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, specializing in breast oncology. My presentation today will be the Role of Endocrine Therapy.

My objectives today are to: list the available adjuvant endocrine therapy options for patients with both invasive and noninvasive breast cancers; to analyze the data supporting adjuvant endocrine therapy; and finally, to describe the rationale for choosing adjuvant endocrine therapy in specific patient populations.

Endocrine therapy options vary based on whether patients have invasive or noninvasive breast cancer. For noninvasive breast cancer such as ductal carcinoma in situ or DCIS, treatment options include the antiestrogen, tamoxifen, and also the aromatase inhibitor, anastrozole. For invasive breast cancer, we have a couple more options. We also have the antiestrogen, tamoxifen, as a primary treatment option. However, there are also therapies such as ovarian ablation or suppression in premenopausal women, such as surgically removing the ovaries through oophorectomy, or utilizing luteinizing hormone releasing hormone or LHRH agonists, such as goserelin or leuprolide to reduce circulation estrogen. Aromatase inhibitors are primarily used in postmenopausal women or in premen --- in premenopausal women in combination with ovarian suppression. And examples of aromatase inhibitors include anastrozole, letrozole, or exemestane.

The National Surgical Adjuvant Breast and Bowel Project or NSABP initiated a prospective randomized clinical trial which evaluated the use of adjuvant tamoxifen in patients with DCIS. All patients in the trial underwent lumpectomy and breast irradiation and were then randomized to receive tamoxifen, daily for five years, or placebo, daily for five years. Investigators concluded that compared to placebo, tamoxifen given for five years decreased the risk of invasive breast cancers as well as ipsilateral and contralateral breast cancers.

In a subsequent publication with additional follow-up, investigators discovered that after breast-conserving surgery, radiation and tamoxifen reduced the 15-year cumulative risk of invasive ipsilateral breast cancer by 1.5% and the 15-year cumulative risk of death by less than 1%. And while these numbers may seem small, it should be noted that all-cause mortality is low in this patient population. And in fact, in this trial, 15-year overall survival exceeded 85%. So these patients actually have a --- a very good prognosis.

Aromatase inhibitors have also been evaluated for patients with DCIS. The NSABP B35 results were presented at the American Society of Clinical Oncology or ASCO meeting in 2015. And after a lumpectomy and radiation, more than 3,000 patients with ER-positive DCIS were randomized to receive either tamoxifen, daily for five years, or anastrozole, daily for five years. After more than nine years of follow up, 10-year point estimates for breast cancer-free
interval favored the aromatase inhibitor over tamoxifen. And because of these results, the authors concluded that anastrozole is an appropriate option for adjuvant therapy in postmenopausal women with DCIS, specifically in women age 60 years or younger but understanding that they have to be postmenopausal in order to receive the aromatase inhibitor. It’s very important.

For invasive breast cancer, the American Society of Clinical Oncology and the College of American Pathologists have developed guidelines for the determination of ER PR status for invasive breast cancer. So, E --- ER is estrogen receptor, and PR is progesterone receptor. These guidelines recommend that ER and PR status should be determined on all newly diagnosed invasive breast cancers. And this is to determine whether they would be a candidate for adjuvant endocrine therapy. ER and PR status should be determined by immunohistochemistry, not the older ligand-binding assays. The guidelines also recommend to consider endocrine therapy in patients whose breast tumors show at least 1% ER positivity or PR-positive cells. This is a little bit of a change historically. We have considered patients to be ER or PR-positive if the percentage is greater than 10%. So there is some controversy here. And finally, the guidelines recommend to consider the risks and benefits for endocrine therapy for each patient. So even though these therapies are well tolerated by most patients, they are not benign and side effects can include hot flashes, bone loss, and long-term toxicities, which will be covered in a subsequent presentation.

There are two major targets for endocrine therapy. We can either block the effect of estrogen or we can lower the circulating estrogen. And so antiestrogens block the effect of estrogen at the cellular level. So an example of this is tamoxifen. Other agents such as LHRH agonists in premenopausal women, aromatase inhibitors in postmeno --- menopausal women, and removing ovaries in premenopausal women cause a functional decrease in circulating estrogen, thus, having the effect of starving the tumor of estrogen.

Tamoxifen has been evaluated through many years as a way to reduce the risk of occurrence in women with ER-positive early stage breast cancer. A meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group provides compelling evidence regarding the benefits of adjuvant tamoxifen. This analysis included more than 10,000 women with ER-positive breast cancer who received either five years of tamoxifen or no therapy. As you can see by the Kaplan-Meier curve on the left, this shows the risk of recurrence with a 13% absolute benefit at 15 years in patients who received tamoxifen versus patients who received the control. On the Kaplan-Meier curve on the right, you can see the decrease in breast cancer mortality with tamoxifen producing approximately a 10% decrease in breast cancer mortality at 10 years, compared to no therapy. So this certainly shows the benefit of tamoxifen in this patient population.
There have been many questions regarding the exact length of therapy that patients should receive their adjuvant endocrine therapy. Two studies have evaluated giving tamoxifen for longer than five years. So the aTTom and ATLAS study randomized patients to receive either five years of adjuvant tamoxifen or 10 years of adjuvant tamoxifen. And as you can see by the table, the ATLAS study had a significant improvement in breast cancer mortality, whereas breast cancer mortality was not significantly different in the aTTom trial. However, when both of these results were combined, breast cancer mortality was significantly improved in patients who received 10 years of tamoxifen compared to patients who received five years of tamoxifen. And results from these two studies have changed the national guidelines.

Aromatase inhibitors have also been evaluated in the adjuvant setting for women with ER-positive early stage breast cancer. Another Early Breast Cancer Trialists’ Group meta-analysis was performed comparing tamoxifen to a regimen including an aromatase inhibitor. If you look at the curves on the left, this includes trials that contain tamoxifen for five years compared to utilization of an aromatase inhibitor for five years. The curve on the right evaluated trials which compared patients who received tamoxifen for five years compared to patients who started out with tamoxifen for two to three years then switched to an aromatase inhibitor to complete five years total. Both of these graphs show the risk of recurrence. And what you can see from the graph on your left is there is approximately a 3.6% benefit in the decreasing the risk of recurrence in patients who received anastrozole or aromatase inhibitors compared to patients who received tamoxifen. In the graph on the right, the benefit is less drastic. At seven years, there was a decrease in the risk of recurrence of 0.7% with the addition of an aromatase inhibitor.

Because of the interest and success of aromatase inhibitors in postmenopausal women, there was an interest in evaluating aromatase inhibitors in premenopausal women but, of course, they must have ovarian suppression. The SOFT and TEXT trials both evaluated this hypothesis. Patients received ovarian suppression with either triptorelin, which is an LHRH agonist, oophorectomy, or ovarian radiation, and were randomized to receive either tamoxifen for five years or exemestane for five years. At 68 months of median follow-up, the five-year disease free survival was improved in patients who received the aromatase inhibitor, exemestane, with ovarian suppression compared to patients who received tamoxifen and ovarian suppression. The toxicities in each arm of the study were what we would expect for each agent. Patients who received aromatase inhibitors experienced increased risk of fracture, musculoskeletal symptoms, vaginal dryness, and decreased libido. Patients who received tamoxifen were more likely to experience venous thromboembolism, sweating, hot flashes, and urinary incontinence. Because of the results of these trials, ovarian suppression in combination with aromatase inhibitors have been included as a treatment option for premenopausal women in the most recent National Comprehensive Cancer Network Guidelines®.
Our major choices for adjuvant endocrine therapy are dependent on the menopausal status of the patient. For premenopausal women, options include tamoxifen. They also include ovarian suppression in some fashion, either surgical removal of the ovaries or using an LHRH agonist. In addition, ovarian suppression has been studied with tamoxifen as well as aromatase inhibitors in the studies that we just discussed. For postmenopausal women, options include the use of tamoxifen, aromatase inhibitors, or some sequential combination of these, such as starting out with tamoxifen and switching over to an aromatase inhibitor.

Because it’s so important to know the menopausal status of the patient in patients who receive an aromatase inhibitor, the National Comprehensive Cancer Network® or NCCN Guidelines® actually include a definition for menopause. So the guidelines state that patients are considered to be in menopause if they have had a prior bilateral oophorectomy, so removal of the ovaries, or if they are greater than or equal to 60 years old. Women who are younger than 60 years old are considered to be postmenopausal if they have been amenorrheic for 12 months or longer in the absence of chemotherapy, tamoxifen, toremifene, or an LHRH agonist, and their FSH and plasma estradiol are in the postmenopausal range. So this is very important clinically.

In addition, if patients are taking tamoxifen or toremifene and they are younger the 60 years old, the FSH and plasma estradiol should be in the postmenopausal range. The guidelines also have a couple other important points. They state it is not possible to assign menopausal status to women receiving LHRH agonists. So you actually have to stop the LHRH agonist and see if they have a resumption of their ovarian function. In addition, a very important point in women who are premenopausal at the time of adjuvant chemotherapy, amenorrhea is not a reliable indicator of menopausal status. And so many of these patients have low residual ovarian function. So the blood work is very important.

This is an algorithm from the NCCN Guidelines® specifically for premenopausal women. And so the NCCN Guidelines® recommend that patients be started on tamoxifen, daily for five years, with or without ovarian suppression. At five years you determine whether the patient is still premenopausal or has gone into menopause. If the patient is still premenopausal, you could consider tamoxifen for an additional five years, to complete five years, or you could give the patient no further therapy. If the patient goes into menopause after five years of tamoxifen you have two choices. You could either start an aromatase inhibitor for an additional five years or you could complete 10 years of tamoxifen. And with the SOFT and the TEXT results that we discussed, you’ll see the footnote, "an aromatase inhibitor plus ovarian suppression for five years may be considered as an alternative option". So this is directly from the results of these studies.
For postmenopausal women there are many choices that we have for adjuvant endocrine therapy. Patients can receive an aromatase inhibitor, daily for five years. Patients may be started on tamoxifen for two to three years and switch to an aromatase inhibitor to complete five years of therapy. Patients may be treated with tamoxifen for approximately five years and then switch over to an aromatase inhibitor for an additional five years. Patients may complete 10 years total of tamoxifen. Patients who are started off on an AI but have significant symptoms such as joint or muscle aches, or osteoporosis; patients --- these patients may be switched after two to three years to tamoxifen to complete five years of therapy. And if patients have a contraindication to an aromatase inhibitor such as severe osteoporosis, tamoxifen for five or 10 years could be considered.

This is information from the ASCO Practice Guideline for adjuvant endocrine therapy but it also provides an excellent summary of this topic. First of all, endocrine therapy is effective only among patients with tumors that express ER and PR. So there is some argument regarding the exact percentage that is required. However, more than 10% for ER-positivity is clearly an indication to receive endocrine therapy. Additionally, women who are pre- or perimenopausal at the time of breast cancer diagnosis should be treated with tamoxifen. And it should be noted that these guidelines were developed before the results of the TEXT and the SOFT trials were available. So I would add that an aromatase inhibitor with ovarian suppression could potentially be an option for these patients as well. Next, most postmenopausal women should consider taking an aromatase inhibitor to lower recurrence risk or receive 10 years of tamoxifen. So both of these are options. And then, finally, and as you can see from the many options that we have, the optimal timing and duration of endocrine therapy are unresolved. So we have many different ways that we can appropriately administer this endocrine therapy. This concludes my presentation. Thank you for your attention and we welcome your feedback.