Program Title: Hormonal Therapies for Breast Cancer
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**This program was presented in partnership with Northern Westchester Hospital, Northwell Health.*

Guest Speaker: Dr. Lev Davidson, **Medical Director of the Cancer Treatment and Wellness Center at Northern Westchester Hospital.** Dr. Davidson is Board Certified in Internal Medicine, Hematology and Medical Oncology and actively participates in ongoing research in this field. Dr. Davidson joined the staff of Northern Westchester Hospital in 2016 where he leads an excellent team of oncology physicians and staff.

Program Description: Hormonal therapies, commonly used to treat estrogen-receptor positive breast cancer, may be used at different points in a treatment plan and to treat various stages of breast cancer. This webinar addresses the following topics: An overview of the different hormonal therapy options; possible side effects and how to manage them; the latest research; how recommendations have changed; how long should this treatment continue.

NOTE: You may find it helpful to view and listen to the slides from this webinar (which are posted on our website and YouTube channel) while reading through this transcript.

Robin Perlmutter Good evening, everyone. I'm Robin Perlmutter peer counselor here at Support connection. I would like to welcome you all to our Nationwide webinar on hormonal therapy for breast cancer with Dr. Lev Davidson. This presentation is in partnership with Northern Westchester Hospital Northwell Health.

Remember that. Dr. Davidson is sharing his expertise any information from tonight or questions pertaining to individual concerns should be discussed with your doctor.

It's with my great pleasure that we have. Dr. Lev Davidson Medical Director of the Cancer Treatment and Wellness Center at Northern Westchester Hospital. Dr. Davidson is board-certified in Internal Medicine Hematology and Medical oncology, and he actively participates in ongoing research in this field.

Thank you Dr. Davidson for sharing your time and expertise with us tonight.

Dr. Davidson Thank you so much. Before I begin the discussion tonight. I would like to take a moment to thank Robin and the Support Connection for inviting me here and all their help in setting everything up. Most importantly I would like to thank tonight's participants for allowing me this opportunity to speak with you. I am not sure if we as doctors tell you enough that you have at least an equally great impact on our lives as you may think we do on yours. And also how much inspiration we draw from you.

Therefore, at this time. I would like to begin our discussion regarding hormonal therapies for the treatment of breast cancer.

Tonight's discussion matter is in regards to treatment of breast cancer with hormonal therapies, otherwise known as endocrine therapy. Hormones are present in every woman's body. But the most important ones for the purposes of this conversation are estrogen and progesterone. The reason for this is that they can fuel some forms of breast cancers.

This can help breast cancer cells grow, divide and spread. If the tumor cells from a biopsy or a surgical sample contain estrogen receptors, the cancer is called estrogen receptor-positive disease or ER positive. Approximately 80 percent of all breast cancers contain estrogen receptors. The majority of these types of cancers will also contain receptors for progesterone otherwise called PR+ disease. When both receptors are present on the cancer cells, we typically call that hormonal receptor-positive disease or HR positive.

I do not want you to get too worried or overwhelmed by this graphic. I'm going to focus on the upper half of this representation particularly and I will come back to it several times during this discussion. For our purposes now, I would like for you to note the green estrogen molecules in the upper right-hand corner. You can see them binding and activating estrogen receptors and then make note of those estrogen receptors activating a cascade of reactions that eventually will lead to the cancer cell replicating as genetic material and dividing and forming new cancer cells.

In the last 10 to 15 years targeted therapies have become the cutting edge of cancer treatment and research. If you think about it from the last slide how these hormonal medications work, they are one of the earliest forms of targeted therapies that we use in cancer care. The goal of any hormonal medication is to block the effect of these hormones on the cancer cells.

So there are two main mechanisms by which these medications can accomplish this. The first is to interfere with the interaction between the hormone and its receptor. Examples of medications that work this way include Tamoxifen and Faslodex. Tamoxifen is what we call a SERM(S-E-R-M) which stands for a selective estrogen receptor modulator. It's the modulator portion of the description, which is particularly important and should be noted. What this means is that depending on the organ it can either block the effects of estrogen or behave like estrogen. This is important to keep in mind as this will later explain some of the risks and side effects associated with this medication.

The other mechanism by which these medications can work is to prevent the production of estrogen and some of the examples are given in this slide. It is important to take note at this time that the aromatase inhibitors which are a very important medication in the treatment of breast cancer are not effective at blocking production of estrogen by the ovaries. This will later explain why they cannot be used themselves in premenopausal women. I also put in the surgical removal of ovaries just as a reminder that not only medications can help control levels of estrogen.

And speaking of side effects, why don't we go over some of them now. Let's start with Tamoxifen. Remember what we previously said that it's a modulator of estrogen. So when you look at its effects on the liver, it actually behaves like estrogen. We make clotting proteins and cells in our livers. Estrogen increases the production of these clotting factors and increases the risk of blood clots and strokes. This is the same mechanism by which estrogen-based oral contraceptive pills cause increased clotting. In the uterus Tamoxifen also behaves like an estrogen. So it is constantly stimulating the uterine lining which can lead to an increased risk of uterine cancers. Other side effects include cataracts, mood swings, depression, and loss of libido.

Tamoxifen tends to be the medication of choice for men who develop breast cancer and some of the side effects that men experience are listed there as well. Fulvestrant also known as Faslodex, works by decreasing the number of receptors for estrogen on the breast cancer cell surface. Some of the side effects are listed there as well.

Now, let's take a look at the aromatase inhibitor group of medications. Remember what I said, they are ineffective at blocking the production of estrogen in the ovaries. Therefore, they cannot be used by themselves in women with functional ovaries, meaning premenopausal women. As you can see there is an increased risk of heart attack, heart failure, and high cholesterol. Bone loss is also another important issue and the most common reason for which women stop medications are joint pains. Mood swings and depression can also worsen while on these treatments.

At this time, I am going to pause a moment and discuss what has become a very important topic regarding the use of Tamoxifen. Tamoxifen is metabolized in the liver by a specific pathway called the CYP2D6 pathway. Tamoxifen by itself is what we call a prodrug. This means that it is less active as a cancer treatment than the parts that it is broken down into by this liver pathway.

One of the byproducts of metabolism is called endoxifen, which is really the substance that does most of the work of treating breast cancer. So a group of antidepressant medications known as SSRIs can inhibit this pathway. Paxil is notorious for this, Zoloft is less so and we think that Effexor and Celexa are relatively safe for you so long with Tamoxifen. These are an important class of medications as patients being treated for breast

cancer are often dealing with depression and we often use these medications to deal with hormonal therapy side effects.

Other commonly used medications that can interfere with the production of endoxifen and potentially decrease Tamoxifen's effectiveness include Quinidine, which is commonly used in cardiology, Benadryl and Tagamet which are over the counter medications. With these kind of interactions, it always shocks me to think that these are over-the-counter medications.

Next, let's take a look at which settings we do use endocrine therapy in. The first is called neoadjuvant treatment. This means that the treatment is received before the definitive surgery. The goal for doing this is to reduce the size of the breast tumor and to allow for a better surgery and for surgery that could reduce the amount of breast tissue removed.

The second setting in which endocrine therapy is used is called adjuvant therapy. This is given after definitive surgery has already been performed. The goal in the setting would be to reduce the risk of the same breast cancer returning and also to reduce the risk of developing a new cancer in either the same or opposite breast.

Lastly, the third setting would be when the disease is more advanced or has recurred in a previously treated breast, chest wall, or nearby lymph nodes or the disease has spread to other organs known as metastatic disease. The addition of specific targeted therapies in that situation have now become the standard of care. And I will cover that a little bit later in the discussion. So let's take a look at the first setting which we discussed which was the neoadjuvant setting. Again, the goal here is to take what maybe an inoperable cancer at diagnosis and try to convert this into an operable tumor. This can also be performed to try to achieve a better cosmetic outcome. Typical findings for taking this approach include larger tumors, involved lymph nodes, locally advanced disease that is invading into other structures.

A landmark study called the NSABP 18 trial proved by giving the same treatment before surgery did not affect the long-term outcomes negatively and that preoperative treatment was an acceptable approach. Particularly in postmenopausal women endocrine therapy for hormone receptor positive tumors has been found to be a viable option. However, data in premenopausal women suggest that overall preoperative therapy should be in the form of chemotherapy.

GEICAM is a collaboration group of breast cancer researchers in Spain. They looked at preoperative treatment with either chemotherapy or endocrine therapy with the response rates being significantly better in the preoperative chemotherapy group. With data such as this endocrine therapy in the preoperative setting has typically been reserved for postmenopausal women, particularly ones with other significant medical conditions that would likely make them poor candidates for chemotherapy.

Current research is suggesting that this can be a viable alternative for other postmenopausal women. As you can see reviews that pulled the data from 20 different studies together adding up to approximately 3,500 patients showed similar response rates, surgical outcomes and radiological outcomes when endocrine therapy was compared to chemotherapy in postmenopausal women. These reviews also showed that aromatase inhibitors tended to have better outcomes than Tamoxifen in this group of women.

So naturally, the next question should be how long should we continue women on endocrine therapy prior to performing the surgery. The answer to this question is not definitively known. However, given the endocrine therapy usually takes longer than chemotherapy to show its beneficial effects, the majority of us will prescribe it for about three to six months before surgery. Some may even continue it up to 12 months if the person is showing a continued response to this type of therapy.

At this point, I would like to discuss something that has changed the way we assess and treat breast cancer after it is surgically removed. What you see on this slide is an Oncotype Dx report. There are others like it but this tends to be the one most commonly used. This is a predictive model. It's based on 21 genes that have been associated with breast cancer. Each of these genes carries a different significance or weight. Based on this a score is calculated. The score typically falls into a range of either high, intermediate or low risk for

recurrence. This test is typically performed on a surgical sample after it has been removed, but it is also possible to perform this on a biopsy sample.

As you can see in the first box is the actual score. The second box tells you what the risk of the disease returning at nine years after having taken endocrine therapy for a total of five years. And lastly, the third box tells you what the additional benefit of adding chemotherapy to endocrine therapy may be.

On the grid right below those three boxes is an explanation of chemotherapy benefit. The first thing you should notice is that there are different levels of benefits depending on the age with a cut-off of being at 50 years. On both extremes with a recurrent score of 15 or less and 26 or greater, there is either very low benefit or a significant amount of benefit to adding chemotherapy respectively.

It is the midline group of scores between 16 and 25 that shows some differences based on age. It is that middle group that has been better defined by recent studies such as the TAILORx trial.

The last bullet that I presented on the prior slide is what is being investigated currently. If the Oncotype Dx study is performed in a biopsy sample and it shows that the woman is at low risk for recurrence with chemotherapy likely to be of little benefit, then can we use this information in the preoperative setting to decide if endocrine therapy may be the better option in that patient.

I will now move on to the second setting in which we may offer women endocrine therapy. This is what we called adjuvant treatment after definitive surgery has already been performed. Again, I will break down the discussion into two groups pre and postmenopausal women. I will start with the treatment of premenopausal women. We will also need to break this group down further into two separate sub groups: Women who are at high risk of recurrence and ones that are at lower risk of recurrence.

The women who are at higher risk are typically defined by age of less than 35, larger primary breast tumors, lymph node involvement, a high recurrence score such as the TAILORx as we discussed in the prior slide, and people who are candidates for or have received chemotherapy.

Two relatively recent and large anticipated trials named the SOFT and TEXT trials established that these group of patients at high risk for recurrence stood to benefit even more if the function of the ovaries was suppressed in addition to taking medications such as Tamoxifen or an aromatase inhibitor. Please remember back to what I had said earlier about aromatase inhibitors being contraindicated in premenopausal women without the suppression of ovarian function. This step is a must if premenopausal women are going to be offered an aromatase inhibitor.

Women who do not meet high-risk criteria define the low to average risk group of patients. Studies have shown that these patients may carry a very small risk of breast cancer spreading to other parts of the body. Therefore, the addition of ovarian function suppression may not be a large enough benefit to justify the possible added toxicity of adding this type of treatment.

Therefore, Tamoxifen tends to be the preferred agent in this group of women. If menopause has achieved during treatment with Tamoxifen, then the additional benefit of an aromatase inhibitor can still be obtained by switching to an aromatase inhibitor at that time.

So what is the optimal duration of treatment for premenopausal women. Surprisingly, there have not been large number of studies addressing this exact question. The information that we have available to us tends to be extrapolated from the post-menopausal group of patients.

We know that minimum duration of treatment for endocrine therapy should be at least five years. The higher risk group of women we defined earlier obviously tends to benefit the most from extended therapy. And it is not unreasonable to consider a 10-year course of treatment for them.

Conversely, it's not clear that there is a significant enough risk in the lower risk group to justify the possible side effects of extending treatment beyond five years.

I will now move on to the next topic which is adjuvant treatment in postmenopausal women. This is a much better defined group of patients. There is sufficient data that state that the aromatase inhibitor group of medications are the preferred agent over Tamoxifen. The benefits seem to be maintained at any stage or tumor size. So women even with a one millimeter or a two millimeter tumor stand to benefit.

As you can see on the slide, there are three main agents in this group as listed. As we discussed earlier, the way they work is to suppress the production of estrogen. Looking at pool data from multiple studies, the aromatase inhibitors have an additional 20 to 35 percent reduction in risk of breast cancer recurrence when compared to Tamoxifen.

There is also a 15% reduction in the risk of dying from the disease at 10 years. As I mentioned in the earlier slide, studies have shown that if Tamoxifen is the initial medication started then switching within the first two to three years to an aromatase inhibitor, if possible still preserves, the added benefit of these medications.

Is one of these agents superior to the others? It does not appear to be so. As you can see from the graphic a trial of 1800 women that were randomly assigned to each of these three agents for five years did not really show any significant differences. The side effect profile may be a little bit different with Aromasin showing a greater tendency towards gastrointestinal side effects. Whereas, the other two agents show greater tendency to high cholesterol levels.

Let's take a quick look at the possible side effects from aromatase inhibitors. First and foremost, I would like to state that these can be very well-tolerated medications. Some of the possible side effects include those related to musculoskeletal symptoms as listed. As a group of complications we call them aromatase inhibitor musculoskeletal syndrome. Some of the maneuvers that seem to benefit women when they experience these side effects include twice-weekly supervised resistance and strength training as well as monitored aerobic exercise for 150 minutes per week.

The use of anti-inflammatory medications can also be beneficial. These medications can be stopped for even up to two months to alleviate these symptoms. The same medication can be retried or a different one in the class can be prescribed after resolution of symptoms. Acupuncture has also been shown to have some benefit in alleviating the symptoms.

I'd like to just say I'm lucky to work in a treatment center that also has a wellness program. The wellness program incorporates complementary treatments such as acupuncture and I personally have seen people benefit from this tremendously at times.

Another approach if all else fails is to stop the aromatase inhibitor and just switch to Tamoxifen as it does not have this type of side effect. We may also see an increase risk of vaginal symptoms and or painful intercourse. Generally, we recommend hormonal options such as those listed. And vaginal estrogens tend to be avoided as there is evidence that they can be absorbed into the bloodstream. And obviously, this is not a desired effect. For hot flashes the same goes that estrogen therapy is to be avoided. We can use a number of medications including the SSRI group of antidepressants that we mentioned earlier. They do not interfere with metabolism of aromatase inhibitors like they do with Tamoxifen. And again acupuncture may be beneficial as may Internet Cognitive Behavioral Therapy.

Some additional side effects are listed in the following slide, which include osteoporosis, increased risks of fracture, increased risk of cardiovascular disease, diabetes, high cholesterol levels, fatigue, forgetfulness, and some hair thinning has been seen. Despite all these side effects that I have listed, I would still like for people to keep in mind that as I mentioned earlier, these can be very well-tolerated medications.

So at this point, we've established earlier that the aromatase inhibitors go even beyond the benefit of Tamoxifen in the treatment of postmenopausal women in the adjuvant setting. However, sometimes it's not possible to treat with an aromatase inhibitor as it may not be well tolerated or contraindicated due to some of its possible side effects. Having said that it is important to note that Tamoxifen is still a very potent medication. Studies have shown that we can reduce the risk of breast cancer recurrence by almost 40% at 15 years. They have also shown a near 30% reduction of death from breast cancer at 15 years' time. Again, please keep in

mind the interaction with other commonly used medications that we have discussed before. And I have again listed some of the side effects related to Tamoxifen as a reminder.

So the next question to ask is, what is the optimal duration of endocrine treatment in the adjuvant setting? Again from current studies we noted that it should be minimally for five years of treatment. We also however know the risk of recurrence can steadily continue for even up to 15 years beyond the completion of treatment. Based on this information endocrine therapy beyond five years may be an option for some women with invasive breast cancer. This decision should be based on the balance of risk of recurrence versus the risk and side effects of continuing these medications for a longer period of time. High-risk features appear to be lymph node status with three positive lymph nodes being of particular high-risk. Tumors that are greater than 2 centimeters in size and a high-grade tumor. What this is referring to is the appearance of the tumor under the microscope. Tumor cells that look less and less similar to the cells from which they are derived are considered to be high grade.

Similar to neoadjuvant setting, gene predictive models such as the Oncotype Dx are being looked at to see if they can be useful in selecting out a population of patients who are not likely to benefit greatly from extended treatment and therefore avoid the additional side effects.

Two recent large trials called The ATLAS and aTTom trials look at extending Tamoxifen for five to ten years of therapy in the adjuvant setting. These were positive trials and show that doing this improved the risk of recurrence and even the risk of dying from breast cancer. There was also a further significant decrease in the risk of developing a new breast cancer in the opposite breast. And as one would suspect, the risk of side effects such as clotting and uterine cancer persisted throughout the duration of treatment with Tamoxifen.

Trials looking at combined modality treatment meaning starting on Tamoxifen at some point during the duration of the course of treatment whether it be a two, three or five years, switching to an aromatase inhibitor showed increased benefit when compared to completing a course of Tamoxifen only for five years. To this point trials looking at extending aromatase inhibitors beyond five years have not consistently showed an improvement in survival outcomes. Some of these trials have shown a decrease in recurrences or new breast cancers but again not in survival times.

Additional therapy does come at a price including more side effects related to bone pain, fractures and new onset osteoporosis. Some have even looked at different approaches including a shorter overall course of treatment or intermittent use of these medications without any significant difference in outcomes.

Next, I would like to try and summarize the adjuvant treatment of hormone receptor positive breast cancers on the following single slide. I found a schematic on an internet resource, which I think is an excellent summary and algorithm for the adjuvant treatment of breast cancer. I know it looks very busy. However, I will go over with you and I think it can simplify the discussion we just had about the topic.

Please look at the top two rows. The most important question there is if the woman is premenopausal. If she is not, then the data we discussed has shown aromatase inhibitors are the medication of choice. If she is premenopausal and simultaneously younger than the age of 35 given the very high risk of recurrence very serious consideration should be given to suppressing the function of the ovaries and offering the added benefit of an aromatase inhibitor.

If she's older than the age of 35, but still premenopausal, then the next step is to see if she falls into the category of high risk for recurrence. As you remember, these are the women with the larger primary breast tumors, lymph node involvement, high Oncotype Dx scores and ones that were considered for or given chemotherapy. If this is the case, then again consideration should be given to ovarian suppression with the use of an aromatase inhibitor.

If she is not in the high-risk category, then Tamoxifen can be given. If menopause happens during her treatment with Tamoxifen, then switching to an aromatase inhibitor can be considered to get the same benefit without the added side effects of ovarian function suppression. I think that this is the most important part of this whole schematic.

I will now move on to the final setting in which we use endocrine therapy. And that is in the advanced or metastatic hormone receptor-positive breast cancer. The first point on this slide, maybe the most difficult statement for us to have to make as we sit across from and discuss the approach to treatment with our patients. But I believe it is unfair to the person in front of us if we do not tell them the complete truth on which they will base further decisions regarding their health care and plan their lives going forward.

The goals of treatment with endocrine therapy in this setting therefore are to reduce tumor burden and symptoms with minimizing side effects, especially when compared to chemotherapy. In recent years, the addition of new targeted agents to endocrine therapy have shown substantial improvements in progression-free and even overall survival benefits in some of the trials. This approach therefore has become the standard of care for this disease. The three main group of targeted medications are listed on this slide. There are the cyclin-dependent kinase or as we call them CDK 4/6 inhibitors. And the three FDA-approved ones are listed there. There are also the PI3K Inhibitors and the one that is approved for treatment of breast cancers listed. As well as the mTOR inhibitors with one approved for breast cancer treatment being listed on my slide.

Chemotherapy is usually reserved for patients with cancers that appear to be either not responding to endocrine therapy or have extensive symptomatic organ involvement. The reason for this is that chemotherapy may show its beneficial effects more quickly than endocrine therapy and allow for relief of symptoms and prevent further organ dysfunction in a more timely fashion. There have been no studies that have shown adding chemotherapy to the previously mentioned combinations improves overall survival and therefore we generally avoid taking this approach.

Okay, does everyone have this slide committed to memory? I am bringing back this dreaded diagram to try to better understand how these new targeted agents interact with endocrine therapies. Hopefully some of these terms in the diagram are now a little bit more familiar to you.

Please make note of the box in the upper left hand corner that shows you where the PI3K and mTOR inhibitors work. When there are abnormalities in these targets they can interact directly with the estrogen receptor, even without estrogen being present and activate the pathway that will eventually lead to the breast cancer cell growing, dividing and spreading. It is almost like a switch has been flipped to the on position. This is one of the explanations for why breast cancer cells can become resistant to endocrine therapies.

These inhibitors can flip the switch back to the off position. As you can see when given together with endocrine therapy, you're blocking that pathway at multiple points. Please look at the CDK 4/6 molecule. This is a target for activated estrogen receptors to initiate the downstream growth process. Blocking the action of the CDK 4/6 also blocks this downstream cascade that again leads to growth of the breast cancer cells.

Studies looking at the CDK 4/6 inhibitors along with the aromatase inhibitors have shown often times an improvement in progression-free time by over 10 months with a total interval lasting for over two years. No one aromatase inhibitor in combination with these medications seems to be superior to the others. Some of the additional side effects attributable to these medications when combined with the aromatase inhibitors are listed and usually, the low white blood cell counts are the most pronounced.

Let's take a look at the next set of targeted agents that are highlighted in red the PI3K inhibitors. And again the dreaded diagram just as a reminder of how these medications work. As you saw from the prior diagram this pathway plays a significant role in mediating cell growth, survival and new blood supply formation. Mutations in these pathways have to be tested for on the tumor tissue and if present are targets for these medications. Mutations have been found in approximately 40% of all estrogen receptor positive breast cancers.

When these mutations are present, the medications are used in combination with Faslodex after a woman has failed therapy with an aromatase inhibitor with or without a CDK 4/6 inhibitor. Studies have shown a near doubling in the progression-free intervals in these settings. Some of the more common side effects attributable to these inhibitors are listed.

The last of the group of targeted medications are the mTOR inhibitors. Afinitor has been shown to be effective in combination with either an aromatase inhibitor, Tamoxifen or Faslodex as an option for postmenopausal women who have become resistant to aromatase inhibitors by themselves or in combinations such as with a

CDK 4/6 inhibitor. The side effects are listed. However, stomatitis seems to be the more prominent one. There have been recent studies showing a significant improvement in the severity and frequency of this side effect when people were given a course of preventive steroid mouthwash called Decadron. And as you can see from the slide, the best optimal sequence of these medications has yet to be established outside of using CDK 4/6 Inhibitors with an aromatase inhibitor as frontline therapies.

The final topic which I would like to touch upon tonight is the treatment of metastatic disease in the premenopausal woman. Ovarian suppression allows premenopausal women to take full advantage of the addition of targeted agents that have been evaluated in the postmenopausal setting. If this is chosen, then treatment options are similar to those described in postmenopausal setting previously. Some studies have shown that this approach may have a better progression-free time than some chemotherapies with improved tolerability's. The other option is if a woman does not wish to take the additional medications and possible side effects, Tamoxifen by itself as a single agent is also a reasonable alternative. A review of combined studies showed a response rate of 45 percent for Tamoxifen by itself.

This concludes my presentation on hormonal therapies for breast cancer. And, I would just like to leave you with a quote from Ben Franklin: "Tell me and I forget. Teach me and I remember. Involve me and I learn." I hope this information is useful to the people participating tonight and opens up the avenue for additional discussions with your treating doctors. At this point, I would be glad to take any questions. And again, thank you for allowing me to be involved in this discussion.

Robin Perlmutter Thank you. Dr. Davidson. Okay. We have a question in the chat. "Do the drugs Benadryl and Tagamet interact with AI's as well as Tamoxifen?"

Dr. Davidson Very good question. They typically do not because again the metabolic pathway, the way that these medications are metabolized are different between the group of aromatase inhibitors like I mentioned Femara, Arimidex, Aromasin as compared to Tamoxifen. It's really Tamoxifen and the metabolic pathway that the liver uses to break it down into its active agents is what's affected by Tagamet and Benadryl and obviously, the SSRI antidepressants are a big culprit of that.

Robin Perlmutter Okay. Thank you. We also have another question. Someone wants to know "If it's okay to stop taking Femara after 7 years or should they continue for 10?"

Dr. Davidson Yes, and another excellent question. As one of the slides shown that I presented. As of today there is no clear-cut evidence that there is a survival benefit for extending from 5 to 10 years. Certainly, there is an argument that could be made because there is a reduction in recurrence rates and new primary cancers. Everything really is based on an assessment of what the risk of the disease of returning coming back versus what are the risks of continuing on these medications for longer period of time. And that's very different for each individual. Obviously, if the risks are higher than the disease recurrence are higher than the risks associated with taking the medication, it may be something that I would certainly talk to my patients about considering continuing.

Robin Perlmutter "Do you ever see a time to stop taking Arimidex?"

Dr. Davidson Well, yeah, absolutely. I mean obviously, it depends on what the circumstances are. You know, unfortunately with metastatic disease, if you're treating a person in that setting then they're probably as long as the medication is working for that person and it's being well-tolerated there really isn't a role for discontinuation at this time.` However, if you're using it in as we talked about neoadjuvant or adjuvant setting. Again, just as a reminder that's before surgery or after surgery to prevent a relapse not that the person has widespread disease then again, it is really again a discussion. The current data suggests that five years is adequate but those who may be at a significantly higher risk of recurrence, you know could really consider extended therapies as I mentioned before.

Robin Perlmutter Okay, thank you.

"Is ovarian ablation a better option than suppression?"

Dr. Davidson Excellent question. So for suppression, as we talked about this is a pharmacological meaning a medication-based approach. So typically a woman could be given injections on a monthly basis to suppress ovarian function. Sometimes up to three, four month injection can be given however obviously surgical removal would obviate the need for continued medication. So my general approach is to initially start women on suppression, and if it's well-tolerated along with the aromatase inhibitor if that's our goal, which is you know to convert somebody who may not be able to take an aromatase inhibitor into someone who can take and get the extra benefit of an aromatase inhibitor. If the medications are all well tolerated and the side effects are manageable then you can have a discussion about having the ovaries removed and therefore not having to continue on additional medications.

Robin Perlmutter Okay, thank you.

"Does a premenopausal woman with only 20% estrogen-positive breast cancer benefit from Tamoxifen and AI's?"

Dr. Davidson Absolutely another fantastic question. So basically what the question is asking at what point do we consider women to be estrogen positive? So anything one percent or greater, we actually do consider to be estrogen positive. We do see that the majority of benefit tends to come from women who show approximately 10% or greater estrogen receptor positivity on their pathological samples. It's that gray area between one and nine percent, that's a little bit of a bigger question. But, we still do offer women hormonal based therapies if there's staining score is a 1 percent or higher.

Robin Perlmutter Okay, Thank you.

Someone's mentioning that "they are going to be taking Letrozole because they did not tolerate Arimidex, and is that an okay route to go?"

Dr. Davidson Yes, of course, it is. So there are two types of aromatase inhibitors. I kind of alluded to it when I presented the side effect where with Aromasin there's more gastrointestinal side effects and you know as I mentioned, hypercholesterolemia or high cholesterol levels, cardiovascular issues more so with the other two. And the reason for that is their molecular structure. So Femara and Arimidex tend to be a little bit more similar molecularly. So it's not inappropriate to try the other one, but there is a reasonable possibility that the same side effect may be experienced. At that point, I would try Aromasin because again molecularly it's slightly different. It's called a steroidal, aromatase inhibitor. So the structure chemically is a little bit different than the other two.

Robin Perlmutter Okay. Thank you.

"When taking Tamoxifen, is there a side effect monitoring protocol specific for the risk of uterine cancer or the development of blood clots?"

Dr. Davidson It's all based symptomatic. So close gynecological follow-up is a must. I have all my patients if they are not established with their gynecologist, absolutely re-establish. So minimally once a year evaluations and Pap smears, to see for any kind of abnormal cells being shed.

Robin Perlmutter "Could you stay on Arimidex forever?"

Dr. Davidson Theoretically yes. Would I necessarily recommend that, again, it also depends on the setting. So I mean these medications do certainly have side effects and you know, if as I mentioned let me give you one example osteoporosis new-onset osteoporosis is a very very real thing. I've had many many women have very significant bone density loss and if that increases your fracture risk that in itself could actually affect your lifespan as well. There have been very well-done studies in medicine that show for instance a hip fracture clearly One Survivor (in-audible). So everything has to be balanced off. But in the adjuvant setting I would not at all recommend something.

Robin Perlmutter Okay, "Are the side effects of these medications generally reversed once discontinued?"

Dr. Davidson Yeah, absolutely, absolutely quite feasible to have those reversed. And as I think I mentioned in one of the slides that it's not uncommon for us to have to stop the medications for a number of weeks and a lot of us have even stopped a medication for a month or two to allow for resolution of the side effects before resuming them or you know, considering a different agent.

Robin Perlmutter Okay, "Is removing ovaries in premenopausal women too risky versus taking AI's?"

Dr. Davidson You can't in premenopausal women. You cannot really initiate aromatase inhibitor therapies. Again, because as I mentioned, the ovaries are functional they're producing estrogen and the aromatase inhibitors do not affect their ability to do so. So what may happen if you put a premenopausal woman on an aromatase inhibitor, we have feedback loops in our body, hormonal loops. There may be an initial slight drop in estrogen levels, which will send a signal to the ovary while the levels are dropping, so let's increase production and you may get the exact opposite of what you're trying to accomplish. You may actually bump up the levels. That's why it's so important to prevent the ovaries from being able to produce additional estrogen. And as I said, it could be done one of a number of ways, giving medications that do that or removing the ovaries obviously is another option.

Robin Perlmutter Okay, thank you.

Another question. "How much of a risk are heart problems with Anastrozole and how to know if they are occurring?"

Dr. Davidson That's a long term question meaning obviously the day you go on your cardiovascular risk doesn't really increase. It's over a period of time and this was really, you know seen in women on these medications probably for you know, at least a year or two before you know that was assessed. So that that is a question that we as oncologists also have to get the person's cardiologist involved. You know, obviously if there is a recent heart attack and stents were placed obviously clearly that risk is much higher. If a person has a distant history of heart disease, let's say they had a heart attack 20 years ago, but have been fine since on medical management it's certainly you know a consideration and again everything in medicine is balance. So if the risk is high enough of breast cancer recurrence, whereas the cardiovascular risk is stable or you know, not overly significant, it may still be the most optimal medication for that person. If the cardiovascular risk is high and the breast cancer risk is lower than I would certainly think about different options.

Robin Perlmutter Okay, thank you.

Another question. "If you take a break from an AI due to side effects, is it appropriate to extend treatment beyond the total of five years?"

Dr. Davidson That can absolutely be considered because really it's still a five years' worth of treatment. And as I mentioned, we have studies that have shown even, slightly extended treatment two years instead of additional five years or even that approach that I showed you where the woman takes it for nine months on three months off. They actually showed reasonably good outcomes. Not a whole lot different than women who continued on it for an additional five years even.

Robin Perlmutter Okay, here's a question. "If you are on KISQALI. I'm going to spell it K-I-S-Q-A-L-I, can you take a break from the Femara for metastatic disease, finding the side effects from the AI very debilitating?"

Dr. Davidson Yeah, yeah. No. No, of course. That's a wonderful, wonderful question and there's not an absolute answer. But some data that's available some of these medications by themselves, you know may not be as effective because if you remember that diagram, I called it the dreaded diagram, they work in unison. This is all one big loop, one big mechanism that these medications work maybe on different parts of it and a lot of times one medication is dependent on the other to work equally well. There have been some studies with some of these targeted agents tried on their own or even combination with other targeted agents. And you know, the data is not as impressive as let's say the aromatase inhibitors with a CDK4/6 inhibitors as well.

Caller #1 Yes, if a person is on Anastrozole and it's recommended that they start participating in the every six months of a Prolia shot, what are the studies on how beneficial that Prolia shot is as opposed to the side effects of it?

Dr. Davidson I am going to assume that we are discussing in the adjuvant setting, meaning that the primary treatment for the breast cancer, let's say whatever was necessary surgery, radiation, chemotherapy has already been completed and that person is now on hormonal therapies endocrine therapies we discussed tonight. So there is data. Some of the data originates from Memorial Sloan Kettering here not too far.

And as a matter of fact, if you actually take a look at the NCCN guidelines or the National Comprehensive Cancer Network guidelines which you know, the majority of us consider typically, the gold standard in guidelines. Even women lacking any form of bone density disease, so I mean either osteoporosis or osteopenia, based on that data actually gain improvement in breast cancer-specific outcome. So yes, there is definitely data to support it again in the adjuvant setting about two to three years' worth of these kinds of medications. There's denosumab which is Prolia and then there's also Reclast with zoledronic acid part of the bisphosphonate group of medications. So there is clear cut data to suggest that you know breast cancer-specific outcomes independent of you know, bone density are improved with these medications. And again, probably for somewhere around two to three years' worth of use.

Caller #1 Thank you.

Dr. Davidson Of course.

Robin Perlmutter "Would you ever take Tamoxifen and Lupron?"

Dr. Davidson Absolutely, it can be done. Again there was a slide that I showed that's yet another approach. Again, if there is a contraindication to you know, aromatase inhibitors actually adding ovarian suppression with medications, like Lupron to Tamoxifen has also been shown to increase the benefit from hormonal therapies as compared to Tamoxifen by itself. So answer, yes, you can absolutely consider that.

Robin Perlmutter Okay, we have another question. "How quickly do I need to decide if I am going to be treated with hormonal therapy?"

Dr. Davidson General answer to that question is that with anything you're better off starting sooner rather than later. And you know, this kind of data is constantly developing. I see in our journals, you know, the number dropped from three months to one month then from one month to three months and then up to six months. So there are studies out there, you know that are showing maybe even up to you know, six months later, there's still benefit. I'm not encouraging people to wait that time period. I'm just saying if for whatever reason there was a reason that the medication couldn't be started. I wouldn't say well, it's too late don't bother starting it. But if you've made the decision and all is clear, I would certainly, you know, try to start the treatment sooner rather than later.

Robin Perlmutter I just want to take this opportunity to thank Dr. Davidson for your passion dedication and commitment to the cancer community and to all of you that came on the line tonight to become educated on this very important topic. I wish you all a great night.