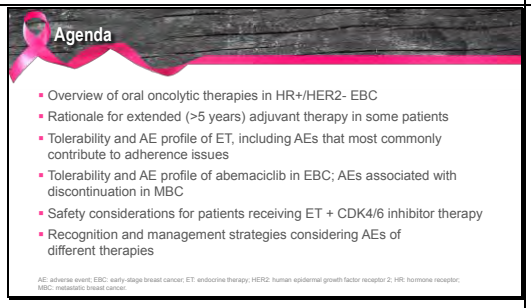
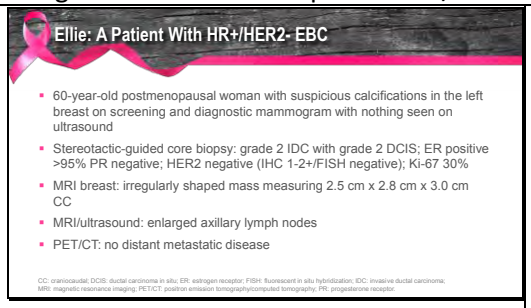
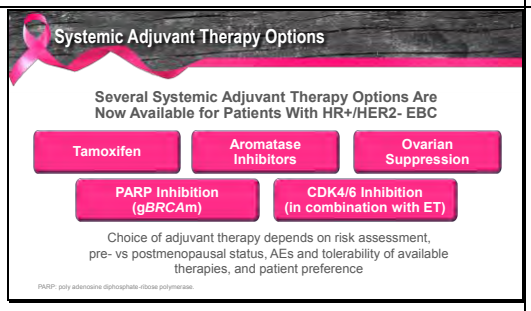
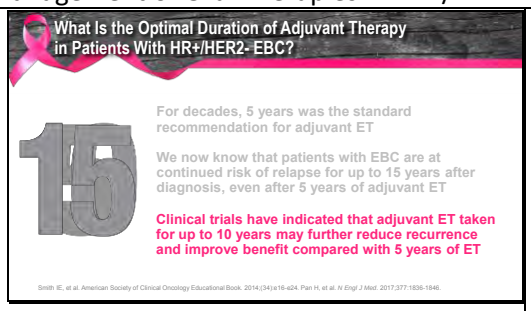
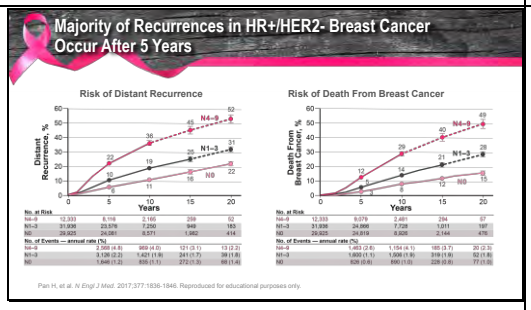
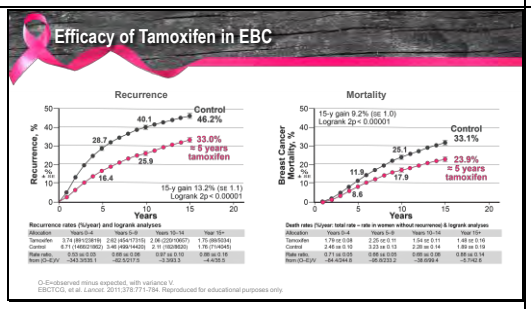
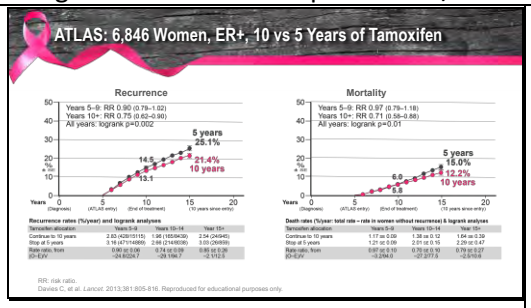
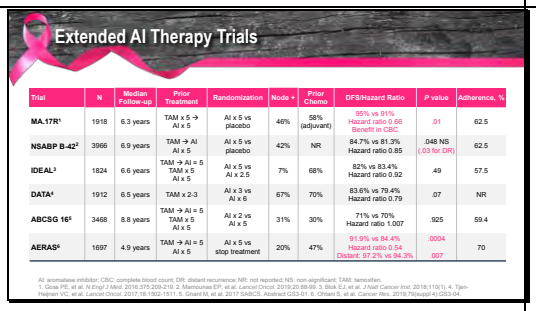
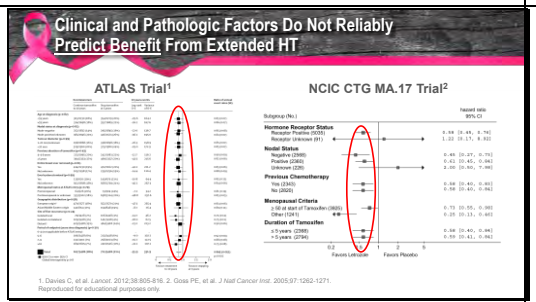
Optimizing Oral Therapy in HR+/HER2- Early Breast Cancer: Nurse-led Strategies to Improve Adherence and Persistence

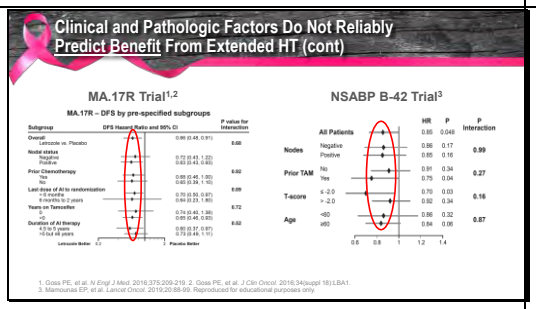
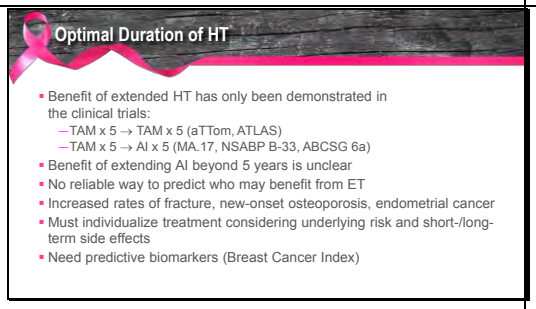
Adverse Event Management of Oral Therapies in HR+/HER2- EBC

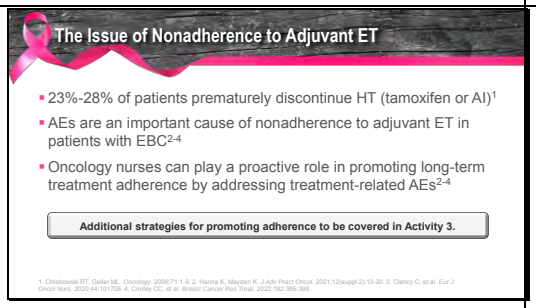
1		Hi, I'm Sarah Donahue, and I'm here to talk to you about adverse event management of oral therapies in hormone-positive/HER2-negative early-stage breast cancer. I am a nurse practitioner at the University of California in San Francisco.
2		Welcome.
3		So today I'll give you an overview of the oral oncolytic therapies in hormone-positive/HER2-negative early-stage breast cancer. We'll discuss the rationale for extended hormone therapy beyond the 5 years for certain patients. We'll discuss the tolerability and adverse event profile of endocrine therapy, including adverse events that most commonly contribute to adherence issues. We'll discuss the tolerability and adverse event profile of abemaciclib in early-stage breast cancer, and the adverse events associated with discontinuation that we've seen in metastatic breast cancer. We'll discuss safety considerations for patients receiving endocrine therapy, plus abemaciclib therapy. And we'll discuss management strategies for the different adverse events for the different therapies.

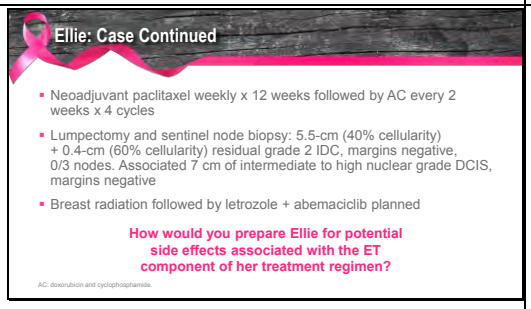
4		So we're going to start with a case study. Ellie is a patient with hormone-positive/HER2-negative early-stage breast cancer. She's 60 years old. Postmenopausal. She had a suspicious calcification in the left breast on screening and diagnostic mammograms. And nothing was seen on her ultrasound. So she went and had a stereotactic-guided core biopsy that found grade 2 invasive ductal carcinoma with grade 2 DCIS. The invasive disease was estrogen receptor-positive, progesterone receptor-negative and HER2-negative. The Ki-67 was 30%. MRI of the breast showed an irregularly shaped mass measuring 2.5 by 2.8 by 3.0 cm. An MRI ultrasound also showed enlarged auxiliary lymph nodes. The PET/CT did not show any distant metastatic disease.
5		So there are several systemic adjuvant therapy options for these patients with hormone-positive/HER2-negative early-stage breast cancer. We have our hormone therapies; tamoxifen, that's our oldest medication that's available. We have the newer aromatase inhibitors. And we also have ovarian suppression that we can give to patients to go along with their tamoxifen or aromatase inhibitor. We now have 2 additional therapies to give with the endocrine therapy—PARP inhibition and CDK4/6 inhibition. So the choice of adjuvant therapy depends on the risk assessment, pre- versus postmenopausal status of the patient, adverse event profile, and the tolerability of the available therapies for that individual patient, and the patient's preference, always.

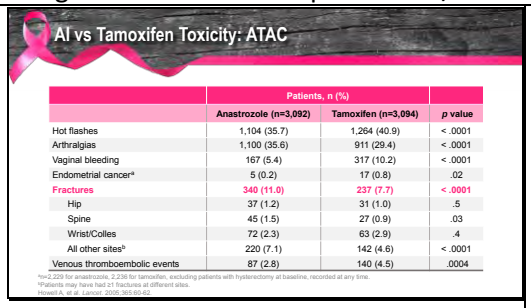
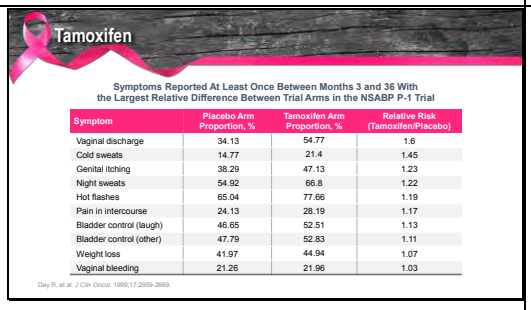
6		So what is the optimal therapy for patients with early-stage breast cancer that are hormone-positive? For decades, it was always 5 years of adjuvant endocrine therapy. But that has changed. We now know that patients with early-stage breast cancer are at continued risk of relapse for up to 15 years after diagnosis, even after the 5 years of endocrine therapy. So how do we protect them longer? There have been clinical trials that have shown that adjuvant endocrine therapy taken for up to 10 years may further reduce recurrence and improve benefit compared with the 5-year benefit there is for some patients.
7		So who are these patients that need to be watched more closely and given more therapy? We know that patients with more nodes of their disease involved have higher risk of recurrence. And that risk of recurrence continues on out to 15+ years/20 years. So you see here that the node, in negative patients, their risk is much lower than the risk in patients with 4 to 9 positive nodes. So we need to really protect our higher-risk patients.
8		Tamoxifen has been shown to reduce the risk of recurrence of breast cancer by about 40%. You can see here, if you follow this line up, at 10 years, it's about 40%. And it's been shown to increase overall survival.

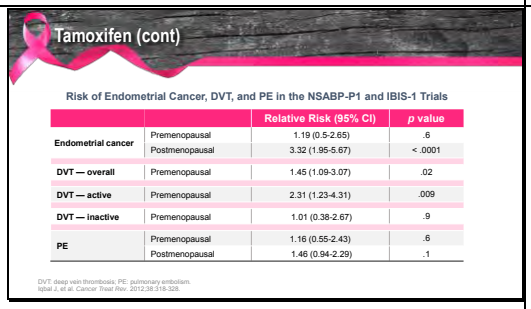
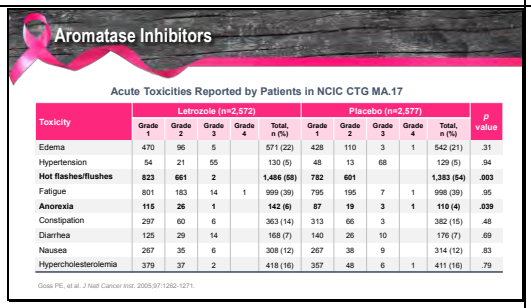
9		The ATLAS trial looked to see if 10 years of tamoxifen would be better than 5 years of tamoxifen. And they did show a benefit across all women enrolled.
10		So now how about the aromatase inhibitors? We know that aromatase inhibitors can reduce risk of recurrence by about 60% in women. Can we have patients take more aromatase inhibitor therapy for 10 years and reduce their risk further? So there's been several trials looking at that. They're all listed here. Two of those trials actually found a benefit in the patients they enrolled. And in those trials, some patients started on tamoxifen for a certain amount time, maybe when they were early stage or possibly when they were premenopausal. And then transitioned over to the aromatase inhibitor once they became postmenopausal; or they had ovarian suppression added in so that they could go on the aromatase inhibitor. A variety of situations occurred. But then for the last 5 years, they all went on aromatase inhibitors. And they found in the MA.17 and the AERAS trial that there was improved overall survival and reduced risk of recurrence.
11		So were there patients in these trials, in the tamoxifen trial, the ATLAS trial, or the MA.17 trial, the aromatase inhibitor trial, that benefited more from having longer duration of endocrine therapy? And they found that it didn't matter if patients were younger or older, didn't matter if they were node-positive or node-

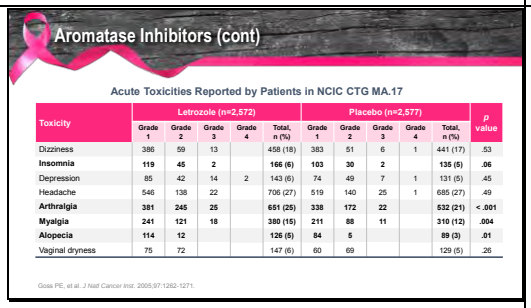
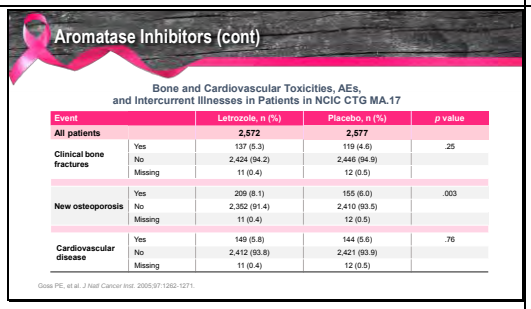
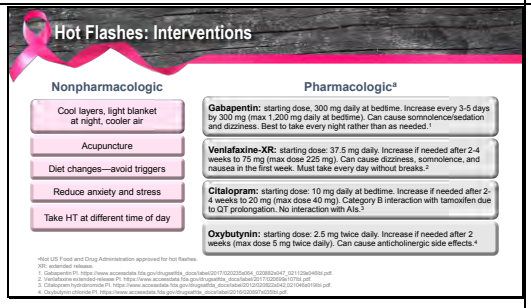
		negative. All patients benefited, even those that had had chemotherapy prior versus those that didn't. There really was no difference. Everybody benefited. The only group here, if you look, that didn't benefit were the people that were hormone receptor-negative. So that group. But that would make sense because they're not going to have those receptors to block.
12		The MA.17 trial, similarly, didn't have a difference in the benefit by node status, by age. NSABP did see some benefit in the B-42 trial. They also didn't have a difference.
13		So the optimal duration of hormone therapy, if you took all of these trials together, wasn't demonstrated across the board. However, there were some things that we do know, that tamoxifen for 5 years, followed by tamoxifen for another 5 years is beneficial to most patients. And there were 3 trials that did show a benefit in the longer duration of aromatase inhibitor. So the benefit of extending aromatase inhibitors beyond 5 years is a little bit unclear. However, we do have some trials that show a benefit, so we do consider it longer duration in our higher-risk patients. However, what is the higher risk? There's really no reliable way to predict benefit from longer duration endocrine therapy. We do know that there's increased rates of new onset of osteoporosis, increased rates of endometrial cancer in certain patients on tamoxifen longer term.

		So we really need to think about each patient individually and discuss their risks, their short-term and long-term risks of continuing on therapy. We need predictive biomarkers so that we can determine who would benefit from longer-term endocrine therapy because it's a little bit unclear still. There's one available right now called the Breast Cancer Index. That is a test where they take tissue from the surgery, and we send it out for genomic testing at this company. These tests can predict benefit of endocrine therapy of beyond 5 years, as well as the risk of patients developing a late recurrence of their breast cancer. So there's sort of 2 outcomes with that test. There was a recent trial that did further validate the BCI, or Breast Cancer Index, so you may see that being used more often in practice.
14		Thinking about patients receiving endocrine therapy, I like to focus on just getting them through that first 5 years and then sort of approaching the next several years of hormone therapy, if I'm going to be recommending it at a later date. So we know that 23% to 28% of patients prematurely discontinue their hormone therapy, whether it be tamoxifen or an aromatase inhibitor. The biggest issue that I've found for nonadherence to these medications or discontinuation is the adverse events that are associated with endocrine therapies. So as nurses, I feel that our role is to ensure that patients stay on their hormone therapy. Like I said earlier, it reduces their risk of recurrence by between 40% and 60%, so it's incredibly important. And we can play a very large role in helping patients reduce that risk by

		treating those adverse events and discussing strategies to help them. We'll be discussing that more with Activity 3.
15		So what are the side effects of endocrine therapy?
16		Let's go back to Ellie. She's been diagnosed with this hormone-positive/HER2-negative early-stage breast cancer. We decide that we're going to give her neoadjuvant chemotherapy. We give her paclitaxel weekly for 12 weeks. Then we follow that with AC every 2 weeks, times 4 cycles. She then goes on to have a lumpectomy and sentinel node biopsy. She's found to have 2 areas of residual disease—1 that's 5.5 cm and 40% cellularity, and the other is 0.4 cm and 60% cellularity. It's grade 2. The margins are negative. There were 3 sentinel nodes removed; none of them had cancer in them. She also had some DCIS in the breast tissue that was removed. The margins for that were negative. She then goes on to have breast radiation followed by letrozole and abemaciclib. How would you prepare Ellie for potential side effects associated with the endocrine therapy portion of her treatment?

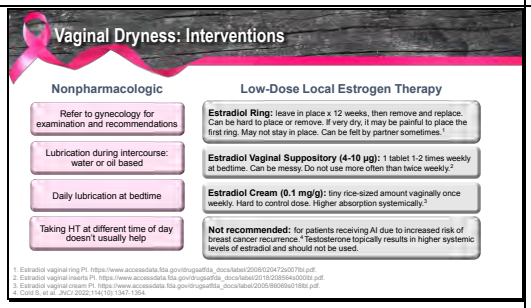
17	 Patients, n (%) Anastrozole (n=3,092) / Tamoxifen (n=3,094) / *p* value Hot flashes 1,104 (35.7) / 1,264 (40.9) / < .0001 Arthralgias 1,100 (35.6) / 911 (29.4) / < .0001 Vaginal bleeding 167 (5.4) / 317 (10.2) / < .0001 Endometrial cancer[a] 5 (0.2) / 17 (0.8) / .02 **Fractures 340 (11.0) / 237 (7.7) / < .0001** Hip 37 (1.2) / 31 (1.0) / .5 Spine 45 (1.5) / 27 (0.9) / .03 Wrist/Colles 72 (2.3) / 63 (2.9) / .4 All other sites[b] 220 (7.1) / 142 (4.6) / < .0001 Venous thromboembolic events 87 (2.8) / 140 (4.5) / .0004 [a]n=2,229 for anastrozole, 2,236 for tamoxifen; excluding patients with hysterectomy at baseline, recorded at any time. [b]Patients may have had ≥1 fractures at different sites. Howell A, et al. *Lancet*. 2005;365:60-62.	So what are the side effects? We know that both the aromatase inhibitors and tamoxifen can cause hot flashes. Joint aches and stiffness are seen with the aromatase inhibitors, but you can see that a little bit with the tamoxifen. Vaginal bleeding and endometrial cancer are really associated more with tamoxifen than the aromatase inhibitors. And we'll discuss that a little bit more later and what that means. But you see that these rates of endometrial cancer are actually quite low compared with the incidence of vaginal bleeding. So it doesn't always indicate endometrial cancer when a patient has vaginal bleeding. Aromatase inhibitors are associated with higher rates of osteoporosis. However, the fracture risk is not that much greater than with tamoxifen. It is increased, but not at a large amount. Venous thromboembolic events have been seen with tamoxifen as well.
18	 Symptoms Reported At Least Once Between Months 3 and 36 With the Largest Relative Difference Between Trial Arms in the NSABP P-1 Trial Symptom / Placebo Arm Proportion, % / Tamoxifen Arm Proportion, % / Relative Risk (Tamoxifen/Placebo) Vaginal discharge 34.13 / 54.77 / 1.6 Cold sweats 14.77 / 21.4 / 1.45 Genital itching 38.29 / 47.13 / 1.23 Night sweats 54.92 / 66.8 / 1.22 Hot flashes 65.04 / 77.66 / 1.19 Pain in intercourse 24.13 / 28.19 / 1.17 Bladder control (laugh) 46.65 / 52.51 / 1.13 Bladder control (other) 47.79 / 52.83 / 1.11 Weight loss 41.97 / 44.94 / 1.07 Vaginal bleeding 21.26 / 21.96 / 1.03 Day R, et al. *J Clin Oncol*. 1999;17:2659-2669.	Tamoxifen was studied in a trial, one of the earlier trials, NSABP, where they compared tamoxifen with placebo in patients, and they found that there were higher rates of vaginal discharge. Usually it's like a clear/yellowish discharge. Higher rates of vasomotor symptoms like cold sweats, night sweats, and hot flashes. They also found that patients had a slightly increased experience with some incontinence, with stress incontinence and other types of incontinence. They found that weight loss was harder to achieve in patients on the tamoxifen arm, just by a small amount.

		And like I said earlier, there is this risk of vaginal bleeding, but it actually wasn't that much higher in the tamoxifen arm. And just to be clear, tamoxifen, if a patient is premenopausal and they get tamoxifen, they will have their periods. That is normal. It's the abnormal vaginal bleeding that we are discussing here.
19		Endometrial cancer in this trial was noted and found, but it was seen only in the postmenopausal patients. That is the group that was driving the endometrial cancer risk. Deep vein thrombosis was seen in patients on tamoxifen. However, they found that if the patients discontinued the tamoxifen, that risk went away. So those on active therapy with tamoxifen had this increased risk, but once they stopped the medication—they became inactive on the tamoxifen—their risk reduced. And pulmonary embolism was seen in both groups, the pre- and the postmenopausal patients. Low rates, but certainly significant.
20		Acute toxicities in patients on the MA.17 trial with aromatase inhibitors were seen. Hot flashes were more likely to be seen in patients on the letrozole arm. And there was a slight trend toward issues with weight loss. I actually have not seen that in practice, so I find that to be really interesting. Patients will often ask you about hypercholesteremia while on the aromatase inhibitors, but really there was no difference in the placebo versus the aromatase inhibitor arm of this trial.

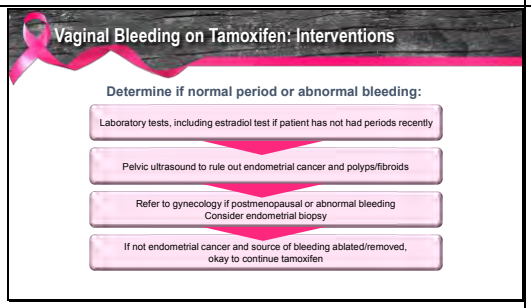
		Usually we don't have patients having GI toxicities, such as nausea, diarrhea, and constipation. I have not had issues with patients having hypertension, and nor do they in this trial.
21		In addition, insomnia was seen more in the patients that received the aromatase inhibitor. And the joint aches and stiffness, as we discussed earlier, more so in the patients receiving the aromatase inhibitor. Hair thinning was also more likely to occur in the patients on the aromatase inhibitor. And it's not like a full loss of hair; it's really just thinning. And it can settle down after about 1 year. All of these symptoms, I've found, can settle down after about 1 year. The beginning is usually the hardest part.
22		As you know, aromatase inhibitors can lead to decreased bone density. They did not see a difference in patients experiencing fracture in the placebo versus the aromatase inhibitor arm. But they did see a higher incidence of osteoporosis, or the development of new osteoporosis in the aromatase inhibitor arm. And there was no difference in cardiovascular disease.
23		So how do we manage these side effects? For hot flashes, there's a lot of nonpharmacologic things that we can do to help patients, and I always start there when I'm treating patients for symptoms. Just because it doesn't add a new medication that could have other side effects. And patients often prefer to have something that's not a medication-based treatment.

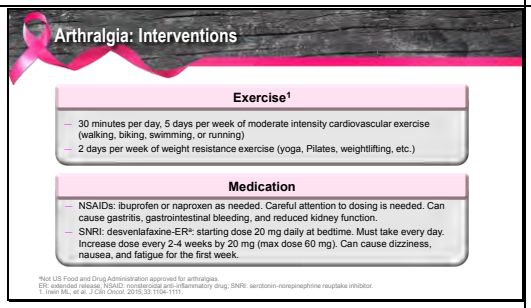
		So I tell them cool layers, like blankets at night; cooler air, like A/C if they have; windows open; fan on. Acupuncture actually has been shown to reduce hot flashes. Diet changes, like avoiding triggers. I have patients that tell me all sorts of things about what triggers them—wine, coffee, spicy foods. I have a patient that tells me that sugar really gets her to have a hot flash pretty quickly. So she avoids that, which is fine by me. Stress and anxiety can increase hot flashes, so really working on methods of reducing stress and anxiety, meditating—those things can really help. And then, taking the hormone therapy at a different time of day. So some patients might notice the first 5 or 6 hours after they take their aromatase inhibitor or their tamoxifen, they're having their hot flashes. So I have them, instead of taking it in the morning, take it at night. But if it's making it so they can't sleep through it, then I tell them to take it in the morning. So it's such a simple thing; just moving around when they take it so when they do have their hot flashes, it's a little bit more tolerable at that time of day. We have all these medications—I'm just going to pull them up all here—that can reduce hot flashes. These first 3 have been shown to reduce hot flashes by about 50% in trials: Gabapentin we start at 300 mg at bedtime. It is definitely really good at helping people get sleepy at night, as well as reducing the intensity and the frequency of the hot flashes.

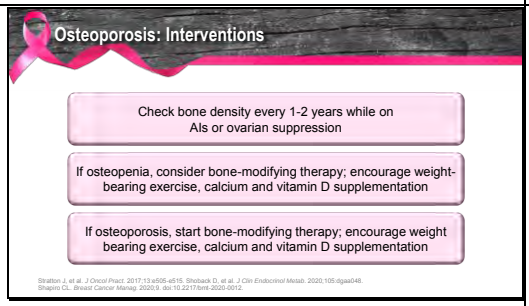
		I do allow them to increase the dose every few days. It really takes a few days to know what is happening at night. So I don't want them to increase it too quickly. It can make them groggy in the morning and feel dizzy. So I definitely have them move it up before bedtime. Like if it's 9 PM, take it at 7 PM. That can help. Sometimes I have to start patients on the 100-mg dose because 300 mg is too much. I start at 300 mg in most patients though because that's the dose that I find to be actually effective; 100 mg can be kind of like a drop in the bucket, it doesn't help much. And it's best to take it every night rather than as needed. It really works better. But you don't have to take it every night. It's not habit-forming. It doesn't cause negative side effects if it's not taken every night. Venlafaxine is an SNRI that patients can take to reduce their hot flashes. For anxiety and depression, the starting dose is 75 mg, but for hot flashes we can start them off at 37.5 mg. They can take that morning or night. We increase it after about 2 to 4 weeks, depending on how they're doing. We double the dose to 75 mg. The maximum dose is 225 mg a day. This medication, the side effects are generally seen in the first week, and that's dizziness, somnolence, and nausea. But then they get used to it and that gets better. So I always tell patients, try to stay on the medication for at least 2 weeks before stopping and deciding that you don't tolerate it, because those side effects do go away most of the time. This medication needs to be taken every day without breaks. If you start and stop,

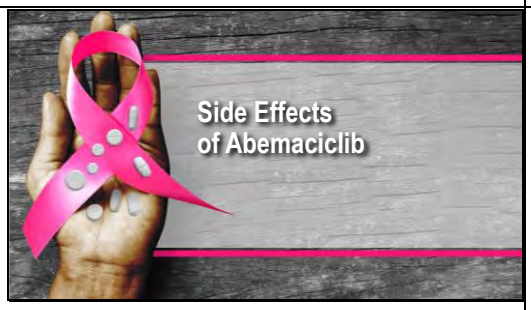
		it can cause a lot of negative side effects, specifically around mood. Citalopram is another antianxiety/antidepressant. It's an SSRI. We start at 10 mg at bedtime. And similar to the venlafaxine, you can increase it every 2 to 4 weeks. Max dose is 40 mg. It does interact with tamoxifen, so it cannot be taken with that medication. But it does not interact with the aromatase inhibitors. And finally, oxybutynin. This one has been shown to reduce hot flashes by about 70%. So very, very effective. Starting at 2.5 mg twice a day, and then you can increase it as needed after the first 2 weeks for a max dose of 5 mg twice daily. It does cause some dry mouth, so I have patients often discontinue it. However, it works so well. So it's always in my back pocket if these first 3 don't work.
24		Vaginal dryness is a very common side effect with the aromatase inhibitors. I don't see it as much with tamoxifen. We have, again, nonpharmacologic solutions. One is, I make sure that they're tied in with gynecology because the gynecologist often has really great ideas and ways of improving vaginal dryness. They also can actually do the pelvic exam and make sure there's nothing else going on. I have patients lubricate during intercourse with something that's water- or oil-based. They use coconut oil. They use all those things that are out on the market for water-based lubrications. And I also have patients do a daily lubrication at nighttime. That can really help. And it's best to start that off early on, to prevent the dryness. So it can really help the mucosa stay nice and plump. One example is taking a vitamin E tablet and

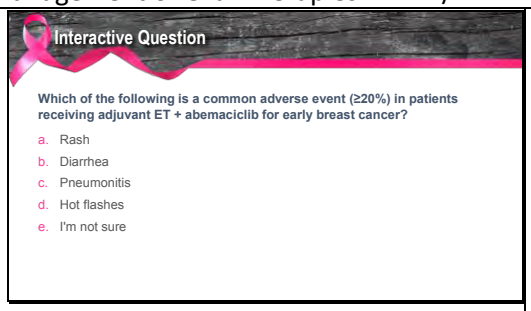
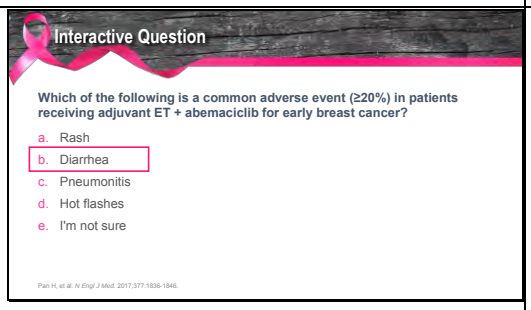
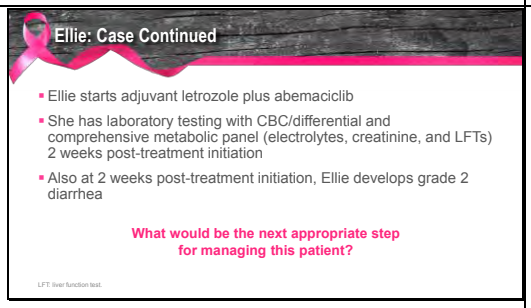
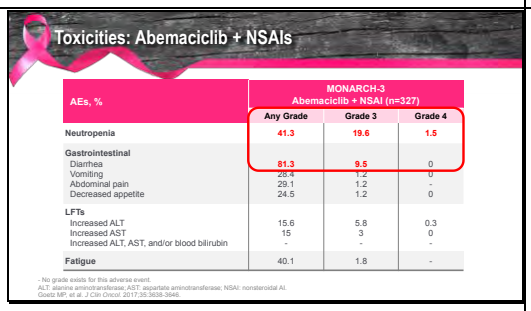
		breaking it a little bit and then placing that vaginally at bedtime, but wearing a panty liner. Or putting some coconut oil vaginally. You can make little ice cubes of that, but using a panty liner as well because it can get a little messy. And then, taking the hormone therapy at a different time of day doesn't usually help, but you can always try that. There are some low-dose estrogen therapies that we feel comfortable with. They've been studied in some trials. Not all of these have been studied yet. And they haven't been shown to increase serum estradiol levels by much. So the estradiol ring. This one has been studied. This is a ring that contains a low dose of estrogen. It's placed vaginally. It's left in place for 12 weeks and then removed. And then you replace it. Some issues with that are it can be hard to remove or place. It's a very stiff ring. If you already have vaginal dryness, placing it that first time can really be very difficult, so you have to use a lot of lubrication. Once you start using it, the mucosa is nice and plump and it usually is not an issue after that; it's just that first placement. Sometimes the gynecologist can place it for the patient in the beginning. The partner can sometimes feel it during intercourse, so patients sometimes want to remove it—just so that they know they can do that and put it back in. They don't have to get a new ring. The estradiol vaginal suppositories are very useful. You can use them 1 or 2 times weekly. Patients without breast cancer are using those daily. We do not do that with breast cancer. They wear a panty liner. They do it at bedtime.

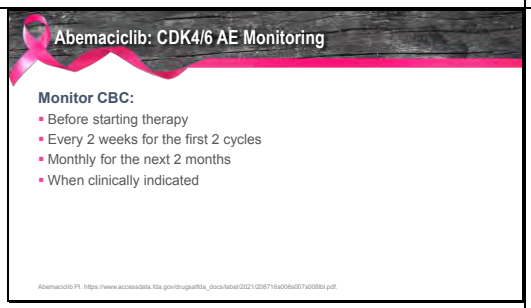
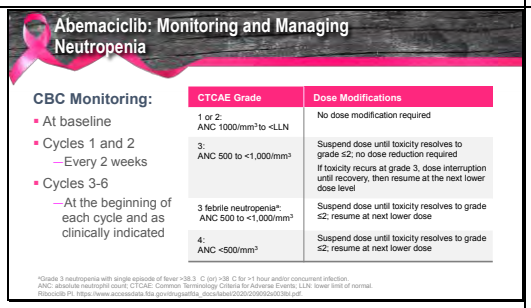
		There's also estradiol cream. This is my least favorite one because it's really hard to monitor how much the patient's using. But they can use a rice-sized amount vaginally 1 to 2 times a week, similar to the suppository. And that one may have a higher absorption systemically, so I try to avoid that one. However, if that's the only one that works for a patient, I let them use it; I can monitor their estradiol, their serum estradiol if I want, like every 2 weeks, every month, just to make sure that they're not having a lot of updates as well. So that can reassure patients. We don't recommend topicals like testosterone. They definitely increase serum estradiol by quite a bit. So we don't recommend that.
25		So vaginal bleeding on tamoxifen can be a normal period. But we need to determine if it's abnormal bleeding if a patient is telling you that. Some of these patients have had chemotherapy recently, and so their periods stopped. Then they do their radiation or whatever comes next, and then you put them on their tamoxifen and they start having their periods again. So how do you know if that's abnormal vaginal bleeding versus normal vaginal periods? So we can do a laboratory test with the estradiol test to see if their ovaries have turned back on. So if it's elevated, then you know that their ovaries have turned back on and this is a normal period. If it's not, then you start to wonder, is this something else? So then you can get a pelvic ultrasound that can look for thickening of the endometrial lining; that would indicate possible hyperplasia or risk for endometrial cancer. Or you can see if they

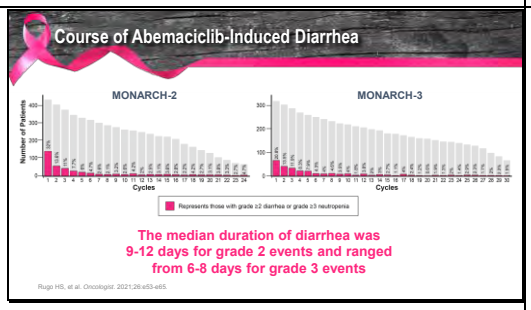
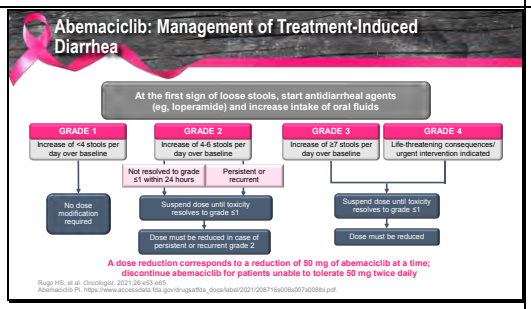
		have a polyp or a fibroid that's enlarged because of the tamoxifen that could itself be bleeding. The important thing is to have them tied in with gynecology at the start of taking their tamoxifen. So you're referring them back to their gynecologist when there's abnormal bleeding. And then the gynecologist can do that biopsy. And then, if the biopsy's negative—say, they find a polyp, they remove the polyp or they do an ablation, and the patient stops bleeding, they can actually continue the tamoxifen. As long as there's no endometrial cancer, it's fine to take tamoxifen if the bleeding item is removed.
26		So for arthralgia, this is super common in patients taking aromatase inhibitors. Like I said earlier, some trials found it to be 40% of patients, others 50%. Very, very common. We know that these joint aches and stiffness are likely going to occur in our patients. What we have found, there was a trial called the HOPE trial, where they looked at exercise and they measured how much exercise the patients were doing and they found that quite a bit of exercise was needed to reduce patients' experience of arthralgia. So it was 30 minutes a day, 5 days a week, of moderate intensity cardiovascular exercise, like walking, biking, swimming, or running. And 2 days a week of something with weight resistance, like yoga, Pilates, or literal weightlifting. There are many other options. But all of this is what they found to reduce the experience of arthralgia. So this seems like a lot. I tell patients to start slow if they're not doing anything. Do

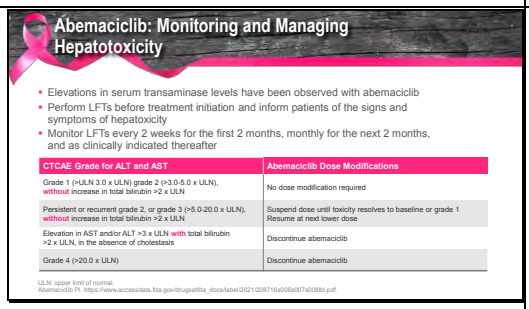
		it 1 or 2 days a week. And then slowly have a goal of building up. I also tell them, exercise by itself has shown to reduce the risk of breast cancer, and so that really motivates them. It also keeps their heart healthy, which is something that we maybe as a breast cancer nurse I don't think about a lot, but it's something that patients should be thinking about. It is one of the leading killers in the United States. Medications can help with arthralgias. I tend to try to avoid them and start with exercise as the mainstay of therapy. But you can have patients take ibuprofen or naproxen as needed. We need to make sure they're taking that with food. And we need to make sure that it's not affecting their kidneys negatively. And then there is one SNRI that's actually been shown to reduce joint aches and stiffness for patients on aromatase inhibitors specifically, and that's desvenlafaxine. I start patients at 20 mg a day and slowly, over 2 to 4 weeks, can ramp up. The max dose is 60 mg. It can cause dizziness, nausea, and fatigue that first week, but if they can get through that, usually those symptoms get better.
27		Osteoporosis: For patients getting aromatase inhibitors, osteoporosis is a concern. We check the bone density every 1 to 2 years while they're on the aromatase inhibitor, or ovarian suppression, actually, because that can reduce their estrogen and therefore increase the risk of decreased bone density. If they have osteopenia and they're on this aromatase inhibitor, we consider a bone-modifying therapy. Encourage weight-bearing exercise. That's any exercise,

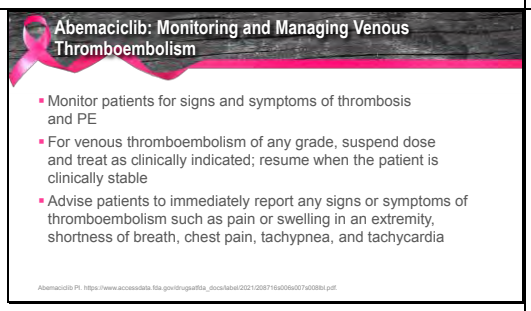
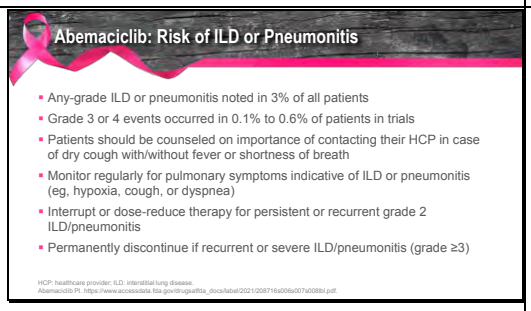
		except for swimming, that's been shown to improve bone density—so anything really that requires gravity; walking is weight-bearing. Calcium with vitamin D supplementation can be very helpful as well. We check vitamin D levels as well, just to make sure we don't need to give them extra vitamin D. If they have osteoporosis, we definitely will start bone-modifying therapy and encourage weight-bearing exercise, as well as the calcium and vitamin D. The medications that we use for increasing bone density (the bone-modifying therapy) is zoledronic acid; that's given every 6 months, for a maximum of 5 years. So my feeling about osteoporosis and osteopenia in patients taking aromatase inhibitors is that it's something that we should be watching. It is a negative effect of our therapy. But their rates of fracture were not that high in the studies. And so, I try to reassure patients that I'm not worried about them fracturing, unless they're somebody that falls a lot or somebody that's doing some contact sport. But generally, that's not most of my patients.
28		So now we'll talk about side effects of abemaciclib.

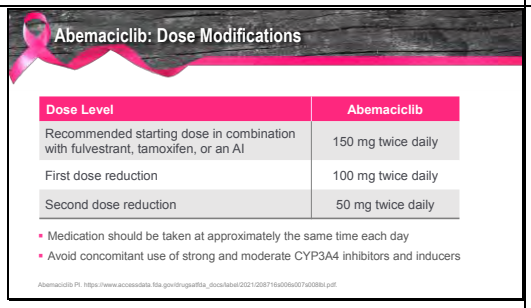
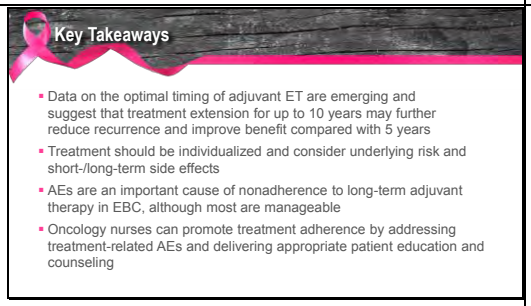
29		So which of the following is a common adverse event in 20% or more patients receiving adjuvant endocrine therapy and abemaciclib for early breast cancer? a) Rash b) Diarrhea c) Pneumonitis d) Hot flashes e) I'm not sure
30		The answer here is diarrhea. We do see rash, although rare, with abemaciclib. Pneumonitis is rare as well, something to be monitoring; we'll talk about that more. And hot flashes, you would see those with any patient on endocrine therapy; it wouldn't be specific to the abemaciclib.
31		So we're going to talk about Ellie again. She starts adjuvant letrozole and the abemaciclib. She has laboratory testing 2 weeks after with CBC/differential and a comprehensive metabolic panel. That panel includes electrolytes, creatinine, and liver function tests. She also, at 2 weeks post-treatment initiation, tells you that she's had some diarrhea. It's been grade 2, meaning 4 to 6 episodes in a 24-hour period. What would be the appropriate next step for managing her?
32		So let's just go over the MONARCH-3 trial adverse events that were reported. They found that 40% of patients experience neutropenia; about half of those had grade 3 or grade 4 neutropenia. GI side effects: Most common was diarrhea and that was occurring in 80% of patients. Only 10% had grade 3 diarrhea, so that would be 7 or 8 stools in a 24-hour period. But there was diarrhea in most patients.

		Liver function test abnormalities occurred in about 15% of patients. A low portion of those experienced grade 3 or grade 4 liver function abnormalities. It's usually the ALT and AST. And fatigue was experienced in 40% of patients.
33		So before starting therapy, every 2 weeks for the first 2 cycles, and then monthly, the CBC/differential should be monitored. And then also when clinically indicated.
34		So when monitoring the CBC, you're looking at the absolute neutrophil count. If it's greater than 1000/mm^3, you just continue at the current dose; you don't have to change anything. If a patient experiences ANC at 500 to 1000/mm^3, you would hold the medication, the abemaciclib. Continue the endocrine therapy. Wait for their neutrophil count to rise above 1000/mm^3. And then resume at the previous dose. However, if that happens again, next time you get labs, they're down below 1000/mm^3 but above 500/mm^3, you then hold the medication, wait till they get to be above 1000/mm^3, but then you resume at the next lower dose level. And we'll talk about the dose levels a little bit later in the talk. If they have febrile neutropenia, which was rare in this trial, but it did occur, and they have this ANC that's below 1000/mm^3 but above 500/mm^3, you would stop the medication, wait till they recovered, wait till their infection, if they experience that,

		is resolved, and then resume at the lower dose. And if they have an ANC of less than 500/mm^3, you would wait, stop the drug. Wait till they get above 1000/mm^3 and then resume at the next lower dose.
35		For diarrhea, what they found was that it was higher during the first cycle. It usually occurs pretty quickly after patients start treatment, after a week or so. And what they found was that, as cycles went on, the diarrhea got better, in both the MONARCH-2 and the MONARCH-3 trial. And whether that's because the toxicity actually decreases with the drug or because patients become a little bit better at taking loperamide—sometimes they're taking it preventively, like a half tablet of loperamide every day, or they're taking it more quickly, as soon as the diarrhea occurs—it's unclear if this is just better management or decreased toxicity over time. If patients experience diarrhea for grade 2 events, it usually lasted 9 to 12 days; if it was grade 3, 6 to 8 days in the trials.
36		So how do we manage this? At the first sign of loose stools, we have patients start their antidiarrheal agents, like loperamide, as I discussed previously, and increase their oral fluid intake. I also, just in addition to that, have them change their diet to more of a BRAT diet, those bland foods, avoid spicy things, avoid a lot of acidic foods. That can help a lot. So if they're experiencing grade 1 diarrhea, no more than 4 stools a day, they can just continue the medication and take their loperamide.

		But if they are, like Ellie, who is having grade 2 diarrhea, she had 4 to 6 stools per day over her baseline, you would stop the medication, wait till she has less than 4 stools a day. We'd be starting her on loperamide to get to that point. And then, you could resume at the previous dose. However, if you resume at the previous dose and she again goes right back to having 4 to 6 stools per day, then you'd want to stop the medication, wait till she has less than 4 stools a day, and then go to the next lower dose level. If the patients have grade 3 or grade 4 diarrhea, 7 stools a day or more, you would stop the medication. Wait till their diarrhea reduces to less than 4 a day, and then you would reduce the dose. So the dose reductions, like I said, we'll be discussing in a later slide.
37		The elevations in the transaminases were seen in patients taking abemaciclib. So we do this comprehensive metabolic panel, and we check their LFTs every 2 weeks for the first 2 months, and then every month after that. Patients that had a rise in their LFTs that was greater than 3 times the upper limit of normal, but they had a total bilirubin that remains no greater than 2 times the upper limit of normal, you could continue the medication. However, if their LFTs rise even further, although the total bilirubin is still doing okay, you could just stop the medication, wait till they have a reduction in their LFTs and then resume at the next lower dose. If they're having a rise in their AST and ALT, as well as their total bilirubin, they can no

		longer be taking the medication; you have to stop the abemaciclib. And if they're having grade 4, obviously, no more abemaciclib.
38		So venous thromboembolism was seen in low rates, but it was seen in the trials. So deep vein thrombosis or pulmonary embolism. So what we do is we talk to the patients about what to look for, and we work it out pretty quickly if they have shortness of breath, chest pain, swelling in 1 leg. We stop the medication. We treat the clot, and then once the symptoms are better, shortness of breath or chest pain or leg swelling, we can resume the abemaciclib at the previous dose. But if that happens again, of course, we're not going to be continuing the medication. Usually it doesn't because they're on a blood thinner at that point.
39		ILD or pneumonitis was seen in patients taking abemaciclib at only 3%. But it's something that we should be careful of because the grade 3 or 4 events did occur in the trial; at small rates, but these are deadly situations. So we make sure that we monitor for this and catch it quickly. So we counsel patients. We tell them what to look for— shortness of breath and cough. They need to tell us that between visits. Every time they come in, we ask them about those symptoms again. And then if we do think that they might be having an experience of pneumonitis or ILD, we have them stop the medication right away. We work them up for it. We get the chest CT. And then if they do have pneumonitis, we treat them with steroids. Sometimes we can, again, try, if it's a mild case of pneumonitis or if it's mostly

		asymptomatic, we can put them back on the abemaciclib again. However, if it recurs, or if they have a lot of symptoms, we would not be able to continue the abemaciclib anymore.
40		For the dose modifications, I keep referring to this slide and here we are. A starting dose is 150 mg twice daily. There are pills out there for taking 200 mg twice daily, but that is for monotherapy without endocrine therapy, so make sure that your patients are not getting that dose. It's 150 mg twice daily. And the first dose reduction is 100 mg twice daily. And the next dose reduction is 50 mg twice daily. And after that, you discontinue the medication because it's no longer thought to be efficacious at doses lower than 50 mg twice a day. It also should be avoided with strong and moderate CYP3A4 inhibitors. So having the pharmacist really help you with looking at the medications for each patient and adjusting those medications so the patient is not experiencing more toxicity from the abemaciclib or reduced efficacy of the abemaciclib.
41		So key takeaways: Data on the optimal timing of adjuvant endocrine therapy, 5 versus 10 years, are emerging. And we may further be able to decide which patients would benefit with a longer duration of endocrine therapy. The Breast Cancer Index is certainly hopeful. Treatment should be individualized, and we should be considering the underlying risks, the short- and long-term side effects for each patient.

		Adverse events are an important cause of nonadherence to long-term adjuvant therapy in early-stage breast cancer. But most of these side effects can be managed. And it is our job as oncology nurses to promote treatment adherence by addressing treatment-related adverse events and delivering appropriate patient educate and counseling.
42		Thank you very much for joining me today.