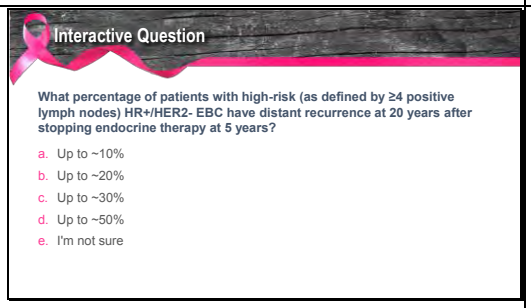
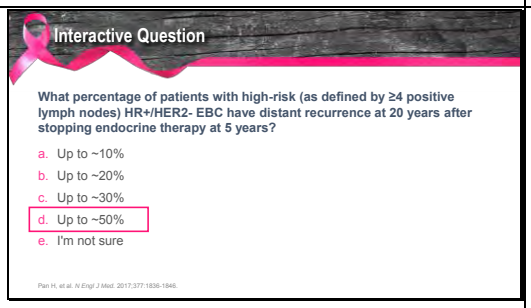
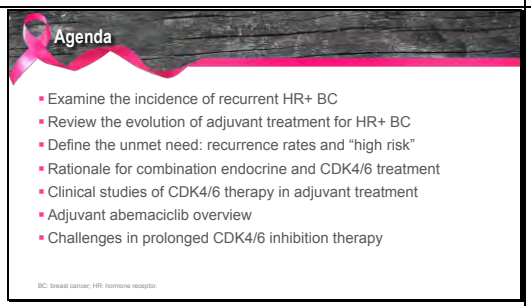
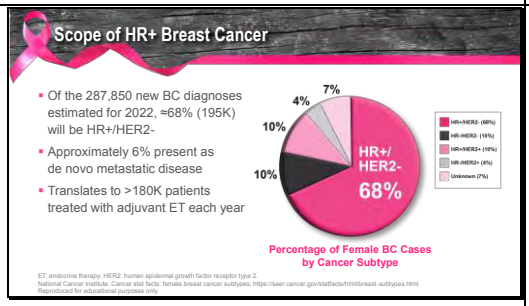
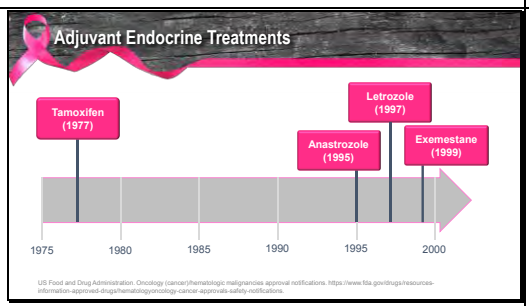
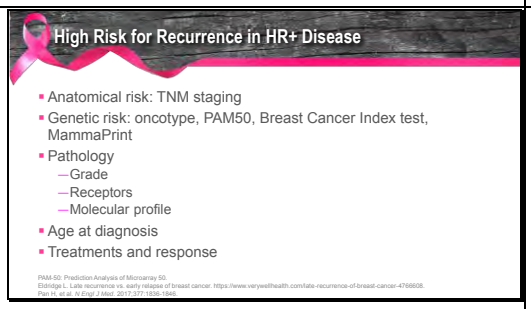
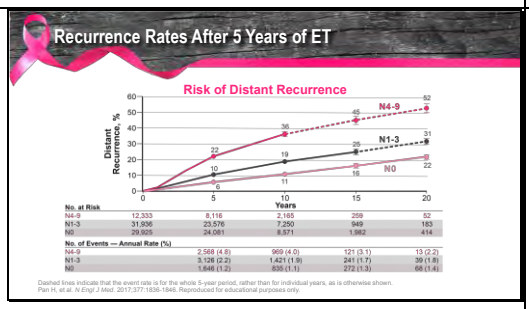
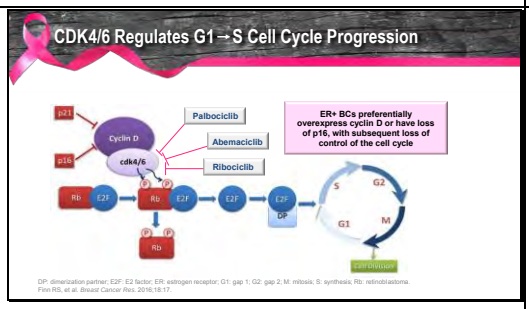
Optimizing Oral Therapy in HR+/HER2- Early Breast Cancer: Nurse-led Strategies to Improve Adherence and Persistence

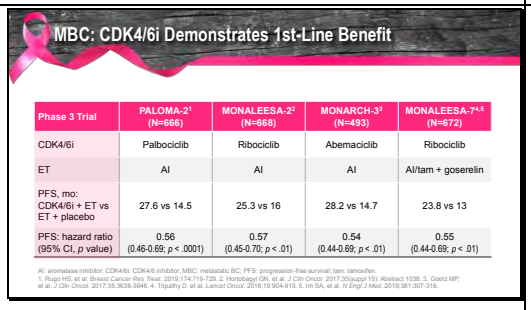
CDK4/6 Inhibitors in HR+/HER2- EBC: Updates in Adjuvant Therapy Paradigms for High-Risk Disease

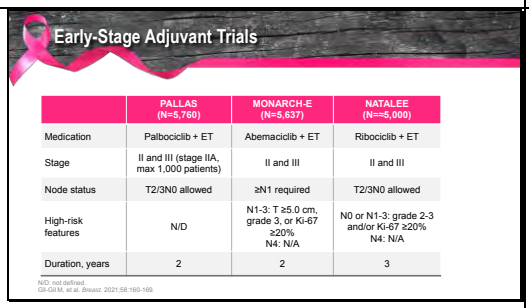
1		Hello, and welcome to this program on CDK4/6 inhibitors in hormone receptor-positive/HER2-negative early breast cancer. And basically, this is part of an update on adjuvant therapy paradigms for high-risk disease.
2		My name is Mikel Ross. I'm a nurse practitioner at Memorial Sloan Kettering Cancer Center on the breast medicine service.
3		
4		
5		So what we're going to go through over the next several minutes is, here on the agenda slide, we're going to examine the incidence of recurrent hormone receptor-positive breast cancer: How big is this problem? How big is this unmet medical need?

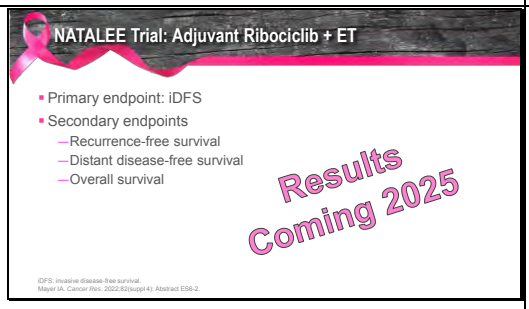
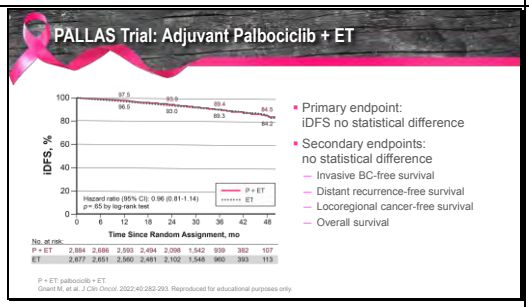
		We will review the evolution of adjuvant treatment for hormone receptor-positive breast cancer. Then we're going to define that unmet need: how often do people recur? Who is actually defined as high risk? And then we'll talk about the rationale for combining endocrine therapy with CDK4/6 inhibitor treatment. We'll review the clinical trials on CDK4/6 therapies in adjuvant care. And then, ultimately, we'll take a look at abemaciclib, currently the only CDK4/6 inhibitor approved for early-stage breast cancer adjuvant treatment. And then look at some of the challenges in staying on those therapies to ensure we have the maximum risk reduction.
6		So how common is hormone receptor-positive breast cancer? In any one year, approximately 290,000 cases of breast cancer are diagnosed, of which almost 70% (latest data, 68%) are identified as hormone receptor-positive/HER2-negative. So if you take out the 6% of patients who present with de novo metastatic, this translates into almost 180,000 patients that are treated each year with adjuvant endocrine therapy.
7		And what are the tools that we've had to treat these patients and give them that extra layer of insurance of hormone endocrine targeting? The first tool we had in 1977, tamoxifen, and then very quickly 3 aromatase inhibitors, starting in the mid- to late 90s. However, it's been very quiet since then, and we have had only these 4 therapies, 2 classes of drugs to sustain us

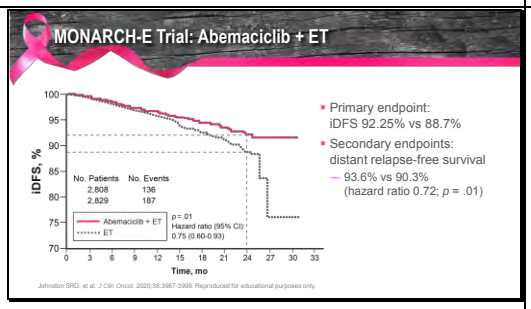
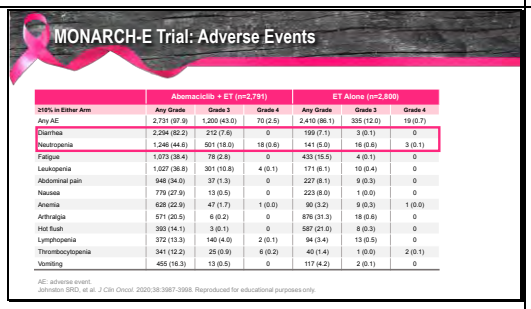
		all the way through the first 2 decades of the 21st century.
8		Now, with those tools, let's talk a little bit about our high-risk patients, because those are the ones that we're up at night for when we're clinicians. How do we define high risk? When I talk to patients, I say there are really 2 ways to think about risk primarily. First of all, there's the anatomical risk—how big is it? Where has it gone? And that's the tumor, node, and metastases staging—so, T1, T2, how big is the tumor, and how many lymph nodes are involved. The larger the amount of disease, the higher the stage, the greater anatomical risk. There are now also many ways we look at genetic risks. What are the genes that are part of this cancer that confer or make it more likely to be something that comes back in the future? We look at oncotypes that tell us yes/no in terms of chemotherapy benefit. And then we also look at PAM50. And even more recently added onto the NCCN guidelines is the breast cancer index test, which tells us yes/no in terms of extended adjuvant therapy—do we go for a second 5 years? And also, MammaPrint. Pathology in terms of grade; so, the higher grade—a grade 3—confers more risk than a grade 1 that looks more like normal breast tissue. Receptors: how positive is it? If it's estrogen-sensitive, how positive is it? There's a very big difference between 5% versus 95%. Same with progesterone. And then the molecular profile. With many people understanding that based on the type in terms of luminal versus basal type, the risk that comes with those cancers. Age at diagnosis is a risk factor. Younger people tend to have a higher risk of

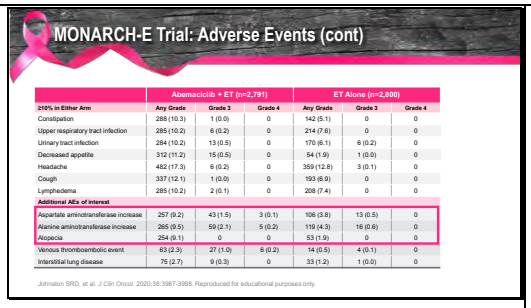
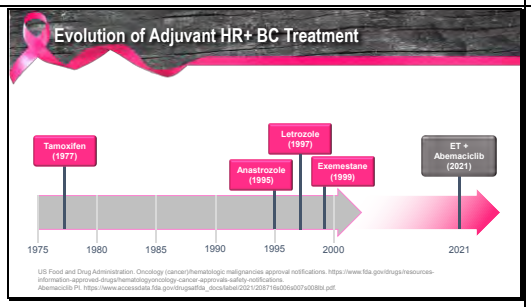
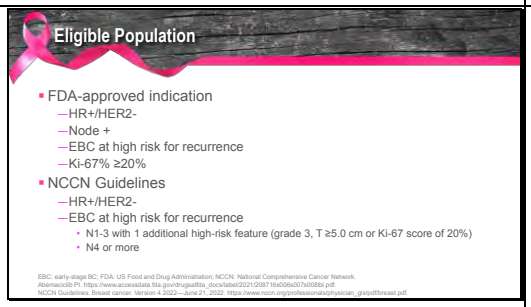
		recurrence than people that develop a breast cancer at an older age. And then, of course, their treatments—if they respond to it; if they receive adjuvant chemotherapy, is there a complete response? And even the time between diagnosis and being able to start on therapies. All of those things create a way to look at what is this individual person's risk, whether it's anatomical, genetic, the pathology, or their age and individual factors.
9		Despite our best efforts with those therapies, tamoxifen and the aromatase inhibitors, we do know that a certain number of patients will have recurrence. Here, almost a seminal paper that was published in the *New England Journal of Medicine* that says, based on nodes—so, that anatomical risk—what are the recurrence rates long-term over 20 years? You see even for a node-negative population, if you look through here, as high as 22% may recur within 20 years. And if you're talking T2 and of 4 or more nodes, up to 50% of patients may recur at the 20-year mark. So we think about those 180,000 patients that benefit or we utilize endocrine therapy and then we look at these recurrence rates, and we know that there is a huge need to do better than using the tools we've had to date.
10		So why might CDK4/6 be one of those tools that we would add on to traditional endocrine therapy? Here, we have the mechanism of action of a CDK4/6 or the CDK4/6 process and where CDK4/6 inhibitors—here you see palbociclib, abemaciclib, and ribociclib—where they come into play and how might this complement and increase the advocacy in

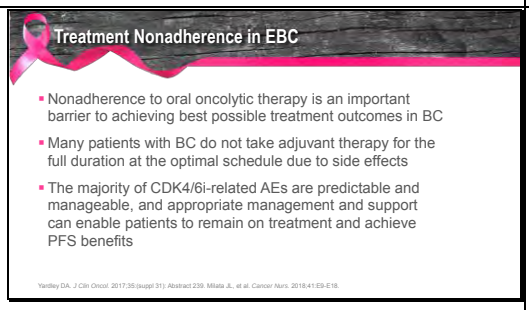
		an early-stage breast cancer. Well, it all comes down to what is going on here with RB protein, retinoblastoma protein. This protein is a tumor-suppressor protein. When it is activated and hooked on to EF, which is transcription factor, it is doing this job of suppressing and the cell cycle is slowed and controlled. What happens in a breast cancer? In a breast cancer, we know that hormone-sensitive/estrogen-positive breast cancers will overexpress cyclin D. And as a result, cyclin D will complex with CDK4/6—the cyclin-dependent kinases 4 and 6. And, in making this complex, will then phosphorylate the RB protein. When it is phosphorylated, it then goes away, becomes inactive. And the transcription factor, EF, is then allowed to move forward and tell the cell to grow and divide. So in this setting, when cyclin is overexpressed, this phosphorylation and inactivation of the suppressor gene happens too frequently. And then we have transcription factor signaling and aberrant overabundant cell cycle division, which is the hallmark of cancer. CDK4/6 inhibitors work by inhibiting this process of that binding of cyclin to CDK4/6, and then consequently stopping the inactivation of the suppressor protein.
11		Now, that's the mechanism of how these things work. But the first place though where we really saw how adding a CDK4/6 inhibitor to traditional endocrine therapy works is in first-line metastatic breast cancer. And there are data for second line and beyond, but I really want to focus on, in the metastatic setting, do we get benefit. Here are the phase 3 clinical trials, one with each of the marketed CDK4/6

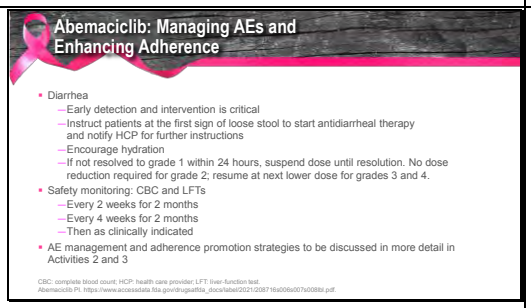
		inhibitors—PALOMA-2 with palbociclib; MONALEESA-2 with ribociclib; MONARCH-3 with abemaciclib; and MONALEESA-7, also with ribociclib, but instead of being paired with only an AI, it could be an AI or tamoxifen, with ovarian suppression. The bottom line is, if we look at what was considered successful, that progression-free survival, all of them, on the order of about 50%, cut the risk of progression by almost 50%. So you see a hazard ratio, for example, in the PALOMA trial of 0.56; means that the risk of progression, if you combine those 2 therapies, is only 56% as much as if you had the aromatase inhibitor alone. So all of these trials were successful, all of them with significant improvements in PFS, and almost doubling of the time in terms of progression-free survival. So for example, here in the MONALEESA, 25.3 months versus 16. So CDK4/6s in combination with traditional endocrine therapy definitely demonstrate a benefit in first-line metastatic breast cancer.
12		But what about in early-stage breast cancer? Is there a benefit to be had there? Well, we are answering that clinical question. We've answered it for some; some are still being decided. In terms of clinical trials, the PALLAS trial has answered that question for palbociclib. The MONARCH-E trial has answered that question with abemaciclib. And the NATALEE trial is enrolling and will answer that question for ribociclib. Now, there are some differences between these 3 trials in terms of that high-risk patient that we are looking to provide that extra insurance to. Each one of these trials

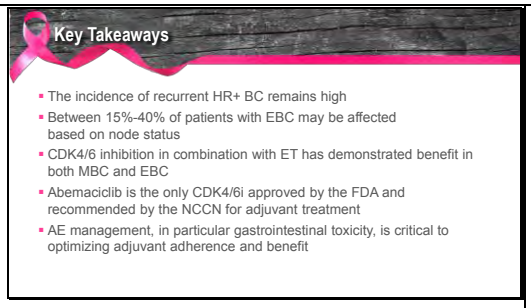
		defines high risk differently. So for example, stage, all 3 trials require a stage 2 or above. However, in the PALLAS trial, stage 2, as defined by a larger tumor, but not necessarily by node positivity, was allowed. And in the abemaciclib trial, for MONARCH-E, yes, a larger tumor was fine, but a positive node was required. So a slightly different definition of high risk. And then in the NATALEE trial, large tumor, but node-negative is still allowed. Additional high-risk aspects of the trial—not defined in PALLAS, MONARCH-E, depending on the number of nodes, the tumor had to be either quite large or a grade 3 or a high proliferation index as demonstrated by a Ki-67. And then in the NATALEE trial, grade 2 or 3 would be needed; so a little bit less restrictive in terms of the grade; [and/or] a higher Ki-67. So what are the results in looking at, does that first-line metastatic benefit also translate to a high-risk population in early-stage breast cancer?
13		The NATALEE trial, looking at adjuvant ribociclib with endocrine therapy, it's not answered yet. Because it is a 3-year look, it's taking a while longer, and results will be coming in 2025.
14		Let's take a look at the PALLAS trial with palbociclib plus endocrine therapy. In this trial, which did not require node positivity, only a large tumor, at the end of 4 years, there was no improvement in invasive disease-free survival at 4 years. The results between the study arm, 80.5, adding palbociclib versus endocrine therapy alone, 84.2, did not reach statistical significance. So for that population, with

		this medication, for that duration of time, no difference.
15		What about the MONARCH-E trial with abemaciclib? A little bit more strict definition, a higher bar in terms of high risk, requiring node positivity and additional high-risk features, such as a higher grade or a higher proliferation index. In this case, there actually was a statistically significant benefit in terms of invasive disease-free survival. Here, at the 2-year mark, 24 months, you see a difference of 92 versus 88/89, and the hazard ratio of 0.75, meaning that the risk of an invasive event was decreased by 25%. So in this situation, in the population as defined by this study, there is a benefit to combining CDK4/6 with traditional endocrine therapy.
16	 AE, adverse event. Abemaciclib + ET (n=2,791) / ET Alone (n=2,800) ≥10% in Either Arm: Any Grade / Grade 3 / Grade 4 / Any Grade / Grade 3 / Grade 4 Any AE: 2,731 (97.9) / 1,200 (43.0) / 70 (2.5) / 2,410 (86.1) / 335 (12.0) / 19 (0.7) Diarrhea: 2,294 (82.2) / 212 (7.6) / 0 / 199 (7.1) / 3 (0.1) / 0 Neutropenia: 1,246 (44.6) / 501 (18.0) / 18 (0.6) / 141 (5.0) / 16 (0.6) / 3 (0.1) Fatigue: 1,073 (38.4) / 78 (2.8) / 0 / 433 (15.5) / 4 (0.1) / 0 Leukopenia: 1,027 (36.8) / 301 (10.8) / 4 (0.1) / 171 (6.1) / 10 (0.4) / 0 Abdominal pain: 948 (34.0) / 37 (1.3) / 0 / 227 (8.1) / 9 (0.3) / 0 Nausea: 779 (27.9) / 13 (0.5) / 0 / 223 (8.0) / 1 (0.0) / 0 Anemia: 628 (22.9) / 47 (1.7) / 1 (0.0) / 90 (3.2) / 9 (0.3) / 1 (0.0) Arthralgia: 571 (20.5) / 6 (0.2) / 0 / 876 (31.3) / 18 (0.6) / 0 Hot flush: 393 (14.1) / 3 (0.1) / 0 / 587 (21.0) / 8 (0.3) / 0 Lymphopenia: 372 (13.3) / 140 (4.9) / 2 (0.1) / 94 (3.4) / 13 (0.5) / 0 Thrombocytopenia: 341 (12.2) / 25 (0.9) / 6 (0.2) / 40 (1.4) / 1 (0.0) / 2 (0.1) Vomiting: 455 (16.3) / 13 (0.5) / 0 / 117 (4.2) / 2 (0.1) / 0	Adverse events we would want to take a look at I have highlighted here in a bar. The most common ones that we see clinically: diarrhea and neutropenia. Now, all of the CDK4/6 inhibitors do have neutropenia as a side effect, but you see a rate of any grade of 44% versus 5%. There's well-defined monitoring regimens watching neutropenia during the first 2 cycles of abemaciclib. I think we're all pretty familiar with that by translation from the metastatic setting. Diarrhea, 82% versus 7%. This does tend to be a challenge. In subsequent modules in this training program, there will be discussions about minimizing diarrhea and really helping patients take advantage of this benefit from adding this therapy. And then other things, pretty much the same.

17		Another one though that I would want to highlight, which is part of our monitoring program, and then what patients will also experience, we do see some increased changes in liver function tests—not a huge amount, but certainly more than the control. And then an alopecia rate of 9% versus 2% with endocrine therapy alone. And certainly you'll get that feedback from your patients. But when educated properly, when closely monitored for the most significant clinical side effect that the patient will feel—well, not the neutropenia, they don't feel, but they will feel diarrhea—you really can optimize this therapy and get patients on it successfully and keep them on it successfully.
18		So the evolution goes on. We had a 2-decade break in terms of therapies to treat our hormone-sensitive breast cancer patients, and in particular those who were at high risk for recurrence. Now we've added on a new paradigm, which is combining endocrine therapy with a CDK4/6 inhibitor. And we know by doing that, if we believe the data—and there's every reason we would—that we can decrease by an additional 25% the risk of recurrence; the risk of recurrence remains quite real even in node-negative populations, but certainly in node-positive populations.
19		What are those eligible populations? Based on approval, ones that when you seek insurance approval for the coverage of this oral oncology medication, if you read the FDA approval word by word, it is for hormone receptor-positive/HER-negative breast cancers that are node-positive in early breast cancer at high risk for recurrence, and a high Ki-67 greater than or equal to 20% is included within that labeling.

		The NCCN though are slightly more liberal and allow a few more patients to come into the treatment group. Still hormone receptor-positive/HER2-negative, but they actually give us a definition of high risk as either 2 criteria: if there are 1 to 3 nodes—so an N1 disease, then you need an additional high-risk feature, such as a high grade, grade 3; a quite large tumor of 5.0 or higher; or a high proliferation index of Ki-67 20% or higher. However, if you have 4 or more nodes, one does not need one of those high-risk pathology features.
20		Now, with every therapy we give, whether it's IV, which we have really good insight into, but more importantly orals, there are challenges with adherence. Nonadherence to oral therapy can be a very big barrier, and that has been researched extensively in terms of how to optimize that for people. Many patients, and we know from patient report and studies that are done with breast cancer, do not take adjuvant therapy for the full duration or the optimal schedule due to side effects. However, when patients have been properly educated, when they understand the benefits that accrue to them, and I find in particular patients on CDK4/6 inhibitors, those side effects, which you can explain to them, plan for, closely monitor for, they are predictable, they are manageable. And in really supporting them in those first 4 to 6 weeks of therapy, we really do get them on that, and get them on that successfully. And then we really do have every reason to believe that we are going to translate what we see clinically in terms of progression-free survival benefit into what their experience would be in

		providing them with extra insurance and a lower risk of recurrence.
21		Abemaciclib in particular, I've talked about it quite a bit up until now—diarrhea, and this is in the package insert—patient education, early detection, and intervention is critical. I have found that the diarrhea does tend to start almost immediately, if they're going to get it. So at the first sign of diarrhea, I tell them to call us. Here is the initial plan that, based on what you've experienced, we may tweak it some. So start your antidiarrheal therapy, but also call us and we will optimize your plan. Encourage hydration. And then if not resolved rather quickly, then we can hold the dose and consider if we want to dose-reduce in order to allow patients to get on this therapy. Safety monitoring is outlined here as we talked about. It can get pretty busy for the first 8 weeks. And I tell them, “We're going to be really good friends for the next 8 weeks.” Every 2 weeks for the first 2 months, blood counts and LFTs. Every 4 weeks for 2 more months. And then as clinically indicated. I will say that adverse event management and adherence promotion strategies will be discussed in greater detail in additional activities in this program, activities 2 and 3. So you will be sure to want to tune in to those.

22		So key takeaways for the last several minutes: the incidence of recurrent hormone receptor breast cancer does remain high, affecting tens of thousands of women a year. Between 15% to 40% of patients with early-stage breast cancer that is hormone sensitive may be affected, may have a recurrence based on their node status. Combining CDK4/6 inhibition with endocrine therapy has demonstrated benefit, both in the first-line metastatic setting and now in 1 clinical trial early-stage breast cancer setting for higher-risk patients. Abemaciclib is currently the only CDK4/6 inhibitor approved by the FDA and recommended by the NCCN for adjuvant treatment in this population. And we really do allow these patients to get the benefit of this additional therapy by good, aggressive toxicity management—in particular, GI toxicity—and therefore optimizing adherence and optimizing outcomes.
23		I want to thank everyone for listening in for these few minutes. I hope that this has been a summary that helps contextualize the challenge, but also then contextualizes that we have moved further down the road in terms of improving outcomes for early-stage breast cancer patients with the addition of CDK4/6 inhibitors. Please make sure that you tune in for subsequent modules as they will provide more insight on how to address the challenges and the opportunities in this population.