**Transcript Details**
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/from-risk-to-resilience-best-practices-for-improving-outcomes-in-early-stage-erher2-breast-cancer/32681/

Released: 06/02/2025
Valid until: 06/02/2026
Time needed to complete: 90 minutes

**ReachMD**
www.reachmd.com
info@reachmd.com
(866) 423-7849

---

From Risk to Resilience: Best Practices for Improving Outcomes in Early-Stage ER+/HER2- Breast Cancer

**Announcer:**
Welcome to CME on ReachMD. This activity, titled *From Risk to Resilience: Best Practices for Improving Outcomes in Early-Stage ER+/HER2- Breast Cancer,* is provided by AXIS Medical Education and supported by an independent educational grant from Lilly USA, LLC.

This replay of a live broadcast discusses best practices for optimizing outcomes in early-stage ER+/HER2- breast cancer.

**Chapter 1**
**Announcer:**
Please welcome Theresa Gillespie, Kristi Orbaugh and Kimberly Podsada.

**Dr. Gillespie:**
Well, good evening and welcome. We're so glad everyone is here. We're very excited about our program tonight. It is From Risk to Resilience: An Interactive Sharing of Best Practices for Improving Outcomes in Early-Stage ER-Positive, HER2-Negative Breast Cancer. If you came to the wrong presentation, just stay anyway. We're happy to have you. And I noticed that there's wine, so this is really a very special evening.

So, I am Theresa Gillespie. I'm going to be moderating the session tonight. I'm a Professor in the Department of Hematology and Medical Oncology and in the Department of Surgery at the Emory University School of Medicine, and also in the Winship Cancer Institute in Atlanta. I'm a long-time oncology nurse.

With me tonight, we have two very distinguished speakers, Kristi Orbaugh, who is an Adult Nurse Practitioner, Community Hospital Oncology Physicians in Indianapolis, Indiana. Also, Kimberly Podsada, who is an Oncology Nurse Practitioner at the University of California, San Diego Comprehensive Breast Health Center in La Jolla, California.

So, these are our disclosures.

So, these are our learning objectives. They seem like a lot, but we have planned them all out and we hope to cover all of them.

So, I'm now going to go ahead and turn the podium over to Kimberly Podsada, who's going to be talking about the importance of assessing risk of relapse in early-stage ER-positive, HER2-negative breast cancer. Kimberly?

**Chapter 2**
**Dr. Podsada:**

Thank you, and it is good to be here. If I told you about my morning getting here and just making it on time, I am very happy to be here. So, thanks to the organizers for inviting me. It's a real honor to be here. And thanks to all of you who chose oncology and are sticking with oncology. Thank you.

I am going to start with my patient. A 40-year-old premenopausal female presented with a palpable left-breast mask. Imaging and biopsy of the breast and the lymph node revealed a clinical T2 N1 Grade 2, strongly hormone-positive, HER2-negative by IHC and FISH and invasive ductal carcinoma.

She enrolled in a clinical trial but was not eligible because of a low MammaPrint, but staging scans showed no metastatic disease. So, what test would you consider ordering next? This is not a polling question, nor is it a trick question. So, Oncotype DX, genetic testing, NGS molecular testing, or a breast cancer index BCI?

Oh, I guess it is a polling question. Cool. OK, so the majority did choose genetic testing. Great. And that is correct, so that's what I would definitely order for her. We're going to talk about some of the other tests, but genetic testing for young women, of course, is very important and a key piece of how we may treat her, and options we may offer her.

The Oncotype DX, I'll review in a second. NGS molecular testing is usually done in the metastatic setting to see if there are any targetable mutations in the metastatic setting.

So, for Oncotype DX, it's a very good test. It's predictive and prognostic and it really helps us to understand if someone would benefit from chemotherapy or not. Same with MammaPrint. MammaPrint also gives us an idea whether someone is at low risk and does not need chemotherapy, or high risk and does need chemotherapy.

The Breast Cancer Index is a great test that we have been using more regularly now for women when they're completing their 4 to 5 years of their endocrine therapy, and we want to know whether they're high risk for recurrence.

And an additional 5 years of therapy would be beneficial for them.

Prosigna is just looking at postmenopausal women, and honestly, EndoPredict I've never used and it has 12 genes, so we tend to do more of the Oncotype DX or the MammaPrint.

So, the Oncotype DX gives us that recurrent score. Again, it’s prognostic and predictive. You have a low, intermediate, or high risk. Again, this is really telling us whether someone is at risk for recurrence, and chemotherapy can help to reduce that risk. MammaPrint gives you just a good low score or a poor high score. And like I said, the Breast Cancer Index is also prognostic and predictive, so it will let you know whether you are at high risk and if you'd have a benefit to continuing endocrine therapy.

So, when we think about our patients or a breast cancer patient, or any cancer patient in general, we're thinking also about the individual and their lifestyle and some of the things or factors associated with an increased incidence of breast cancer: being a woman. We are at 100%-fold greater risk than men. Genetics. Whether someone is BRCA 1 or 2 or has another mutation within that gene positive, and that accounts for about 5 to 10% of all breast cancers. Majority of breast cancers are random. Family history. So, about 15 to 20% of women with breast cancer have a family history. Someone's lifestyle. Obesity after menopause is an increased risk, not just for cancer but other diseases as well. Alcohol consumption. Even moderate consumption, but definitely excessive consumption. Lack of physical activity. And hormones. Whether someone has increased or abnormal hormone levels, especially when we think about postmenopausal women on HRT.

So, we do know there is still a fact that using HRT in the postmenopausal setting does increase one's risk for breast cancer. And also, reproductive. Early menarche, late menopause, no children, or giving birth at a later age. These are all individual risks that potentially increase one's risk of a breast cancer.

So, this patient, her mother had breast cancer at age 30. She had G3 P3 22-years-old with her first delivery, hysterectomy at 37 years old due to menorrhagia, but her ovaries are in place. And her breast cancer diagnosis was at 40 years old, so she's young. No previous history of breast biopsy. History of smoking, but she quit about 7 years ago. Occasional alcohol use, but very rarely. No Jewish heritage. BMI is 44, so she is overweight. No current exercise routine with a sedentary lifestyle. Plus, we need to think about her additional factors

once we know more about pathology.

So, we're looking at the potential individual risk factors and then there are risk factors associated with someone's pathology as well.

So, she did her genetic panel, 19-gene panel, completed. No actionable mutations, so her BRCA gene was normal. As a reminder, we all have a BRCA gene. It's normal or it can be mutated, and that's where that high risk of breast cancer comes from. She proceeded with a bilateral mastectomy and left axillary lymph node dissection with immediate deep reconstruction.

Her pathology revealed, surprising to everyone, PT2 N3b. Five of 26 lymph nodes were positive. Mixed invasive lobular, 90% and ductal, 10%. Continued to be hormone-positive, HER2-negative, Grade 2. Extensive lymphovascular invasion and dermal lymphatic involvement.

So, at this point, she went on to receive dose-dense AC-T, and then afterwards, she had Goserelin for her ovarian suppression and anastrozole during radiation. During radiation during this time, adjuvant abemaciclib was approved by the FDA and she agreed to start 150 milligrams BID daily for 2 years.

**Chapter 3**

So, some of the things we consider risk for breast cancer were current, so now we're kind of looking at the whole picture. Her characteristics as well as potential pathology characteristics that increase her risk for recurrence. So, approximately 30% of patients with high-risk early breast cancer experience recurrence by 5 years of follow. So, things that affect that risk; young age at diagnosis, her tumor morphology – ductal versus lobular, a larger tumor size, high-grade tumor, symptomatic at presentation, presence of the LVI, lymph node involvement, whether someone's ER-negative or HER2-positive, positive or close margins, PR negativity, that high Ki67 proliferation rate, or metaplastic carcinoma.

So, there's this unmet need and gaps in the current treatment strategy for hormone-positive, HER2-negative early breast cancer. Primary endocrine therapy resistance in early breast cancer develops within the first 2 years of adjuvant therapy, which may result in local and regional recurrence or metastatic, which is incurable. So, a total of about 12% of high-risk patients with hormone-positive, HER2-negative early breast cancer experience recurrence within 2 years of follow-up. High-risk patients are 3-times at risk of recurrence or death compared to non-high-risk patients. It's imperative to identify these patients with primary endocrine resistance. Hormone-positive, early breast cancer are those high-risk patients for risk of recurrence. And administer additional therapy to prevent or delay recurrence or progressive disease.

CDK 4/6 inhibitors have demonstrated success in reducing the risk of recurrence in our hormone-positive, HER2-negative early breast cancer patients when administrated with a combination of endocrine therapy.

Again, really trying to drive home this picture of some of the tumor characteristics as well as the individual characteristics. We have to look at both of these things to see whether someone is a high-risk patient and whether they really would benefit from additional intensification of therapy.

So, a high-grade tumor, patients with lower-grade tumors show up to 41% longer survival than high-risk tumors. PR-negative. The lack of PR expression was associated with a 60% higher risk of recurrence. Lymph node involvement. Increased lymph node involvement was associated with 11 to 31% decreased survival. Increase in tumor size associated with 13 to 33% decreased survival. LVI also, like our patient had, associated with 21% reduction in survival rates. And again, going on that high Ki-67 proliferation rate or a luminal subtype. Subtype luminal A tumors have a better 5-year survival compared to our luminal B's or our triple-negatives.

In patients with hormone-positive early breast cancer at risk for both early and late recurrence. So, this top graph is showing the dark purple are the hormone-positive patients, and we can see that within that 5-year period, it does increase and then tapers off that long tail, that’s our late recurrence. So, approximately 50% of the recurrence occurs early within the 1 to 5 years of diagnosis and that risk of recurrence remains beyond 20 years.

The bottom graph is showing lymph node positivity and that majority of that risk of recurrence remains irrespective of nodal status. So, that bottom line is showing N0, and that top line is showing N4 to 9. So, although yes, with increased lymph node involvement, we do see an increased risk of recurrence, and with lower lymph node involvements, there's still a risk of recurrence.

So, earlier recurrences are an urgent concern regardless of the nodal status. A recent data from control arms of Phase 3 trials of adjuvant CDK 4/6 inhibitors in patients with hormone-positive, HER2-negative stage II and stage III early breast cancer show that the risk remains regardless of nodal status. So, N0 up to 11% of patients are at risk, N2 to 3 approximately 24 patients are at risk of experiencing an invasive disease event within 3 years of starting standard-of-care adjuvant therapy. So, 1 in 8 women treated with endocrine therapy alone are expected to have an invasive disease-free event by 3 years in the NATALIE trial, and that looked at ribociclib and endocrine therapy in the adjuvant setting.

So, our ultimate goal is to reduce the risk of early and late recurrence while balancing medication symptom set. So, when we are thinking about prescribing abemaciclib or ribociclib to our patient in the adjuvant setting, we need to review medications common and rare, the serious side effects, the dosing schedule, monitoring and management strategies. Kristi is going to go into detail about this, so we'll be able to hear from her much more in depth about this. And then, how are we going to help manage these patients on therapy and what other options do we have for them to make treatment tolerable and also give them this benefit of reducing their risk of an early recurrence and late recurrence?

So, consider abemaciclib dose escalation with the intention to reach that maximum dose, or dose-reduce if you start at the full dose. Consider ribociclib dose-reduction or hold as indicated. And we also are going to be spending our fireside chat really talking about addressing obstacles to adherence and creating that individualized, tailored plan to ensure compliance and include the rationale regarding adjuvant therapy and reducing that risk of cancer recurrence. It's going to be important to have those really good relationships with our patients and again, reminding them about why we are asking them to go through additional treatment and additional side effects is to reduce their risk of their cancer coming back, especially in a metastatic setting.

So, it is my pleasure now to present Theresa. She's going to be discussing recent, current and emerging evidence supporting CDK 4/6 inhibitors in the adjuvant therapy for hormone-positive, HER2-negative early breast cancer.

**Chapter 4**

**Dr. Gillespie:**

Thank you so much, Kimberly. That was an excellent presentation. So, my task tonight is really to walk you all through some of the current and emerging evidence that would support why we're using CDK 4/6 inhibitors in the adjuvant setting for HER2-negative, HR-positive early breast cancer.

So, I'm not going to assume everyone in the room is a breast cancer expert, and I also think it's really important that we all understand mechanisms of action and how these particular agents might differ from other kinds of breast therapies. And why is this class of agents important that we're spending this time talking about them.

So, we have three approved agents in this class of drugs: palbociclib, ribociclib and abemaciclib. And believe it or not, the first drug in this class was approved by the FDA 10 years ago, so it's been in practice for quite a while. The mechanism of action is a little unique, but it works by inhibiting the phosphorylation of the retinoblastoma protein which deactivates the tumor-suppressor protein and in turn, prevents cell proliferation.

And this particular checkpoint is often overexpressed in HR-positive breast cancer cells, so it was seen as a target that could be key in terms of some therapeutic development.

So, the initial approvals were all for advanced and metastatic breast cancer and there was recently a pooled analysis of seven different trials representing more than 4,000enrollees that were all on these different agents. And what we found from this pooled analysis was that progression-free survival was increased sort of regardless of the type of endocrine therapy, and that there was increases in median progression-free survival in all of the different kinds of subgroups that were looked at, as well as for pre- and postmenopausal patients.

I want to just point out that the results of this pooled analysis of these seven different trials was limited because of the way that the enrollment went, and really, there were only sufficient numbers of White and Asian subgroups in order to really apply the findings to those group, because there was lack of representation from others. So, I really want all of us as we leave this room, just to think about what you can do in your own practice to encourage and motivate and find ways to increase representation on clinical trials so that the findings can be generalizable to all of our populations.

Chapter 5

So, now I just want to review some of the recent data for CDK 4/6 inhibitor use in early-stage breast cancer. So, we're switching from that advanced meta static setting to the early-stage that Kimberly was alluding to.

The first is the PALACE trial. This is a prospective, randomized Phase 3 study, and the eligibility was for HR-positive, HER2-negative early-stage breast cancer and the randomization was palbociclib with adjuvant ET, versus ET alone. And the primary endpoint was invasive disease-free survival. And what was found at 4-years point of analysis was similar results between the two treatment groups, so there was no statistical difference. And there were also, not any differences by subgroup.

So, the conclusion of this is that the addition of adjuvant palbociclib to standard endocrine therapy did not improve outcomes compared to endocrine therapy alone.

So, we're going to see some of these survival curves. So, this is a Kaplan Meier curve. And you can see here, this is for invasive disease- free survival. Those curves are basically superimposed on themselves, which tells us that there was no significant difference. And this is overall survival. And you can see essentially the same thing at 48-months.

The second try I want to talk about is the PENELOPE-B trial. And this was also a randomized, placebo-controlled trial. And in this one, the patients were HR-positive, HER2-negative but they had residual invasive disease after having neoadjuvant chemotherapy, and they were also considered at high-risk for relapse.

So, here, the trial design was randomized to adjuvant endocrine therapy with palbociclib or placebo. And the primary outcome again was invasive disease-free survival. Here again, we saw no significant improvement in IDFS with the addition of palbociclib. It was not a significant difference, and there was also no differences between the subgroups.

So, in this particular study that was looking at women who had residual disease and also considered high-rate for recurrence. You can see here, this is at the4-year mark, and these survival curves are basically superimposed on each other. However, if you take these out, we may see that there is some difference over time but we don't have those data mature yet.

Now, the MONARCH-E trial that Kimberly also alluded to was abemaciclib for adjuvant therapy in early-stage breast cancer. And here the participants were randomized to either abemaciclib with the physician’s choice of whatever kind of ET they wanted to use versus ET alone. And again, the primary outcome was invasive disease-free survival.

Now, here, the eligibility was both men and women. They had HR-positive, HER2- negative. Node-positive, resected, early-stage breast cancer. And they also had some of those clinical and pathological characteristics that we heard from Kimberly would indicate a high-risk of recurrence.

So, here's the results of this. There were over 2,000individuals that were randomized on this study and what they found at 36-months of follow-up was there was a significant difference and a benefit for those who were receiving the abemaciclib as well as ET, versus those receiving ET alone. And there also was shown to be some distant relapse-free survival when they were followed for a longer period of time. However, overall survival did not show a significant benefit.

So, here, you can see this is for the invasive disease-free survival and the separation of the survival curve. So, that tells us that, just by looking at it, it looks like it's a significant difference. But here, this is overall survival. And this is at 72 months and that's a pretty long period of time, but not showing any significant difference there.

The other thing that the MONARCH-E trial did is it looked at subgroups, and they were particularly interested to know if older patients, those over 65, versus younger patients received the same level of benefit. And in fact, that was found to be true. So, that was a really good finding because we knew that regardless of age, we could treat patients in the same way.

The last trial I want to go over is the NATALIE trial, and this is with ribociclib. Again, randomized, Phase 3 trial for early-stage breast cancer. And here, this was for HR-positive, HER2-negative, stage II or III breast cancer, but they could have received prior adjuvant or neoadjuvant therapy, and they were randomized here, to ribociclib with a nonsteroidal AI versus an NSAI alone. And they had a wide

variety, pre- and postmenopausal women included.

And what they found was that at three years, the invasive disease-free survival did show an advantage to the combination of the ribociclib with NSAI versus NSAI alone. So, the conclusion is that that drug combination significantly improved invasive disease-free survival for this particular set of patients.

So, here we can see, this is at the 3-year mark, that there is a separation of the curves as well. The other thing that the NATALIE trial did is, it looked at a number of subgroups and their prior systemic therapy. So, they looked at people who had had prior adjuvant therapy, neoadjuvant therapy, no chemotherapy. And this was really done to see if there might be a potential role for CDK4/6 inhibitors as being therapy without giving the people chemotherapy. And if this is true, then this could be a great advantage for those diagnosed with breast cancer. And so, those studies remain to be done and reported.

So, a summary of the four trials that I presented. The first was the PALACE, and the other was PENELOPE-B. Those both used palbociclib, and neither of them showed survival advantage with the combination of those drugs with some kind of ET. The MONARCH-E trial showed improved invasive disease-free survival, as well as distant relapse-free survival and for the abemaciclib as well as ET in the adjuvant setting. However, not for overall survival. And then the last one is the NATALIE trial with ribociclib plus and NSAI, which did show a significantly improved IDFS in patients who had early-stage breast cancer. However, overall survival results are still pending.

The one thing I want to leave with you tonight is that these were four different trials. They were with different drugs. They were different sample groups. Different eligibility. So, you cannot just say, well, this drug showed this, and this drug showed that, and therefore this drug is better or worse or anything. None of these trials are head-to-head comparisons. And that would be the only way that we could really say one drug was superior to another.

But again, these particular samples in the eligibility criteria did vary, so just keep that in mind. Each trial sort of stands on its own, and we learned a little bit more about these drugs as well as the best way to treat women with or men in some cases, with early-stage breast cancer.

So, I'm now going to turn the podium over to Kristi and she is going to address how best to manage these adverse events of the CDK 4/6 inhibitors, and she has a lot of great strategies to share. Kristi?

**Chapter 6**
**Dr. Orbaugh:**
We just have learned a lot so far this evening. I sure hope you feel like that. So, Kim walked us through really understanding. Let's look at that patient. Let's look at their disease characteristic. Let's look at the characteristic of the patient itself. What makes a high-risk patient?

Then we looked, Teresa really walked us nicely through those studies. So, we understand now what was taken before the FDA and what was approved and hopefully, we understand those indications. But now what we're going to zero in on, I hope after hearing that, you understand the benefit of these drugs in the appropriate patient, in the appropriate. But what's that going to cost the patient? And I don't mean in terms of money, that's not what I mean at all. I mean, in terms of toxicities.

So, what we have done is we're going to key in on six toxicities. We're not at all pretending that these are all of the toxicities that we see. But certainly, what the faculty felt that were important ones.

We're going to talk about diarrhea, QT prolongation, neutropenia, ILD and pneumonitis, hepatotoxicity and venous thrombotic events.

Alright, I want you to meet my patient, Darcie. So, Darcie started on abemaciclib and a gonadotropin-releasing agonist and an aromatase inhibitor for her high-risk breast cancer. Three weeks after starting abemaciclib, the patient develops a Grade 2 diarrhea. Now, just kind of think in your own practice how that patient would be treated. OK? So, we know she's got that Grade 2 diarrhea. What would we do? Would we give her two loperamide after the first loose stool, then maximize that dose in 24 hours? Hold her abemaciclib if no improvement in 24 hours? Or consider dose-reduction if diarrhea occurs? Or all of the above?

All right. The answer is: All of the above.

So, let's talk about diarrhea. OK? First of all, I know we're eating. We're nurses, it doesn't even bother us does it? So, we know that both drugs do have at least some risk of diarrhea. So, when you look at ribociclib, about 19 to 35% will develop diarrhea. We know, however, with abemaciclib, that's higher. In fact, about 80 to 90% of patients will develop at least some degree of diarrhea. And what's interesting about this diarrhea is it tends to be worse. And this graph will demonstrate that. It tends to be worse during those first 8 to 10 weeks. So, what that says to us as nurses is this is when we need to lean in. We need to walk if that's the drug that the doctor chooses, we need to walk with that patient through those first few weeks and they need to have a plan, so they are able to stay on drug and benefit from it.

We know that we need to have visits with them and support them, whether it's phone visits or whatever. But after that 2- to 3-month period, you really see the diarrhea trickle downward.

So, here's what we need to do, right? Anytime we have a toxicity, patients have to have a plan. So, I'm from Indiana, and in Indiana we have a rule, or patients have a rule. Nobody ever, ever, ever gets a toxicity Monday through Friday 9:00 to 5:00. OK? Is that just in Indiana? So, patients need a plan. We know when we study adherence and compliance, one of the biggest reasons why patients don't comply with our rules is they don't understand them. So, we really need to work on that education. We also have to know baseline. How can we ever react to someone's toxicity if we don't know where we started? Right? So, we need to know their baseline. And then, how many number of stools over that baseline.

And let's talk about that medication management. How many of you have ever had a patient come in, tell you they have diarrhea and you ask them how many loperamide have you had today? Yeah. Or a half of one because no one wants to be bound up. Right? That's always a big problem.

Also remember, it doesn't have to be loperamide. There are other drugs that we need to think about. There's Lomotil, Colestipol, bulk-forming agents. A lot of things to think about. And then, remember when we had to take nutrition class in nursing school? Remember those techniques as well. It is not the first two months you're on abemaciclib. It's not the time to go to the Denver State Fair and eat from every fried food truck. It's just not. OK? You need to think about those kinds of things and help walk people through that. Talk to them about the importance of hydration. Talk to them about maybe eating a little bit of a more bland diet right at the beginning.

And we need to monitor those electrolytes for a variety of reasons, and think about hydration status. There might be a patient that calls in and has diarrhea, and you want to bring them in and check their electrolytes and maybe give them fluids if need be. But here's the big one. Just because you start at that dose, you don't have to live there. And here's the wonderful thing is, multiple analysis have really looked at that MONARCH-E data and we know that we don't lose efficacy if we lower the dose. However, if we don't lower the dose in those patients that need it, we certainly might lose patient's adherence. OK?

So, here's kind of an algorithm of how we would manage it. If someone has diarrhea, make sure you get them started on the appropriate medication, increase fluid, that type of stuff. If it doesn't decrease after 24 hours, hold the drug. Let that gut settle down. And many times, you can just resume the drug. If not, you may have to reduce the drug.

QT interval prolongation. How many of you are cardiologists? OK. Me either. So, let's talk about why that's important. The QT prolongation, when we're looking at both of these, is kind of unique to ribociclib. It tends to be kind of dose dependent. So, just so we're all clear on – and what is a QT prolongation. I'm sure you all know. But the period between the Q and the T is when the heart repolarizes. OK? And if it takes too long for that heart to repolarize, you start getting arrhythmias. And so, that's really not something we want to set patients up for. We also know that certain electrolytes are used to repolarize that heart, so it's very important that we make sure we're monitoring their electrolytes. We've got to monitor those, and we've got to normalize them before we start, if at all possible.

The other thing we want to make sure is that we're doing EKG's before we start and 14 days in with that first cycle and then as clinically indicated. And we only want to treat those patients or initiate treatment, if their QT interval is less than 450 microseconds.

We talked about collecting or correcting those electrolytes. And also, know the patient. Do they have a cardiac history? If they have a cardiac history, who's managing that? And do we need to talk to their cardiologist just to have them on board, just as the multi-team disciplinary approach, right? And make sure ribociclib is not to be used in combination with tamoxifen, and the reason is the prolonged QT interval.

Here's the other thing. Know the other medications they're on. That's so important. Both of these drugs are metabolized via the CYP pathway and a lot of drugs are metabolized that way and we need to know if any other drugs that the patients are on have the potential to prolong that QT interval.

Neutropenia. OK. So, when we look at abemaciclib, we see neutropenia a bit less than ribociclib. And in about 37 to 46% of the patients on the MONARCH-E, you're going to monitor those labs, right? You're going to check a CBC before they start, 2-weeks in for the first 2 months and then monthly for the next two. And then as clinically indicated. Now, ribociclib, because it has a little bit higher incidence of that neutropenia, you can see about 94% of those folks will develop neutropenia and about 45% are going to be a Grade 3 or 4. So, we're going to monitor those CBC's a bit longer. So, we're going to monitor the CBC prior to therapy, every 2-weeks for the first 2 months, and then monthly thereafter. And with both drugs, we can consider dose an eruption if needed or dose reduction. OK?

So, our neutropenic strategies, Grade 1 and 2 we are just going to monitor and there's going to be no dose modification required. If we have a Grade 3, we're going to hold whichever drug it is, allow them to resolve to at least a Grade 2 or smaller, no dose reduction is required. It's where we have those recurrent Grade 3s or those Grade 4s that we need to definitely reduce the dose.

**Chapter 7**

OK. ILD and pneumonitis. Just for a minute, let's forget that we're talking about CDK 4/6s, OK? So many of the drugs that we give in oncology have the potential to cause ILD or pneumonitis. So many of them. All of the CDK 4/6s. The mTOR inhibitors, the anti-HER2 drugs. A lot of the TKI's we use. And then, there's that drug class, maybe you've heard of it, immunotherapy? Right? Yeah. And the potential to cause pneumonitis. I say all that to say, we're really good when we do patient teaching about asking them, hey, what are your baseline bowel habits? But how many of you ask patients on a regular basis, do you have COPD? Do you have adult asthma? Do you have? Do you have? We need to know those baseline pulmonary things as well. Very, very important for a variety of drugs, not just for the CDK 4/6s.

So, there's for our management of ILD. I'm clicking quicker because I talk too much.

Let's think about hepatotoxicity. Remember, these drugs are metabolized via that CYP pathway, so we need to make sure that we're following their CMP's along. Definitely want to look at those ALTs and ASTs. So, for abemaciclib, we are going to, really for both of them, we're going to check the CMP's before we start every 2 weeks for those first 2 months and then, monthly thereafter with abemaciclib for two other months, for ribociclib, for four other months. OK? And again, if you run into difficulty, consider dose interruption or dose discontinuation.

Also, if someone comes in and they suddenly have bumped their liver, also question, did you start anything different? What's new in your life? I just had this case happen last week in clinic. Someone had been dialed in forever and suddenly the ALT and AST had increased and they had just come back from Florida for spring break. I had no idea that Florida did that to your liver functions, but evidently it does. OK, just. I guess it's a state thing, any of you Floridians in here.

OK. Venous thrombotic events. Alright. Anytime we combine CDK 4/6s with endocrine therapy, we can increase the risk for venous thrombotic events by about two- to three-fold, so it's really important that we're having that talk with patients. First of all, we need to know that history. Do you have any clotting history? And we need to make sure that they're telling us. Does your calf hurt? Is your calf swollen? All of those types of things that are very, very important that they know to report to us. And the risk of arterial events still has not been defined. OK?

So, to tie that up in a bow. I know that was a lot. But just think about the data that we've looked at and how exciting these two drugs are as we utilize them in a population that is at high risk. So, as nurses, it's our job to walk with them through this journey and help get them through those toxicities. Whether you all know it or not, you go to work every day with this big toolbox and in that toolbox, you have so many skills to deal with these toxicities and so don't forget that. We need to be vigilant in monitoring these toxicities, so patients can be adherent and remain on therapy.

Alright. So, I'm going to turn it over to Kim, and we're going to have a fireside chat. Sounds kind of fun, doesn't it?

**Chapter 8**

**Dr. Podsada:**

So, I'm going to kind of start us off at the next part of this evening's event, and this is where we're looking really more for everyone to get involved. Either send in your questions or come up to the microphone. I'm going to talk a little bit about unlocking best practices for CDK 4/6 inhibitor patient management and boost adherence and persistence. So, just a couple of slides to get us set up for our next discussion.

So, my patient, going back to the original patient case, she experienced significant joint and muscle aches with menopause-associated mood changes and fatigue. Remember, this is a 40-year-old woman that we have just forced into menopause. So, anastrozole was discontinued and Exemestane was prescribed, as was bupropion 150 milligrams daily. Once abemaciclib was started, she reported diarrhea and increased heartburn.

So, what are going to be some of the things that factor adherence? So, we have a variety of issues, patient-related. What are her perceptions about the necessity of this medication and making sure that we're reviewing that information? How's our quality of life? Is she forgetting to take her medication? Has it not become a routine yet? What about her moods? Is she depressed or anxious, and is that affecting when she takes or doesn't take her medication? What about the side effects of medications? The complexity of how many pills to take. That pill burden. And the duration of various therapies?

What about other comorbidities? Other priorities that she may have in her life? And then there's us and the system. So, we don't start to see patients as much anymore. We're spreading out our visits. They're not getting that routine contact. And maybe other people are starting to get involved; covering nurses, different APP's, so now there are different people involved with her care. So, that relationship that we had initially is starting to separate, and so this is really where we need to continue that relationship with our patients, that trust-building relationship, and stay in touch with them.

What about younger or older age? This young patient, she's got three kids. She's a single mom. She has a lot of other priorities. How can we help her? We also have older patient population. Do they have a good support system? Is anyone there helping them? So, interventions to think about, to improve adherence. And we know there is no one strategy that's going to work for every patient, so we really need to learn our patient and how they best learn and how we can be involved in helping to facilitate adherence.

So, therapy-related interventions. Simplify the routine. Put a calendar. Get an app.
Educate about the use of medications. Can she take the medications at the same time? Can she take it with other medications? Yes, you can. Providing those clear instructions. And that continuous monitoring and reassessment? I use Epic. Many of you probably use Epic, and within that there's the reminder. And I'm like, OK, I'm going to remind myself in 2 weeks to call her because she just started this medication. I'm going to CC my nurse, so that both of us are aware, this patient gets back on our radar because we get forgetful also and we have a lot of patients we're taking care of. So, try to set yourself those reminders as well.

As far as the patient goes, we need to make sure that we're addressing any misconceptions that she has about treatment or who else has her ear. Is she around people that are encouraging to her to talk to her doctor? Or are they saying I saw this on TikTok and you've got to try this? I've had this happen, so it's like, I thought we were building a trusting relationship and now you're turning to TikTok. So, anyway, that reminds me, I need to reinforce that trusting relationship with the patient. How does she like to learn? Does she want something sent to her by e-mail? Does she want to read something? Does she want a patient brochure or there's a variety of different things that may cater to the way her style is of learning.

And that behavioral and motivational intervention? We need to be their cheerleader, but we also need to do that in a factual manner, where these are the risks of not taking therapy. This is why we really want you to try therapy. And we have ways to help you handle the side effects.

And self-management and patient accountability. I want my patient to be involved in this process. I don't want to have to care more than they do about their health and their care, and that becomes very challenging. We can be their cheerleader, but they're doing this at home. They have to find the motivation to do this and we have to encourage them to be accountable. And also, fill in those blanks. What might they be missing? What have they not heard? What's their readiness? So, we know we're going to be having a lot of conversations with our patients early on and we have to remember, gosh, she keeps asking the same question. Didn't she hear it the first time? No, she wasn't ready then. And so, when she asks you again, take the time to explain it, and this time, it may sink in.

And the impact of dose reductions on efficacy of abemaciclib for high risk patients with early breast cancer. We've all kind of alluded to

this. And so, the risk of recurrence for these patients with hormone-positive early breast cancer is up to 30% at 5 years despite chemo, endocrine therapy and radiation. The MONARCH-E was designed to evaluate addition of 2 years of adjuvant abemaciclib 150 milligrams twice a day with endocrine therapy, in our hormone-positives, HER2-negatives, node-positive, high-risk adjuvant therapy. And dose reductions are commonly used to manage treatment toxicities, and the goal is maximizing treatment adherence. And so, the impact of dose reduction on drug efficacy is important for patients and providers. I am thrilled to know that based on multiple analysis, the efficacy of adjuvant abemaciclib in MONARCH-E was not compromised by dose reductions. So, this means that dose-reducing a patient is not going to compromise the efficacy. So, I as a provider can have this confidence when I dose-reduce someone that they're still going to be getting an effective therapy.

So, do we start at a low dose and go up to make it more tolerable for them, or we confidently know that we can reduce doses as well and still have them reap the benefits of therapy?

And in the NATALIE trial that looked at ribociclib, these patients had stage II or III hormone-positive, HER2-negative advanced breast cancer. Some of them had no nodal involvement and are still at risk for recurrence decades after initial diagnosis. Now, ribociclib was dosed at 400 milligrams daily. It's once a day, 3 weeks on and 1 week off for 3 years. Now, the metastatic dose is 600 milligrams, so at the 400 milligrams, we are seeing that there is an improved tolerability as well as maintaining that efficacy. So, the lower dose of ribociclib has made a difference for patients tolerating therapy. And the extended treatment, the 3 years versus the 2 years for abemaciclib – again, they're two separately designed studies so we can't compare. But the thought process was important to prolonged cell cycle arrest and drive more tumor cells into irreversible senescence.

Let's talk toxicities.

**Chapter 9**
**Dr. Gillespie:**
Well, we're going to talk more, OK? This is quick, I promise. I want to come back to Darcie. Don't forget about my friend Darcie. Just to give you a little bit more about her case. So, she's 40. She's premenopausal status post chemotherapy with lumpectomy and radiation therapy. You'll see she's a PT3, PN 2, M0, so she's high-risk. She's high risk. I call these people the patients that keep me up at night. You worry about them. So, Darcie started on abemaciclib and a gonadotropin-releasing hormone, as well as an aromatase inhibitor.

Now, here's more about her. Here's what's really important about her. She's married, she works part-time and she cares for two young children. She's very active on social media, the beast cancer sites. Do you ever hear that? And she several members of those groups have suggested that she asked about supplements, herbs and vitamins. Yeah, I'm seeing a lot of shaking of the heads. So, Darcie shares with her healthcare team that she's really preparing to start some of these things that were recommended to her. Not on TikTok, but on Facebook. OK? That probably just showed my age, didn't it?

So, at her first routine follow-up, we already talked about her diarrhea, and we did the appropriate management. We started on Loperamide, increased her fluids, and reduced the dose if necessary. But here's another thing. She's fatigued. We didn't even talk about that. Right? How many of you hear that when patients come in? I'm just tired. I am tired. And she's tired for a lot of different reasons. You're all tired and you're not on antihormonal therapy and a CDK 4/6, right? And so, that's really important. It's really affecting her quality of life.

She's got hot flashes. They're annoying. It keeps her up at night. It happens at the most inappropriate times, like maybe when she's standing in front of a group of people speaking. I'm just saying, I've heard it happens. It isn't happening here, of course. And she's really, really interested in taking those supplements, because guess what? Supplements and herbs and vitamins, they're all natural. They're all natural, so they're not hurtful. The thing we need to remind patients over and over and over again is when the good Lord made us, we just have a couple different ways to metabolize things, right? Liver and kidneys for the most part. And if we are taking in a lot of things that are all metabolized via the same way, we can really run into some difficulties. Certain drugs may make certain drug supplements, whatever, may make the abemaciclib or the ribociclib not metabolize as quickly, so they become more toxic because they're not getting them out of their system. The exact opposite can happen. It can make them be metabolized I think I just said that backwards. Can make them be metabolized slower so they have more toxicities, or it can be metabolized quicker so they're not getting the whole benefit.

And I don't know how many of your mothers told you to eat grapefruit because it was healthy for you. She lied to you, OK, because grapefruit interferes, and it's metabolized via that same pathway, so we do need to make sure that they're staying away regardless of

which one of those drugs they're on, staying away from grapefruit products, OK?

OK, so now we're going to get to some of your questions and hopefully we can really talk about Kim's patients and my patient as well.

**Chapter 10**
**Dr. Gillespie:**
So, we've had a lot of questions that were submitted. I can't tell if some of them are from the virtual viewers or from people in this room. We're going to go through those questions. I'm going to direct them to people on the panel. But if you have additional questions, that's what the microphones are for. But also, some of these questions are pretty broad and just asking like, well, what do people do? So, I would really encourage people in this room to share your own tips and strategies and help other people to figure out how to answer these.

So, I'll start. And this is to Kimberly. You mentioned there was 50% breast cancer risk if there is a family history. Please define family. Does it include just the mother? How about the aunt on the father's side, crossover, if there was ovarian cancer in the family?

**Dr. Podsada:**
So, that means, what I meant was typically, it means more first degree relatives. So, your mother, of course, or even aunts starts to get to 2nd degree. But if you're seeing a trend within your family that are closer relatives.

So, not your second cousin. Not who you're married to, etcetera, uncle. So, really more of those first degree relatives. Your mother, father, aunts and uncles.

**Dr. Gillespie:**
OK. Yeah. The next question is also to you, Kimberly. Does someone have a question? No? OK. You mentioned the luminal subtype. Does that show up on the pathology report, or is that special testing?

**Dr. Podsada:**
So, that is just a classification for further classification of breast cancer. So, a luminal A is the most favorable and that is the strong hormone- positive. When you have a luminal B, now we're talking about estrogen. It might be positive, but progesterone might be negative. Or that's also considered triple-negative or HER2-positive. So, the luminal A is the most common type. That's the hormone-positive. And then our luminal B's become more of a challenge or more aggressive. General answer.

**Dr. Gillespie:**
So, the next question I'm going to direct to Kristi, but I would encourage anyone in the room who has a thought or a similar experience to please share that. So, the question is, three patients in our clinic developed ascites requiring paracentesis after taking CDK 4/6 inhibitors. One of our oncologists is reluctant to use one of the certain drugs after this. Do you have any thoughts?

**Dr. Orbaugh:**
I guess the first question I have is, did the patient have metastatic disease?

I haven't seen a ascites with early stage, but certainly have with patients that have metastatic disease. So, that would be my first thought. And we didn't make a big deal out of it when we were speaking, but both of those drugs do have indication in the metastatic setting as well.

**Dr. Gillespie:**
Right. And the ascites may be related more to the disease process than the location.

**Dr. Orbaugh:**
Right. So, perhaps they have abdominal carcinomatosis or they have significant liver metastasis and they just have portal hypertension, that type of thing.

**Dr. Gillespie:**
Mm-hmm. So, I don't know if the person who asked that question is in the room or if anyone else has had somewhat similar experience

and wanted to share, but please feel free to give further details if you'd like.

OK, I think this is to you, Kristi. Would you automatically take someone – this is referring to prolongation of QT. Would you take them off any other drugs that also tended to prolong QT, like ondansetron?

**Dr. Orbaugh:**
Absolutely. Absolutely. You would need to make sure. And here's the wonderful thing about having two different drugs. That's why we need to do baseline and really understand our patient. Does the patient have irritable bowel syndrome coming in? Do they have Crohn's Disease coming in? Clearly, that's probably not a patient that's appropriate for abemaciclib. But thank goodness we also have ribociclib, right? If a patient comes in and we realize they have significant cardiac issues, maybe because of whatever, they are on several medications that can cause or at least increase QT prolongation, then maybe ribociclib isn't the right drug for them. So, that's kind of the wonderful place we're in right now with both of these drugs, is we have a choice.

**Dr. Podsada:**
I would also just add that if someone is having nausea or vomiting and they are on ribociclib, I would not prescribe ondansetron because of that QTC interval. So, I would just think about the other drugs that they are on, and I would choose a different antiemetic as well.

**Dr. Gillespie:**
OK. The next question is; In the case study, the patient developed diarrhea 10 days post starting treatment. Would you not want to also rule out infection as they may also be neutropenic?

**Dr. Orbaugh:**
Absolutely. You don't want to make that mistake with any drug, right? We don't want to blame a toxicity on a drug when we haven't really worked the patient up completely. And that's one of the very first questions we need to ask when someone comes in and they have diarrhea, does anyone else in your family have it? Your work partners, have they had a similar issue? Did you eat anything? I have the cutest little patient that happens to be on abemaciclib and she is we'll just tell you she's addicted to ice cream and she's lactose intolerant. OK? So, she is being treated actually for metastatic disease and has been on abemaciclib for several years. And she'll still call me and tell me she has diarrhea intermittently and the very first thing I say is how much ice cream are you eating?

**Dr. Gillespie:**
So, Kristi, I think this is for you as well. Can you give filgrastim for the neutropenia with abemaciclib?

**Dr. Orbaugh:**
Well, I guess I would just reduce the dose. I would just reduce the dose. And fortunately, with either of the drugs and that neutropenia, you don't see a lot of febrile neutropenia. It's not like when someone comes in and they've just had AC and their white count is 0.8 and you're very, very concerned about febrile neutropenia. I've been in oncology a long, long time and we use CDK 4/6s by the truckloads. And I don't just see breast cancer, I should say that. And I haven't seen febrile neutropenia yet, which means Monday morning I will.

**Dr. Podsada:**
But I've heard of some people actually using GCSF and I guess that's not the wrong decision, but we can dose reduce. I mean, we want to make the medication tolerable for someone. I tend to just follow the guidelines and if neutropenia continues to happen then you dose reduce. So, the body is kind of declaring itself, that's not the right dose and now we have all this robust information that says you can reduce the dose and still have efficacy.

**Dr. Gillespie:**
So, this question is for Kimberly. Many of our patients who are ER-positive, HER2-negative, early-stage of breast cancer believe that they have a great prognosis and they hang on to the 5-year mark as sort of their goal. How do you communicate with them that they are still at risk of relapse after 5 years?

**Dr. Podsada:**
Absolutely. So, this is a change of thinking when we look at our early-stage breast cancer patients now because you can't confidently say that an endocrine therapy alone is enough. So, we're really talking about these high-risk and this is why we are strongly recommending these additional CDK 4/6 inhibitors because of that risk of not just an early recurrence but the later lines of recurrence. It

is a challenging conversation to have, but what is unique to this patient population is they are high risk, so we can point to all of these characteristics we reviewed, especially in their pathology; their tumor size, their grade, how many lymph nodes were involved, their young age. We can point to all of those things and really say these are those things that will make you, unfortunately, at higher risk for early and late recurrence. So, it is being factual, it is then being hopeful, but we have these therapies, and we'll help you to manage side effects. We can dose reduce. We really want you to get through 2 years or 3 years of this, so that you significantly reduce that risk in the future.

Nothing is 100%, so we're talking frankly with them as well. But this can reduce the risk. And right now, that's what we have, and we didn't even have these before. So, it's really great that we have tailored treatment now to early breast cancer. Instead of just using this in the metastatic setting, now we're offering this in the early setting because these women are so high risk for recurrence.

So, it's not an easy conversation. Some of our stage Is do not need ribociclib or abemaciclib, but our stage II or IIIs that have all of these other high-risk features, now have an option to reduce their risks. And this patient population is really kind of changing my thinking as well because all of a sudden, their oncotype score is coming back low. Oh, great. This means they don't need chemo. This means they're low risk. No, it means they just don't need chemo. They need the targeted therapies. They need their endocrine therapies. And now, they really would benefit mostly with the CDK 4/6 inhibitors.

**Dr. Gillespie:**
OK. The last question that's come in is to you, Kristi. So, patients often fear if they report AE's, they will be taken off of therapy or their dose will be reduced. If they have something like neutropenia, they can't change that because that's a lab value, but how do you encourage someone like Darcie to accurately report her diarrhea?

**Dr. Orbaugh:**
Well, I think this comes right back to good nursing education, right? When we're setting down and talking to them about the drugs, whichever one we're putting them on, and we go through the toxicities, again, we want to tell them this is the dose we're starting at but there's data that says we can reduce the dose to keep you on the drug so you can benefit from it. And making sure that they understand that. And I get it from a human standpoint, right? I mean, if I know that I'm high risk – I know enough to know that – and the doctor and my nurse practitioner in my oncology nursing team has said you're high-risk; you need to do this. And then you tell me I have to reduce that dose? If someone hasn't kind of started that conversation earlier, I'm really, really anxious and I'm going to be honest, I'm going to lie to you like a little rug and tell you and tell you that I'm OK when I'm not, because I want that drug. But I know just looking out at these faces, I can just imagine the wonderful nursing education you give to these folks, and let them know we may really be reducing your dose in a, whenever, a month, two months, three months. Whatever down the road, and that's OK. There's data that supports this. There really is.

**Dr. Podsada:**
Right. And then I will have people go, well, if that's the case, then I want to start at the lower dose and it's a very rational and reasonable conversation to have. You're absolutely right. And then I usually have the conversation with them, if you are someone that does need to dose reduce, we know we can do that confidently in you. However, if you're someone that is tolerating the full dose, we don't dose-reduce you. So, again, these dose reductions, these alternatives are really for the individuals we need to keep on therapy and they're struggling at that dose. So, that's always a challenging conversation. Well then, start me low and take me up. And it's like, well, OK I mean, we can do that also, but with the goal of getting them to the full dose.

**Dr. Gillespie:**
In all transparency, I have had patients before – and just to kind of dovetail on what Kimberly has said – that have been on the Breast Cancer Support websites or whatever. TikTok. Wherever they got the information. And they haven't even started a drug yet and they come in with toxicities before we ever start. And I've had a fair amount, if doctor has said we're going to start on abemaciclib, and they've said, Oh well, I'll get diarrhea, and they come in with diarrhea and we haven't given them abemaciclib. I have started low, and I have in – but with the caveat to that patient just exactly what Kimberly said. This isn't the dose I want you at. We're going to start here and see how we do, but we're going to try to increase the dose if at all possible.

**Dr. Podsada:**
Right. But that's also a part of that trust-building relationship with our patients and being very present and not thinking about what's next or where I just was or what I forgot. But being there with them and listening to their concerns. If I have someone that comes in with

Crohn's, if I have someone that comes in and they say they are sensitive to every medication that they have ever taken, I'm going to believe them. I'm going to listen to them at face value and I'm going to negotiate where I can negotiate. But also, we still have the data showing, I really want you on this medication because I don't want this coming back and I know you don't either because you want to see your kids go to high school and graduate and get married and have babies.

**Dr. Orbaugh:**
And get off the payroll. Sorry, I didn't mean to say that out loud.

**Dr. Gillespie:**
One last question. One last question has come in. So, we generally discharge patients after 5 years, assuming their non-extended AI. Would you be following these high-risk patients longer?

**Dr. Podsada:**
Absolutely, yes. Absolutely. One of the things that I do in our clinic is I am our Survivorship Nurse Practitioner as well, so often the docs will start sending patients to me around that 2 years to share visits, and then we follow all of our hormone-positives for 10 years. So, if they are still on that endocrine therapy, yes, I'm definitely continuing to follow them. And even if they finish their therapy at 5 years, I still continue to follow them because again, there are survivorship issues after the 5 years of medications that they've been on that still need to be addressed.

**Dr. Orbaugh:**
That's what we do as well.

**Dr. Gillespie:**
So, thank you again for coming and for your questions and attention. But I also want to just thank every one of you for what you do in oncology nursing. I've been an oncology nurse a long, long time. Many people in this room have been a long, long time. I haven't done the whole 50 years, but in that range. And I am never I can't even find the words to explain the level of how impressed I am with the quality of your clinical care, the depth of your compassion, and how much you really care about your patients, and their ability to access and get good quality of care and educate yourself so that that happens all the time. So, thank you again. Thank you for everything you do and have a great rest of the evening.

**Announcer:**
You've been listening to a replay of a live broadcast discussing *From Risk to Resilience: Best Practices for Improving Outcomes in Early-Stage ER+/HER2- Breast Cancer.* This activity was provided by AXIS Medical Education and is supported by an independent educational grant from Lilly USA, LLC.

To receive your free CME/CE credit or to download this activity, go to ReachMD.com/CME. This is CME on ReachMD. Be Part of the Knowledge.