Hello. My name is Diane Hecht and I’m a clinical pharmacy specialist in the Division of Pharmacy at The University of Texas MD Anderson Cancer Center. Today, I will be presenting the Role of Chemotherapy in Breast Cancer Survivorship.

After completion of this lecture, participants will be able to: describe the current prognostic and predictive factors with clinical utility for breast cancer; interpret the rationale for systemic treatment of early stage breast cancer; recognize patients with operable disease who are likely to benefit from systemic treatment of chemotherapy and/or biotherapy in addition to local therapy;...

...identify chemotherapy and biotherapy regimens which have demonstrated benefit in the treatment of early stage breast cancer and are, therefore, considered standard of care; and, lastly, outline the current treatment approach with systemic chemotherapy and biotherapy in patients with operable disease.

Breast cancer is not one disease. It’s rather a diverse or very heterogeneous disease. And it’s driven by multiple genetic alterations and molecular events resulting in identification of the unique subsets of patients, and tailored treatment based on risk versus benefit principles.

Unique subsets of patients, therefore, required a varied approach --- a varied treatment approach based on prognostic and predictive factors. Prognostic factors are those in the absence of systemic therapy include correlation with the natural history of the disease, reflect the inherent aggressiveness of the cancer, and are associated with the likelihood of distance --- distant recurrence. Predictive factors, on the other hand, are associated with response or lack of response to a specific therapy.

Specific prognostic factors utilized in clinical practice today include the following: axillary lymph node status, tumor size, the histologic subtype and/or grade, tumor cell proliferation in disease, as well as patient characteristics. Established primary factors include the lymph node status and the tumor size. Regardless of lymph node status, the size of the primary tumor remains an independent prognostic factor for distant recurrence.

Now, let’s review the predictive factors in clinical practice. And these include the hormone receptor status, which are the estrogen and progesterone receptor. And they predict the response to hormone therapy. Likewise, we now know the Human Epidermal Growth Factor Receptor 2. Its amplification or overexpression is also involved in certain subsets of breast cancer. And, therefore, predict response to trastuzumab therapy which is a monoclonal antibody directed against that HER2 receptor. It’s also possibly predictive of the response to anthracycline chemotherapy as well.

The use of prognostic and predictive factors allows us to limit the use of potentially toxic drugs to most --- to patients most likely to benefit. And, likewise, it saves patients not likely to benefit from significant toxicities and comorbidities. Evidence-based computer
modeling is also utilized today, which combines tumor and patient-related factors to predict clinical outcomes. The risk versus benefits of additional systemic therapy after local treatment can be reviewed.

Genetic profiling or gene expression-based prognostications predict the likelihood of recurrence in node negative patients.

All patients with invasive breast cancer unfortunately are at risk of the development of metastatic disease. Clinically detectable cancer has had an opportunity to establish distant micrometastases even in the early stage. Likewise, there is no ordinary pattern of tumor cell dissemination; although we know the bloodstream is important. Recurrence following local regional therapy is most common at distant sites.

Reduction of risk requires systemic treatment with chemotherapy, endocrine therapy, and/or biologic therapy along with the local treatment.

The systemic treatment approach is utilized in both early Stage I and II as well as locally advanced or Stage III breast cancer. These patients need to have no evidence of metastatic disease but have a high likelihood of recurrence. The goal is curative or to improve long-term survival and the systemic treatment reduces the likelihood of both local and distant recurrence. Adjuvant therapy and neoadjuvant therapy are both utilized in systemic treatment approaches of early stage breast cancer. Adjuvant therapy occurs following local therapy.

Whereas, neoadjuvant therapy is administered preceding definitive local therapy. Randomized phase III trials have demonstrated that the preoperative approach is equivalent to the postoperative therapy in terms of disease free and overall survival.

Neoadjuvant therapy includes chemotherapy plus or minus biotherapy, as well as hormonal therapy, although much less frequent use of hormones. The National Surgical Adjuvant Breast and Bowel Project, which is a cooperative group in the United States, had two large trials, the B-18 and B-27, which tested preoperative chemotherapy and included a 16-year follow up. The results included achievement of a pathologic CR in the breast and negative axillary nodes, and clearly predicted favorable long-term outcomes and disease free and overall survival.

Additional benefits of neoadjuvant therapy are that it can render an inoperable tumor resectable; it can increase the rate of breast-conserving treatment; and it can determine response to therapy in vivo. We do need accurate baseline tumor assessment for staging and post-treatment assessment. So imaging studies and pathologic assessment of the tumor tissue is essential prior to preoperative therapy.

The benefits of chemotherapy are not distributed equally across all patients. And, again, this is going back to the previous slide which described the unique subset of patients and the diversity within breast cancer. The challenge is identifying those patients most likely to benefit. So we have to balance recent advances about the
disease with results from existing evidence from meta-analyses. A --- an Early Breast Cancer Trialists' Collaborative Group or EBCTCG was formed in the mid 1980s and essentially they've collected data worldwide and run these meta-analyses on adjuvant systemic therapy trials. And they have reported 10-year and 15-year effect on recurrence and survival. There was a publication in Lancet 2000 and there's recently been a publication this year, in 2012, with some updates.

In the 2000 overview analysis polychemotherapy versus no chemotherapy was reviewed. Polychemotherapy is defined as combination chemotherapy which for the most part, during those years, included the regimen CMF or FAC or FEC. So, either using doxorubicin or epirubicin in combination with fluorouracil and Cytoxan. This overview analysis included 29,000 woman randomized by the year 2000 to trials started in 1995. Most of the time, the patients received either 6 or 12 months of the CMF or the anthracycline-based chemotherapy. And, at this point, remember there were no taxanes or biological agents. So this was strictly chemotherapy only. And few women over the age of 70 were included in the trials. Significant improvements in the absolute risks of both recurrence and breast cancer mortality, taking all ages together, were found. The relative risk for recurrence was 0.77 and for mortality 0.83.

The absolute benefit from chemotherapy for both younger and older patients appeared most significant in the ER or horm --- hormone negative populations.

This slide depicts the 15-year probabilities of polychemotherapy versus no chemotherapy in the EBCTCG 2000 overview. Benefits in the risk of recurrence and breast cancer mortality remain significant at 15 years for both younger, or those less than 50 years, as well as the older, those age 50 to 69 years. The absolute benefit at 15 years was about 3 times better for the younger versus the older age women, and also better for recurrence versus mortality. However, the older women also benefited. The benefits also included both node negative and node positive, regardless of age.

And, this is shown on this next slide with the following graphs. On the left, we have the younger patients, those less than age 50, showing breast cancer mortality of the control versus the polychemotherapy. And the right graph is the older women, ages 50 to 69, control versus polychemotherapy. So that you can see where these two graphs are running a lot closer on the older women. Yet, there is still a 15-year gain of 3% whereas in the younger women there was a gain of 10%.

Likewise, polychemotherapy for 12 to 24 weeks was reviewed. And we look the --- the authors looked at single agent versus combination regimens as well as the timeframe or the length or duration of treatment of chemotherapy. So, firstly, the age-standardized effects of single agent regimens were significantly less favorable than the combination chemotherapy reg --- regimens for both recurrence and mortality.

In terms of longer versus shorter duration regimens, the weighted mean treatment duration was 10.7 versus 5.0 months. And, this included mostly CMF-based regimens. But this demonstrated little long-term gain with longer durations. The recurrence rate
was 8.3 versus 8.7% per year and the death rate ratio was 0.98. This gave us information about how long we needed to treat these women with chemotherapy and were eventually biotherapy. And it showed us that we didn’t necessarily need to continue it for a longer period of time in order to achieve the same results.

And it also confirmed, as we suspected, that combination therapy is actually significantly better than single agent, and, hence, our recommendations of using those combination therapies today. Regarding the specific regimens, there’re a number that have been evaluated in phase III clinical trials and are considered appropriate. I recommend that you review the NCCN Guidelines for Breast Cancer and where the St. Gallen International Breast Cancer Expert Panel Guidelines on this topic.

On this next slide I do have a list of the cytotoxic drugs which are used alone or in combination and they include drugs in the anthracycline, alkylating agent, antimetabolite, and now today, the taxanes.

Anthracyclines are a key class of cytotoxic chemotherapeutics in the adjuvant and neoadjuvant setting today. The 2000 analysis confirmed modest, but highly significant benefit of anthracycline-based regimens for approximately 6 months, as compared to the CMF regimen, also given for 6 months. The absolute benefit at 15 years was a 3.4% in recurrence and 3.3% reduction in mortality. This was seen in both younger and older groups and it was independent of hormone status.

The taxanes were --- are a more recent class of chemotherapy. And these also now provide the backbone for current adjuvant and neoadjuvant therapy. Multiple large, randomized trials with docetaxel and paclitaxel have also been reported. And they’ve tested the sequential taxane after an anthracycline-based regimen in addition to a concurrent taxane and anthracycline regimen. We’ve also looked at whether or not taxanes can replace anthracyclines. And, at this point, you know, there is some information. And, again, it goes back to this notion of unique subsets of patients need unique or personalized therapy. And so, therefore, we can’t as of yet today, we don’t have data saying that taxanes can replace anthracyclines. However, there may be patient populations whereby taxanes combination chemotherapy without anthracyclines is appropriate.

In a 2008 meta-analysis evaluating the addition of taxane to anthracycline-based regimens, there was an absolute risk reduction at 5 years. Now, again, we don’t have, you know, 10 and 15-year data yet at this point but we will. And so, at this point, at 5 years, there was a reduction in recurrence of 5% and in death of 3%.

This next slide represents the curves of these taxane-based trials and on the left is the cumulative estimate of the probability of disease free and overall survival up to 2 --- 5 years --- [excuse me] --- derived from the stratified pooling of trial data. The control is in blue and the taxanes are in yellow. On the right-hand side is the estimated absolute risk reduction at 5 years, gained by the addition of taxane to anthracycline-based
adjuvant regimens, again showing an approximate 5% benefit in disease free survival, and 3% benefit in overall survival.

Now, let’s move to adjuvant biologic therapy. Again, like the taxanes, the biologics are much newer group of drugs. But, they are currently standard of care for those patients who have amplification or overexpression of the HER2 receptor, which occurs in approximately 20-30% of patients with breast cancer. We know that the HER2 over amplification is associated with increased tumor aggressiveness, increased rates of recurrence, and increased rates of mortality. Therefore, HER2 testing is done in all newly diagnosed patients. We, also, luckily, have a monoclonal antibody against this HER2 receptor protein, called trastuzumab, which was approved by the FDA in 2006 in the adjuvant setting. It was initially approved in the metastatic setting. And the appropriate clinical trials have been done in the adjuvant setting, showing its benefit in this area as well. These were for node positive or node negative and tumor greater than 1 cm.

There’s a meta-analysis including five clinical trials with 9,739 patients, so almost 10,000 patients, we’ve been able to look at with benefit of adjuvant biologic therapy. And that was trastuzumab in combination with chemotherapy versus chemotherapy alone. And these showed a significant survival benefit with the combination of trastuzumab and chemotherapy. In terms of disease free survival, there was a 0.62 reduction in relative risk, which is a 38% lower --- [excuse me] --- a 0.62 relative risk which is a 38% lower relative risk for disease progression or death, and for overall survival, a 0.66 relative risk which is a 34% lower relative risk for death from any cause.

Next is a forest plot of the disease free survival. And on this slide you'll see the 5 different trials listed and the relative risk and essentially, if the value is lower than 1, then it’s a beneficial effect when combined with chemotherapy. And so you can see for all studies, the effect was --- was very beneficial.

Adjuvant therapy for HER2 positive breast cancer essentially is being given for one year unless there’s a contraindication. We administer it weekly or every 3 weeks. It’s used either concurrently with a taxane or after the completion of chemotherapy. But we generally have weighed giving it along with anthracyclines, although there are some studies and some trials that have been done where they’ve been used together in younger, healthy patients or younger patients with non-cardiac comorbidities. However, a thorough cardiac assessment which includes either an echo or a MUGA is required in all patients prior to and during trastuzumab treatment. And this is because there’s a black box warning for either clinical or subclinical cardiac failure. Now the mechanism of this tends to be different from the anthracyclines. But, nonetheless, we generally, at this point in time avoid using the two drugs together because the highest absolute incidence occurred when given in combination with an anthracycline.

Now we’ve also tested trastuzumab in the neoadjuvant setting and this includes trastuzumab again in combination with chemotherapy. And we’ve documented high pathologic complete response rates as well as disease free survival rates. So there
was a study actually done here at The University of Texas MD Anderson Cancer Center of 42 patients. And these women had Stage II to IIIA invasive breast cancer but non-inflammatory. And they received 24 weeks of trastuzumab in combination with neoadjuvant chemotherapy versus the neoadjuvant chemotherapy alone. There was also a second cohort of 22 additional patients treated with the combination so that we could get additional information on the combination. Likewise, in Europe there was a study of 235 patients with locally advanced or inflammatory breast cancer which also, well actually which utilized one year’s worth of trastuzumab in combination with neoadjuvant chemotherapy versus neoadjuvant chemotherapy alone.

These were both positive trials so neoadjuvant trastuzumab is now supported by the NCCN and the St. Gallen Guidelines for the treatment of HER2 positive early stage breast cancer.

Ongoing studies, however, are looking at the optimal duration of trastuzumab, the timing of trastuzumab initiation and relationship to chemotherapy. So, do we give Herceptin plus the taxane first or do we give it after the usual chemotherapy? And then, we are also combining it with investigational tyrosine kinase inhibitors and other monoclonal antibodies.

So, in summary, I’d like to finish with the fact that breast cancer, again, is a very diverse or heterogenous disease. The benefits of systemic treatment with chemotherapy and biotherapy differ across different patient subsets. So the decision regarding the use of chemotherapy and/or biotherapy is based on an estimated risk of recurrence and benefit of therapy. Biologic features play an expanding role in the systemic treatment decisions that we are making. And meta-analyses of randomized trials with adjuvant chemotherapy and biotherapy demonstrate reductions in the odds of both recurrence and death. Thank you for your attention today and we welcome your feedback.