

**Update on San Antonio: Breast Cancer in Young Women**  
**A YSC Young Perspectives Teleconference**  
**January 13, 2005**

**ANNA CLUXTON**: Good evening and welcome to "Update on San Antonio: Breast Cancer in Young Women," a YSC Young Perspectives Teleconference. My name is Anna Cluxton. I am a YSC board member and a young breast cancer survivor. I will be your moderator for tonight's call.

Every December, the San Antonio Cancer Institute sponsors the San Antonio Breast Cancer Symposium, an international scientific symposium for the interaction and exchange of information among basic scientists and clinicians in the breast cancer community. It attracts nearly 700 oral and research presentations and over 6800 attendees from all over the world. This year the conference had a mini-symposium on breast cancer in young women. The inclusion of this mini-symposium speaks to the growing recognition by clinicians and researchers that young women form a special subset of the breast cancer population and should be viewed and studied as such. In addition to this session, there were a number of presentations and posters throughout the conference that focused on premenopausal women.

Tonight we have two esteemed presenters joining us who have graciously taken the time to help us make sense of all of the information discussed at San Antonio. Dr. Rita Kramer is Associate Professor at the Baylor College of Medicine and Dr. Minetta Liu is Assistant Professor of Medicine and Oncology at the Lombardi Comprehensive Cancer Center within Georgetown University Hospital.

Before we begin the teleconference, I'd like to tell you how the call will work tonight. Tonight's call is being recorded and will last approximately 90 minutes. The first 30 minutes of the call will be presentations by our panel. Each panelist will summarize the presentations and abstracts from San Antonio relevant to young women and will explain what they mean to you as a young woman affected by breast cancer. In addition, many of you have submitted questions in advance, and both Dr. Kramer and Dr. Liu will try to incorporate the answers in their presentations.

After we hear from our speakers we have allocated approximately 50 minutes for you to ask the panelists questions. Finally, this call is operator-assisted, so when we open the line for questions our operator, Morgan, will give you instructions on how to answer your questions. Due to the format of these calls it's difficult for us to answer questions that address specific cases or individual circumstances. If you have questions of a personal nature we will try to address them in more general terms. If we run out of time and you still have questions for the panel you can submit them to [info@youngsurvival.org](mailto:info@youngsurvival.org). We will do our best to get an answer back to you.

A transcript will be made available on the YSC website, [www.youngsurvival.org](http://www.youngsurvival.org), in about three weeks. Additionally, tonight's call is being taped and will be available as a command performance call for about two weeks. We'll have more details coming out to you later. Finally, I would like to thank Aventis for helping us to make this teleconference possible.

Our first speaker is Dr. Rita Kramer of Baylor College of Medicine in Houston, TX. Her clinical focus is on breast cancer risk assessment and the evaluation and treatment of breast cancer. Dr. Kramer's research interests are breast cancer prevention and recovery after treatment for breast cancer. Recently Dr. Kramer conducted a study on chemotherapy-induced amenorrhea and secondary side effects. Many YSC constituents completed this survey. Dr. Kramer, if you want to share any preliminary results with us, please feel free to do so.

**Panelist One: Dr. Rita Kramer**

The data that we received with the support of the YSC membership has been used to prepare an abstract that we hope will be accepted for presentation at the upcoming American Society of Clinical Oncology meeting. Our data indicates that women who get a taxane chemotherapy after adjuvant Adriamycin/Cytosin-based chemotherapy have a higher chance of experiencing premature menopause, but we learned from those who filled out the questionnaire that many women stopped having their periods transiently and that their periods will restart after that initial temporary cessation. So it's teaching us that a woman's menstrual cycle is a little bit of an unreliable marker about whether or not she's actually permanently in menopause, because many women's periods will restart.

**CLUXTON**: Now we will hear from Dr. Minetta Liu from the Lombardi Comprehensive Cancer Center at Georgetown University Hospital in Washington, D.C. She is involved in clinical and translational research with a particular focus on the development of new methods to detect breast cancer and increase our understanding of the molecular mechanisms underlying chemotherapy responsiveness. Dr. Liu is firmly dedicated to the care and education of women with breast cancer and uses an individualized multidisciplinary approach to patient management.

**LIU**: Dr. Kramer, do you want to go ahead talk about the mini-symposium and some of the exciting new information that was presented at San Antonio and then I can go through some of the interesting abstracts?

**KRAMER**: Yes, thank you. I had the pleasure of working with Dr. Richard Elledge, a co-member of the planning committee for the San Antonio Breast Cancer Symposium. We were interested in putting together a mini-symposium about special issues in the treatment of breast cancer in young women. Our first speaker was Dr. Aron Goldhirsch, who has done a lot of work in clinical trials in Europe. We asked him to talk about the biology of breast cancer in young women, how that might be different from breast cancer in other women and what that might mean regarding treatment.

Dr. Goldhirsch did a fabulous introduction for us. He helped remind everyone that it's important to evaluate the basic biology of breast cancer in every woman of any age. But he also reminded us that the likelihood of a woman's breast cancer being responsive to hormones increases as she ages. So, statistically if a woman is diagnosed in her 70s, her breast cancer is much more likely to express a target we can use to direct hormonal therapy at, as opposed to a woman diagnosed in her 30s or 40s. He reminded us that it's important to evaluate each individual woman, however, and to look at not only the size of the tumor, but also whether or not there's lymph node involvement under the arm. And finally, he also emphasized the need to look at protein targets that might be used as a way to direct our therapy.

I'm going to talk a bit about those protein targets. The three we routinely measure in patients

diagnosed with breast cancer are the estrogen receptor, the progesterone receptor and the HER-2/neu receptor. These are protein receptors on the cancer, kind of like finding a keyhole in the door. The estrogen receptor is probably easiest to understand. When we find that target present on a cancer we know we can actually manipulate it by using medicines. We can use Tamoxifen, which would work like putting duct tape over the keyhole. That is an option for women of any menopausal status.

We know that Tamoxifen will help women of any age whose cancer expresses an estrogen receptor. One of the other ways that we can manipulate that target is to deprive the cancer from ever seeing estrogen. For most women the ovary is the major source for the production of estrogen in their body. But, even after we've gone through menopause or had our ovaries removed, we still produce estrogen in our bodies. In some cases the breast tissue itself is a little factory that can produce estrogen. We have learned to block that production of estrogen by tissues other than the ovary, using an enzyme inhibitor called an aromatase inhibitor. That drug prevents other hormones in the body, like testosterone, from being turned into estrogen. So, it's a way to deprive the body of estrogen, or to deplete the estrogen levels in the body.

Now, that works really great for a woman who's postmenopausal or who has stopped having periods. But the drug is not strong enough to result in a lowering of estrogen levels or depletion of estrogen in a woman who still has her ovaries. In fact, for women still having periods, an aromatase inhibitor can actually cause problems because the body is designed with feedback mechanisms. If a premenopausal woman is given one of the aromatase inhibitors it can cause the ovary to work harder and cause side effects like facial hair or acne and she may not get any real benefit from the drug. Other ways we can lower estrogen in premenopausal women is to take their ovaries out, or give medicines, in the form of shots, to turn off the ovarian production of hormones. In Europe they sometimes actually give radiation to the ovaries. We don't do that very often in the US. There's also something called an LHRH agonist that can be given to turn off ovarian production of hormones.

Dr. Goldhirsch did a wonderful job of outlining over 20 years worth of research showing that in premenopausal women Tamoxifen is very effective. He highlighted some of the most important

questions that we're examining for women whose cancers express the estrogen receptor. For example, if Tamoxifen is great therapy, would we get even better results if we combined some of these treatments? What if we gave Tamoxifen plus a shot of medication that stopped ovarian production of hormones?

I think Dr. Liu's going to talk more about some of those research trials. We're very excited about those studies and think they're a way to improve treatment for young, premenopausal women. I think it's important that all premenopausal women whose cancers are estrogen receptor positive understand that they can't take an aromatase inhibitor by itself. If they have their ovaries in place and they're having regular menstrual periods, then taking an aromatase inhibitor alone ... really Dr. Kent Osborne describes it like just taking a glass of water, because the drug is not strong enough in its mechanism of action to overcome the ovaries' production of estrogen.

Another thing that Dr. Goldhirsch really highlighted was that chemotherapy can be effective for all women with breast cancer, but that young premenopausal women are at a little higher risk of having unique side effects from chemo.

So, for example, if I see a woman who might be 70 or 80 and I give her chemotherapy I am very worried about how she may tolerate the therapy while I'm giving it. So I'm concerned that she may experience acute side effects from chemo. She may not tolerate the fatigue that comes with chemo as well as a younger, healthier patient. But that 70-year-old woman has already stopped having periods and the chemo that I give her is not likely to push her into early menopause.

Early menopause can be a really really big deal. We see a lot of patients in our clinic who have lots of side effects as they finish chemo, such as hot flashes, not sleeping very well and sometimes mood swings and depression. I bet Dr. Liu sees that, too. She'll let us know when she talks a little bit later. But it's important that we sort out what happens when a woman gets chemo, not just after she's finished with the nausea and the vomiting and her hair is all grown back. But what happens down the road? What happens five years later, 10 years later, and those sorts of things?

Dr. Goldhirsch reminded everyone that a young woman who goes into menopause early is at risk of later problems like weakening of the bones, or osteoporosis, and that we need to pay attention to that because we don't want to have women be at risk of falling and breaking a hip. [It's] fabulous to have been cured of breast cancer, but we want to pay attention to later side effects so that we don't leave women at risk of hip fractures and things like that at a young age.

Whether or not a woman goes into premature menopause is kind of a big deal because if her tumor was estrogen receptor positive, as she finishes chemo she and her physician will talk about hormonal therapy options. It can be kind of tricky. What really happens with your period is kind of a poor marker of what's really going on in the ovary. Believe it or not, as much as we've learned in medicine, menopause still holds a lot of mysteries for physicians.

There's something called "perimenopause" that I'm sure many women could have told us about. It's a stretch of time during which women can have irregular periods and some menopausal symptoms, but maybe not so many. One thing we're learning is that the aromatase inhibitors probably aren't effective in perimenopause. So, if we've given a patient chemo and we're seeing her as she finishes that treatment to discuss hormonal therapy, we'll err on the side of using Tamoxifen if there's any doubt she may restart her periods and that her ovarian function has not permanently ceased. We do that because we know an aromatase inhibitor would be ineffective.

One thing that Dr. Liu and I heard at the conference that may be helpful for women going from perimenopause into menopause as they age is to start Tamoxifen. Then after they've taken the therapy for three to five years they could switch to an aromatase inhibitor.

I guess another thing to talk about is some of the information about the ability to have a child after you've been treated for breast cancer. We were thrilled to have Dr. Oktay from the Weill Medical College at Cornell come and talk to us about options for preserving fertility. Any time we talk about this we always get lots of questions about whether it's safe for a woman who's had breast cancer to consider having a child. I think that there's a lot of concern about that, and there's not a whole lot of large studies. There aren't studies of thousands and thousands of women who've chosen to do this.

But in general we think that if a woman's cancer was an early stage and she has a very good chance of being cured of this disease, and she wants to have a child, that that's a reasonable choice for her. So many things go into the decision about whether or not to have a child. Lots of things are involved. Dr. Oktay did a great job of highlighting the fact that some of our older chemo agents, like Cytosan, really can affect the ovaries. Not only does a woman's hair fall out. Each follicle in the ovary gets that chemo and that damage can make it harder to get pregnant.

Dr. Oktay also talked about taking a small piece of the ovary out and putting it in a freezer. We've all heard of sperm banking, but we're just beginning to learn about ovary banking. A woman's eggs don't tolerate freezing like sperm does, it hasn't really been very productive. But what holds great promise is taking pieces of the ovary tissue out, freezing it and then giving the woman treatment, and then re-implanting that ovarian tissue. That's an option for a woman who may be without a partner when she's initially diagnosed with breast cancer and may want to look at what her options would be to conceive a child down the road. Dr. Oktay showed very interesting slides of a woman who had ovarian tissue taken from the freezer and surgically placed in her forearm, and pictures of that ovarian tissue ovulating. It made all of us laugh because we know what cramps feel like when you ovulate and we wondered what it would feel like if your arm was ovulating.

One other thing that Dr. Oktay talked about was couples committed to having a child in the future can harvest embryos for in vitro fertilization. One participant asked, "Is there any way to harvest eggs without doing estrogen?" Actually there is. Dr. Oktay presented information about harvesting eggs with the use of Tamoxifen, which we thought was pretty interesting.

One of the final things that I'll talk a bit about is the last speaker in our mini-symposium, Paula Rauch from Mass General, who talked to us about the impact of breast cancer on parenting and on the children. This was a topic of great personal interest to both my co-moderator in the session, Dr. Richard Elledge, and to me, because we've had several young women caring for very young children. There's a lot of concern about how to help our patients communicate with their young children about what's going on, as well as the whole process.

Dr. Rauch gave a fabulous presentation. She pointed out to the entire audience how perceptive children are, how there's really no hiding from a child that things are different in the home, that a mother is given treatment and that the entire family may be more stressed. She pointed out that children are going to find out that their mother has cancer and that one of the important things to do is to be very honest and open about it.

Her specific comment was that the child will learn that his or her mother has cancer. It can be learned from the parents in an environment where they feel comfortable asking questions, or they can learn it from their teacher or from the next door neighbor or from an older cousin they only see every six or eight months. She pointed out that one lesson most parents want to teach is that the child is important, and that important things will be discussed with the child because the child is important. It's important just to be right up front with things.

She also pointed out that sometimes it's important for people to set aside some family time. But sometimes I see such wonderful support given to newly diagnosed women and it can be a little overwhelming as they try to juggle it all. Dr. Rauch pointed out the importance of trying to preserve some routines, to set aside maybe certain nights of the week when a family can eat dinner together, and try to maintain a little structure in the child's life.

We also talked about some of the really hard things, like how a parent or a mother might tell a child that therapy is not going well. Dr. Rauch had some great comments. She pointed out that the parents might say it's the doctor's job to worry and do everything possible to make things turn out well, and that the child wasn't to be the one to worry. There were people whose job it was to worry. If things changed the parents would tell the child and keep the child keyed in to where things were at any point in the process.

She also pointed out that lots of times people expect a teenage child to kind of take on adult responsibilities when there's stress in the family and that sometimes it's important not to put those kinds of expectations on a teen, that they may not really be able to take on more adult roles at a time when there's so much stress.

I'm looking to see if I talked about everything that I had scribbled notes about, and I think I took my whole time, didn't I?

**CLUXTON**: You did great. (Laughter)

**KRAMER**: I'm rattling on, and I'm not sure what I missed. But hopefully people will ask questions.

### **Discussion**

**CLUXTON**: To our listeners, if you'd like to see more discussion about dealing with children as a breast cancer survivor, the transcript from the YSC's previous teleconference, "My Mommy Has Breast Cancer," with Dr. Wendy Harpham, is available on the website, [www.youngsurvival.org](http://www.youngsurvival.org) as is, I believe, a fertility transcript from another teleconference that featured Dr. Oktay as well.

**KRAMER**: We thought that was such an important session.

**CLUXTON**: It was.

**KRAMER**: Because physicians want to be helpful but we feel all thumbs and elbows.

**CLUXTON**: Exactly.

**KRAMER**: I think many of us don't really know how to be helpful there, and we don't realize that sometimes just listening [can be helpful].

**CLUXTON**: I thought it was very interesting that Dr. Rauch said that that program developed out of a physician satisfier program, that the medical oncologists lacked the tools to be able to talk with parents who were cancer survivors. That it was very troubling to them and they needed

something to sort of take the ball and run with that (Overlap), which was very interesting.

**KRAMER**: To provide support for a situation in which we felt that we were inadequate, I think.

**CLUXTON**: So Dr. Liu is going to discuss other research relevant to young women as it was presented at San Antonio. Dr. Liu?

**Panelist Two: Dr. Minetta Liu**

I just wanted to thank Anna and the Young Survival Coalition for asking me to do this and also all the participants for joining. I know it's late in the evening and there are kids to be put to sleep and dinners to be had. So thanks for joining us.

I have this daunting task of going through the exciting data that was presented at the San Antonio Breast Cancer Symposium and trying to synthesize it, in particular for young women. So I'm just going to kind of review a number of studies briefly that I think have huge relevance for our young premenopausal women. I'm not obviously going to be able to go into detail about everything, and if there are more questions feel free to e-mail us and we can provide some more explanation as needed.

So I thought I'd talk about screening and prophylactic measures, then things related to early stage breast cancer diagnosis and treatment, and then, importantly, as Dr. Kramer was talking about before, some of the unique after -treatment effects that premenopausal women have to deal with.

There's some interesting data just with reference to breast density actually as a risk factor for breast cancer. We know that it's a marker for estrogen production and estrogen levels. With increased breast density there is difficulty in detection with mammography. So there was some interesting data about that, and there will be more studies ongoing related to that.

That also leads into the work with breast MRI, which is having an increasing role in screening for our high-risk patients, particularly young women. Several large studies have been done.

There was a very elegant presentation by Ms. Warner from Canada actually. Knowing that there's a low sensitivity of mammography as well as ultrasound in screening, they looked at very high-risk women including women with BRCA-1 or 2 mutations, as well as those without mutations but a calculated high lifetime risk of breast cancer. [The study] included pre- and postmenopausal women who were getting ultrasounds and mammography and then added on MRI as well.

There was a significant increase in the number of breast cancers diagnosed by MRI as opposed to the other two modalities. It's very sensitive. In other words, we pick up a lot of abnormalities on MRI. They're not always cancer, so that does lead to more biopsies and sometimes what we call false negatives, meaning things look suspicious on MRIs, but biopsies prove they're benign. We're getting better with follow-up and better at really reading and understanding MRIs now. So it's going to have an increasing role, I think, in screening women, particularly those with high breast density but also with mammographically occult disease, disease that's not palpable, or disease that's not detectable on ultrasound. There were certainly some other studies that looked at the breast MRI surveillance, and they pretty much go along with that study that I just talked about.

There's also a growing technology called "transepithelial electrical impedance analysis," which basically looks at the electrical wiring in the breast relative to risk for breast cancer by looking at the tissue at a completely different level. It's not an invasive technology, and it looks like there may be changes that correlate with the risk for breast cancer. Again, there are a couple of studies looking at that, that identified breast cancers that were not otherwise picked up by other means. So those are some exciting things just in terms of screening.

One participant asked a question in reference to mastectomy related to diagnosis of breast cancer in one breast: Whether there's a role for prophylactic mastectomy on that contralateral breast, and [if] that really relates to the baseline risk of breast cancer. Certainly patients who have BRCA-1 or 2 mutations are at a much higher risk for contralateral breast cancer. So, often times it is recommended they undergo a prophylactic mastectomy. Outside of that, there are often cosmetic issues. If mastectomy is done on one side and tissue reconstruction is requested for

symmetry, sometimes women will choose prophylactic mastectomies on the other side. There are also issues of "followability" for mammographically occult breast cancer, which highlight the concerns about how to follow the other breast. That may be obviated by the growing use of breast MRI. But these are things to consider.

There are issues about assessing prognosis once breast cancer diagnosis is made. We use tumor size and lymph node status, but there are other factors we can use to help guide our treatment recommendations, which in turn are guided by what the risk of a recurrence is. We have factors that we already use including Ki67, presence of lymphatic or tumor emboli. These two things relate to how fast cancer cells are trying to divide or if there's evidence that they're trying to lose their so-called stickiness and trying to go through the channels by which they can escape the breast.

There's growing interest in using new technologies other than routine pathology analysis. This new Oncotype DX or 21-gene panel has gotten a lot of press. To be clear, this study [of Oncotype DX] only looked at women with small tumors, node negative and hormone receptor positive breast cancers. This test has not proven to be accurate for those women who have hormone receptor negative breast cancers or involved lymph nodes, and that's because of the population of patients involved in the studies by which this assay, or this test, was developed.

Basically [the test] doesn't require any more from patients after surgery. We're able to use the routine tissue from pathology to assess the expression or the level of expression of 21 different genes. They're really reflective of things we already study: HER-2/neu status, estrogen receptor [status], and proliferation or how fast the cancer cells may divide. There's also what's called an "invasion score," [determined by the] known genes that reflect the invasiveness of breast cancers. The bottom line looked at two different patient populations, one where all patients received tamoxifen. Was this 21-gene score going to reflect prognosis or how women were going to do in general?

They were, again, all treated the same way, and there certainly was prognostic value, at least in the initial studies that have been done. Then, in comparing women who had gotten Tamoxifen

versus those who did not—who received a placebo on these trials—there was certainly a benefit to Tamoxifen. That benefit was greatest for those who had a low or intermediate risk of breast cancer [recurrence] based on this score, as opposed to a high recurrence rate risk, suggesting maybe those women should get chemo in conjunction with endocrine therapy or Tamoxifen.

They also looked at chemo and Tamoxifen versus Tamoxifen alone. Chemo benefited the high-risk population using this score, more than the intermediate-risk population where there was more question. The key in terms of chemo in these trials was that the regimens studied were not the anthracycline- or the Adriamycin-containing regimens often recommended for women with early-stage breast cancer. So the data with the chemo, I think, is going to be a little bit more difficult to use right now. But certainly, I think, a lot of people are going to start asking for this test and it's important for us to use it in the right patient population.

In terms of treatment there are two major forms, as Dr. Kramer was talking about. One is the endocrine therapy, which interferes with how estrogen can interact with cancer cells. And Tamoxifen is the mainstay of therapy for women who continue to menstruate, for the reasons that Dr. Kramer discussed before.

There is growing interest, actually, in rendering women menopausal as a form of therapy as well. There are a lot of questions in terms of whether using drugs like Lupron or Zoladex, which are injections that sort of fool the body system into shutting down the ovaries temporarily, will add to Tamoxifen, or should be used in place of Tamoxifen, or will open the door for the use of the aromatase inhibitors in premenopausal women.

There are studies that are ongoing right now. They're nicknamed the SOFT trial and the PERCHE trial. The SOFT trial in particular is really looking at comparing these different forms of endocrine therapy. [It compares using] Tamoxifen alone versus using those injectable medications that induce menopause, with Tamoxifen versus those injectable medications with an aromatase inhibitor. Then the PERCHE trial is actually looking at inducing menopause and using Tamoxifen versus chemotherapy, as well.

There was an abstract that was presented at San Antonio that did look at what we call ovarian functional suppression or using these injectable medications in conjunction with or in comparison with chemo. That chemo was CMF, which is again not necessarily what we use at this time. We tend to use more Adriamycin or [and Cytosin], AC, as it's abbreviated. But there was equivalence in inducing menopause versus chemo in patients who had hormone receptor positive and node negative breast cancer. So it remains a question.

Something we have to remember is that actually the first systemic treatment for breast cancer was actually removal of the ovaries in 1896 when a very wise surgeon decided to do that as a form of therapy. So the question remains. I think these trials are incredibly important and will hopefully answer the questions. They're ongoing and accruing patients right now.

In terms of chemo, I think the bottom line in adjuvant therapy is that in those patients for whom chemo is recommended and indicated, it offers significant benefits. There's growing evidence that taxanes, drugs like Taxol and Taxotere, when used in conjunction with drugs like Adriamycin or Epirubicin offer a benefit in terms of survival, as well as recurrence, in terms of decreasing recurrences and increasing survival from breast cancer.

There's also evidence that if we give chemo before surgery in the right patients that adding the taxanes to the Adriamycin-type regimens will increase the success of completely shrinking the tumor away, such that when surgery is done we can't find anything anymore. We know that that's a very good prognostic factor. In other words, that suggests that the chemo was working very well and that the risk of breast cancer coming back is much smaller.

There have also been questions about the benefit of giving taxanes or chemo in general for hormone receptor positive versus hormone receptor negative breast cancers. There was a very elegant review about the trials that have been done in adjuvant chemo for breast cancer patients showing that there's a clear benefit for chemo in patients who have hormone receptor negative breast cancers, node positive breast cancers.

For hormone receptor positive patients there is a benefit, it's just a delayed benefit, simply

because those patients can receive drugs like Tamoxifen. Endocrine therapy and Tamoxifen are really the mainstays of therapy for hormone receptor positive breast cancer. So that's exciting... sort of verification for the fact that we use chemo quite frequently in young women.

Then lastly, just in terms of the unique side effects that young women can experience with treatment, there's an abstract from the Young Survival Coalition looking at menopausal symptoms in young breast cancer survivors. They polled YSC members about different side effects they were experiencing in relation to treatment. I think the most interesting thing to take out of this was that women who were still menstruating, whether they were on Tamoxifen or had received chemo before, were still experiencing symptoms of menopause: hot flashes, vaginal dryness... we can't assume they're not there in patients even though they're menstruating. They're things that we can certainly address. We know from our menopausal patients that we have means of managing hot flashes and vaginal dryness. [These are] things that we need to talk to our premenopausal patients about.

In terms of bone density, it is an issue. We know chemo in and of itself can induce accelerated bone density loss. The secondary effects on the ovaries in inducing menopause can ... even temporarily inducing menopause... increase the risk of developing osteoporosis later on. There are a number of trials looking at using drugs like Zometa, which we use routinely in women who have metastatic disease to the bones, to try to decrease the effects, pain or fractures that can be related to bone metastases. The thinking here is that if we use Zometa during the course of chemo can we strengthen bone and not have problems with accelerated bone density loss?

So there's an ongoing trial right now for premenopausal women ages 40 and above who are receiving chemo, who will also receive Zometa for two years in conjunction and then after chemo to see if we can help prevent bone density loss.

Then the other question is: if we do use drugs, like Lupron or Zoladex, to induce menopause in conjunction with Tamoxifen or the aromatase inhibitors, can we also use those to help prevent bone density loss? There has been at least one study now that shows that A – it's safe to do and B – it can also help prevent significant bone density loss with these treatments.

The bottom line is there's a lot of exciting information for all women with breast cancer, but also growing focus on premenopausal women with breast cancer, and there's certainly more to come in the coming years.

**CLUXTON**: Thank you, Dr. Liu. If I could just ask you and Dr. Kramer, did you think there was any new information on treatment of metastatic disease, particularly maybe some treatments that would have lower side effects than some of the really aggressive forms out there?

### **Discussion**

**LIU**: I think that's a growing focus in metastatic breast cancer, which is not necessarily just focused on young women, but for all women with breast cancer. There's this growing interest in targeted therapies, trying to find treatments that are going to be directed only at cancer cells and trying to spare normal cells. It's really when we affect normal cells that we get side effects. Then there are also ways of trying to modify known chemo drugs to decrease side effects. So there's excitement.

Actually Abraxane was just FDA-approved yesterday. Abraxane is a formulation of Taxol that we've known and been using for several years. It's a formulation that allows us to A -- give an increased dose of drug, and B -- decrease the risk of having reactions to Taxol. There are a lot of changes and there's also a lot of research just looking for new targets to try to target.

**KRAMER**: I think that your question was about therapies for metastatic cancer, but one of the themes of this meeting over the last couple of years has been to try to make local therapies less difficult for women as well. So we had a nice presentation about different ways of doing reconstructive surgery last year. Then during this year's meeting there were several presenters who talked about longer follow-up data with the sentinel lymph node procedure. Both of those directions of research are really intended to allow women to have the best possible surgery with the least risk of having a complication from that procedure years later. So the sentinel lymph node procedure for women who are a candidate for it is just a fabulous advance and decreases the risks of lymphedema. We're learning more and more about that.

**CLUXTON**: Great. Actually just to touch back on your talk, Dr. Kramer. In talking about perimenopausal status in terms of either fertility concerns or even the use of aromatase inhibitors, what are the ways that some of our listeners could expect to be tested to see if they have gone into menopause? Or is there a way? (Laughs)

**KRAMER**: That's a fabulous question. Thank you for asking it and giving me the opportunity to kind of fuss at physicians. At the moment we don't have a single test that is a definite, written in stone test that tells us that a woman is menopausal. Part of the challenge of finding the perfect test is actually related to a woman's physiology. We're pretty complex individuals, and we have multiple hormones that rise and fall in relationship to each other. If we have a single ovarian follicle or a single egg, one egg left, the odds that we could get pregnant with that egg would be very, very low. But, if our blood work were strong just at the particular time when that one single egg made its cycle, then the lab work would show that we were premenopausal.

So at our center, we will occasionally look at levels of estradiol and FSH and an LH. But we're very, very leery of hanging our hats on the pattern of those lab results to really confirm for us that a woman has gone into menopause, and in particular a woman who's just finished chemo. We know that those hormonal levels fluctuate, and while the lab that we draw this month may look like the woman is postmenopausal, several months later those hormones may change and really indicate to us that she isn't postmenopausal. Interestingly enough some of the medicines that we use as endocrine therapies can also kind of influence how these labs all look. So individuals who are on Tamoxifen and have labs done to try to see if they've gone into menopause, some of those labs are unreliable.

So we really think that a woman has gone into menopause if it's more than a year since her last period. That's our clinical definition. But, we've also had women who've been on Tamoxifen whose periods have stopped and we've assumed that they're menopausal—only to find that when they stopped the Tamoxifen their periods restarted. So defining menopause is still very much a challenge, in particular with women who've gotten chemo and are within a year of that treatment. So we're still challenged by what should and probably does seem like something that would be a

little more simple. We can put a robot circling Mars, but we're still trying to define menopause.

**CLUXTON**: Well, in one sense it's complimentary to be such a challenging case for all of our medical oncologists, but it's also frustrating as survivors.

**KRAMER**: Yes, definitely. Definitely.

**CLUXTON**: Before we open it up for questions from the audience, Dr. Liu, there was a question submitted about long-term surveillance in somebody diagnosed at a young age. I thought a way to address this would be talking about some new surveillance measurements, medical management of high-risk women, women who are BRCA positive, anything like that.

**LIU**: I mean, in terms of routine surveillance I think many of us still rely on the standard, the CAT scans, bone scans. Physical exam is I think of the most importance, listening to patients and their systems. We do routine blood work. There are tumor markers, the so-called tumor markers, the CEA, the CA 15.3 and CA 27-29, which are not entirely reliable, although a lot of oncologists do draw the blood work routinely, the thought being that if they are elevated that that would prompt a further investigation for identification of metastases. But what we know is that they can be normal and breast cancer can still recur, and they can be elevated for reasons other than breast cancer. So they have to be taken with a bit of a grain of salt.

There are other tumor markers that are certainly being developed, simple blood tests, none of which are coming to the forefront yet, but with increasing molecular technology we may be able to identify those. Again with breast imaging, mammograms, increasing use of ultrasounds, but also particularly MRI, which I think will be really important in looking at breast cancer recurrences. There are other technologies like PET scan or PET in conjunction with CAT scan that are being used now.

Some facilities and some oncologists are using them more than others. I think as we understand the technology better we'll be able to interpret the results better. The problem with these new technologies is that we often are so sensitive in picking things up that it leads to 'there's

something there but it's too small to biopsy' or 'we can't really find it and so we need to follow it.' So, those are some of the difficulties, but also some exciting things that are coming down the pike.

**CLUXTON**: I once heard a physician say that some of his best diagnoses came from the "doorknob diagnoses." So it was literally as he was going to leave the room after, "Okay, so everything's fine, blah blah blah, see you in six months." And he had his hand on the door knob to walk out of the room and the patient would say, "Well, there is this persistent cough that I have," or ...

**LIU**: Exactly.

**CLUXTON**: ... you know, something like that. So I think I would encourage our callers to always have questions ready for your doctor and to be ready to talk about any sort of weird things or ongoing symptoms.

**KRAMER**: I think you're right on target, Anna. I actually reviewed a lot of literature in preparation for a writing project and found that the most reliable indicator that a woman had recurrence of her disease with spread to another part of her body was her history. The next most reliable thing was the doctor's physical exam, though people are always asking us at the breast center about getting follow-up bone scans and a PET scan.

**LIU**: Exactly.

**KRAMER**: We really don't advocate that. We really put a lot of faith in how our patient feels and faith in our physical exams. There's been no study that has shown that getting a bone scan every year picks up anything any quicker than listening to our patient. So we really need to be developing the sort of relationships where if somebody is having a problem they just pick up the phone and say, "I need to come in even though my appointment is not scheduled for another two months. Something's concerning me so I'm calling to come in." Physicians need to listen. We don't draw the tumor markers here because we don't ...

**CLUXTON**: I'm so glad to hear that. (Laughter)

**KRAMER**: ...I've had so many patients whose lives were turned upside down with an abnormal tumor marker that was drawn when my patient felt absolutely fine, had no symptoms, no problems. Many, many, many, many x-ray tests later we find no sign of any problem and the patient is followed and never has a problem. So, we don't really draw those tumor markers in anyone we're following because they *might* have cancer come back in their body later. We use those blood tests in the situation in which we know someone has had a recurrence of their cancer, maybe in their bone, and we follow that test over time to help us know whether our therapy is working. So we wouldn't make a change on any one blood test. I agree completely with Dr. Liu. It's not a great test. So we would look for a pattern in the test. What were the last three values? How did they compare versus just one isolated value?

**LIU**: The bottom line, I think, is that women really know their bodies better than anybody else.

**KRAMER**: I couldn't agree more.

**LIU**: And better than any test.

**CLUXTON**: I believe there was a pretty large study done several years ago where they took one group of patients and did every single test they could possibly do, and then another group and just followed them as is the standard, and the group that was the standard actually did not find any recurrences or new primaries sooner than the group that was so closely followed. That's absolutely right

**KRAMER**: I think it's important that we be aware that women are at risk of a brand new breast cancer and that one of our focuses is to make sure that we're doing all those things to screen for a new breast cancer, be it mammography or ultrasound. Or, Dr. Liu mentioned, in women who have a high high chance of that happening, we're starting to use MRI.

**LIU**: And clinical breast exams are incredibly important still.

**KRAMER**: Definitely.

**CLUXTON**: Definitely. Well, we have about 20 minutes left for questions. The operator, Morgan, will instruct you on how to indicate that you have a question. I'd like to request that each person ask only one. Again, try to remember that Dr. Liu and Dr. Kramer will try to address your question in a general sense so that it can be more applicable to the rest of our listeners. Morgan, do we have any questions?

### **Question and Answer Session**

**MORGAN**: We will take our first question from Houston, Texas. Go ahead, please.

**QUESTION 1**: *My question is regarding ovarian suppression. I'm one year out of treatment. I've been on Tamoxifen now for one year. I'm doing really well. I've been one of those people that haven't had problems with Tamoxifen, and I'm very thankful for that. It even lowered my cholesterol, which ....(Laughter) But I'm very stressed about the whole ovarian suppression thing. I would prefer not to do it because I did go into menopause for a short time during chemo and it wasn't extremely pleasant. I'm worried about bone loss and things like that. But, of course, if I think that it would really improve my chances for not having a recurrence then almost anything is worth that. What I'm wondering is I know the trials are just beginning, but would there be any type of an update, maybe even in one year? Will they come out and say, okay, here's what we're seeing so far? Or are we just not going to know the answer for another five years?*

**CLUXTON**: Dr. Liu? Can you address that?

**LIU**: There is no planned release of data typically in these types of trials after a year. I mean, there have been a number of trials, small trials, that have tried to look at answering this question. But the trials that are ongoing should hopefully answer the question in the long term. How old are you?

**QUESTION 1, continued:** *Thirty-four.*

**LIU:** I mean, you wouldn't be eligible for those trials now just because of the time since you started Tamoxifen. To do it certainly is a discussion probably between you and your oncologist. There are pluses and minuses to doing it. But there is no demonstrated benefit yet in doing it. So no one could guarantee that it would be better, or it would be worse, the toxicities or the side effects that you might experience.

**QUESTION 1, continued:** *One thing I'm very interested in is taking Tamoxifen for five years, enjoying estrogen for four more years, since I've already been on it one, and then having the ovaries removed or shut down to do the aromatase inhibitor. But I understand they don't really know about that yet either.*

**LIU:** Correct.

**CLUXTON:** I think what's important for both of those questions is to keep in mind that the longer that we wait for data to come out the better it is for all of us. By the time that you finish your Tamoxifen who knows what information will be available. So it's just a matter of sitting back, unfortunately, and having to be patient.

**KRAMER:** I'm thrilled to hear she's not having side effects with Tamoxifen.

**LIU:** Yes. I'm amazed. (Laughs)

**KRAMER:** In fact, the majority of women don't. It's hard for us to convince patients of that, but many women don't experience side effects. So hip, hip, hooray for the fact that she's not.

**CLUXTON:** The only ones I tend to encounter, like in support group and in discussions, are hot flashes, and those are alleviated with so many other medications. Any other questions?

**MORGAN**: Yes, next question is from Fairfax, Virginia. Go ahead please.

**QUESTION 2**: *I am on Arimidex. Actually I just started last week. Is there any research which shows that Arimidex works better or worse in situations where the patient is a little overweight—in terms of fat increasing the amount of estrogen?*

**KRAMER**: Let me try this one. Dr. Liu, chime in. Are you postmenopausal?

**QUESTION 2, continued**: *Well, I'm on Lupron.*

**KRAMER**: So you would be taking a combination of Lupron and Arimidex?

**QUESTION 2, continued**: *That's correct.*

**KRAMER**: I don't think there are studies yet where the data has been analyzed according to weight and effectiveness of the aromatase inhibitors. Part of the challenge is that this enzyme, aromatase, certainly is found in fat cells. But breast tissue also has this enzyme. One of the things we're struggling with is that the level of estrogen that we draw from your blood, the level we measure there, may not be reflective of what the level is actually in the breast tissue. Just like most other things, there's probably going to be some variability that some women have more of this enzyme, for example, in breast tissue, than others.

So certainly we think that women who are overweight have higher circulating levels of estrogen in their blood, and women who are very overweight, who meet the criteria for obesity, actually do worse if they're diagnosed with breast cancer, we think maybe in part because they have high levels of estrogen in their blood. But the effectiveness of the aromatase inhibitors may be very much influenced by what's going on actually in the breast tissue itself. That's more challenging for us to measure. So I don't know if I really answered your question. Just trying to point out it's a little more complicated. (Laughs) Who knew that the breast could make its own estrogen?

**LIU**: There are also questions in terms of concentration of the aromatase enzyme in the

peripheral fat. So, does it correspond? In which case aromatase inhibitors should work just as well. Those are things that need to be looked at.

**MORGAN:** Yes, next question from Midlothian, Virginia. Go ahead, please.

**QUESTION 3:** *What is the difference between estrogen positive and progesterone positive? The first time I was diagnosed I was estrogen negative, progesterone negative, HER-2 negative. The second time I was estrogen negative, just barely progesterone positive and still HER-2 negative. Now it's come back five years later a third time and it's metastasized. So I'm just wondering what drugs are going to work for me. I'm still premenopausal. I'm still having periods.*

**CLUXTON:** Can I clarify for the doctors, were these three recurrences in the same breast? Were they metastatic? Were they new primaries?

**QUESTION 3, continued:** *The first one, same breast for the first two. Then just in the last six months it's gone to my lungs, my brain and my liver after having been disease free over five years.*

**LIU:** What was the interval of time between your original diagnosis and the in breast recurrence?

**QUESTION 3, continued:** *About 13 months.*

**LIU:** One thing about how hormone receptors are assayed or studied by the pathologist is that definitions of negative and positive, there's variability from different labs. Even if you take the same tissue in the same lab sometimes the percentages ... because most labs now have the technology by which they can actually give a percentage as opposed to just plus or minus. So that's something to take into consideration. If it's just slightly progesterone receptor positive at time two that whether it's truly positive or not ...

**QUESTION 3, continued:** *Right, it came back five percent.*

**LIU:** So five percent to some is still considered negative. I think because technology is getting better, some people would consider five percent positive. There's very much a grey zone with respect to that. I'm assuming you haven't had a biopsy of your most recent recurrence.

**QUESTION 3, continued:** *Yes, and it was the same thing.*

**LIU:** It was a little bit progesterone receptor positive?

**QUESTION 3, continued:** *Five percent.*

**LIU:** Certainly endocrine therapy is something that can be tried even with patients that are estrogen receptor negative and progesterone receptor positive. The studies didn't really grade how positive progesterone receptor was. But [patients] can derive a benefit from endocrine therapy.

**QUESTION 3, continued:** *We tried Tamoxifen and it didn't work. I've tried Xeloda and that didn't work. This week I started on Gemzar and Navelbine. Everybody seems kind of confused on what to do with that progesterone part out there, and I'm wondering are there some things... since it acts like it's positive but the estrogen is negative. Is there something different or unique ... for the metastatic disease that's not ...*

**LIU:** That's not chemotherapy or ... ?

**QUESTION 3, continued:** *Well, chemo that's maybe not used all the time because of the negative estrogen but negative or positive progesterone depending on who's looking at the number.*

**LIU:** Well, we know the progesterone receptor doesn't in and of itself really do much. It actually makes the estrogen receptor work better. They kind of are in conjunction. So even

though tests are negative it should suggest there's hormone responsiveness. So it can be considered whether one endocrine therapy is going to work better with just a slightly progesterone receptor positive breast cancer. We really don't know that. I don't know if Dr. Kramer has an addition?

**KRAMER:** I think Dr. Liu pointed out one of the most important things the pathologist can help us with: measuring these receptors and measuring them accurately. Craig Allred has done lots of work in this area. He looks for two things. He looks at all the breast cancer cells on a slide to see how many of them show the receptor. Then, the second question he asks is, of the ones that show the receptor how strong is it?

I think when your pathologist or physician tells you it's 5%, what they're unfortunately telling you is that 95% of the cells don't express the progesterone receptor. So it's never a problem to have a second opinion on that assay if you have any doubt in it at all because it's so extremely important. But if you did not respond to Tamoxifen I probably wouldn't recommend other hormonal therapies because I think you're more likely to respond to a chemo agent.

**QUESTION 3, continued:** *I asked yesterday about the new one that's coming out, and I understand it's 45 days before it will be manufactured and out to the physicians' offices and hospitals. Have you all heard any more on a date for that Abraxane?*

**KRAMER:** I don't know. Dr. Liu, have you talked to anybody about when we can expect Abraxane in our local pharmacies?

**LIU:** I don't know. I think they're just giving literature at the FDA approval now. How easy it is to get? I'm not quite sure when it will be available.

**KRAMER:** One thing you could do is ask where you receive your treatment if they could inquire to their chemo drug suppliers because they'll probably be able to give some information about when they expect to put that first order for the drug in.

**MORGAN**: Next question from Chicago, Illinois.

**QUESTION 4**: *I have a question about Tamoxifen and time frames. We know that three years isn't as good as five years. We know that 10 years is worse than five. There are a lot of us on Tamoxifen who are still getting our periods, who've been unable to start a family or try because of the Tamoxifen. Some people decide to go off after three or four years, instead of doing the full five, because they're sort of watching time tick. Do you have any thoughts on four versus five years on the drug? And, secondly, if a woman does decide to go off a bit early what are the thoughts on going back on to finish the five-year course after having a baby?*

**CLUXTON**: Dr. Kramer, why don't we direct that to you.

**KRAMER**: I think the studies that have been done have been three versus five years. I don't think we've ever studied four versus five years. I can empathize with wondering about that biologic clock. I think if a woman has a low-risk breast cancer and she's very interested in having a child that it would be reasonable to stop the Tamoxifen, conceive, deliver the child and then start back on it. There aren't many studies of delayed Tamoxifen, of not starting it right away but waiting and then starting it later. It seems that it still can be effective. Having a child is a complicated decision, but I think if you wanted to stop Tamoxifen for a year and then start back on it, as a physician I'd be perfectly willing to start my patient back on it to finish the five years.

**LIU**: I agree. There's no right answer to any of this. The studies were looking at two versus five years of Tamoxifen. We often use two years as a cut-off just to at least get Tamoxifen because we know there are good benefits from it. Also the risk of a recurrence decreases after two years and then again significantly at five years. A lot of it has to do with time of life and sort of situations. So the flip side to this, too, is the question: Does getting pregnant increase the risk of a recurrence irrespective of Tamoxifen for hormone receptor positive breast cancer patients? There really is no data to suggest that there it does, at least at this point in time.

**CLUXTON**: Speaking from personal experience, I know that it's so important to really have

that comfort and trusting relationship with your oncologist, and be able to talk to them about those decisions and involve them. My medical oncologist, when I chose to stop taking tamoxifen after two years to try and get pregnant, we haven't been successful. Now looking at going back he said, I have no standard by which to go through this. There's no window that's going to close to where I can't put you back on Tamoxifen as far as I'm concerned. So it's really just having that relationship with your oncologist and trusting in what they're telling you and making the best decisions for you and your quality of life. I think we probably have time for one more question.

**MORGAN**: Our next question is from Oak Park, Illinois. Go ahead, please.

**QUESTION 5**: *Thank you for the conference. I'm a 28-year-old with ER positive, HER-2/neu negative stage IV disease with mets to my liver and bone. My question is what is the panel's opinion on single sequential agent approach to chemotherapy in stage IV disease? I'm asymptomatic essentially from all of my mets and I've been doing single agents, Taxol initially which failed and now currently on Adriamycin. I just wanted to know your opinion.*

**LIU**: I'm a huge fan of sequential single agent therapy. There have been two randomized, Phase III trials looking at single agent versus combination therapy. The combinations evaluated were: Xeloda versus Taxotere versus Taxotere alone, and then Gemcitabine and Taxol versus Taxol alone. Although both studies did show a slight survival benefit to doing combination therapy versus single agent therapy they didn't actually look at sequential therapy.

If you actually look at the patients who got Taxol or Taxotere alone, a number of those women actually didn't either get more therapy afterwards or certainly didn't go on to the agent they didn't get. In other words, didn't go to Gemcitabine or didn't go to Xeloda afterwards. So those studies were not necessarily a fair comparison of combining versus sequencing those single agents. Then, we know there's a lot more side effects associated particularly with Xeloda and Taxotere together, although response rates are good. In other words, we see tumor shrinkage that correlates into a slight survival benefit. But, would that same thing happen if we did those drugs in sequence? I really don't see anything wrong with single agent therapy in the right situations.

**CLUXTON**: Dr. Kramer, do you have anything to add to that?

**KRAMER**: Let me just clarify. Could you tell me again what your estrogen receptor was?

**QUESTION 5, continued**: *Sure, it's ER positive and HER-2/neu negative. Taxol put me in exactly I guess menopause based on ... I didn't have a period from March until two weeks ago. Then I restarted my period, and I just, along with my Adria, which is my new agent that I've been switched to, I have taken the LHRH agonist today.*

**KRAMER**: I think one very important thing would be the ability to tell which of those agents is benefiting you. You're on two different treatments right now, a chemo agent and a hormonal therapy. I don't know exactly where you are in the chemotherapy, but I might try the hormonal therapy alone. There's very good evidence that individuals with estrogen receptor positive breast cancer will respond to hormonal therapy. I don't know if you've had Tamoxifen already.

**QUESTION 5, continued**: *I haven't, but while I was in presumed menopause from the Taxol and the Adria, I took a brief break from chemo with an aromatase inhibitor. I had tumor progression on aromatase inhibitor alone. But as I heard from you guys before, not having a period is not necessarily the best indicator that you're in menopause.*

**KRAMER**: And the fact that your periods started back.

**QUESTION 5, continued**: *(Overlap) maybe my ovaries were waking up at that time. Obviously that would produce a lot more estrogen in my body (Overlap).*

**KRAMER**: I think you may just have started on the most effective therapy out there for you, which is a hormonal therapy. I might argue to give you Tamoxifen rather than the LHRH agonist because I think it will cause you less side effects. When someone is asymptomatic it's very hard for us to beat that. Almost any drug we give will cause one symptom or another. I think the LHRH agonists are going to cause you to have hot flashes and probably a little trouble

sleeping at night and maybe some other symptoms. I think the Tamoxifen might have fewer side effects. I'd be a big advocate of doing either hormonal therapy or chemo. In someone who doesn't have many symptoms I'd really go for the hormonal therapy. Your cancer expressed the target these medicines work through, so I'd take advantage of those 20 odd years of research that we have that show that this therapy can really benefit you.

**QUESTION 5, continued:** *That's great. I appreciate that. Thank you.*

**CLUXTON:** Thank you all so much for your enthusiastic questions, which made this teleconference a success. We hope you've found it helpful and that your questions were answered. If you have more questions, or if you were not able to ask your question tonight please send them to [info@youngsurvival.org](mailto:info@youngsurvival.org) and we'll get them answered for you. The transcript from tonight's call will be available.

The YSC is here to provide you with the information you need as young women with breast cancer. The YSC is here as a support and to serve as a point of contact for you. If you're registered on the YSC website, and I assume most of you are, you'll continue to receive information about upcoming programs, newsletters and announcements. If you're not on our mailing list, visit [www.youngsurvival.org](http://www.youngsurvival.org) to register. If you've registered and you're not receiving this information please e-mail [info@youngsurvival.org](mailto:info@youngsurvival.org) to ensure we have the correct e-mail or mailing address for you. To help us reach out to young women in the community with breast cancer please contact us and we can tell you how to become part of our Adopt-A-Hospital program.

This concludes our program for this evening. Again, I'd like to thank our presenters, Dr. Rita Kramer and Dr. Minetta Liu, for joining us and sharing your knowledge, time and experience. Thank you to Aventis for sponsoring tonight's teleconference. Thank you, Morgan, for facilitating as our operator. Finally thanks to all of you.

We hope you will be joining us for future programming, including the Fifth Annual Conference for Young Women Affected by Breast Cancer on February 19th and 20th, 2005 in Philadelphia.

For more information on the conference please go to the conference dedicated web site at [www.youngsurvivorsconference.org](http://www.youngsurvivorsconference.org).

Good night, everyone, and please be well.

(END OF TRANSCRIPT)