

**Y-ME ShareRing Network
November 15, 2006
7:00 pm Central Time**

Tonight's program is supported by an unrestricted educational grant from Novartis Oncology. Our topic is, "Early Breast Cancer in Postmenopausal Women: Know Your Treatment Options" and our speaker is Dr. William Gradishar. Dr. Gradishar is Professor of Medicine in the Division of Hematology and Medical Oncology, Department of Medicine, at the Feinberg School of Medicine at Northwestern University in Chicago, Illinois, and a Member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. He also serves as Director of Breast Medical Oncology, Associate Director of the Lynn Sage Comprehensive Breast Program and Program Director of Northwestern University's Hematology/Oncology Fellowship Training Program. His research focuses on the development of novel therapeutics for the treatment of breast cancer and we welcome Dr. Gradishar this evening. You may begin.

Dr. William Gradishar: Thank you very much and as the opening comments suggested, what I'll do over the first part is just give a rather broad overview of the use of endocrine therapy for breast cancer patients who are postmenopausal and then as we get into a little bit more detail, focus on some of the newer therapies and then in the final part allow anybody who is listening to answer some questions, ask some questions relevant to the topic.

So for most patients who develop breast cancer, despite media attention justifiably for sometimes more dramatic cases that occur in younger patients or very, very young patients, the vast majority of breast cancer actually occurs in postmenopausal women. The characteristics of breast cancer in that population

are a little bit different than breast cancers that occur in premenopausal women and the most striking difference I suppose one might say is that more commonly breast cancers occurring in older patients in the postmenopausal population tend to be sensitive to the effects of hormones. One of the treatment strategies that has always been explored and developed has been somehow interfering with the effects of hormones on breast cancer and that's where the phrase, "Anti-hormone therapy" comes from. The first thing I think people should be aware of if they are not already is when oncologists or you read in lay literature that a patient is receiving hormone therapy, 99% of the time what they're actually receiving is anti-hormone therapy. I think it's an important small detail to recall that we're actually not giving hormones for most patients but rather trying to interfere with hormones that are made by the body or interfering with the effects of hormones at the level of the tumor cell. Just as a way of sort of historical interest, you can use, actually use hormones to treat breast cancer. In the past we used estrogen as a treatment for breast cancer and depending on the dose that is used, it's actually a relatively effective therapy for patients who have hormone sensitive breast cancer, but one of the problems and the reasons that estrogen was largely abandoned and to a great extent even progestin's was we have far more effective therapies that are better tolerated. For all intents and purposes as we go through this discussion, as opposed to hormone therapy what we're really going to be talking about is anti-hormone therapy.

For women who are diagnosed with early stage breast cancer, which generally means the disease is restricted to the breast or the lymph nodes in the armpit area, the first step for most women is to undergo local therapy which includes surgery and based on the information that is gained from looking at the

specimen, we determine whether or not the tumor was hormone receptor positive which means estrogen or progesterone receptor positive and if that is found to be the case then at least one piece generally always of adjuvant therapy, which is defined as therapy given after local therapy to get rid of any microscopic disease that might still be around, one piece of adjuvant therapy is universally going to be anti-hormone therapy. Whether a patient gets chemotherapy or not is really a discussion for another day, but focusing just on the anti-hormone piece, if a woman has hormone receptor positive disease, it's been demonstrated for the last 25 years we've known that giving an anti-hormone reduces the risk of the disease coming back and the anti-hormone therapy that most people think about when we go back anywhere beyond five years from the present time all the way back 25 years is tamoxifen and tamoxifen is an anti-hormone therapy that interferes with the effect of estrogen at the level of the tumor cell. So if a tumor cell has an estrogen receptor, what Tamoxifen does is rather than the estrogen attaching to the receptor, sort of like a lock and key, tamoxifen attaches to the receptor and rather than stimulating the tumor cell to divide and spread, it actually interferes with growth signals and as a result basically shuts down the tumor cell.

What has been demonstrated is that in patients with metastatic disease, which is advanced disease, not a topic for today, women who get tamoxifen have significant decreases in the size of their tumor in a significant fraction of patients. When it was used in patients with early stage breast cancer, it reduces the risk of recurrence and improve the overall survival and we've subsequently learned that giving tamoxifen as a prevention strategy before a woman even develops breast cancer if she has high risk, reduces the risk that a woman would ever develop

breast cancer. So tamoxifen is a very well established drug. It has been around for a long time. Used worldwide probably more than just about any other anti-cancer therapy and those are all of its attributes, but some of the downsides that we've recognized for a long time are that in a small fraction of women there can be some rather significant side effects. The most troubling ones in terms of medical consequences include blood clots which can occur in a few percent of all patients that are treated and in women who have a uterus and they go through the course of their life, probably 1 in 1,000 women can develop uterine cancer. If you take tamoxifen it can become 2 to 3 out of 1,000, so the risk doubles, but the numbers are still very tiny, but it's still obviously a very troubling side effect. Then there are some quality of life issues of course that occur with tamoxifen. There can be increase in hot flashes that have been demonstrated in some trials in some patients. Whether it's women undergoing menopause, change in metabolism or the effects of tamoxifen, some women will complain of weight gain and there are a whole list of rare side effects that can also occur. As a result of sort of this side effect profile, there were a lot of efforts that were made over the years to see if one could improve on tamoxifen. There were a variety of drugs that were like tamoxifen but with only subtle changes made in the structure that were evaluated to determine if they could improve the outcome not only in terms of reducing the risk of the tumor coming back, but also making the drug more tolerable and for all intents and purposes those small variations were basically a wash, things looked mostly like tamoxifen.

The other strategy rather than interfering with the tumor cell directly by blocking the receptor was to get rid of the thing that actually stimulated the tumor cell which was estrogen. So the focus of our discussion is really postmenopausal

women and at first blush one might think that in that population of women there's no estrogen because the ovaries don't work or they've stopped functioning for all intents and purposes, but in reality, estrogen is still made in small quantities, generally not from the ovaries, but from tissues different than the ovaries. Basically what happens is a precursor or something that has turned into estrogen is done so by an enzyme that actually converts precursors into estrogen and that enzyme is called aromatase and aromatase has been known about for a long time. There were actually efforts many, many years ago to interfere with that enzyme and drugs that we no longer use like aminoglutethimide were used 20 years ago. The reason that drug really didn't continue on in widespread use was because of the side effect profile of that drug and really in the late eighties/nineties, there were a whole panel of new drugs that were referred to as Selective aromatase inhibitors that came online. They began to be developed in patients with advanced disease and unique property sort of across the board about these drugs is they affected strictly the aromatase enzyme and they didn't affect anything else that was really going on in the body in terms of enzymes and as a result they could be appropriately called "selective" and the net effect was that they really decreased what little estrogen was around to even a lower level and the consequence of that, of course, is that there is less estrogen to stimulate tumor cells.

So in patients with metastatic disease, these different aromatase inhibitors, the newer ones, were all shown to be as effective or better than any of the previously used drugs for metastatic disease for anti-hormone therapy, things like progestins like Megace, as good or better than drugs like tamoxifen. So once it was demonstrated that they had not only significant benefit in terms of an effect

against the tumor, but also that they were generally well tolerated and specifically what was demonstrated was for most patients they were very well tolerated with relatively few side effects and specifically fewer issues with blood clots, fewer issues with vaginal symptoms and endometrial cancer. Of course, in a patient population that has advanced disease, patients may not unfortunately be on therapy for as long a period of time because of the nature of their disease. So where you could really judge the effect of these drugs were in patients with early stage disease where like tamoxifen we give drugs for multiple years at a time, similarly the trials that were designed for the aromatase inhibitors were designed to put women on these drugs for five or more year and that would be an opportunity not only to look at the long-term affects of the drugs in terms of the tumor, but also tolerability, how well patients tolerated these drugs.

So from the late eighties to the present time there have been numerous trials that have been conducted looking at the aromatase inhibitors in comparison to tamoxifen or in sequence with tamoxifen to determine if they reduced the risk of breast cancer coming back to a greater degree than what tamoxifen was able to achieve. When we're talking about aromatase inhibitors though, I'll focus my attention on what's available in the United States, although there are other drugs that are either being evaluated or are available outside the United States. The three that we have available here are referred to as Anastrozole or Arimidex, letrozole which is Femara or exemestane which is Aromasin and these are all oral drugs which makes them also very attractive and they're all similar in the sense that you take a single pill per day and the trials that were conducted in early stage breast cancer really followed the idea that women would receive an aromatase inhibitor initially for five years and that would be compared to

tamoxifen. There were also trials that looked at a group of patients who were getting tamoxifen for five years, which is sort of the standard, and that would be compared to a sequence in which patients started with tamoxifen and then after two to three years they were switched to an aromatase inhibitor. Then finally, there was a trial in which the issue of long-term therapy was evaluated and there have been some successors to that trial as well and basically the question that was asked in this trial was you get five years of tamoxifen and at that point patients were randomized to no further therapy or to receive letrozole for an additional five years and there has been a similar trial, smaller in size, with Anastrozole as well.

So I'm not going to talk in great detail about each of those trials because those are sort of almost long lectures, but I can basically try and convey to you what the results of that experience has been to date. Sort of to jump to the punch line, when aromatase inhibitors have been integrated into the adjuvant therapy of patients with postmenopausal breast cancer, who are sensitive to the affects of hormones, in other words, hormone receptor positive early stage breast cancer, sort of the consensus from all trials is that integrating an aromatase inhibitor either instead of tamoxifen or to follow tamoxifen has resulted in a better outcome for patients and better outcome is basically translated into a reduction in the number of recurrences that occur. So the strategy that most oncologists in the United States use is that they may start a woman on tamoxifen and then after a period of a couple of years switch that woman to an aromatase inhibitor or based on data from some trials that start out with an aromatase inhibitor; they may simply elect right from the get go to start with an aromatase inhibitor and continue it for five years. At the present time there are many different nuances

and issues that still revolve around these trials. Among the questions that are always raised: Well which one of the ones that are available is best? Which one should I make sure my doctor puts me on? And, quite frankly, it's very difficult based on the trials that have been conducted to date to say that one is better than another in terms of reducing the risk of breast cancer or reduce the risk of breast cancer returning. Whenever we talk about the effectiveness of a therapy, and by that I'm referring to reduction in risk of the disease recurring, the flipside of the coin is what are the side effects of the drug and as a class these drugs have sort of a similar profile and, again, there might be nuances between the different drugs, but as a group one can say, "Number one, they're well tolerated and number two, in contrasting it to tamoxifen, there are certainly fewer patients that develop blood clots; there's certainly not the risk of uterine cancer that we see with tamoxifen." On the other hand, or in general, any of the vaginal symptoms that may occur with tamoxifen, but in contrast, there are some issues with bone health that we have to recognize with the aromatase inhibitors, specifically any of these drugs as a class have the potential to cause a decrease in bone density over time. So we have to be very aware of that when we treat patients and we establish a baseline bone density, we make sure that women do the right things in terms of bone health, in terms of exercise, calcium intake, etcetera, and then we check the bone density generally annually to make sure that patients aren't developing osteoporosis, but that is a potential risk, osteopenia/porosis with any of these drugs.

At this time we have data to support any of these drugs as adjuvant therapy and there are several trials that are still being completed that may offer additional information in terms of how best to use them or which drug to use optimally in a

certain situation. As an example, there's probably a diminishing number of patients who started out on tamoxifen many years ago, have completed five years of tamoxifen and the question comes up, should I switch or should I at this time even if I've been off of tamoxifen for a few years go onto an aromatase inhibitor, might there be additional benefit even though I've completed five years of tamoxifen? One of the trials that has been completed that included letrozole actually did demonstrate that prolonged durations of therapy, meaning beyond five years, five years of tamoxifen and then five years of an aromatase inhibitor clearly further decreased the risk of the disease recurring. We also know that even if the interval between completing tamoxifen and starting an aromatase inhibitor is measured in years, patients may still accrue a benefit from a late start to an aromatase inhibitor. So I think that the general consensus again is that the aromatase inhibitors have made a difference for post menopausal women and I think that's a key point, you have to be confident the woman is postmenopausal if she is going to start on this kind of medication and for most oncologists, if a woman is premenopausal before starting say chemotherapy, we generally when we get to the anti-hormone therapy piece of her therapy will start with tamoxifen because many women despite stopping their menstrual periods, we aren't shocked when six months later their menstrual periods can resume. So I think the important point is you have to be absolutely confident that the woman is postmenopausal and for many of us we start with tamoxifen switching to an aromatase inhibitor down the line and also checking hormone profiles to be confident the woman is postmenopausal. As a result of this sort of data in the metastatic disease setting and then the discussion we just had about its use as an adjuvant therapy, there are trials underway to evaluate these drugs as

prevention therapies to prevent breast cancer from even developing, but there's no data at the present time.

So I guess I've sort of spoken for the desired allotted time, not to spend too much time talking about lots of data, but just to give sort of a broad overview regarding the use of endocrine therapies in postmenopausal women with early stage breast cancer. So what I'll do now is stop and if there are specific questions about this topic, I'm happy to answer them.

Our first question comes from Nancy from Virginia. Please go ahead.

Nancy:

Hi. I've taken, my question is whether or not after five years of tamoxifen and five years of Arimidex and ten years that I have taken Fosamax, if I should switch to Avastin or raloxifene, which has not yet been approved for breast cancer preventive, but has been approved for osteoporosis.

Dr. William Gradishar: Right, so if a woman with early stage breast cancer has already gotten ten years of adjuvant endocrine therapy as what you're describing, we don't know that more is better. There is certainly absolutely no rationale for putting a woman on Avastin and at this time if you're...

Arline Kallick: I think she meant Evista raloxifene.

Dr. William Gradishar: Oh okay.

Dr. William Gradishar: Well I heard raloxifene; I didn't know if it was, you're not.

Nancy: Right, you're right.

Dr. William Gradishar: Well I'll just make the comment. Avastin, no absolutely not, but Evista which is the commercial name for the generic raloxifene....

Nancy: Right that's what I mean.

Dr. William Gradishar: ...is a drug that has been shown to be beneficial as a prevention agent as well as for treating bone health. There is data in animals that women who have gotten five years of tamoxifen and then go onto raloxifene actually can have an increased risk of developing breast cancer and that's based on animal models. So our first thought would not be to switch a woman who has had tamoxifen who has had Arimidex back to raloxifene as a prevention strategy, particularly if she seems to be tolerating and benefiting from a bone builder like Fosamax.

Nancy: Okay that's, I had not asked my oncologist that, but I had decided not to switch for the time being. Thank you very much.

Dr. William Gradishar: You are welcome.

Operator: *Our next question comes from Priscilla from New Mexico. Please go ahead.*

Priscilla: **Yes, Doctor, I'd like to ask what the role of radiation is. Is that commonly prescribed for people with say a small, a very small tumor and that has not**

metastasized or appeared in the lymph nodes? Is that pretty standard to give the radiation along with the Arimidex?

Dr. William Gradishar: Well it's not so much; well I guess the first question is the setting where radiation is generally used is a woman who has had a lumpectomy for invasive breast cancer. The standard recommendation is she should have breast radiation and if a woman has had a mastectomy the circumstances might be that if she had a lot of axillary lymph nodes or a bigger tumor then even having had a mastectomy we give radiation. In terms of giving the radiation at the same time as anti-hormone therapy be it tamoxifen or one of the aromatase inhibitors, quite frankly it makes no difference and we're happy if a woman starts on it at the same time that she initiates radiation. We always give the radiation therapy physician, if he wants to wait a few weeks that's fine with us, but there's no data that suggests it's bad to combine it.

Priscilla: Thank you very much Doctor.

Operator: Our next question comes from Marie from New York. Please go ahead.

Marie: **Hi. I've been 2½ years on tamoxifen and I recently, a few days ago, my oncologist switched me to the Arimidex. Am I going to age now because the estrogen production has totally stopped?**

Dr. William Gradishar: No you still have residual even with the affect of the aromatase inhibitors and in this case Arimidex, you will have a lowering of the estrogen levels, but they

probably won't hit zero; there will still be some residual estrogen. Most women don't note a dramatic; you are not going to turn into a 95-year-old woman...

Marie: Yes right.

Dr. William Gradishar: ...in the next three weeks, so I wouldn't worry about that. Sometimes women will comment that the texture of their skin or something might change, but you have to keep in mind even though you're on letrozole, you're also at the same time you are aging and time does pass, which in the setting of breast cancer that's a great thing, but one would not expect you to have dramatic changes in your appearance or even subtle necessarily changes in either how you feel or your appearance simply by virtue of taking an aromatase inhibitor.

Marie: Okay good. **Now can I take the Arimidex for five years on top of the 2½?**

Dr. William Gradishar: Well that's an unknown, so the way I answer that question, it's sort of hedging is we'll see in 2½ years. It gives me 2½ years to figure that out, but the reality is there is no trial that has been done where it's been evaluated 2½ years of tamoxifen followed by an undefined period of an aromatase inhibitor. Most of the trials were a total of five years of therapy, but the reality is in practice when we're getting these women out to five years, if they don't have problems, many of us just continue them on the aromatase inhibitor beyond 2½ years.

Operator: *Our next question comes from Kathy from Virginia. Please go ahead.*

Kathy: Hello, Doctor, thank you for answering our questions. **My question is the differences or the marginal differences between tamoxifen and Aromasin. I was on tamoxifen for three years and now my oncologist has switched me to Aromasin and the side effects of both of those and is there a marginal difference?**

Dr. William Gradishar: Well all of the aromatase inhibitors are probably somewhat better than tamoxifen in terms of reducing the risk of breast cancer returning, so that's across the board. In terms of side effects, it's a tradeoff, you avoid some of the side effects that we equate with tamoxifen, the blood clot risk, the endometrial cancer risk, but you may buy an alternative problem which is bone health, so we have to monitor that. I mean for most women this is well controlled; we can treat that; we monitor it with bone density exams and we can supplement calcium and give drugs like Fosamax or other similar drugs to try and build bone. But on balance it is probably an incremental improvement over tamoxifen using aromatase inhibitors because you further reduce the risk of the disease recurring.

Kathy: Okay thank you very much.

Operator: *Our next question comes from Carolyn from Pennsylvania. Please go ahead.*

Carolyn: **Yes, I had taken tamoxifen and I developed the uterine cancer and then I was given Arimidex and now I'm taking Femara. Is that what you mentioned aromatase?**

Dr. William Gradishar: Yes both Arimidex which is anastrozole and Femara which is letrozole, exemestane which is Aromasin, those are all, all three of those are aromatase inhibitors. I'm not sure what the circumstances were for switching from one aromatase inhibitor to the other, but there may have been specific circumstances that are specific to you. But for most women we generally keep them on one and continue through their course of therapy, whatever that might be, and for whatever reason if there was some issue about tolerating the drug we might consider switching to another one, but generally we stick with one through the total duration of therapy.

Carolyn: **And that's usually five years, is that what you're saying?**

Dr. William Gradishar: That's the working concept right now, but, as I mentioned earlier, there are trials that are underway that are looking at even longer durations of therapy, ten years of an aromatase inhibitor. So I think the support for doing that isn't there yet just because we don't have enough data, but there's certainly an interest in looking at that.

Carolyn: Okay thank you.

Operator: Our next question comes from Peggy from Texas. Please go ahead.

Peggy: **I was wanting to find out what about if you are negative?**

Dr. William Gradishar: If you're hormone receptor negative?

Peggy: Yes.

Dr. William Gradishar: If a patient has a tumor that is hormone receptor negative there would be no benefit from anti-hormone therapy. So the general strategy is we wouldn't use that and I'm speaking of tamoxifen, aromatase inhibitors, any sort of anti-hormone therapy and depending on the risks the woman has it may be that chemotherapy is the more appropriate choice.

Peggy: **Okay because that's what they told me to take through chemotherapy. Hello.**

Dr. William Gradishar: I didn't hear the last comment.

Peggy: **I'm sorry. They said that I was going to need to take the chemotherapy.**

Dr. William Gradishar: And that's probably why because, as you already mentioned, you had a tumor that was hormone receptor negative.

Peggy: **Right and it was small, it was about 1.6 centimeters.**

Dr. William Gradishar: That's a dimension where many physicians will think the risk is sufficiently high where chemotherapy would be used.

Peggy: **Okay and that should take care of that then. I mean that should help it I mean.**

Dr. William Gradishar: That's the idea. That's why they are recommending it to you.

Peggy: Okay. All right thank you.

Operator: *Our next question comes from Mary from Texas. Please go ahead.*

Mary: Hello, Doctor, and thank you for your time. **I'm like the lady that you just spoke to. I'm ER and PR negative. I was on Adriamycin, Taxotere and Cytoxan. I am now in remission. My quick question is have you heard has Tycurb* been approved yet?**

Dr. William Gradishar: No, Tycurb is not approved yet. That's a drug that will likely be approved at some point and will work in patients with HER2 positive disease.

Mary: **That's what I have, yes.**

Dr. William Gradishar: And it'll, it's anticipated that sometime in the next year that'll be available.

Mary: **Next, it's going to be a whole year?**

Dr. William Gradishar: Well I don't know that, but sometime in the next year I would anticipate it will be approved.

Mary: Okay. **My doctor is going to be starting me since I'm in remission. He is going to be restarting me on Herceptin and he said that I'll probably be on**

that for about two years, taking it every three weeks. Does that sound like the general?

Dr. William Gradishar: Yes the standard, the standard therapy even if Tycurb gets approved will be that Herceptin is still used...

Mary: **Oh really.**

Dr. William Gradishar: ...as the preferred drug in the setting that you're describing and the standard right now today is for one year of therapy.

Mary: **One year.**

Dr. William Gradishar: Right.

Mary: **And it's every three weeks.**

Dr. William Gradishar: Every three weeks is acceptable yes, that's perfect.

Mary: **That's perfect and one last question and I thank you for your time, Doctor, very much. Would it benefit me at all to take Evista in addition to Herceptin to make, try to make sure that I minimize my chances of getting this again?**

Dr. William Gradishar: We would generally not recommend that, but, again, since your tumor was hormone receptor negative and you're still in the midst of your anti-cancer therapy with Herceptin, I wouldn't, I didn't think that adding raloxifene in this kind

of setting would be the sort of strategy we would use for most patients. We would generally give chemo Herceptin and then call it a day.

Mary: **And then call it quits?**

Dr. William Gradishar: Yes.

Mary: Okay and I thank you greatly for your time in taking time out of your evening, sir, to spend it with us.

Dr. William Gradishar: Sure I'm happy to.

Operator: Our next question comes from Sarah from Tennessee. Please go ahead. Sarah from Tennessee. I'll go to our next question. Mary from Texas, please go ahead.

Mary: **Hi, Doctor, my name is Mary and I'm an almost five year breast cancer survivor and my question is I've been on Femara now for almost five years, it will be five years in December, and I've only had I know one bone density test. Should I have another one?**

Dr. William Gradishar: Well the issue about how frequently to get bone density tests is not set in stone, but generally speaking if we place a postmenopausal woman on a therapy that has the potential for affecting her bone density we would want to check it at least whether it's every year or certainly every couple of years and the consequence is that if your bone density is declining significantly, and it may not be, it may be

perfect, is that you'd want to intervene so that you're not at a higher risk for developing a fracture and some of the medications that other callers were mentioning such as Fosamax, these are medications that build bones, so if we saw that a woman's bone density was declining over time we'd certainly want to get that on board, so to speak, to try and slow or prevent bone loss that could lead to osteoporosis and an elevated risk of fracture.

Mary: **Okay and one more question. Is one of the side effects of Femara joint aches because my joints have just really started to ache here lately?**

Dr. William Gradishar: Well it's I suppose a little bit surprising if you've been on it approaching five years, it's a more recent phenomena, so whether that's the Femara, whether it's arthritis is hard to know, but, again, across the board, Femara, Arimidex, exemestane, they can all cause some aches and pains in some patients and then of course you always have to tease out from this in a postmenopausal patient population is there a piece of that that is arthritis or is it the drugs, so you always have to try and sort through which of the two or both it is.

Mary: Okay thank you very much.

Dr. William Gradishar: You are welcome.

Operator: *Our next question comes from Kathy from Mississippi. Please go ahead.*

Kathy: Hi, thank you very much Doctor. **I am, I am a HER2 positive person. I've gone through all the therapies and now he finally put me on, it's not, he was**

going to put me on the aromatase inhibitors because my bone density was at osteopenia point, almost osteoporosis, so he put me on tamoxifen. Do you think that is better to put on or do you think that, then I thought about maybe Evista would be better? Also, if I were put on something else, would that be better and then if I got to the point that it was worse, do something else or what would you do?

Dr. William Gradishar: Well it's a judgment your doctor makes. He looks at what your risk of the disease coming back is, what your bone density is and I don't think anybody would tell you that tamoxifen is a lousy drug; it's a very good drug, but the newer ones are slightly better and when your oncologist sees any patient, he is going to decide - well I want to get the best therapy to prevent the disease from coming back. The patient who had very bad osteoporosis right at the start, he may decide in the big scheme of things that tamoxifen, which has close to the same benefit in terms of reducing the risk of disease coming back and may help build bone for a specific patient that might be the right choice as opposed to using an aromatase inhibitor which might be slightly better than tamoxifen for reducing the risk of the disease coming back, but if the woman already has horrible osteoporosis, she could have a greater risk of developing a fracture with an aromatase inhibitor. So I don't know the circumstances or any of the numbers with regards to your particular situation.

Kathy: Well really what I saw.

Dr. William Gradishar: But the issue is he has to, he has to weigh all of those things before making a decision.

Kathy: **Yes. Well yes and he is not just one specialist in that area, he has to do the therapy for an area of about 80 miles circular wide for all kinds of cancer, which makes it probably hard on him, you know?**

Dr. William Gradishar: Oh I suspect it does.

Kathy: **Yes and he travels from town-to-town, which is kind of bad in a way too. But I was wondering if you ever were, if I was put on like the Femara or something like that or the aromatase and my bone mass got better, I mean do you do anything like that sometimes? I mean is that a possibility?**

Dr. William Gradishar: Well for most patients it either stays the same or declines a little bit. Generally if people are taking one of the aromatase inhibitors all by itself, they don't build bone.

Kathy: **Oh they don't build bone, oh okay.**

Dr. William Gradishar: No, no.

Kathy: **Okay and also one other thing I was going to say, does this with a lack of hormone cause more, they call it chemo brain because I am losing everything? I mean I've lost my cap. I was going to the dentist and I seem to be misplacing things and real slow.**

Dr. William Gradishar: Yes it's not clear. I mean there is a phenomena that people describe referred to as chemo brain where their sharpness, so to speak, of how people think may be a little blurry and it's not very well understood. Some people think it is related to chemotherapy. It's not clear what the anti-hormone therapy contributes to that and, of course, people can have other medical problems, other medications, they can be aging as they go through this, so it's a very difficult problem to tease out in terms of what the effect of the drug is compared to just people getting older or compared to other illnesses people might have.

Kathy: And I'm 52, but I seem to be getting a lot worse and I've had the adjuvant therapy of Herceptin. I just finished the last of August. I mean it takes me all day to even get ready to do anything. My husband has given up on me. He won't take me anywhere anymore.

Dr. William Gradishar: **Yes, well I think that it is a real phenomena. Which of the therapies you've received is contributing to it is hard for me to say.**

Kathy: Yes, who would you go to see about that?

Dr. William Gradishar: **Well I would see your oncologist and then have him refer you if there's an issue that might be addressed by a neurologist perhaps.**

Kathy: Yes, okay thank you very much.

Operator: *Our next question comes from Jilana from New Jersey. Please go ahead.*

Jilana: Oh hi. I had another Herceptin question. I'm also, I'm actually premenopausal, but I am HER2 positive and so I'm listening to the tamoxifen discussion, but I guess it's this question of the interaction of Herceptin and I've heard several other women ask this question. Herceptin with tamoxifen versus Herceptin with aromatase inhibitors, of course, realizing that I would probably not go on the aromatase until after I became menopausal.

Dr. William Gradishar: Yes, right now we don't have a reason to think that giving tamoxifen at the same time as Herceptin is somehow going to either cause a bad reaction or result in a less than optimal result. So for women who are hormone receptor positive and HER2 positive where they are going to get Herceptin, we generally start the tamoxifen at the same time and just continue it through.

Jilana: I understand. There really haven't been enough studies yet about the interaction or which one prevents more recurrence, etcetera, in that kind of setting.

Dr. William Gradishar: Do you mean not giving the Tamoxifen?

Jilana: Or, yes or does the aromatase work better with the Herceptin?

Dr. William Gradishar: Oh no that kind of trial has not been done and I doubt it ever will be.

Jilana: Oh okay. Thank you.

Arline Kallick: Before we break into groups I would like to thank you, Dr. Gradishar, for the excellent program this evening and I'm sure you've realized already how our callers have appreciated your presentation and your kindness in listening to the questions and answering them so well. So we thank you very much for being with us this evening. .

Dr. William Gradishar: Okay it was my pleasure. Everybody have a good night and I wish you all good luck.