



**Advanced Breast Cancer in Young Women:  
What's New on the Medical Front?  
A Young Perspective Teleconference  
December 19, 2006**

*Please join **Clifford Hudis, MD**, Chief, Breast Cancer Medicine Service, Solid Tumor Division at Memorial Sloan Kettering Cancer Center and YSC Medical Advisory Board Member, as he presents medical advances and promising research in the areas of young women and metastatic breast cancer. Upon his return from the 2006 San Antonio Breast Cancer Symposium Dr. Hudis will discuss any breakthroughs in specific and varied metastases and the overall treatment of advanced breast disease. Gain insights to develop questions to discuss with your healthcare team. An interactive question and answer segment will follow his enlightening presentation.*

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**ANNA CLUXTON:** Good evening, and welcome to "Advanced Breast Cancer in Young Women: What's New on the Medical Front," a Young Perspective Teleconference hosted by the Young Survival Coalition (YSC). The YSC is the only international, non-profit organization dedicated to the critical concerns and issues unique to young women and breast cancer. My name is Anna Cluxton. I am an almost six-year survivor, diagnosed at the age of 32. I'm a national board member of the YSC and chair of the Central Ohio chapter, and I will be your moderator for tonight's program.

Tonight we are very excited to present this teleconference, as the medical treatment of metastatic breast cancer is of great interest to a large part of our constituency. Tonight's teleconference is going to be engaging and extremely enlightening, and we're so pleased that so many of you are able to join us during this busy holiday season. We chose strategically to host this teleconference immediately following the 2006 San Antonio Breast Cancer Symposium to provide you with some of the more recent outcomes and research occurring in the field of breast cancer in young women.

The San Antonio Breast Cancer Symposium is designed to provide state-of-the-art information on the experimental biology, etiology, prevention, diagnosis and treatment of breast cancer and premalignant disease. This international symposium is directed towards academic

and private physicians and researchers involved in breast cancer in the medical, surgical, gynecologic and radiation oncology fields as well as breast cancer advocates.

The format for tonight's call is as follows. The first part of the call will be a presentation by Dr. Hudis. We will then open the call to your questions, and at that time there will only be about 25 minutes to cover all of your questions, so please try to keep them brief. If we run out of time and you still have questions for the panel, you may submit them to [rsvp@youngsurvival.org](mailto:rsvp@youngsurvival.org). We will do our best to get an answer to you.

This evening we are so pleased to present Dr. Clifford Hudis, chief of the Breast Cancer Medicine Service, associate attending physician at Memorial Sloan-Kettering Cancer Center in New York City and YSC Medical Advisory Board member. Dr. Hudis is an associate professor of medicine at the Weill Medical College of Cornell University. He is also co-leader of the Breast Disease Management Team at Memorial Sloan-Kettering Cancer Center, co-chair of the Breast Committee of the Cancer and Leukemia Group B, past chair of the Internet Services Committee of the American Society of Clinical Oncology and past president of the New York Metropolitan Breast Cancer Group.

He received his B.A. from Lehigh University and his M.D. from the Medical College of Pennsylvania following the completion of a six-year combined B.A. and M.D. program. From 1983 through 1987 he trained in internal medicine at the Medical College of Pennsylvania and served as the chief medical resident. His hematology/oncology training was completed at Memorial Sloan-Kettering Cancer Center in 1991, where since then he has been a member of the Breast Cancer Medicine Service and has conducted a large number of clinical trials.

His research interests include chemotherapy development, hormone therapy, novel targeted therapeutics and supportive care. A particular focus has been the integration of newer agents into the treatment plan for patients with early-stage disease. In addition to his

practice and clinical research, Dr. Hudis has served in a number of capacities at ASCO and as a member of the editorial boards of several journals. He is also a member of the breast committees of the Radiation Therapy Oncology Group and the National Comprehensive Cancer Network.

Dr. Hudis, thank you again for your willingness to join us. And now here's Dr. Hudis.

**CLIFFORD HUDIS, MD:** Thanks very much. It's a real pleasure to join all of you tonight. My job is a fairly diffuse one, and that is to in some ways summarize some of the interesting results, especially, I think, the clinically relevant ones, that were presented at the 29th Annual San Antonio Breast Cancer Symposium over the last few days, ending on Sunday. By way of introduction, these kinds of meetings are taking place all of the time. Of course there is the America-centric view, if you will, that highlights just ASCO and San Antonio, but the truth is that new data has been presented at ESMO, at the European Breast Cancer Conference and a variety of other settings around the world on a not quite continuous, but I would say, more frequent than every six-month basis.

I think it's important when talking about new data to put it in context. So as I go through my talk I'm going to first introduce each topic by highlighting what is standard and known about the area of research, and then I'm going to focus on what is new and how that might change things. In broad outline, I'm going to cover the results of the TAnDEM trial, which focuses on the combination of Herceptin and hormone therapy for advanced breast cancer. I'm going to talk about the EFFECT trial, which talks about the specific hormone therapy selection in the metastatic setting.

I'm going to focus a little bit on the role of new taxanes, especially a drug you probably know as Abraxane. And I'm going to talk about it compared to Taxotere; I'm also going to talk about it in combination with Avastin. Then I'm going to talk at the end about some new data regarding alternatives to Herceptin for people who have been on Herceptin but who have cancer that is growing anyway. That will get us through, I guess, the half-hour and still

should leave plenty of time for questions.

So the first topic really is the combination of hormone therapy and Herceptin. Again, by way of background, we've known for many years that, of course, Herceptin is an active treatment, blocking the growth of a subset of breast cancers, that is, those that are HER-2 positive. At the same time, we know that plenty of HER-2-positive cancers really don't respond to Herceptin. More about that a little bit later. But there's cross-talk. That is, some cancers that are both ER and HER-2 positive seem to grow through, if you will, dialogue between these two receptor systems. Therefore, there's been an obvious temptation to block them together.

Indirectly, in the adjuvant setting, we had tested this, although we didn't necessarily mean to. What I mean is that in the big adjuvant Herceptin trials that you're all familiar with, we had given lots of hormone therapy as well as Herceptin. But we didn't test for it or study it carefully. This year in Istanbul during the ESMO conference just in October, Bella Kaufman from Israel presented the first results of a trial called TAnDEM. This is a long-awaited trial in which patients with metastatic breast cancer getting their first hormone therapy, in this case defined as Arimidex, were randomly assigned to take Arimidex alone or to take Arimidex and Herceptin.

What was interesting about this was that the result was really all in the eye of the beholder. Firstly, there was no real difference in toxicity to speak of. Anybody that's familiar with this knows that if you're on Herceptin you have to come in and get an intravenous treatment with regularity, every week or every third week. But if you discount that, Herceptin is not especially toxic, especially in this setting where it's not being given with chemotherapy. The part about it being all in the eye of the beholder is the following. The average person on the trial got a very modest improvement when Herceptin was added.

However, some people got a very long improvement. What I mean is that there was a significant subset of patients who, given both Herceptin and Arimidex, appeared to have

responsive disease for years, whereas that kind of outcome was not clearly seen with Arimidex alone. So while the average patient, again, didn't benefit very much, some individuals benefited a whole lot. Of course an important question is how do we know who's who going into it so that we can more efficiently direct people to the right treatment. And we don't have the answer.

Questions from the audience really hammered this updated presentation at San Antonio because, while the study showed what I just described, the patients who got Arimidex alone may have crossed over to get Herceptin later, but they did not include their outcomes in the results of the study. Many in the audience wondered in terms of toxicity if it wouldn't just be easier to give people Arimidex, and if it didn't work and when it didn't work, move along to Herceptin as a single agent. That model of two drugs sequentially being just as good as two drugs together has been tested in chemotherapy trials, and in fact, is known to be true. So that's a small weakness of this trial.

The practical result is that clinicians treating many of you, I suppose, really can't yet say for sure that they should or should not give Herceptin when they start first hormone therapy for metastatic disease. And I think that's a decision that they're going to continue to make on an individual basis. But the study results are important, because they provide some information where there was none before.

The second study in the hormone arena that I wanted to touch on is a trial called EFFECT. And this is a pharmaceutical-industry sponsored trial, but that's not a reason to discount it, because I think the results are informative. In this study they took patients who were on treatment like Arimidex, and when the disease got worse they randomized them to either switch to a new kind of hormone therapy called Aromasin. You may know it as exemestane. This is a so-called steroidal aromatase inhibitor. You know that both letrozole, Femara, and anastrozole, Arimidex, are non-steroidal drugs.

Many doctors for many years have thought that by switching from one class of

aromatase inhibitor to another they get responses. Others were skeptical of it, and they would instead prefer to switch to a different kind of drug like Faslodex or fulvestrant. Again, for those of you who are knowledgeable about this, fulvestrant or Faslodex is very different drug. It has nothing to do with aromatase inhibitors. It's sort of like a super tamoxifen.

So in this trial, patients who were developing worsening disease while on Arimidex or on Femara were randomly assigned to take Aromasin or Faslodex. And just to make sure that there was no bias in the trial, it was placebo controlled. So since fulvestrant, Faslodex, is an injectable drug, you got a dummy injection if you were on the Aromasin. And if you were on the Faslodex you got a dummy pill. So everybody took pills and everybody got injections, and the doctors and the patients were both blinded as to what they were really on.

The fascinating thing to me about this trial is that the two arms are identical. That means that after you've been on an aromatase inhibitor you are as likely to respond to a different kind of aromatase inhibitor as you are to respond to Faslodex. The practical meaning is that you can avoid switching to an injectable treatment, which may be a little more painful. And instead you can stay on an oral treatment for longer. That's about it from a practical point of view in this trial. I'm certain that that's not what the sponsor of the study was hoping to see. They were hoping to see that Faslodex was better than the aromatase inhibitors so that they'd be able to sell more of it. I'm sure they'll still sell plenty of it, but it's an interesting result that gives us more options and more reasons to feel like we have flexibility than we had before. This is a reason to really respect randomized clinical trials.

So speaking of randomized trials, I'm going to switch gears again and I'm going to talk about some chemotherapy studies that were updated this year. One of the more interesting drugs of the past few years has been this drug called Abraxane. It's also known as nab-paclitaxel or nanoparticle paclitaxel or nanoparticle albumin-bound paclitaxel or ABI007. It has a lot of names. But what it is essentially is plain old-fashioned Taxol, which, instead of being dissolved

in solvent, is attached to human protein called albumin. This allows it to be given to people without the solvent, and for many of you who may have been experienced with Taxol, it eliminates one of the most famous sees of Taxol, which is the allergic-like reactions sometimes seen. In fact, when we use this albumin-bound paclitaxel, we don't have to worry about using steroids and antihistamines, things that have made treatment with Taxol a little more difficult over the years.

Now, Abraxane is FDA approved and already in fairly broad use for the treatment of metastatic breast cancer and other tumors. But the ideal way to give Abraxane and its relative value compared to some of the other standard treatments is still being established. In the first randomized trial that led to its FDA approval, Abraxane looked a bit better than conventional Taxol. The next step that the company wants to take is to prove that it's also better than Taxotere. And for many of you, again, familiar with this, you'll know that there is a general sense that Taxotere is a little tiny bit better than Taxol, although the differences are somewhat modest.

So investigators beginning this journey wanted to make sure that they were using the right dose of Abraxane. They also wanted to make sure, before they began the study against Taxotere, that they were in the right ballpark. So they conducted what's called a Phase II study. The only difference is this Phase II study was randomized, so patients numbering several hundred were randomly assigned to get Taxotere, that's the control treatment, or to get Abraxane. And if they got Abraxane, they were randomized to get it using three different dose and schedule combinations, one with a standard Abraxane dose given every three weeks. Two of them involved weekly Abraxane, using a high dose or a low dose.

The bottom line from this trial, which came to me as somewhat of a surprise, is that there was a statistically significant improvement in response rate for Abraxane at a low dose given every week compared to Taxotere. And in most ways it was less toxic, and those

differences were also statistically significant. This is interesting, because it raises, to some degree, the question, why do they need to do a randomized trial now. That is, in their Phase II study they were just looking for a hint. But they actually got statistical significant favoring Abraxane.

The answer to that question is that they didn't get data on all of their endpoints. Specifically, they did not report a difference in how long it took cancer to get worse. Therefore, with that as the primary reason to approve a new drug, they're going to go ahead and do their trial. Remember what their goal is from a marketing point of view. They want to be able to tell doctors in the open that Abraxane given at a low dose every week is really better than Taxotere. And to do that they have to do a trial that satisfies the FDA. So that's the next study that flow out of this work.

A related trial was performed and reported at San Antonio this year, and I have to say, this study, I think, is an important one for many of you, because it relates to the use of chemotherapy and Avastin. So you will know, of course, that Avastin is antibody we can give now that helps turn off the formation of new blood vessels. It is the first really effective, broadly available antiangiogenic agent. It's FDA approved for use in a variety of cancers, including lung, head and neck and colon.

There's a history in breast cancer that bears description before we move forward. When the drug was used, Avastin, as a single agent in advanced breast cancer, it was not very active. When it was combined with Xeloda, the pill chemotherapy, again, that many of you are familiar with, in breast cancer in patients who had been treated extensively, there was a signal that it was more active. That is, the patients getting Avastin and Xeloda did better than the patients getting Xeloda alone. But the differences did not achieve statistical significance, and the trial was insufficient to get Avastin approved because the benefit was too small.

The next study, one that I know you heard about in the last year and a half, looked

at the drug combined with Taxol. It was performed by the Eastern Cooperative Oncology Group. It's called ECOG 2100. And this was one of the big news stories from ASCO last year. In that trial, patients getting their first chemotherapy for metastatic breast cancer received Taxol alone or, by random assignment, Taxol and Avastin. That latter group did much better. Their cancers shrunk more often, and they lasted on therapy much longer, suggesting that there was a real benefit to the treatment.

Based upon that, many clinicians believed that Avastin was of greatest value only when given with Taxol and only when given as the first treatment for metastatic breast cancer. I have to say that I took some issue with that, because the definition of what's the first chemotherapy could be influenced by what doctor you saw and what treatment you had before and so on. So I was heartened at San Antonio this year to find the results of a non-randomized trial where patients got Abraxane often as the third, fourth or fifth chemotherapy. So it was obviously a bit further down the treatment line.

In this trial they gave the Abraxane either every week or every other week, and they gave it with Avastin, the antiangiogenic. The response rates were up around 50 percent, so that's as high a response rate, basically, as we see in the first-line setting. I think it really raises the possibility that Avastin, with the right chemo, could be active even in patients who have progressed down the line from getting first- or second-line therapy. I think it should embolden doctors to think about using Avastin a little more broadly than before. So I found that to be an interesting study for all of you to know about.

For the last few minutes I'm going to switch gears and go back to HER-2 and highlight one drug I'm sure you've heard about but another class of drugs that you probably haven't heard about. I'm going to start by asking the following question. Is it the case that Herceptin cures or eradicates metastatic breast cancer even when it's HER-2 positive? And you all know the answer. It's no. There are some people with really remarkable, long-term responses

lasting years and even some people who may appear to be cured, although we're always cautious about that terminology. But the truth is, the sad truth, that most patients on Herceptin eventually will have cancer that grows despite that Herceptin.

In addition, some people getting Herceptin for HER-2-positive breast cancer don't get a tumor response anyway. That is, having HER-2-positive breast cancer does not guarantee a response to Herceptin. So the obvious point is that HER-2 and Herceptin is a much more complex system than one might have initially thought, and we clearly need drugs that will reverse resistance to Herceptin. And we need drugs that will maybe amplify the Herceptin effect.

The first of these drugs to hit the market almost certainly is going to be an oral drug called lapatinib. You'll know it as Tykerb. This was a big news story at ASCO this past summer. This is what's called a tyrosine kinase inhibitor. In contrast to Herceptin, which attaches itself to HER-2 on the surface of the cancer cell, lapatinib, Tykerb, attaches itself to the inside of the cell, that is, to HER-2 on the inside of the cell. What it does, simply stated, is to shut off the downstream signaling. If you imagine HER-2 signaling is one of those complex Rube Goldberg type devices with the levers spinning and the ball falling and so forth, it's interrupting one of those events after the ball falls.

In doing so, it shuts off the signal for these cancer cells to grow. And you've heard already in a randomized trial with Xeloda that Tykerb increased the response rate and the time to progression. This data was updated at San Antonio just now, and I have to say, the difference between the current presentation and the earlier one was nil. So given that, why am I presenting it? It's just to remind you that the study is positive, that the FDA is almost certainly going to approve it, and we will, therefore, have a new kind of anti-HER-2 therapy available some time, I would think, in 2007.

Related to that, we reported from my group activity for a whole new class of

drugs. This drug is called 17-AAG. And this drug works very differently. In order to describe how it works, I have to use some analogies. So imagine that HER-2 is a bed sheet. In order for HER-2 to work right, that is, be deployed at the surface of the cancer cell, it has to get there and be folded into the exact right shape. So it's kind of like saying, imagine a bed sheet is made and put into a bag. What you need to do is get that bag home from the store, open the bed sheet up and spread it out across the top of the bed so that it can be useful, functional. And the system that spreads it out, the system that deploys HER-2 from where it's manufactured to where it's actually functional, is called heat shock protein 90, that is, HSP90. We now have drugs that can selectively target or turn off HSP90, and in doing so it shuts off HER-2.

The first of these drugs is the one I named already, 17-AAG. And we reported now both at ASCO and updated at San Antonio activity for heat shock protein 90 inhibitor, 17-AAG, given to patients whose cancers have grown on Herceptin, so what we're really saying is that there are going to be many new opportunities to increase our ability to target HER-2, all of this deriving from the fact that we know more and more about what it is that makes HER-2-positive breast cancers grow. I think that we're going to be able to provide ever-better outcomes for people with that kind of breast cancer as a result of these ongoing studies.

So I think with this I'm going to end my formal comments, and I've left a significant amount of time, hopefully enough, for some of your questions. Thanks again for inviting me tonight.

**ANNA CLUXTON:** Thank you, Dr. Hudis. Right now we're going to end up queuing up some questions for our listeners. While we're doing that I will go over some of the questions that have been submitted by e-mail. We invite our listeners to go ahead and ask questions. I would like to remind you to please keep your questions of a general nature, as Dr. Hudis will not address your personal treatment questions, but also to make it more applicable to all of the callers, please keep them of a general nature. We've had around 40 questions

submitted prior to the call tonight, so I'm going to take a couple of those and read them off to Dr. Hudis. I believe one I sort of gave you a heads-up before our call started, and that had to do with inflammatory breast cancer, if there was anything new for IBC patients.

**CLIFFORD HUDIS, MD:** There are a whole lot of things happening in terms of inflammatory breast cancer, but most of it is really driven by the increasing pools we have to treat various subsets of breast cancer, that is, biologically-defined subtypes. So what I mean specifically is there's been data reporting activity for lapatinib in inflammatory breast cancer. And Massimo Cristofanilli from MD Anderson reported a non-randomized trial in the preoperative setting of lapatinib combined with Taxol. For those patients, some of whom had inflammatory breast cancer, the combination was highly active, with about four out of five patients having a clinical response.

I think it's important to point out, however, that for inflammatory breast cancer, once metastatic, the treatment approaches really are not unique. That is, metastatic breast cancer is, by and large, metastatic breast cancer. And the physical presentation in the skin, which is what defines inflammatory disease, doesn't change the overall management approach.

**ANNA CLUXTON:** Then also we had a number of questions related to triple-negative breast cancer.

**CLIFFORD HUDIS, MD:** Triple-negative breast cancer is quite sort of a hot topic right now. It's important at the outset to highlight why and how it's defined and what limitations that puts on us to begin with. Right now we define breast cancer essentially in two axes. Is it hormone responsive or is it hormone unresponsive? Secondly, is it HER-2 positive or is it HER-2 normal? Hormone-responsive breast cancer has the ER or PR or both receptors present. HER-2, of course, is HER-2-positive receptor staining. The problem, and the reason I'm highlighting this, is that the staining and testing itself is a clinical endeavor related to using the microscope and the pathologist's naked eye and some very specific things. And it is not at all

foolproof.

So when we talk about triple-negative breast cancer we're talking about a subtype of breast cancer that expresses neither of those three receptors but may well itself be very heterogenous. That means it may itself be a mixture of types of cancer. I actually strongly disagree with the notion that there is such a thing as triple-negative breast cancer. I think it is a collection of things. As an example, last year at San Antonio ... and we updated this a little bit this year at San Antonio as well ... my group described a subtype of so-called triple-negative breast cancer where the male hormone receptor, the androgen receptor, appears to be expressed and turned on.

And in fact we're doing a clinical trial later this year, actually in early 2007, where we're going to give the antiandrogen treatment, bicalutamide, that's used for prostate cancer, to a subgroup of women who have metastatic, androgen-receptor positive breast cancer. That's a subset of the triple negatives. So I don't think that you're ever going to see in a big way a meaningful advance that relates to all of triple-negative breast cancer, because I don't think there's such a thing as all triple-negative breast cancer. Like the rest of breast cancer, I think it's a collection of diseases and we're going to have to parse it out more finely.

**ANNA CLUXTON:** That's incredible. So, let's take our first question from our listening audience.

**REBECCA:** Hi, Doctor. I was wondering if you could comment on the E75 HER-2 vaccine trial and what your thoughts are on how they randomized their group according to the HLA-positive and negative, and what those results really mean.

**CLIFFORD HUDIS, MD:** I think the numbers were relatively small in this trial. In fact, the authors themselves were very conservative in pointing out that essentially what they've proved with their vaccine is that they were able to achieve an immunity. That is, they had immune response, and secondly that the patients appeared to do very, very well, but they

were in no way able to talk about effectiveness yet, and I wouldn't do that either.

**CARLA:** I'm from Glendale, Arizona, and I was diagnosed with triple negative. But I had a question, and it wasn't addressed, in regards to possible vaccination. I know there are studies out there, but do you know anything on that?

**CLIFFORD HUDIS, MD:** So this relates to the previous question, and it gives me the chance to expand even a little further. Firstly, there's a great enthusiasm for vaccinating people against breast cancer. The first challenge that you have to admit is that breast cancer is you, is me. Breast cancers come from us. So it is not like vaccinating against a bacteria or a virus, which is all foreign. Most of what is a breast cancer is from your own body, and therefore it doesn't represent an easily separable target for your immune system. Therefore, we go looking for ways in which breast cancers are on their surfaces different from normal cells. And it's a hit or miss proposition for any one breast cancer to find it.

In order to do this we have identified, over the last 15 years, some targets, and they're called antigens, that are to a greater degree present on breast cancer cells than they are on normal cells. But very few, if any, of these targets are uniquely present on breast cancer cells, that is, only on the breast cancer and never on normal tissue. This is pretty important, and it relates to the last question. If one is to develop an immunity that's permanent against a target, one has to be really sure that there is not going to be some significant health problems. So when we're talking about, for example, vaccinating against HER-2, that's all well and good. But if you have an irreversible to HER-2 and HER-2 turns out to cause heart damage, how are you going to turn that off? At least when we use Herceptin, if somebody develops heart problems we can stop the Herceptin. So this is one of the ways in which this could be a problem.

Now, most vaccine studies that are done well to this date have not yet been ready to really look at effectiveness. They've really been sort of Phase I studies asking the simple question does our vaccine vaccinate. That seems like a dumb question, but what we mean is if

we give the vaccine does it generate a sustainable and meaningful immune reaction targeting the antigens of interest. The way we determine that is by things like skin testing and blood cell testing. The class of vaccine trials available today has largely been locked in that first stage here. As you know, there have been very few or no fully powered randomized trials meant to prove the effectiveness of vaccines. One such trial, I'll point out to you, was the Theradex trial, conducted several years ago. It was negative. It did not show any advantage for vaccinating. This doesn't mean that vaccines are a bad topic for research. It means that we have to pursue it even more rigorously and make sure that whatever we ultimately test on large scale is effective.

**DARIA:** Oh, hi. I had questions about triple negative as well. I guess you kind of answered. I just was wondering if there was anything new on the horizon for triple-negative metastatic breast cancer. It's just kind of disheartening that there are such wonderful things with all of these hormonal things for the hormone-receptor-positive people, but triple-negative patients only have chemotherapy.

**CLIFFORD HUDIS, MD:** I hear you on that. So the first thing is I think it's worth having some perspective in this way. What you say is absolutely right, but the converse is also true. When you look at the impact of chemotherapy, it's greatest in the triple negatives. And that's true in the adjuvant setting, clearly, and it appears to be true in many cases in the metastatic setting. The second thing is that Avastin and the newer antiangiogenic pills that are coming along the pike, there's every reason to think that they will be as or more active in the triple negatives.

Now, very specifically there is a lot of interest in some chemotherapy drugs for triple-negative breast cancer, like carbo or cisplatin. But I guess that doesn't really get away from your issue, which is that you're looking for a non-chemotherapy alternative. I share your frustration, and, in fact, that's why my comments were directed at pointing out that triple-negative breast cancer is really a diagnosis of exclusion. All it means is that we have not yet

sorted out the important targets that almost certainly exist in that population. My group is looking, for example, as I described, at the androgen receptor in that group of patients, and I think that there will be more targets in there, and hopefully we'll get to it soon. But fundamentally I don't think that triple-negative breast cancer represents a defined or distinct entity. I think that that's part of the problem here. I think it is a collection of diseases, and our science job right now is to pull it apart into what it really is.

**ANNA CLUXTON:** Dr. Hudis, I have a comment on that and then I also have a question related to that. My comment is that it's sort of like when somebody is diagnosed with breast cancer at a young age and has a very strong family history and goes through BRCA testing and has gone through genetic counseling and they test negative. I know that they are often told, it doesn't mean that you're not at risk for some type of familial disease going on. It's just that we are not smart enough to know what's going on in your family. It's sort of comparable to that.

**CLIFFORD HUDIS, MD:** I just wouldn't say smart enough, but we just don't know yet.

**ANNA CLUXTON:** There you go. We just haven't found it yet. One thing I wanted to ask you is sort of related to this. So if somebody has been told they're triple negative, and whether they're newly diagnosed or going through treatment, would you recommend that they get a second opinion on their pathology?

**CLIFFORD HUDIS, MD:** Absolutely. I'm glad you brought that up. Because there is nothing more important than that. Estrogen receptor testing and HER-2 testing in America, as good as it is, is not very good. There's every reason to spend a couple of hundred dollars and take the couple of hours it takes to get the pathology retested at least once. You will get surprises. I can give you example after example. I will share with you right now an anecdote from my own practice.

Several weeks ago a woman presented to my practice with newly diagnosed

breast cancer, never known to have it before, that was labeled triple negative on the basis of a bone biopsy. But the disease was clearly widespread in the bones. She had clearly been suffering from it for many, many months, if not years. And it just seemed sort of by pattern of growth typical for a hormone-responsive breast cancer. She needed emergency surgery to fix her hip, and at that time I insisted that they repeat the estrogen and progesterone receptors.

And sure enough, it was positive. I could fill the hour with anecdotes about that. So one should always reconsider not just retesting, but also even doing a second biopsy. There are tissues like bone that sometimes give you false negative results. There are patterns of growth that suggest estrogen positivity versus negativity, and you should be open-minded on this, and your doctor should be, too.

**ANNA CLUXTON:** Right. I was going to encourage that as well with the ... you're certainly not saying anything against your medical oncologist if you're getting a second opinion about your pathology, because that's a totally different physician that looks at that.

**CLIFFORD HUDIS, MD:** Well, I'm going to push it a little further and tell you that a skilled medical oncologist will, from time to time, elect hormone therapy even though the pathology report says it's negative for the estrogen and progesterone receptors. A classic example is the person who has bone metastases a decade after a primary diagnosis, where there's no other reason but bone and the person has been told it's estrogen receptor negative. But that pattern of growth with a late recurrence, bone only, is typical of hormone responsiveness. I wouldn't care what the pathology report said. I would try hormones.

**ANNA CLUXTON:** Especially if you respond. That's the important thing.

**CLIFFORD HUDIS, MD:** Well, that's the point. That's exactly the point. So I know there are a lot of questions about this triple-negative group. I would downplay the hype on that a little bit. Again, I don't believe it's going to hold up in the long term as a single, distinct entity anyway. Secondly, I think that you have to be aware of the fact that all of this testing right

now in America has modest quality at times and always bears repeating.

**ANNA CLUXTON:** Thank you.

**ALIKA:** Actually I'm a supposedly triple negative. I was weakly ER positive. But you actually have answered my question in answering the other ... oh, actually, I do have another question. I've been newly diagnosed with breast cancer, and I was diagnosed initially with Stage IV. I've been reading a lot about young, African-American women with triple-negative disease and them having a basal-like ... What in the world is that? And how do I know if I have that?

**CLIFFORD HUDIS, MD:** When we start to talk about where breast cancer really comes from, we're talking about the tubes called ducts that actually carry milk from the lobule, where it is secreted, to the nipple, where a baby would breastfeed. Picture, if you could, in your mind, the roots of a tree buried underground. Those roots are like the ducts in the breast, and the tree trunk is like the nipple. Breast cancers arise from the cells that line those roots.

So now picture a garden hose, a green garden hose like every one of you probably has had sometime in your life. As you cut that garden hose in half right through the middle of it and look at it on end, it's a round tube. The inner surface of it is called the epithelium. Those cells are called luminal cells. The outer surface, the green outside of it, is called the basal cells.

When we talk about breast cancers, we are beginning to believe that certain kinds of breast cancers arise from those inner cells called luminal and others arise from the deeper cells called basal cells. The difference is that the luminals are more likely to be estrogen-receptor positive and the basal types are more likely to be estrogen-receptor negative. So this is all about trying to figure out the single cell of origin of breast cancer, the stem cell that starts the whole process off and where it comes from in the duct of the breast.

**ALIKA:** Okay, so if pathology came back that was ER positive weakly ... and again I'm not asking you to diagnose ... more than likely one would think that it's probably not ...

**CLIFFORD HUDIS, MD:** Not what?

**ALIKA:** Probably not the basal.

**CLIFFORD HUDIS, MD:** Well, that's where things, of course, get somewhat murky, because there actually are luminal A and luminal B. And the luminal As are strongly ER positive and respond to hormone therapy, and the luminal Bs are said to be weakly ER positive but not so responsive to hormone therapy, whereas the basal are said to be ER negative and unresponsive as we talked about. From a practical point of view, this terminology is of no consequence to any individual right now. All that you care about is what treatment is appropriate to try and what treatment works for me. And some of that remains, as you know, trial and error. You wouldn't use a luminal A or B subtyping or a basaloid subtyping as a justification for skipping or specifically choosing a chemotherapy treatment, for example.

**ALIKA:** Okay. Thank you very much.

**CLIFFORD HUDIS, MD:** Sure.

**TAMAR:** BRCA1, is that one of the subsets that's triple negative? And can you address that specifically? Is that like a subset of the triple negatives?

**CLIFFORD HUDIS, MD:** Not exactly. So BRCA1 and BRCA2 are two of the most commonly defined or found genes that are known in families to cause breast cancer. Specifically when somebody has a BRCA1 abnormality and gets breast cancer, that is more likely to lead to a triple-negative tumor type, although it's not absolute. So these are sort of like overlapping diagrams. If you remember Venn diagrams from grade school, there's a set of tumors that are triple negative or basaloid, and there's a set of tumors that occur in people who have BRCA1 mutations. These two sets overlap but they're not identical.

**ROCHELLE:** Hi. If you have already been treated with Taxotere, is Abraxane still an option for treatment? Or are they too similar to each other?

**CLIFFORD HUDIS, MD:** This question really would not be answerable in a

general way. Specifically there are people who will respond when you switch from one of the taxanes, Taxol, Taxotere, Abraxane, to another. And there are people who will respond when you change the way you give the taxane: high dose every third week; lower dose every week. So it can be worth a trial, depending on the situation. Only a discussion with a doctor could really clarify that.

**ROCHELLE:** Thank you.

**DIKLA:** Hi. My question is more on the circulating tumor cell tests or all of those microarrays that were shown at the exhibits, if they're progressed enough to indicate if treatment is working or to choose a specific treatment for advanced breast cancer.

**CLIFFORD HUDIS, MD:** So those are really two separate technologies and two separate questions. I'll try to answer them both. The first question is the circulating tumor cell technology. For those of you who aren't familiar with it, this basically involves drawing the tube of blood and counting the amount of breast cancer cells, the number of breast cancer cells that are found in it. The simple notion is that the higher the count may be the worse somebody might do by prediction, the lower the count the better; more importantly that a change in the count over a matter of four or eight weeks could predict whether treatment is working or not working.

The problem is the following. There are only a limited number of studies that have actually validated this. And you have to appreciate this without thinking I'm too conservative, I hope. The critical question is when you get that second count, if it has not fallen, which means that you would predict that the treatment you're on might not work, you have no evidence on the earth that making an early change to another treatment is necessarily better. In addition, so far the test has worked most reliably with chemotherapy and less reliably with hormone therapy.

So I remain somewhat conservative on this, and I would not recommend the

routine use of this test outside of a trial. To their credit, the investigators involved in this, after it was published in the *New England Journal*, have launched a prospective, randomized trial where they will get sequential blood draws for the circulating tumor count. And in people whose counts fail to fall, they're going to randomize them to stay on they're already delivered treatment or to make an early switch. And only that study is going to tell us whether it is wise to use this information to guide therapy. Until we get that I don't think we can say it is.

The second question related to microarrays and the ability to predict the benefits of specific treatment. The simple answer is no, it is not yet ready for prime time. We're still learning how to do these microarrays, which cells to do them on, which cells matter, what the relationship between specific expression profiles and response to specific drugs really means. This is a purely experimental approach at present.

**DIKLA:** Okay, thank you.

**JULIE:** Hi, Doctor. My question has somewhat been answered on a triple-negative BRCA1. I know there's an overlap. I know 70 percent of BRCA1s are triple negative. But are they looking at that in terms of it being, say, slightly different? As you said, you think triple negatives are probably comprised of a lot of different variables, just like those that are hormone-receptor positive. Are they looking at it that way in terms of, say, which types of chemotherapy, whether it's the antiangiogenesis or something else, would be most effective in those two groups?

**CLIFFORD HUDIS, MD:** Well, sure. But somebody asked earlier about the bottom line here in terms of how many tools we have available. For right now if it's triple negative our tools are chemotherapy and antiangiogenics. So we're looking at their value in all of the types of triple-negative cancers, if you will. There is not yet anything very special to distinguish the BRCA1 group. The only wrinkle is there's some evidence that the platinum salts, carboplatin and cisplatin, might be better in this group. We are, in fact, exploring that to the best

of our ability. I have to say, you realize that doing clinical trials specifically in people with BRCA mutations is actually very difficult from a logistical point of view, because the eligibility criteria would, by definition, identify them outwardly as being mutation carriers. There are tremendous barriers to doing a trial like that right now.

**JULIE:** Okay, thank you.

**CLIFFORD HUDIS, MD:** Let me expand for a second. If I said I'm going to do a study in triple negatives, that's one thing. But if I said I'm going to do a study in BRCA1 heterozygotes, then every one who signs up for the trial has flagged herself as a gene carrier, and there are some broad societal issues about externally identifying people that way.

**ANNA CLUXTON:** I think we have time for one more question.

**DIPAK.:** This is regarding an ER-positive breast cancer metastasized to the liver after five years. The question is the pros and cons of the two treatment options, chemo, like a Taxol, plus Avastin versus a Lupron plus a letrozole, something, it goes to like a hormonal versus chemo plus Taxol. Could you please comment on that?

**CLIFFORD HUDIS, MD:** There are several issues here. The first one is that as a point of bias, you happen to be asking a doctor who prefers to see people get the least toxic treatments available for whatever their situation may be. In the case of the possibility of responding to hormone therapy, I would always favor the hormone therapy approach first. One can always move along to chemotherapy if one's hand is forced, but it's often the case that hormone-responsive tumors will be stable or shrink for months or years, and all of that time is time where you can avoid chemotherapy. So that would always be my first bias.

Supporting that, a cancer that comes back five years after the original diagnosis has, in part, defined itself as relatively slower growing. It gives you time to, if you will, make a mistake. So if one starts hormone therapy and several months later the cancer is a bit larger, you then go on to chemotherapy and you've truly lost nothing. It feels like emotionally that you've

lost something, but you really haven't. It's no different than if your doctor just found it a few months later. So I don't think that you should be concerned about this. Although I would never be able to give individualized medical advice on this kind of call, it's, I think, always important to explore the hormone therapy options first.

**ANNA CLUXTON:** Thank you for all of those thought-provoking questions, and thank you, Dr. Hudis, for your honest and very informative answers. Do you have any final comments about San Antonio or metastatic disease in general?

**CLIFFORD HUDIS, MD:** I'm not a Pollyanna about all of this, but I do think that these remain exciting times. I think that the burgeoning preclinical sciences, the microarrays, our understanding of the genes and the proteins that the genes make is really expanding our ability to approach this problem. I remain very optimistic, as I have all through my career, that we're going to continue to chip away at this and provide people with both longer life but also better life with higher quality of life and less toxic treatment options.

**ANNA CLUXTON:** Thank you, again, Dr. Hudis. We hope that our callers found it helpful and that your questions were answered. Again, if you have more questions or if you were not able to ask your question tonight, which I'm sure there are many more out there, please send them to [rsvp@youngsurvival.org](mailto:rsvp@youngsurvival.org) and we will do our best to answer them. The YSC is here to provide you with the information you need as a young woman with breast cancer and to serve as a point of contact for you.

If you are registered on the YSC web site, and I assume most of you are, you will continue to receive information about upcoming programs, newsletters and announcements that affect you as a young woman. If you are not on our mailing list, please visit our web site at [www.youngsurvival.org](http://www.youngsurvival.org) to register. Remember that a transcript of this call will be available in three to four weeks and will be posted on the web site. Also in early January we expect to release the next step in our programming for young women living with metastatic disease, which

will be a DVD entitled "The Beautiful Eight." So please keep your eyes open for that release.

Finally, I enthusiastically say this, I hope you will join us for our future programming, including our wonderful Seventh Annual Conference for Young Women Affected by Breast Cancer February 23rd through the 25th in Virginia. Registration, program and scholarship information can all be found at the very specific conference web site, which is [www.youngsurvivorsconference.org](http://www.youngsurvivorsconference.org), and we hope to see you there. I again want to thank our presenter, Dr. Hudis, for joining us and being so eloquent and so willing to share your time and expertise. This concludes our programming for this evening. I want to wish you all the very best holiday season and a safe and happy new year. Good night.

*(END OF TRANSCRIPT)*