Hello and welcome. My name is Chad Barnett. I'm a Clinical Pharmacy Specialist in the Division of Pharmacy at the University of Texas, MD Anderson Cancer Center and I'm very pleased today to be able to talk to you about the Late Effects of Endocrine Therapy.

My objectives today are to: identify the most clinically relevant late toxicities associated with adjuvant endocrine therapy; to describe the incidence and management of these toxicities; and to discuss appropriate monitoring of these toxicities.

There are many late toxicities from endocrine therapy, ranging from osteopenia and bone loss to vasomotor symptoms, decreased libido, and these are all very important. However, because of the interest of time I would like to focus on what I consider to be the three most important counseling points for these patients.

This includes bone loss, endometrial cancer, and vasomotor symptoms.

So let's start out with bone loss. Cancer treatment induced bone loss occurs when the natural balance of bone remodeling is shifted toward bone resorption by osteoclasts and unfortunately this is done by some of our endocrine therapies. This can be rapid and severe bone loss. It is generally more severe than women undergoing a natural menopause. And it can be associated with significant clinical, social, and economic consequences including activities and mobility may be limited after a fracture, and patients may be unable to pay for their medications targeted toward their osteoporosis. Finally and most important, treatment-related fractures can be associated with decreased quality of life and shorter survival. So obviously this is a very important issue in this patient population.

Bone loss primarily occurs through lowering of estrogen. Estrogen is a key regulator of osteolysis. And therefore, physiologic decreases in estrogen levels can place premenopausal and postmenopausal women at a high risk of osteoporosis. Agents that includes are the luteinizing hormone releasing hormone or LHRH agonists, which functionally decrease circulating estrogen in premenopausal women. These include goserelin and leuprolide. Tamoxifen in premenopausal women can also result in bone loss. And aromatase inhibitors in postmenopausal women also lower circulating estrogen leading to bone loss. Examples of aromatase inhibitors include anastrozole, letrozole, and exemestane and are commonly used in postmenopausal women in the adjuvant setting.

This is a table looking at the differences between fracture risk with aromatase inhibitors and tamoxifen. In the first study anastrozole for five years is compared to tamoxifen for five years. And you can see after 68 months of follow-up the risk of fracture is increased by 3% in patients who received the aromatase inhibitor. So obviously this is quite significant. The next two trials compared tamoxifen switching over to exemestane to complete five years, compared to tamoxifen for five years, and tamoxifen for two to three years and then switching to letrozole to complete five years, compared to tamoxifen. And you can see that the fracture incidence was increased as well in patients who received the aromatase inhibitors. What is interesting is this last study. This is the MA-17 study.
and it randomized patients who had completed five years of tamoxifen, to five years of letrozole, or five years of placebo. And you can see that the fracture risk is not significantly different between these two groups. So probably what we are seeing is an increased risk of fracture with the aromatase inhibitors but also somewhat of a protective effect on bone density from the tamoxifen component.

The National Comprehensive Cancer Network® or NCCN® has developed an algorithm for management of bone loss in cancer patients. Cancer patients who are considered to be at risk for bone loss and fracture due to age are recommended to have a history and physical examination, bone mineral density screening through DEXA scanning, and FRAX analysis, which is an online program where you can input patient risk factors and it gives you the incidence of high major fracture or hip fracture. All patients from this point are recommended to be counseled on lifestyle modification, such as exercise and smoking cessation, and recommended to have adequate vitamin D and calcium replacement. Results from here are dictated based on results from the DEXA scan. So for patients with a T-score of greater than -1, no therapy is indicated and it is recommended for them to have a repeat DEXA scan every two years. For patients with a T-score between -1.5 and -1, it is recommended that those patients have a 25-hydroxyvitamin D level checked, in addition to repeating their DEXA scan in two years. For patients with a T-score between -1.5 and -2, in addition to checking a vitamin D level, it is recommended that they consider pharmacologic therapy. And for patients at the most risk for developing a fracture, those with a T-score of less than -2, or a FRAX 10-year fracture risk of greater than 20% for major fracture, or greater than 3% for hip fracture, in addition to checking a vitamin D level, it’s recommended that they strongly consider treatment with pharmacologic therapy. And so you can see that these recommendations, while vague, are important. So strongly consider treatment for those at the highest risk of developing a fracture.

Due to the convenience of the oral dosage form and the low cost, oral bisphosphonates are most often utilized in this setting. So for options we have alendronate, risedronate and ibandronate as oral dosage forms and also there are ibandronate and zoledronic acid administered IV. The IV therapy is often utilized when the oral therapy is either contraindicated or is not sufficient to maintain their bone density.

Denosumab which is a RANK ligand inhibitor has also been investigated in this patient population. This was based on a randomized Phase III clinical trial which involved 250 postmenopausal women receiving an aromatase inhibitor who had osteopenia in the lumbar spine, total hip, or the femur neck. The primary endpoint was the percentage change in lumbar spine bone mineral density, which you can see from the chart, was improved in patients who received denosumab compared to patients who received placebo. So it did meet that endpoint. The fracture risk was not different between the two groups, however, this was a fairly small study. And there were no significant differences in treatment-related adverse events or mortality. And the bottom line here is that for most patients who are at risk for the development of bone loss due to therapy, oral bisphosphonates are typically first line. However, for patients who are refractory, IV
zoledronic acid or ibandronate or subcutaneous denosumab are options for these patients.

So initially, we started talking about the bone loss associated with aromatase inhibitors. Now I’d like to talk about the endometrial carcinoma that is a possibility with tamoxifen therapy. The effects on uterine lining are different based on whether a woman is premenopausal or postmenopausal. In postmenopausal women, tamoxifen can stimulate endometrial proliferation which can result in atypical hyperplasia and endometrial cancer. In premenopausal women, tamoxifen actually has antiestrogenic effect on the premenopausal endometrium. And so atypical premenopausal women taking tamoxifen don’t appear to have this increase in risk of polyps, hyperplasia, or endometrial cancer.

And we can specifically look at the numbers based on this analysis by the Early Breast Cancer Trialists’ Group which compared patients who received five years of tamoxifen to no therapy. What you can see here is that uterine cancer risk is strongly correlated with age. There is little absolute risk of uterine cancer for women who are younger than 45, or who are 45 to 54, and the numbers in patients greater than 70 are very small. However, if you look at the patients who are between 55 and 69, they have almost a three-fold increase in the risk of uterine cancer with tamoxifen compared to no therapy.

This is another way to look at the same information. This was a meta-analysis published in the Journal of the National Cancer Institute and they evaluated the role --- the risk of uterine cancer by the adjuvant endocrine therapy utilized. So if you look on your left, you will see that there were two studies that evaluated --- anas --- aromatase inhibitors for five years, compared to tamoxifen for five years. Three trials that utilized tamoxifen switching over to an aromatase inhibitor for a total of five years, compared to tamoxifen for five years. And one trial in which patients received tamoxifen and were switched over to an aromatase inhibitor for five years, compared to an aromatase inhibitor alone. An analysis of the pooled data demonstrated that longer duration of an aromatase inhibitor was associated with a 66% reduction in the relative odds of endometrial cancer compared to tamoxifen. In other words that, the longer patients were exposed to tamoxifen, the greater their risk of developing an endometrial cancer.

Investigators wanted to know, “Did this risk also occur in patients who receive even longer tamoxifen therapy?” The ATLAS and aTTOM studies evaluated patients who received five years of tamoxifen, compared to patients who received ten years of tamoxifen in the adjuvant setting. As you can see in the ATLAS and aTTOM trials, the risk of endometrial cancer was higher in patients who received ten years of tamoxifen, compared to five years of tamoxifen. And in addition, the risk of death of endometrial cancer was increased in the aTTOM study with the longer duration of tamoxifen.

Recommendations exist for endometrial cancer surveillance from the American Society of Clinical Oncology in their follow-up breast cancer guidelines. They recommend that regular gynecological follow-up is recommended for all women and that women who receive tamoxifen should be advised to report any vaginal bleeding. For postmenopausal women they would be advised to report any vaginal bleeding. And for premenopausal
women they would be advised to report any irregular bleeding or spotting. The guidelines suggest that longer follow-up intervals may be appropriate for women who have had a total hysterectomy and oophorectomy, which makes perfect sense. And importantly, routine screening with vaginal ultrasound or endometrial biopsies in asymptomatic women receiving tamoxifen is not recommended. So that’s actually a very important point of the guidelines.

So we’ve discussed bone loss with aromatase inhibitors, endometrial cancer risk with tamoxifen, and now we will finish on vasomotor symptoms which can happen with almost all endocrine therapy and a wide variety of patients. So it is estimated that hot flashes affect anywhere from 65% to 85% of breast cancer survivors, so obviously a huge portion of the patient population. And the majority of breast cancers are hormone receptor-positive, and therefore, patients will be offered endocrine therapy. Both chemotherapy and tamoxifen can cause more frequent and severe hot flashes than natural menopause. And I think that almost anyone that sees patients in this situation will tell you that hot flashes can significantly affect a patient’s quality of life and it may even affect their adherence to therapy. So patients can --- will actually stop their therapy if they have very severe hot flashes. So that’s obviously very important.

Nonpharmacological options for the management of hot flashes include avoidance of hot flash triggers if patients know what triggers their hot flashes. And also the recommendation to wear loose-fitting clothes or lots of layers, so that patients can take off or add layers as they become warm or cold. In addition, exercise, acupuncture, aromatherapy, and yoga have all been evaluated in the setting to relieve patient hot flashes.

Obviously, we want to avoid any medications that have estrogenic effects for these patients. So we don’t want to supplement estrogen in women who are having hot flashes. So nonhormonal pharmacologic options include, commonly antidepressants, so SSRIs and SNRIs, as well as gabapentin and pregabalin. And clonidine is a very old medication that can be very helpful for some patients who have refractory hot flashes, although the hypotension that comes with it is something to --- to continue to monitor. Herbal supplements may also be taken by patients. However, there is insufficient evidence to recommend these therapies. And because they may contain phytoestrogen, such as soy or black cohosh, they may not be appropriate for this patient population who were are trying to avoid any estrogen exposure.

One point that’s specifically important with tamoxifen is that there is a risk of drug interactions with tamoxifen. Tamoxifen is metabolized through many different enzyme systems, but primarily through cytochrome P450 2d6. And this actually helps to form the active metabolite endoxifen. So the endoxifen is the most important part of the drug combination. Therefore, we would like to avoid any drug interaction that could potentially block the conversion of tamoxifen to endoxifen. The highlighted medications here, fluoxetine and paroxetine, are what are considered strong cytochrome P450 2d6 inhibitors. And, therefore, if possible, we would like to avoid that drug interaction which could potential reduce the effectiveness of the tamoxifen. Appropriate options to avoid
this drug interaction include venlafaxine, citalopram, and escitalopram as well as others, such as clonidine and gabapentin.

These are the footnotes from the previous slide.

In summary, primary physicians should be aware of the possibility of late side effects from endocrine therapy. I've just been able to cover a couple of these. However, there are many, many important late side effects from endocrine therapy. And with prior endocrine therapy and/or chemotherapy, menopausal status and other pertinent past medical history will help to determine the specific toxicities to monitor in each specific patient. So with that, I conclude my presentation. Thank you for your attention and we welcome your feedback.