocked at their diagnosis. And it can be very complicated for them to

understand that you are going to continue to take the letrozole every single day, but the palbociclib they are only going to take 21 days and take a break.

It does not seem that complicated to us, but we do this day in and day out, and that's, in our world, a pretty easy dosing schedule. But I've had ladies come in with all sorts of concoctions that they have somehow gotten from their teaching, which they weren't taught by the advanced practice nurse.

MS. GREENE I had a lady come in and she took it for 2 days, took a week off, took it 2 more days, and she was back to see me. And I don't know where she got that from. However you do it in your practice, maybe give them something visual that they can refer back to.

The take-home message, if you haven't gotten it, is that this combination can cause neutropenia, which Dr. Schwartzberg has already covered, but I put up on this slide, I put together the PALOMA-1 and the PALOMA-3 data, which puts everything that Dr. Schwartzberg presented on one slide that you can see. No matter if you use it with letrozole or you use it with fulvestrant, these patients are going to get neutropenia most of the time. We were talking yesterday in my practice, it's almost a way you can tell that they're taking their medicine, because, again, compliance is an issue with these oral therapies. When they come in and you check their CBCs and you see that they're neutropenic, at least you know that they're taking their medicine.

Because neutropenia is going to be most likely your common side effect, it's very important -- and, again, this is where we shine in terms of taking care of our patients -- you need to make sure that you're checking the CBCs on Day 1 of

every cycle of palbociclib whether they are taking it with letrozole or fulvestrant. And then, for at least Cycles I and II, we need to check their CBCs again on Day 15. You may have to check it on Day 15 or more, with subsequent cycles, but at least the minimum until you see how your patient is going to do, you need to check it Day 1 of every cycle, Day 15 on Cycles I and II.

There are other hematologic toxicities, but those don't tend to be the side effects that you're having to do these dose delays, modifications, or interruptions for. Dr. Schwartzberg and I were talking yesterday, and in my practice and his, we haven't had to transfuse for anemia or thrombocytopenia or anything like that.

The nonhematologic toxicities tend to be GI based, with decreased appetite, stomatitis, nausea, vomiting, diarrhea, fatigue can still certainly be an issue. Alopecia, I want to make one little point. That's usually not something that we have to educate our patients on when we're talking about endocrine therapy, but as you know, for some ladies that can be a very touchy subject. And they have metastatic disease, their quality of life has already been affected, and they don't want to lose their hair. I get it. And they go home and they read or they're on the Internet, and they're going to see alopecia, or hair loss, is a potential side effect, they sometimes can balk at wanting to start this therapy. Or "Can't I just take the letrozole? Why do I have to take the palbociclib too?" But you can have confidence in telling your patients that if they do develop hair loss, it usually is just grade 1, very minimal thinning or patchy hair loss. They're not going to have the total alopecia that you get with cytotoxic chemotherapy.

These are some side effects unique to PALOMA-3. I thought it was good to have it up here so that if you're using this in combination with the fulvestrant and your patient comes in with dry eyes, it probably is from their therapy. But the eye disorders, dry eyes, blurred vision, headache, constipation, rash, and pyrexia can also occur.

Let's dig into the hematologic toxicities. If you are not familiar with the CTCAE grading scale for hematologic toxicities, I heard somebody else say there's an app that you can look it up. But you need to know what a grade 2 hematologic toxicity is so that you can manage these patients appropriately. It's important for us to be able to keep our patients on drug and keep them safe.

So, for grade 1 or 2 hematologic toxicities on palbociclib, there's no dose modifications. We are going to skip grade 3 because it's a little complicated, we'll do that next. But for grade 4 hematologic toxicity, you're going to need to hold therapy no matter where they are in their cycle, monitor them until it recovers to a grade 2 or better, and then resume therapy. But you are going to need to dose reduce. And so you go back to that dose reduction slide we had a little while ago. If they are on 125, they are going to drop to 100.

For grade 3 hematologic toxicities, if you remember back, it's most likely going to be neutropenia, if it's Day 1 of your cycle, you're checking CBCs on Day 1 on all these patients, you're going to need to hold the dose. They can't start that cycle until their toxicity recovers to at least a grade 2. Follow their CBCs more closely, repeat it in a week. When it resolves, and it will, but when it

resolves to at least a grade 2 or better, you can resume therapy and you don't have to dose reduce. You can keep them on their same dose.

When you're checking the CBCs on Day 15, Cycles I and II, if that's when you notice they developed a grade 3 hematologic toxicity, you don't have to stop. If they don't have any complications, they just have a lower white count, which you would expect, you can monitor them. You can keep them on therapy. Repeat the CBC again maybe a week later. And then you want to make sure that that recovers before you start your next cycle.

The only kind of caveat there is if they have this grade 3 hematologic toxicity, and it's a grade 3 neutropenia, which for those of you, that's going to be an ANC between 500 and 999. If they have that grade 3 neutropenia with some type of complication, meaning a fever or an infection, no matter where they are in their cycle, they are going to have to stop. And that makes sense. Stop their therapy. Treat the infection accordingly. If you don't know where their infection is coming from, work up their infection. Monitor them more closely until that neutropenia recovers to a grade 2 or better. Once their ANC gets above 1,000, when you feel it's safe for them to restart, that's when you're going to have to dose reduce. And this is a snapshot here. It's the grade 3 ANC 500 to 999. We need that to recover.

When your patients are coming in and you're getting their CBCs, that's what you need to have in the back of your head. That's what you're looking for.

For nonhematologic toxicities grade 1 or 2, you don't have to make any changes. If you have a nonhematologic toxicity that's a grade 3 or 4, that's

persisting despite medical treatments, so say they are having diarrhea despite diet changes, loperamide, those types of things, you need to hold their therapy, no matter where they are in their cycle. Wait until that recovers to at least a grade 2, and if there are no safety risks that are involved in restarting your therapy, you can do so. But you need to dose reduce by one level.

Some drug interactions -- palbociclib is one of the medicines that you'll have to tell your sweet little ladies that they can't drink their morning grapefruit juice with or to eat their grapefruit. There is an interaction. You need to make sure that you're reviewing patients' medications. And if you're unfamiliar with what might be an interaction, talk with your oncology pharmacist because if they're on these CYP3A inhibitors, they either need to have a dose reduction of palbociclib, which I wouldn't recommend from the beginning. Surely, we can figure out a way to get them on some safer medications. If they're using palbociclib with these CYP3A inhibitors, it can increase palbociclib levels, which then would potentially increase their risk of toxicities.

The inverse is true for CYP3A inducers, it can decrease palbociclib levels, and, therefore, they are not getting effective treatment for their breast cancer. So if they're on any medicines in this class, and I gave some examples up here -- Dilantin, carbamazepine, St. John's Wort -- they need to change to a safer alternative.

This is not something that I've run across in my practice, but if patients are on CYP3A substrates and taking those medicines with palbociclib, taking it in combination with palbociclib can increase those other medication levels in the

body, so most of these probably won't play a role, but one that jumps out to me is fentanyl. If you think your metastatic breast cancer patients that probably have painful boney metastases, a fentanyl patch is a pretty common long-acting medication that is used. Keep in the back of your mind, if you have somebody who has been on the fentanyl patch and they start palbociclib and they are having more sedation or some mental status changes, it could be that there is an interaction here and you might need to think about changing their therapy. Not, hopefully, maybe their pain medication therapy.

For proton pump inhibitors, patients can take palbociclib with proton pump inhibitors, but they need to -- this is where you need to make sure you are educating your patients to take their palbociclib with food. If they take their palbociclib without food and they are on a proton pump inhibitor, it can significantly decrease palbociclib levels in the body and, therefore, they are not getting effective therapy.

Back to our case study. On Cycle 1, Day 1, and Dr. Schwartzberg has recommended starting this therapy, the patient comes back -- and this is another good point with these oral therapies. I'm sure you guys have to deal with this on a regular basis. But sometimes you have to wait a week or longer to get those medications to the patient. Jump through all those insurance hoops. At least in my practice, I like for them to call us and tell us when they have their palbociclib in hand, come in that day or as soon as they can. We'll check a CBC so we know where their baseline is before they get started. Plus, then you make sure you

know that they got their medicine and they're not just out there floating around and you think that they've gotten their palbociclib and everything is good.

She comes in for Cycle I, Day 1. She has essentially normal count, white count 4,800; her ANC is 2,150; no anemia; platelets look good. We review her medicines, and note that she is on a proton pump inhibitor for her GERD and review with her that she needs to make sure she is taking her palbociclib with food.

She comes back in again in 2 weeks, Cycle I, Day 15, for her CBC check. Her white count has dropped. We know she's taking her palbociclib. ANC is 750, so that should be sending up red flags. That's a grade 3 neutropenia. We need to be assessing for infection or fever. She does not have a fever but she does report to you significant upper respiratory tract infection symptoms to the point where we did feel she needed antibiotics to treat that accordingly. And since she had the grade 3 neutropenia, no fever but with an infection, we held her palbociclib.

She went home, took her antibiotics, came back in for Cycle II, Day 1. She finished her antibiotics. She had been off of palbociclib. Her counts have recovered appropriately. White count is up to 4,400. Her ANC is recovered to a grade 2 or higher. Her dose is resumed, but since she had that grade 3 neutropenia with an infection, we dose reduce by one level. She starts Cycle II, Day 1 with palbociclib, but 100 mg/day.

Today, the patient is still on the current therapy. She's had no further dose reductions. She does have some other mild side effects. She's reported some

fatigue, nausea, and anorexia. She did have some intermittent neutropenia, but nothing significant. No further grade 3 toxicities. Clinically, her pain has improved significantly and we got another PET CT. This was in May of this year. Compared to January, you can see, the previous hypermetabolic activity here in the mediastinum, can't see it here anymore. Here, in her hips, these lesions that we saw initially, you almost can't even see her hip ones over here at all. Maybe a little bit there. This femoral lesion is gone. On these axial views, this previously gluteal implant and abdominal -- here's the gluteal much smaller. And here's the abdominal, also smaller.

She's had great clinical benefit and radiographic response. I turn it back over.

DR. SCHWARTZBERG So you can see that these drugs really do work in the kind of setting -- in the real-world setting that we see. And it's very gratifying. We are also gratified by the fact that this, as a class of agents, this appears to be a very important class of agents that can be developed for metastatic breast cancer, and potentially beyond metastatic breast cancer. Because, obviously, the cell cycle, and inhibiting the cell cycle, could potentially be an area that is important in other diseases, in other resistant mechanisms.

There are two other CDK4/6 inhibitors in late-stage investigation: ribociclib and abemaciclib. Ribociclib is a preclinical study of patients that had cell lines with ER-positive or ER-negativity. And the inhibitory concentrations are particularly good in the ER-positive. For this drug, ribociclib, it also appears to be preferentially active in breast cancer, at least in the ER-positive population.

And that led to a series of trials that are very analogous to the PALOMA trials. This series is called MONALEESA. And MONALEESA-2, which was a phase III, double-blind, placebo-controlled study of ribociclib and letrozole was presented about 3 weeks ago at ESMO and subsequently published also in the *New England Journal of Medicine* a couple of weeks ago.

The study design is almost identical to what I showed you for PALOMA-2. It was a 1:1 randomization but it was 3 weeks on, 1 week off for ribociclib. The dose of ribociclib is 600 mg/day with letrozole compared to placebo and letrozole, and the primary endpoint was progression-free survival.

This study was stopped early by the Data Monitoring Committee because it met its endpoint as statistically specified for an interim analysis and that's why the follow-up is relatively short here. But you can see that the hazard ratio is 0.56; the median progression-free survival has not been reached yet for the study combination, and was 15 months for the patients who had letrozole alone. Again, this is in the first-line setting. No previous treatment for metastatic disease.

The third drug is abemaciclib, which is a slightly different drug -- also a CDK4/6 inhibitor. It has more activity, in particularly CDK4 versus CDK6, so it may have clinical implications. And this is a phase I trial, showing you the usual waterfall plot, which shows that patients with ER-positive disease are those that benefit with hormone receptor-positive metastatic breast cancer, not those with hormone-negative status. Interestingly, neutropenia was not the dose-limiting toxicity for abemaciclib and continuous dosing was feasible.

At ASCO this year, we saw the results of the MONARCH 1 trial -- a series of trials that are investigating abemaciclib. This study was different, however, because abemaciclib was given as a single agent, and it was given 200 mg continuous dosing daily as a single agent in patients who had had advanced hormone receptor–positive metastatic breast cancer and could have received several lines of endocrine therapy as well as several lines of chemotherapy. And the median number of lines of therapy in this study was three. These were a much more advanced population. And the disease control rate was 67%, and there was 20% partial response to abemaciclib itself. Another potential way to use these drugs in treating patients. And abemaciclib is also in phase III trials, looking at a very similar design in combination with a nonsteroidal aromatase inhibitor, and we'll see the results of that study in the very near future.

Ribociclib, the study I showed you that was presented and published a couple weeks ago, now is under accelerated review at the FDA, and we'll probably see a decision on that drug in the next few months.

In summary, CDK4/6 inhibitors are really an important new class of drugs for ER-positive breast cancer. The uptake in our clinic for using these, and in my own practice as a breast medical oncologist, has been pretty extraordinary for a new drug. I would say that the large majority of patients now who have first-line metastatic breast cancer and hormone receptor–positive [breast cancer] are getting combination therapy.

The mechanism of action suggests that inhibition of the cell cycle pathway through cyclin I CDK4/6 and then finally on RB reduces resistance to endocrine

blockade by using one of these other maneuvers, either an aromatase inhibitor or fulvestrant as selective estrogen receptor down regulator, but also potentially could be used with tamoxifen as well.

Palbociclib is approved with aromatase inhibition in the first-line advanced breast cancer setting and with fulvestrant following prior endocrine therapy, including adjuvant therapy. You could use the drug with fulvestrant in the first-line setting if the patient has an early relapse and so-called endocrine resistance, if they relapse while they are on an aromatase inhibitor or within 12 months of an aromatase inhibitor -- at least if you're following the evidence based on the clinical trials.

The toxicity, as you've heard, is predominantly hematologic but generally is not clinically serious even when we see grade 3 neutropenia, which occurs frequently. And there is clearly substantial clinical benefit with the addition of CDK4/6 inhibitors added to endocrine therapy and ER-positive advanced breast cancer. And we see that not only for palbociclib, where the data's the most mature, but for the other two drugs in the class that have been tested and that, so far, looks very promising.

I'll just make one other point, which is that CDK4/6 inhibitors may have benefit in other diseases as well. So maybe in a few years, we see this as a general class of drugs that's being used with other tyrosine kinase inhibitors or other pathway inhibitors and possibly other agents as well. A very exciting development for cancer in general.

With that, I want to thank Heather for inviting me to come and be her assistant, and also to thank you all for your attention. We are happy to answer any questions.

QUESTION Maybe I missed this as part of the discussion, but what was the rationale for selecting letrozole as the AI of choice when that's not really, at least in our practice, is not the most commonly used AI in our hormone-sensitive patients?

DR. SCHWARTZBERG That a really good question. I think that was really more of a clinical trial decision rather than a clinical efficacy decision. I will tell you though that there is no difference in the multiple trials that were done previously between the three approved agents, aromatase inhibitors, used in the advanced breast cancer setting -- regardless of prior therapy. Although most of those trials, arguably, were done in patients that had previously not been exposed to endocrine therapy or exposed to tamoxifen.

However, that being said, anastrozole, letrozole, and exemestane have equal efficacy in the metastatic setting.

QUESTION I have a question about a patient that I'm caring for now who has recently been diagnosed with metastatic breast cancer. And she was diagnosed with CLL around the same time she had her breast cancer about 10 years ago. With her recurrence, she has ER/PR-positive HER2-negative disease, although her original cancer was HER2-positive. Any experience in an individual who also has CLL?

DR. SCHWARTZBERG That's a great case for a couple reasons. First, and two important points to make. First of all, I hope you're all biopsying your patients when they develop metastatic breast cancer. I think that's important, and I'm increasingly convinced it's important because there is a phenotypic change in about 10 to 20% of patients. Most commonly we see ER-positive go to ER-negative. And sometimes we see, particularly in the era where we use anti-HER2 therapy now, frequently in the adjuvant setting, or almost universally in the adjuvant setting, HER2-positive to HER2-negative also occurs.

There is still debate about whether you should trust those results and whether there's heterogeneity in a particular place that you biopsy as opposed to others. That answer isn't really clear yet. But, in general, if you have, particularly if you develop a target, i.e., either ER-positive or HER2-positive in the metastatic setting, you should take that seriously and treat those patients accordingly.

That's the first point. The second point is what do you do with an older patient that has comorbidities? And in this case, the comorbidity is another malignancy, a common hematologic malignancy, CLL. That's an interesting problem from a management problem. But the first thing to do, and this you should be doing with any patient, and Heather referenced that we have a number of older patients -- although we have younger patients too who have hormone receptor-positive metastatic breast cancer -- and the question there is, how intensive do you have to be with their therapy and how do you manage their comorbidities? And what are your goals of treatment?

Your goals should always be looking at the patient before you and seeing what their goals are, what they want to get out of it, how much toxicity they are willing to benefit, and what their goals are. So if someone has a comorbidity index that's very high, or a geriatric score that shows that they are not functional, you might be less intensive in your therapy.

For CLL today, as I'm sure you heard through this meeting, CLL is a chronic disease too. And many CLL patients, including patients I still have in my practice, I haven't treated ever for 10 years or more. And not every patient with CLL has to be treated. So I wouldn't necessarily say that you wouldn't be aggressive with that patient from their breast cancer perspective because they have CLL.

But, however, the third point is, if you're going to use one of the new oral agents for CLL, we have to think about what the interactions are. And to be honest, I have no idea of the interaction between palbociclib and ibrutinib, and we'd really have to look that up if that was your goal, to treat patients with all oral therapies for two different cancers at once. That's a real luxury. We never had that conundrum before -- of treating two cancers at once -- how do we do that? And now we are going to have that increasingly. Because we have more people living longer.

QUESTION I'm just new to using palbociclib. I'm from Canada and it's just been approved. And so in one of my patients right now, she developed a grade 3 neutropenia on Day 1, Cycle II. Repeated her CBC a week later, and her neutropenia actually had gotten worse and I'm just wondering, because it went to

a grade 4, what your recommendations would be. I'm rechecking her CBCs on Tuesday, so I'll be curious to see if there's any improvement. There's been no signs of infection, fever, anything.

DR. SCHWARTZBERG Did you check a Day 15 count on that patient during Cycle I?

QUESTION We did. There was a drop, just to a grade 1 neutropenia at that time.

MS GREENE I guess I would just make sure there's not anything -- is she taking any other new medicines? But continue to watch. Sometimes they don't recover all the way and you have to -- off label -- decide what's more important. Again, this isn't the kind of neutropenia that you see with chemotherapy, where you're worried about them getting septic and really, really sick.

Some of them just maintain a low degree of neutropenia and you maybe drop the dose and continue to treat. But that's something you would individually make that decision based on the patient with the rest of your team.

DR. SCHWARTZBERG I agree completely, and in that patient, what I would do would be to drop the dose to 100 when she recovers to grade 2 or less. Now that question it brings up, and we don't have the answer to this, and this is where our pharmacy colleagues could help us, is occasionally I've seen a couple of patients like this that seem to have delayed neutropenia.

So what's happening? Maybe the drug is hanging around, either through an interaction, as Heather said, or maybe it's just the metabolism in that patient.

Remember, pharmacodynamics can be very variable in people with oral drugs. So maybe the drug is still having a long half-life, or a longer half-life in that particular person. You may have to manage her a little bit more carefully. But the simple answer is reduce the dose when she recovers to 100.

I want to make two other points. I've heard in the community that some physicians are starting at 75 mg. I think that's a really bad idea. You should start at 125 and reduce the dose. That's the way the studies were done to get these great results that we see.

You can reduce if it's appropriate. Don't start low and go up high. First of all, probably most of you know that when you do that, you never end up escalating anyway, whether or not you should. And it's just not a good idea, particularly with this class of drugs.

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