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Medical and Quality-of-Life Updates from the 44th Annual Meeting of the American Society of Clinical Oncology

June 13, 2008

Clifford A. Hudis, MD

OPERATOR:

I would like to welcome everyone to the Living Beyond Breast Cancer teleconference. It is now my pleasure to turn the floor over to your host, Elyse Caplan.

ELYSE S. CAPLAN, MA:

Thank you, and welcome, everyone, to Living Beyond Breast Cancer's annual teleconference, reporting the latest updates from the ASCO meeting – the 44th Annual Meeting, I might add, of the American Society of Clinical Oncology. Many of you know that the ASCO meeting is the largest annual medical conference on cancer treatment in the United States. And each year, Living Beyond Breast Cancer hosts a program soon after to report some of the latest research that was discussed and presented that might impact patient care for the future.

I'd like to thank everyone for joining us. I'm Elyse Caplan. I'm the education director here at Living Beyond Breast Cancer, and I'll be moderating the program. Many of you know that LBBC teleconferences are interactive. We will start with a speaker presentation, and after that, we will entertain your questions throughout the balance of the program. As many of you know, ASCO each spring brings together scientists, researchers, oncologists and survivor advocates to hear some of the latest findings in the cancer community. Of course, many of the reports are on breast cancer, but other cancers are discussed as well. More than 30,000 people across the globe gathered in Chicago a couple of weeks ago for this meeting.

Today, our speaker, Dr. Clifford Hudis, will discuss some of the novel therapies that are being studied in early-stage, or adjuvant use of treatment for breast cancer, as well as in the metastatic setting. You'll hear about some of the bisphosphonates, the medicines used for bone building, and their application in early-stage breast cancer, as well as many other areas of quality-of-life and supportive

care issues. As you know, Living Beyond Breast Cancer does teleconferences as one method to get information out to large groups of people across the country and around the world. Many of these programs become transcripts that are found on our Web site [<http://lbbc.org/>].

I'd like to tell you a little about our featured speaker, Dr. Cliff Hudis. He is the chief of breast cancer medicine service and an attending physician at Memorial Sloan-Kettering Cancer Center in New York. He is an associate professor of medicine at Weill Cornell Medical College, a co-leader of the breast disease management team at Memorial Sloan-Kettering, and co-chairman of the breast committee of the Cancer and Leukemia Group B [clinical research group]. He is also chairman of the information technology committee of the American Society of Clinical Oncology, or ASCO. Dr. Hudis's research interests include chemotherapy development, hormone therapy, new targeted treatments and supportive care. He is focused on integrating newer medicines into the treatment plan for people with early-stage disease. Dr. Hudis is a member of the committees of the Radiation Therapy Oncology Group and the National Comprehensive Cancer Network, and, I might add, a very active member of Living Beyond Breast Cancer's medical advisory board. Without further delay, I am pleased to welcome Dr. Hudis.

CLIFFORD A. HUDIS, MD:

Thanks very much. I am really happy to join all of you today. I plan to cover roughly four broad topics in the next half-hour, and then I will leave plenty of time for the usual questions and so forth. The topics that I plan to cover include some conventional chemotherapy development issues, which I think are somewhat passe in this day and age, but I hope they will be of some interest to you, because they may give you some clues about things that are coming. In addition, I'm going to

talk about the very exciting information we heard at ASCO about Zometa in the adjuvant setting. I'm going to talk a bit about bevacizumab – you may know it as Avastin. And I'm going to end up with what I find to be very exciting developments in the area of HER2 positive breast cancer. That's an outline.

Let's start with the chemotherapy story. I think many of you know that the past few years have seen an interesting increase in the drugs that are available to treat metastatic breast cancer. There is always the expectation and hope that the activity seen in the metastatic setting will be something we can translate into improved therapy in the adjuvant setting. There are two protocols – two research studies – that were presented at ASCO this year that are interested in that regard. The first one is very conventional kind of add-on chemotherapy.

If you think back on the history of chemotherapy development in the adjuvant setting, you'll recall that the earlier studies used a single-agent chemotherapy called L-PAM. In the 1960s and '70s, the arbitrary combination of CMF [cyclophosphamide, methotrexate and fluorouracil] was developed. In the '80s, the anthracyclines came along, and to some degree CAF [Cytoxan, Adriamycin and fluorouracil] and AC [Adriamycin and Cytoxan] and so forth all were developed and improved over conventional CMF. Then the taxanes came along in the 1990s, and, therefore, a worldwide standard adjuvant therapy for many, many years has been AC followed by paclitaxel or AC followed by docetaxel, or in many European countries, EC – that's epirubicin – which was used because of a belief that it might be a little bit safer from a cardiac perspective. That's not, by the way, necessarily true. At any rate, the last real change in all of this, of course, was the demonstration that dose-dense scheduling of that same regimen would be better still.

Chris Poole and investigators in the United Kingdom basically took the standard



AC/paclitaxel regimen – four doses of AC and four doses of paclitaxel. There is one subtle difference, and that is that they used EC. And all they asked was whether adding gemcitabine would improve outcomes – simple question. It's basically a comparison of three drugs versus four drugs. The trial was called tAnGo [http://www.lbbc.org/content/news/trial-examines-effectiveness-of-adding-gemcitabine-to-standard-chemotherapy.asp?section_tag=G], and without bothering with the acronym, all that really meant was standard paclitaxel-containing chemotherapy alone or with gemcitabine. This is pretty important to American investigators, because there is a massive NSABP [National Surgical Adjuvant Breast and Bowel Project] trial that – using a dose-dense schedule of AC/paclitaxel – is asking the exact same question.

Now, what they noted in running the trial was that they would need 3,000-plus patients and many years of follow-up to report it. One of our statisticians from the Cancer and Leukemia Group B, Don Berry, however, has demonstrated that in these kinds of trials, if you don't see a significant difference by 36 months, then you essentially never will. So, they took an early look at the data, and at 36 months they saw no difference whatsoever. What that means is that the trial will never be positive, and, therefore, they reported it relatively early – earlier than they would have before. That's one of the take-home messages here: that we're getting a little smarter, even about how we conduct and report our clinical trials in an attempt to be more efficient. While tAnGo was a disappointment in that adding gemcitabine did not improve adjuvant therapy, tAnGo is important because it highlights the way we can more efficiently get the important chemotherapy questions answered quickly.

I emphasize that particular point because of the next study that I want to talk about, a very controversial trial that we did in the Cancer and Leukemia Group B. Hy Muss presented this at ASCO, and the study was called [CALGB/CTSU] 49907 [Read abstract at http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/507 or LBBBC's story at http://www.lbbc.org/content/news/standard-chemotherapy-is-effective-for-women-age-65-and-over.asp?section_tag=G]. This was the first – or, I should say, this was not the first. It was certainly the largest adjuvant therapy trial ever conducted that focused exclusively on older patients. It's worth

pointing out that the median age of breast cancer diagnosis in the United States is 63, yet the typical age of patients in our clinical trials, as many of you will know, is late 40s, sometimes early 50s. While ten years may not sound like a lot, or 15, it is a lot from a physiologic point of view. Clinicians are forced to extrapolate their practices from clinical trials that often enroll younger and, arguably, healthier patients. This causes all kinds of, I think, confusion. Hy Muss has an abiding interest in care of the elderly, so much so that he actually won a distinct ASCO award for these efforts over his career, during this year's meeting.

At any rate, he led a study for us in the CALGB, and in this trial we asked whether we could get away with one of these new oral chemotherapy treatments instead of conventional chemo for older patients. Eligible patients were over age 65, and they were randomly assigned to get capecitabine, a drug you may know as Xeloda, and they got it for six cycles, meaning six of those three-week treatment periods, or they got standard chemo. The interesting thing about this trial was that standard chemo could vary. It was either four doses of conventional AC, which many of you will be familiar with, or it was six cycles of old-fashioned CMF. So, the control arm is an amalgam of two treatment options, and what they are being globally compared against is this novel therapy.

The clinical trial design aspect of this, again, was important. We wrote a study here that did not stipulate a fixed number of study participants. We said we need between 600 and 1,800 patients, and we don't know the exact number because we don't know how the two arms are really going to perform. We monitored the arms of the study, and we could tell by the way the data was unfolding whether the study was going to be positive or negative. We ended up closing the study in December 2006, when 600 patients were on the study. In contrast to many studies you've heard earlier, where there would be so-called "early reporting," we did not report the study back then because we had a hint about the direction the study was going – enough of a hint to be sure with time that we would get an answer, but we did not have the definitive answer then.

We waited a year. This past winter, we looked again, and, indeed, the study was statistically significantly positive, but not the way we had hoped or expected. The capecitabine arm of this trial was significantly inferior to standard chemo. This is important, by the way, from another perspective,

which is, as many of you know, whenever there is a research study, many clinicians in the community will sort of assume that the researchers must know something, and they will start, in some cases, to use this research treatment option even before it has been fully tested. You've seen that in some high-profile examples.

If they had done that in this case, they would have been picking the loser, not the winner. That's another sort of object lesson in the conduct of clinical trials and how to do all of this as safely as possible – that is, to wait for the real result and not to jump ahead. So, those are two somewhat disappointing, but instructive, results. They confirmed for us one other thing: that in older patients, conventional chemo like AC or CMF clearly is effective. I say that because it was statistically significantly superior to the capecitabine in all patient groups, so one cannot argue that chemo doesn't work. One can argue that capecitabine is less effective than standard therapy in that adjuvant setting.

I'm going to switch gears now and talk about what was probably the most newsworthy report at the meeting this year: the study called ABCSG-12. [Read the abstract at http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=35897 or LBBBC's story at http://www.lbbc.org/content/news/pre-menopausal-women-taking-zoledronic-acid-with-hormone-therapy-may-live-longer.asp?section_tag=G] In that trial, premenopausal women were basically treated with goserelin and rendered menopausal. They were then randomized to get tamoxifen or anastrozole, the aromatase inhibitor. That mimics the ATAC study [<http://www.cancer.gov/clinicaltrials/results/ATAC1204/print?page=&keyword=>] that you're familiar with in the past, with the caveat that there were premenopausal women who were being made menopausal to get randomized. Now, that randomization was flat-out negative, with several years of follow-up. There is no difference between the tamoxifen- and anastrozole-treated arms.

It sounds like a third negative study that I'm telling you about, but what's interesting about this is that many clinicians believe, especially for high-risk breast cancer patients, that if they're young, in addition to conventional chemo, patients should have their ovaries shut down and be placed on an aromatase inhibitor because of all of the positive



news you've heard about those drugs in the past few years. This study to some degree undermines that argument, because while it is conceivable that the ovarian suppression in these patients was useful, the difference between tamoxifen and the aromatase inhibitors was zero.

Now, the other aspect of this study is that they randomized the same 1,800 patients to get the bisphosphonate Zometa, or zoledronic acid, which many of you will be familiar with. It's widely used in metastatic breast cancer as well as in other malignant diseases to control bone disease. Of course you know it's the replacement for pamidronate, or Aredia. In this trial, they randomized patients to get seven doses once every six months of Zometa. That's not unlike the once-a-year dosing of Zometa that is being marketed now for osteoporosis around the brand name Reclast. You may see their ads on the evening news and elsewhere.

What has happened is that with the addition of Zometa, there was roughly a 33 percent relative risk reduction in terms of a recurrence of breast cancer. It wasn't limited, by the way, to bone metastases. So, it looked like Zometa was as effective in this case as conventional chemotherapy. This certainly could be a real change in conventional practice for all of us in breast cancer. I think the caveat is that we like to see a second study, especially when we see such unexpected results. We don't have to wait too long. There are multiple – at least four – large, randomized trials testing Zometa and drugs like that as postoperative adjuvant therapy. I think from those studies we should get a clear answer in the next few months, maybe even later this summer.

We're sort of crossing our fingers at this point and hoping to get a bit of confirmatory evidence that Zometa could be useful, independently of everything else, as an anticancer treatment for early-stage breast cancer. So, you can see why this widely used, relatively inexpensive and relatively safe drug could really be a significant breakthrough for our patients.

The third topic I want to talk about is the area of antiangiogenics, specifically bevacizumab. There was a very contentious new drug approval this winter of bevacizumab with weekly paclitaxel for metastatic breast cancer. Many of you who follow this will know that early studies of bevacizumab with other diseases, like head-and-neck cancer or colon cancer and so forth, with a variety of chemotherapy drugs showed that it was an effective

treatment, delaying recurrence or delaying progression of disease. The first study in breast cancer – by Kathy Miller, several years ago [<http://jco.ascopubs.org/cgi/content/full/23/4/792>] – used capecitabine, or Xeloda, in heavily pretreated patients. There were some hints that bevacizumab was active, but it was not enough to call the trial positive.

Much of the development of bevacizumab was slowed down in breast cancer as a consequence. Subsequently, ECOG 2100 [http://www.breastcancerupdate.com/sanantonio/2005/SABCS_05_23.pdf] was a study in which a large number of patients were randomly assigned to weekly paclitaxel alone or with bevacizumab. It was not a blinded study. It was not placebo controlled, and it was not initially set up for purposes of registering the drug with the Food and Drug Administration. However, despite those shortcomings, when it was reported and positive with a near doubling of time to progression for those patients who got bevacizumab, the company, Genentech, filed it with the FDA. They had a special ODAC [Oncologic Drugs Advisory Committee] meeting last winter, and some of you will recall, in February, I think it was, or maybe in January, when the ODAC vote was actually against approval for bevacizumab. The FDA subsequently overruled that voting and voted for approval for bevacizumab.

At that time, we were told that a clinical trial called AVADO [Read the abstract at http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/LBA1011 or the LBBC news story at http://www.lbbs.org/content/news/bevacizumab-plus-docetaxel-may-be-effective-first-therapy.asp?section_tag=G] was about to be reported, and we were told that it was positive and that that would be an important bit of information in this discussion. AVADO was docetaxel, or Taxotere, alone or with a low dose or a high dose of bevacizumab. It was reported by [David] Miles at ASCO just now, and it was positive, but not very. What I mean is that the median time to progression essentially was increased by about one month when bevacizumab was added, and that's a fairly disappointing result, considering all of the hype – and also, frankly, considering the magnitude of the benefit that was seen in the ECOG study. So, that's an important result at this year's ASCO, but it's sort of hard to interpret, because, yes, it's positive, and, yes, it goes the right direction, but it is of a much lesser

magnitude than I think most of us were counting on for this drug.

There are several other drugs that I can mention in that space. There's no real data to update you on, but you should be watching sunitinib, sorafenib and axitinib. The "I-B" ending on all of those names tells you that they're inhibitors – in this case of the tyrosine kinase activity of the VEGF receptor. It just makes the point that there's a whole lot of drug development in that space.

Now, the last broad topic I want to cover for you, before we go to the question and answers, is the area of HER2 positive breast cancer. This is something that has become exciting for many, many reasons. I'll back up and remind everybody that "HER" stands for human epidermal growth factor receptor. There are four members of the HER family: 1, 2, 3 and 4. HER1 is well-known to many people in America because it has a second name, a synonym. That synonym is EGFR, the epidermal growth factor receptor. The EGFR is mutated in some lung cancers, and those are the lung cancers that have special sensitivity to some of these novel anti-EGFR drugs. In addition, many Americans are familiar with EGFR because it is the target of the antibody cetuximab that is made by ImClone, about which Martha Stewart got into trouble. That's HER1.

Now, HER2, of course, is overexpressed: That means it's produced in higher than normal amounts in about 20 percent of breast cancers. Historically, when we saw that a tumor was HER2 positive, or overexpressing, that meant it was a bad cancer; it was more aggressive. The only real tool we had against it was a vague sense that Adriamycin was a particularly good drug for those bad cancers. In the 1990s, Herceptin, or trastuzumab, was developed. That's a monoclonal antibody. It's produced synthetically, of course. It's mostly human, that antibody, but the little tip of it is not human, and that's the part that binds or attaches to HER2. When it attaches, we don't know exactly how it kills breast cancer cells. It may do it through any number of maybe parallel mechanisms or overlapping mechanisms. But one that we think is probably a big part of it is simple immunotherapy. That is, when we give Herceptin, it attaches to HER2 and turns on the body's natural defenses to kill those cells. I will stipulate that other potential activities for Herceptin are sources of great controversy in our scientific community.



Now, the reason for going for all that is that Herceptin has become standard, as you know, in the treatment of metastatic breast cancer and has become standard recently even in the postoperative treatment of early-stage breast cancer to prevent relapse. That's the so-called adjuvant setting. This means that essentially everybody who has a significant risk from HER2 positive breast cancer is getting exposed, at some time or another, to Herceptin. That raises, of course, important questions for all of us about whether we continue Herceptin when the cancer comes back, if it comes back, or whether we should go to other kinds of treatments.

For many years, Genentech has promoted the continued use of Herceptin, so that if a patient got paclitaxel and Herceptin and had progressive stage IV disease, they would recommend Navelbine and Herceptin and then gemcitabine and Herceptin and so on. I will confess to you that I thought that was a bit of a push, because we never had any data that supported that point of view. Last year, or two years ago at this point, at ASCO we heard the first new molecule that targeted HER2 reported. Charlie Geyer presented a study [http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=40&abstractID=90002] in which patients who had progressed on Herceptin either got capecitabine alone or capecitabine and lapatinib, or Tykerb. That's a small molecule that you'd take as a pill. It's an inhibitor of HER2, but it works from Herceptin.

That study was positive, and when that study was positive, it essentially raised more questions than it answered, because it established that HER2 was still an important target, but we didn't know whether the benefit of the anti-HER2 therapy was generic, meaning it could be any anti-HER2 therapy, or if it was specific to lapatinib.

So, Gunther von Minckwitz in Germany did a randomized trial [http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=34562] exactly the same, except he randomized patients after Herceptin to get capecitabine alone or capecitabine and more Herceptin. By the way, we tried to do this trial in the United States and we only ever accrued a total of five patients, which is a bit of a disappointment. At any rate, Gunther randomized more than 100 patients. The study was closed early, because when the lapatinib data became available, the enthusiasm for this approach was diminished.

However, interestingly, there was a near doubling of response rates for the patients who stayed on Herceptin, and in addition to that, there now is evidence of a longer time to progression.

This really muddies our waters. It suggests, again, that the capecitabine/lapatinib study that changed practice in the U.S. might have been positive, but not because of the lapatinib. Instead, it might have been positive simply because of the continuation of the anti-HER2 therapy. This is going to be important in all kinds of ways related to the adjuvant setting where we're testing lapatinib, for example. Now, in addition to that, there are several new classes of drugs that have been shown to be very active in the area of HER2 positive breast cancer.

The first is a drug called pertuzumab. It's also from Genentech. It is distinct from trastuzumab, or Herceptin, in that it attaches or binds to HER2 higher up, away from the cell surface. Picture in your mind a deer's antlers. Down near the skull would be where Herceptin attaches. Up high in the branches of the antlers, that's where pertuzumab attaches, and this makes for mechanical and functional differences. My friend and colleague Jose Baselga, with his collaborators, Pierre Fumoleau from Europe, has shown that in patients with disease that has progressed on Herceptin, when you simply add pertuzumab you get about a 20 percent response rate. This has already led to a big, international, randomized trial of docetaxel and Herceptin alone or docetaxel and Herceptin with pertuzumab [<http://clinicaltrials.gov/ct2/show/NCT00567190>].

The third bit of news in this space is another drug from Genentech called T-DMI. "T" stands for trastuzumab. The "DMI" stands for the name of a chemotherapy drug, maytansine, which is physically attached, linked to the Herceptin. In patients who have been on Herceptin and had progression of disease, T-DMI was given, and again the response rate is about 25 percent. What's interesting about this is we're using the Herceptin as a real targeting drug to deliver the chemotherapy. By having the chemotherapy attached to the trastuzumab, what happens is that the trastuzumab is physically attached to the cell, dragged into the cell. When it gets inside the cell, the chemotherapy, maytansine, is broken off of it and kills the cell. It has kind of been an age-old dream to use antibodies to deliver chemotherapy right to cells. T-DMI does it.

The final drug in this class is something that my group has been fortunate to work on, and it's a novel area of research called heat-shock protein 90 inhibitors. Simply said, when we make these complex proteins like HER2, it takes an energy-dependent system to do that. You have to make the protein, but you also have to fold it and deploy it at the surface of the cell. The system for doing that is heat-shock protein 90. I always describe this as the bed maker. If you buy a sheet at Bloomingdale's, you have a sheet that's fully made but it's not functional. To make it functional, you have to take it out of the bag and you have to put it on the bed and stretch it out and smooth it out and so forth. The bed maker is heat-shock protein 90. If I poison the bed maker, if I poison HSP 90, then my HER2 goes away.

Indeed, we have shown preclinically that that happens, and my colleague Shanu Modi has now shown in phase I and II studies [Reported at ASCO in 2006: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=40&abstractID=32971], including one just updated at ASCO, that about 20 percent of patients who get heat-shock protein 90 inhibitors will have significant shrinkage of their HER2 positive breast cancers. It's exciting to us, because it's in-house science that we've translated. But taken together, the topics I just covered really raise something that we typically are afraid to talk about, and that is the possibility that maybe we could outright cure HER2 positive breast cancer in the years to come, because we have more excited and highly active drugs in that little space than we have anywhere else.

One of the things that I think you have to recognize about this is that there are only 15,000 patients a year with metastatic HER2 positive breast cancer. If all of those drugs are going to be developed and they take several hundred patients per drug, we need to have participation of most patients in the country, in the U.S., in the trials that are developing these agents. It's a really big technical challenge for all of us in the clinical trials world.

I'm going to end my comments there, and I'm going to turn the program back over to the moderator, and I look forward to answering your questions.

ELYSE S. CAPLAN, MA:

Thanks, Dr. Hudis. It's Elyse again. You really zoomed us through life at ASCO as it relates to those of us who are interested in the breast cancer



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updates. I think our participants probably appreciated hearing your broad topics covering the standard chemotherapy and how that has been used in current times as well as some of the more novel approaches to treating breast cancer, the many things that are giving hope to so many women with advanced breast cancer and those following these novel targeted treatments. I imagine you'll get a number of questions related to some of this. Without further delay, I'd like to remind our participants to keep your questions brief and please keep them as broad as possible, because Dr. Hudis will not be able to give a personal consultation, but he can address your broader questions.

OPERATOR:

Your first question is from White Hall, Maryland.

CALLER:

Hi. I'm not sure if you've covered my topic yet. I have triple-negative breast cancer. . . I started treatments last July, and it has continually spread. They haven't been able to stop it with any of the chemos that I've tried so far. I was wondering if you've had any dealings with that specifically...

CLIFFORD A. HUDIS, MD:

Sure. First I want to remind everybody that we can't talk about the individual case management, so please don't misconstrue anything I say to represent specific advice. Triple-negative breast cancer, as many of you will know, is a bit of an odd diagnosis, in the sense that it's being defined by what it is not. What it is not is HER2 positive, and what it is not is estrogen or progesterone receptor positive. So, by process of exclusion, there are probably a group of breast cancers that are being banded together as so-called triple negative. I'm making the point here that it's probably not one specific entity but several.

At ASCO this year, there were smaller presentations that relate to this, and I'll run through them right now for you so that you know what's going on. The first was Lisa Carey, who presented the first results of the Translational Breast Cancer Research Consortium efforts aimed at targeting HER1 [http://www.asco.org/ASCOv2/Meetings/Abstracts?vmview=abst_detail_view&confID=55&abstractID=33786]. If you were on the call when I went through HER2, I started off by describing HER1, the EGFR receptor. I mentioned that Martha Stewart got in trouble

because of cetuximab. Well, we studied cetuximab in breast cancer targeting HER1 because there is some evidence that the EGFR will be particularly useful in so-called triple-negative breast cancer. In our early studies with conventional chemo, we found it to be, frankly, too toxic a drug to give with conventional chemo. It caused a very frequent acne-like rash that most patients really didn't tolerate.

What Lisa did is she gave it as a single agent in a cohort of patients, and she gave it in combination with carboplatin, a drug that is specifically hoped to be active, again, in triple-negative breast cancers. The disappointment, which was not a surprise, was that the antibody cetuximab alone was really not active. The good news was that with carboplatin, there was a significant response rate. Now, of course, this raises the question, is the antibody to HER1, to EGFR, contributing anything or not? And that's a question that will have to be answered in subsequent trials.

The second thing I'll mention is that supporting our belief that triple-negative breast cancer really is not a single entity, there is growing evidence that at least a small number of those triple-negative tumors actually express the male hormone receptor, the androgen receptor. We and a group at M. D. Anderson [Cancer Center] and others have begun to explore this carefully, and while we don't have data yet, I can tell you that we have a clinical trial that is studying the antiandrogen therapy, the bicalutamide that is typically used in prostate cancer for men, in women who have this receptor.

Up until now, the standard management of triple-negative breast cancer really relies on chemo. One of the misunderstandings is that chemotherapy, on average, is more effective in that kind of breast cancer than in others. The second component of the care is the antiangiogenics, which I did talk about. We have, as I say, some modestly good news with the antiangiogenic Avastin, and there are a slew of new drugs in that space.

But to your point, I wouldn't say that this was a big year for big breakthroughs, specifically focused on triple-negative breast cancer at ASCO. It is, however, important to point out that this grouping of breast cancers is the focal point of a whole lot of ongoing research right now.

CALLER:

Thank you.

OPERATOR:

Your next question is from Sandpoint, Idaho.

CALLER:

Actually, I've already had it answered. I was concerned about the triple negative, because that's exactly what I have, and it has come back. I think you pretty much answered. There's really not a lot of hope, is there?

CLIFFORD A. HUDIS, MD:

No. If you heard that, then you misunderstood me. Let me be clear. What I'm saying is that triple negative is an important focus of research right now. It doesn't have a single Achilles' tendon like HER2 positive breast cancer, let's say, or ER positive breast cancer. My personal view is that it's not going to stand as a single entity for too much longer – that you're going to be hearing about subtypes of triple-negative breast cancer, which will have specific and effective therapies for them, like what we see in the other types.

Having said that, I want to, again, emphasize the point I made before. Despite the seemingly bad press that this tumor type gets, the truth is that it is among the most chemo-sensitive types of breast cancer, and in some cases the responses are far greater than what are seen just with conventional chemo than with other types of breast cancer. The antiangiogenics as well as the anti-EGFR therapies are really a focus of ongoing studies right now. This may seem more philosophical than anything else, but I think giving people an extra burden these days by sort of moaning over triple-negative breast cancer compared to others, having treated breast cancer for 20 years, the truth is that metastatic breast cancer is metastatic breast cancer, and triple-negative breast cancers are certainly biologically distinct from the other types, but the prognosis is not as different from these subtypes as people seem to think.

ELYSE S. CAPLAN, MA:

I think that was an important thing to say, Dr. Hudis, because clearly those affected by triple-negative breast cancer often feel isolated as it relates to the research, because over the years so much research has been reported on the hormone-sensitive breast cancers. I'm really glad to hear, number one, you reporting that at meetings like ASCO and the annual San Antonio symposium in December there is a lot of research that's being conducted looking at the various subtypes of breast cancer to try to tailor or personalize



treatments based on the various proteins or targets that are part of an individual woman's disease. I think that does give rise to some hope that there are a lot of things in the pipeline, and the scientists and clinicians like you are working hard to try to get a better understanding of how breast cancer can be managed.

OPERATOR:

Your next question is from Franklin Lakes, New Jersey.

CALLER:

I'm the third person who is also concerned about triple negative, and you have answered a lot of my concerns, but I do have one further question on that. That is, when there is a recurrence rate, is it any different with the triple negative as it is with the other types of breast cancer?

CLIFFORD A. HUDIS, MD:

Let's be precise. In the postsurgery adjuvant setting when we're worried about cancer maybe coming back, there is a very different pattern of recurrence, which I think is part of what fuels some of this concern. Let me start with something that is not so obvious. If you compare estrogen receptor-positive breast cancer against estrogen receptor-negative breast cancer for three decades of follow-up, 30 years, the overall risk of recurrence and the overall risk of death are the same. That comes as a bit of a surprise to people who have always been taught that triple negative was worse and that ER positive was so much better. The aggregate risk of a return of that cancer is the same.

What is very different about those two cancers is the timing of the return. This is what makes the ER/PR negative cancers worse in the short run: They have their highest risk of recurrence in the first few years after diagnosis. I always describe this to patients as the difference between a fixed-rate mortgage and an adjustable-rate mortgage, albeit a funny one. What I mean is that ER positive breast cancer is like a fixed-rate mortgage. Every year, a small but steady percentage of patients, unfortunately, have a recurrence, and that's why over 30 years they have the same risk of recurrence as the ER negatives.

In the ER negative setting, the risk of recurrence is like an adjustable-rate mortgage, with an early spike. In the first five years, most of the recurrences will happen. The paradox is that for the patient with the so-called bad breast cancer, the triple negative, who gets to five years, the odds that that patient will ever have a recurrence at that

point are much lower than the risk for a patient with the better breast cancer at five years. You see?

The distribution of the recurrences is what's different. Triple-negative breast cancers tend to recur early or not at all, whereas ER positive breast cancers tend to occur at a very steady rate, literally over decades. Does that answer your question?

CALLER:

Yes, thank you so much. So, if one does not have a recurrence in the first five years, then her chance of recurrence is slighter?

CLIFFORD A. HUDIS, MD:

Well, that's right. Oncologists are conservative, and nobody ever will say "cured," and nobody will ever guarantee anything, because one can't do that and be honest. But there is a real difference. For example, in the ER negative breast cancers, maybe 90 percent of all of the lifetime recurrences will happen within those first five years, but for the ER positives, it might be only 30 percent of them. You see?

CALLER:

I see. I see, yes. When do you consider looking at the timing? Is it from the diagnosis? Is it from the time that you finish treatment, radiation and chemo?

CLIFFORD A. HUDIS, MD:

We usually talk about it from the time of surgery. The truth is, that's one of those peculiar questions that are never completely settled. But over the span of years and decades, it actually doesn't matter if you're talking about July or September.

CALLER:

Mm-hm. So it's really the time of surgery?

CLIFFORD A. HUDIS, MD:

Yeah.

CALLER:

Thank you very much.

CLIFFORD A. HUDIS, MD:

That's the typical timing that statisticians and scientists use in this question.

CALLER:

Thank you so much.

OPERATOR:

Your next question is from Atlanta, Georgia.

CALLER:

First, thank you so much, because I'm learning so much, and it's very helpful. I have stage IV or

metastatic breast cancer. I travel around to some of the different clinics, the centers in America. Do you all share with each other? If you're going to MD Anderson or you're going to Sloan-Kettering or Dana-Farber, Duke, whatever, for metastatic, is this information on the trials and everything shared? Or is it something that we need to be constantly looking at who's doing what at each center and kind of jump around?

CLIFFORD A. HUDIS, MD:

I'm going to give you my idealized answer and then what I think is the truth. The idealized answer is we are a community of people who, regardless of which institution we work in, are really all focused on the same thing. The breast cancer world, in particular, is very collegial. We have these cooperative groups that do joint research across institutions, and we have multiple versions of those kinds of cooperative groups. In addition, we have deep friendships and associations spanning decades and institutions, in many cases. So, I would hate to believe that there is significant information at one place that is not available at another.

In addition, the federal government and other organizations that are funding research increasingly make it transparent what they're funding and where they're funding it, and they make disclosure of the research, of course, a requirement for that funding. That doesn't mean it's easily accessible; sometimes you have to dig around on the web a little bit.

The other part of science that I think is often misunderstood is, contrary to what people think, when somebody has a breakthrough, that person generally wants to get out there in public as fast and as early as possible, because, frankly, he or she wants the ego gratification and the credit for having been first and right. It is not the case that people at Memorial Sloan-Kettering are sitting on the answer for triple-negative breast cancer and are hiding it from their colleagues. In fact, if they think they have the answer, the risk is actually greater in the other direction that they would prematurely reveal it because they're worried about being scooped. Market forces, if you will, really kind of work against keeping the secrets.

That doesn't mean that sometimes I might not be completely aware of a particular phase II trial at MD Anderson or vice-versa, but to a large degree we're very aware of what everybody is doing, and we're often collaborating on many of these projects.



CALLER:

That was my other question, and thank you for that answer. When you're doing clinical trials, I noticed ... I've been very fortunate. I'm alive 4.5 years later after having this, and doing well. But when these trials are being handled, I notice trials aren't always at each center, so you really have to pick and choose, I guess, where to go, because ... and how did they choose that, like where you go?

CLIFFORD A. HUDIS, MD:

You raise a really great question. It touches on a broader issue that can be hard for people who don't live in science to grapple with, but you don't have a basis for that choice. If you have three new drugs in a particular research setting, then you have three drugs where you don't know how they perform yet. When there is some certainty about how they perform, then of course your choice is made easier. So, while your question is a good one – "How do you choose?" – there really is no answer, and there can't, by definition, ever be one.

CALLER:

Thank you.

ELYSE S. CAPLAN, MA:

Thanks for your great question.

OPERATOR:

Your next question is from New York, New York.

CALLER:

Thank you so much. This is related to triple-negative breast cancer as well. I'm curious where you think maybe the leading research is being done or clinical trials on triple-negative breast cancer. I know you mentioned Lisa Carey, and I know Eric Winer with the Triple Negative Breast Cancer Foundation, but I'm curious about what you're hearing.

CLIFFORD A. HUDIS, MD:

Well, it's being done everywhere. In my group we're focused on two things. For example, there's a drug called a Src inhibitor. It inhibits a specific cellular pathway that may be important in triple negative, and we have, in addition, this whole androgen receptor project. Lisa Carey's focus has been largely on the EGFR, and the Triple Negative Breast Cancer Foundation, which funds research – and I'm participating in that effort – is trying to direct resources at people and scientists and clinical investigators with specific projects, but I don't think it's possible to pick a frontrunner right now. If it were, believe me, you wouldn't need me to tell you.

CALLER:

Thank you.

ELYSE S. CAPLAN, MA:

And wouldn't you agree, Dr. Hudis, that women, whether they have triple-negative or estrogen receptor-positive breast cancer, if they're interested to know about other research trials going on outside of the hospital where they're getting their care, they can always ask their oncologist to assist or brainstorm, if there are other second opinions, for lack of a better word, of other places to explore more of the research that might be relevant.

CLIFFORD A. HUDIS, MD:

I, of course, couldn't agree more, and in addition I think there are some nice resources on the web, even the simple things like the old H&R Block-sponsored site, PDQ, with all of the clinical trials. There are any number of resources, and they're getting more and more transparent and useful. Many of the big cancer centers, for example, have web sites that simply list all of their protocols. Some of them have referral services that, if you call and tell them your situation, they actually can match you up with protocols and the clinicians running those protocols as a new patient referral. There are a lot of opportunities there.

CALLER:

Thank you.

OPERATOR:

Your next question is from Lake Worth, Florida.

CALLER:

Yes, hello. Thank you very much. When you started this, you mentioned having bone buildup during treatment. I'm wondering if you have anything for bone buildup after, posttreatment.

CLIFFORD A. HUDIS, MD:

Let me be clear: The study I described, the ABCSG trial, which caused a big ruckus at ASCO this year because it was so unexpected and good, gave the bone-strengthening medicine Zometa after surgery. Now, what's a little unusual about the patient population is that they did not use chemotherapy, even though they were young patients. They also did not worry about their bone health. In other words, they didn't screen people and only give the bone-strengthening medicine to people with weak bones or osteoporosis. They gave it to everybody, regardless of outcome.

What I'm suggesting is that you watch that particular treatment space carefully, because this summer there may be the results of a second, similar trial. If that trial is similarly positive, I think we will have an answer, and I think that in the postsurgery, postchemotherapy period, maybe stretching for several years, you will see a broad usage of Zometa and the other bisphosphonates, maybe even like Boniva, which you see Sally Field advertising, I don't know. But I think there will be an uptick in usage.

A small study that I didn't highlight before but which is relevant is a study that we did in the CALGB [http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=31982]. Charlie Shapiro was the PI [Principal Investigator, or lead investigator]. This is a study that looked at younger women getting chemotherapy where they often have ovarian failure from the chemo, and as a result they often have bone mineral density loss. Charlie's study looked at the use of Zometa empirically there once every three months, and the Zometa was given at either the end of chemo or a longer period after. We don't yet know which of the timings was better, but we do see that the bone mineral density loss that is normally expected with chemo was abrogated by the Zometa, so that's not a breast cancer-specific endpoint; that's a bone health endpoint, but it's all pointing in the same direction, and I think it's a little time yet before we will be routinely recommending bone-strengthening medicines for everybody after treatment.

CALLER:

Thank you very much.

OPERATOR:

Your next question is from Lawrenceville, New Jersey.

CALLER:

My question concerns patients with HER2/neu positive breast cancer, but my question is about Herceptin in the adjuvant setting. I know there was a clinical trial that began, I think, about 2000 or 2001. In one arm of that trial, women received AC plus Taxol and Herceptin either with Taxol or immediately beginning after Taxol. I was wondering if there was any update in survival rates or any other information about that trial. I am one of the women who received Herceptin, so I was a little interested to know how things have turned out.



CLIFFORD A. HUDIS, MD:

You're referring to the North Central Cancer Treatment Group, the NCCTG study.

CALLER:

I believe so.

CLIFFORD A. HUDIS, MD:

I know you are. Edith Perez was the PI. This was one of the two large studies [<http://content.nejm.org/cgi/content/full/353/I6/I673>] that were sponsored by the National Cancer Institute, the NCI, and they were bunched together and reported, I guess, in 2005 by [Edward] Romond?

CALLER:

That's the trial I'm referring to; yes.

CLIFFORD A. HUDIS, MD:

I know. I know. I know. The thing about it, the reason I'm reminding you of this, is that the study you're describing had three arms, and it was AC and then weekly paclitaxel [also called Taxol]; AC, weekly paclitaxel, then trastuzumab [also called Herceptin]; or AC/paclitaxel with trastuzumab. The second study that was bundled with it was simply AC/paclitaxel alone or with trastuzumab. They took the two arms that were the same, AC/paclitaxel alone, AC/paclitaxel/trastuzumab, and they reported them out, and that was one of the pivotal studies that clearly demonstrated that trastuzumab was effective therapy in the adjuvant setting.

The problem was when they stopped the studies to report those two arms, that third arm was left dangling, because it was not yet mature enough to report. The initial reports suggested that the late use of trastuzumab alone might not be so effective. The problem was, at the very same ASCO meeting or shortly after, we got the results of a European trial called HERA [<http://content.nejm.org/cgi/content/full/353/I6/I659>]. In HERA, standard chemo was completed, radiation was completed, and only then were patients randomized to get or not get Herceptin. Lo and behold, Herceptin worked, and it worked to the same degree as in the American trials, so now we have slightly different results. In the American trial, AC/paclitaxel then trastuzumab might not be so useful. But in the European study, AC and then trastuzumab was very useful.

A French trial called PACS-04 [http://www.abstracts2view.com/sabcs07/view.php?nu=SABCS07L_661&terms=] that was presented at San Antonio last winter, in 2007, was similar to HERA. While it suggested a favorable impact for trastuzumab, it was not statistically significant. So, we have kind of a mixed message in all this, and right now what we like to suggest is that if patients are getting trastuzumab, they should get it overlapping with the paclitaxel. We just don't know yet whether it's as useful to give it completely after the chemo or with the overlap. We're sure it's effective with the overlap, but we're not as sure after. This study was not updated at ASCO right now, and the reason for that is a good reason: There simply are not enough events, meaning bad things happening, on the study to distinguish the arms any more now than two years ago.

CALLER:

Thank you very much. That was very helpful.

OPERATOR:

Your next question is from Pleasanton, California.

CALLER:

Hi, my question relates to the Austrian Zometa study [<http://clinicaltrials.gov/ct2/show/NCT00295646>] and triple negative. You mentioned that all of the women were hormone receptor-positive. Was that because hormone receptor-positive cancer tends to go to the bones more? You also mentioned that there was an improvement in even other sites. So, is Zometa possibly effective with triple-negative cancer also? Finally, was there anything new on BRCA mutations?

CLIFFORD A. HUDIS, MD:

You ask a great question. The ER positivity was selected in this trial upfront because they were asking about hormone therapy. There were two separate randomizations in this trial, one having nothing to do with the other. But the first one was between tamoxifen and anastrozole, or Arimidex, and it had to be in premenopausal patients who were rendered menopausal with goserelin. For that question, they couldn't take anybody with ER/PR negative breast cancer, obviously. Now your question is why didn't they essentially have a broader second cohort just for the Zometa question?

Here I think you're touching on the issue, which is that historically, ER positive breast cancer

tends to recur in bone to a greater degree than other types of breast cancer, and therefore, if there was going to be a bone-specific effect, they'd be more likely to see it. But it raises the question, doesn't it? Because if the drug is effective against bone metastases in ER positive breast cancer, it should be effective in ER negative cancer, and bolstering that is the fact that they observed a decrease in metastases to sites other than the bone. It almost suggests that Zometa might have a specific anticancer effect even independent of its bone activity.

This is very speculative. Believe me, Novartis [manufacturer of Zometa] would like nothing more than for that to be true. They've talked about it in the science world for several years. But I think that essentially, as a follow-on to the ABCSG trial, we're going to have to see some studies in ER/PR negative breast cancer to see if it recapitulates this difference seen in the ER positives.

Your final question was with regard to BRCA, and certainly there were no big breakthroughs reported this year with regard to BRCA1 or BRCA2 breast cancer. I think the biggest breakthrough this year really relates to the description of what are called SNPs – single nucleotide polymorphisms. These are genetic variations, some of which are common enough and associated enough with breast cancer that there is beginning to be a belief that we could use them like we've used BRCA1 or 2 to at least identify some of the high-risk cohorts that we currently test and don't see genetic abnormalities in. That's not really an ASCO-specific finding; that's something that was published in the *New England Journal [of Medicine]* [<http://content.nejm.org/cgi/content/short/359/7/722>] earlier this year.

OPERATOR:

Your next question is from Albany, Georgia.

CALLER:

Yes, some of my questions have been answered, but I'm a triple positive, and I was looking for a way to be one of those 15,000 patients who get used for a trial. Apparently my cancer center only has room for like 12 people in different trials, and nothing I've been able to do fits that. But I took TCH [docetaxel, or Taxotere, and carboplatin combined with trastuzumab, or Herceptin]. I'm almost through with my Herceptin, and my ovaries have come back alive. I've moved from taking Arimidex back to taking tamoxifen. I guess my question is how can I



participate more and make myself more educated on this?

CLIFFORD A. HUDIS, MD:

Without giving advice to any specific patient, you give me the opportunity to make two points. The first one is that – and I don't mean to offend anybody here, but I can't help but point this out – Arimidex and aromatase inhibitors simply should not be prescribed for patients who had their periods when they began chemo. Many doctors around the country believe that if your period stops with chemo, that's the same thing as being menopausal, and the story we just heard is a typical story for a patient whose ovaries are temporarily shut off by chemo and then wake up, and we really do recommend against any use of aromatase inhibitors in patients who were not already, by definition, menopausal before their breast cancer diagnosis – just to make a fine point on that. The definition of menopause in the U.S. is 12 months no period and no medical reason for no period, meaning it's not because you took your uterus out and it's not because you got drugs. You do allow me to highlight an important educational point, which is that tamoxifen remains the standard therapy for premenopausal women, even if their periods stopped during chemo.

On the question of protocol participation, the good news for the caller is that she's through therapy and, therefore, there is no clear benefit to her participating in any study. One hopes that she never needs to participate, because that would really only be possible if, unfortunately, her cancer returned. That's something we hope against.

CALLER:

Thanks for that.

OPERATOR:

Your next question is from Washington, DC.

CALLER:

Hi. Thank you, Dr. Hudis, for your presentation. I wondered, if a patient has early-stage, premenopausal, ER positive breast cancer and is taking tamoxifen and goserelin and wants to take Zometa at this point, would it be a reasonable choice even though the data are not perfect? And could you comment a little more on the study that is coming out this summer and how that might affect the decision? I also just wondered how the researchers described the effect of Zometa. How do they think it's working to attack metastases in locations other than the bone?

CLIFFORD A. HUDIS, MD:

I'll start with the last question. They didn't address that, and that's a real science question at the moment. I think it all was a bit surprising. On the question of the routine use of Zometa, there is a little bit of a cheat: If you do bone mineral density testing and your bone mineral density is falling, you essentially already have an excuse for using these medications. The AZURE study [<http://clinicaltrials.gov/ct2/show/NCT00072020?term=NCT00072020&rank=1>] and others, some are very similar in design. The patient populations vary a little bit. But some of them are asking about different schedules of Zometa versus nothing. Some of them are comparing different bisphosphonates like Zometa or clodronate. I don't know that one of them will be reported this summer, but there is a lot of speculation about this.

I think the timing on this is probably not the biggest issue. One of the nuances of the ABCSG trial is that the overall event rate was very, very low. They picked a very good-risk group of patients. If I remember correctly, and I don't have the data in front of me, at three years it was something like a 96 percent and a 97 percent chance that patients were free of recurrent breast cancer, and that's a very high, thankfully high, statistic. But it makes it a little bit hard to generalize the results to higher-risk cohorts, and that's one of the things we're waiting for.

CALLER:

Thank you.

OPERATOR:

Your next question is from Auburn, Washington.

CALLER:

Yes, I got in kind of late on the teleconference. I had hopefully a general question, and I don't know if it's something that was addressed. Are more oncologists looking toward a low-dose metronomic dosing in terms of bringing about more complete remissions? Are they looking into that as far as for future treatments? Also, are you seeing more central nervous system metastatic breast cancer with HER2 positive patients, in your experience?

CLIFFORD A. HUDIS, MD:

These are two good questions, and they're separate. I mean, they're unrelated, in a way.

CALLER:

Okay, yeah. Sorry.

CLIFFORD A. HUDIS, MD:

No, that's okay. We'll take them one by one.

CALLER:

Okay, great.

CLIFFORD A. HUDIS, MD:

Metronomes, for any of you who took piano lessons, are little devices that sit on top of your keyboard and go tick-tock, tick-tock, tick-tock. It's a bad name. All chemo essentially fits that, whether it's every week or every day or every three weeks or whatever, it's tick-tock, right? It's like a new sexy name, in a way, that's been put on a very old idea. We have experimented with various drugs for decades using variations in dose and schedule. For example, with paclitaxel, not only did we develop high-dose, once-every-three-week treatment, but we also ultimately developed and advanced low-dose weekly, i.e., metronomic paclitaxel. That's something that was just published this spring.

There are new theories all the time about whether one or the other dosing will be better. For many years, the argument was that a high dose would kill more cells. More recently the argument has been that low-dose, regularly spaced treatments would somehow be antiangiogenic. I don't believe that, frankly. I think the real issue is, for somebody with incurable breast cancer, what is the least toxic way to deliver the maximal treatment benefit? It is not clear that any of these manipulations really drive more patients into complete remission, and I have to also add that it's not clear that complete remission means as much as patients think, because complete remission, frankly, means there are not millions and millions and millions of cells so that you can't see them by scan. It doesn't mean that the cancer is gone. We know that because in the era of bone marrow transplant, which was all through the '90s, the complete remission rates were very high with bone marrow transplant, and yet the overall outcome was essentially, as you know, unchanged. So, I think that might be a little bit of a misleading goal to pursue.

On the other question, about that HER2 positive breast cancer and brain mets, it's becoming pretty clear that there is a slight increase in brain metastases in patients treated with anti-HER2 therapies, specifically Herceptin, or trastuzumab. However, I think it's really important to think in terms of absolute numbers rather than in terms of proportions. The best evidence that explains it



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is the HERA trial, which Ian Smith presented several years ago at ASCO [http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=40&abstractID=90003]. In that trial, trastuzumab was given alone after chemo or not, and there was an overall reduction in the risk of recurrence and the risk of death from breast cancer – so far, so good.

What was interesting is that the absolute number of patients who relapsed with brain metastases was identical. Herceptin doesn't get into the brain very well – that's the point – so we do see a relative – that is, a proportionate – increase in brain metastases, but I'm not convinced that we're seeing an increase in the absolute numbers. It's simply that we're doing better outside of the brain, leaving the brain behind as what's called a sanctuary site where HER2 positive breast cancer, unfortunately, grows untreated.

CALLER:

Thank you. Actually, I am a low-dose metronomic success, so I have been doing very well. I had [inaudible].

CLIFFORD A. HUDIS, MD:

No, that doesn't mean that it isn't effective therapy, but we showed that low-dose weekly paclitaxel is the best way to give it, and we just published this in March 2008 in a big, randomized trial in the JCO [<http://jco.ascopubs.org/cgi/content/abstract/26/8/1216>], but having pioneered that myself, I still sort of object to the over, if you will, "sexification" of it. It's just old chemo. CMF was low-dose metronomic, if you will, back in the 1960s. It's just dosing schedule variations, and I think we have to resist a little bit of hype.

ELYSE S. CAPLAN, MA:

That sounds good.

CALLER:

Well, thank you.

OPERATOR:

Your next question is from Katonah, New York.

CALLER:

Hi. Thank you so much for all the information. While we're talking about brain mets, can you say what else you might have heard about potential chemotherapies that would get into the brain for mets?

CLIFFORD A. HUDIS, MD:

The question sort of presupposes that chemo doesn't get into the brain, and, in fact, that's a widespread myth. I'm going to give you an anecdote, and then I'm going to tell you the data. When I was a new attending at Memorial in the early '90s, there was, and still is to this day, a preeminent neurooncologist by the name of Jerry Posner there. If you ever go look for the textbook of neurology in America, it's Posner's book. And he is appropriately widely respected for his clinical skills. I was a brand-new attending, and I had a brand-new patient with new brain metastases, and I did what I had been trained to do, which was send her to neurology so that they could organize her whole brain radiation therapy.

Jerry Posner sent her back with, in those days, a handwritten note. He said, "Give her Adriamycin." I remember I went to my mentor, Larry Norton, and I said, "What's this about? We radiate multiple brain mets. We don't give chemo. We don't think it gets in well." And Larry, sage that he was, said, "If Jerry Posner told you to give chemo, give chemo." And I did, and this patient went 18 months with a good response to the chemo. The lesson is that the standard chemotherapy drugs we give, in fact, do get into the brain. What don't get into the brain are the big antibodies like Herceptin. Chemotherapy for the brain is really no different from chemotherapy for the rest of the body.

In most cases, when breast cancer progresses in the brain – I'm not talking about HER2 and Herceptin, but in most other cases – when it gets worse in the brain, it also gets worse elsewhere. In fact, we see responses in the brain with conventional chemotherapy like I just described all the time. Having said all that, there is now an interest in accruing patients specifically with brain metastases and even specifically after radiation has stopped controlling their tumors to test new drugs that might be favorable in terms of their toxicity profiles.

There was a report of a drug called patupilone, which is somewhat like the Bristol-Myers drug Ixempra that you've heard about in the past year, because it was the first epothilone that was approved in breast cancer. Patupilone is also an epothilone, and in preclinical studies it has a relatively favorable ratio of drug in the brain versus drug in the rest of the body, which suggests that it could be strong in brain mets. Cleveland Clinic and our group in collaboration are doing a

trial with that drug, and many others are being studied as well. I would focus not on the brain and specific chemotherapy drugs, but I would take a broader view and point out that drugs that work everywhere tend to also work in the brain.

CALLER:

Hmm. Okay. Thank you.

OPERATOR:

Your next question is from Mason, Ohio.

CLIFFORD A. HUDIS, MD:

Before we go to that, I want to bring you back to something I just thought of. About a year ago, I was asked to give advice to a company that wanted to develop a drug for brain metastases, because it showed what it said was a favorable accumulation. Yet what its chemotherapy drug had done was fail to shrink cancers in the liver and the lungs, and the point I was making, indirectly just before, was just that: Because the drug didn't work in the liver and lungs, it had no chance to be effective in the brain. That was the advice I gave to the company, and others did, and I think it appropriately abandoned it. I think there's a little bit of a trap in thinking about the brain as somewhat different. What's different about it, though, is the significant impact that even small amounts of disease can have there, because it's an enclosed space, obviously. Anyway, sorry. I didn't mean to cut you off there. Your question?

CALLER:

I, too, am triple negative, and I know that your presentation today was about HER2 and whatever, and I know that you've had a lot of triple-negative calls. But I didn't know that there was a triple-negative foundation, so I was very interested to hear you say that. I'll research that on the web later. But what I have tried to do is find a mentor who has lived beyond five years with triple-negative breast cancer. I have done it through The Wellness Community, Cancer Treatment Centers of America, the American Cancer Society, the one that used to be Y-Me and is now [Breast Cancer Network of Strength], like six different sources that offer support groups and matching you with someone, and I cannot find – they keep calling me back and saying, "We're still looking. We're still looking." I can't find anybody.

CLIFFORD A. HUDIS, MD:

I have these patients in my practice.

CALLER:

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CALLER:

Yes, your Survivors' Helpline is working on it through me, Living Beyond Breast Cancer. They are working on it . . . They have not found a match either. I'm 51 years old. I was diagnosed last December.

ELYSE S. CAPLAN, MA:

All I can say is we will definitely do our best to match you to a volunteer. Just to give you the resource to make it simpler and for anyone else on the call who is interested, the Triple Negative Breast Cancer Foundation's Web site is [<http://www.tnbcfoundation.org/index.html>]. We partnered with it, actually, on a teleconference just two months ago in April. Dr. Lisa Carey, as Dr. Hudis mentioned, who has been doing some research in this area, was our speaker. There will be a transcript available [<http://www.lbbc.org/data/transcript-file/LBCCtriplenegative09.pdf>]. Anyone interested in more in-depth reports on triple-negative breast cancer can definitely access that on LBBC's Web site [<http://lbbc.org/>] or by calling us...

OPERATOR:

Your next question is from Rockford, Illinois.

CALLER:

Hi. I would like to touch on the need for getting patients for clinical trials and studies. I'm an odd case. I've had two types of breast cancer ten years apart, and the second one was a . . . typical medullary carcinoma. In the back of my mind, I think I need some information on how the databases of cancer patients are kept. Is it by type and subtype? I think what I'm looking for is someone to put together a database of all of us rare types so that you can study us all together and at least begin to figure out what might work and how to help each other. I just think if we can study the rare ones, we can maybe unlock the other ones. How the databases work is my basic question.

CLIFFORD A. HUDIS, MD:

Yeah, you're asking a really loaded question,

because they don't work at all the way you imagine. Firstly, institutions typically keep databases, usually with a purpose. In other words, they're not open-ended. Databases may exist to allow us to store tissues so we can study it in the future or to look at outcomes and so forth. But because of the privacy laws that are enforced around the United States, there actually is not a global sharing of databases like you might imagine, and it's not even possible to do that. The only data that can be shared are the data that are generated from patients who prospectively give informed consent and allow for their information to be transmitted, and that is virtually always in the context of a prospective clinical trial, like we've been talking about through the call. There is not a mass amalgam of all patients, all 200,000 per year, for example. It's not possible under the current legal system to even do that.

CALLER:

Would there be a way to get a movement started to ask clinicians to ask for prospective, informed consent and permission to share [inaudible]?

CLIFFORD A. HUDIS, MD:

There would be, actually. Let me say, though, that it would be a significant, costly undertaking, and I've stayed away from the political, but it happens to be a raw wound for me. The investment in cancer research in the United States of America is the largest in any developed country or any country in the world, and it is trivial. The entire federal budget of the National Cancer Institute is \$5 billion a year – and I'm rounding up to give you that number. That represents a fraction of a percentage point of the entire federal budget for a disease – not just breast, but cancer – that kills one-third of Americans. The resources are simply not there.

The [slack] funding at the NCI since the year 2000 means that in real terms the purchasing power at the NCI has fallen by 20 percent. The cooperative group funding, which pays for the Cancer and Leukemia Group B, the NSABP, the SWOG [Southwest Oncology Group], all of those groups that do the big studies, was actually cut in the past two years. It was only because of a massive effort on April Fools' Day in 2007 in the *New York Times* with a page of editorials that we managed to restore the second year's cuts, meaning we had to live with the first year's cuts. That was our big success. The entire budget for cooperative

group trials was \$161 million a year in the year 2000, and it was cut to \$147 [million]. We avoided the cut to \$136 [million]. In all fairness, those numbers are trivial. They don't begin to cover the cost of what you're describing.

CALLER:

I think it's disgraceful. Actually, "criminal" is not really too strong a term. What can we do?

CLIFFORD A. HUDIS, MD:

Well, I think you're going to have to talk to your elected officials, because the irony, or at least the disappointment, for me is that it's terrible here. There's non-existent federal funding around the world. I mean, the NCI and the NIH are still sort of the gleaming towers of hope, because other countries don't fund anything. It's all on the project side through industry. I think this has to be a movement. You've certainly seen the call for the candidates to come to a cancer forum. Many of them refused to come, the presidential candidates. It somehow just doesn't seem to gain traction. I am as frustrated as anybody, as you can imagine, over this.

CALLER:

That just is infuriating.

CLIFFORD A. HUDIS, MD:

Right. Welcome to my club.

ELYSE S. CAPLAN, MA:

Keep taking that passion and keep talking about it, because it's clearly something that many of us are feeling out there on the consumer end as well as the clinician end. We have to keep bringing this issue forward and hopefully make a difference over the long haul.

CALLER:

Would there be anything to the theory that you could unlock the more common cancers, like my first one, by studying the more rare ones like my [inaudible]?

CLIFFORD A. HUDIS, MD:

No, no. It could go in either direction. Quite frankly, from a science point of view, who knows? I'll give you a couple of sobering counterpoints. Not that I want to be a naysayer, but I want to highlight for you that it doesn't always work out as you hope. When we discovered BRCA1, really at the beginning or the middle of the last decade, there was an expectation in many circles that by understanding how that gene was malfunctioning, we would unlock the key to all breast cancer, and



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that just didn't happen. It turns out that BRCA1-mediated breast cancers really are unique in some ways. The biology there didn't transmit.

Similarly, understanding HER2 positive breast cancer has really not unlocked the key to all of the other types of breast cancer. Going back more than 100 years, ER positive breast cancer hasn't unlocked the non-ER positive. So, I don't know that the rare types would necessarily fuel or enhance understanding of the common ones. I don't know that it wouldn't, but I think it's probably not that simple.

CALLER:

My last question, if I could ask it: By cell types, like basal and luminal and all that, are they going to start sorting that way, by cell types?

CLIFFORD A. HUDIS, MD:

What the caller is asking about really is the result of using gene expression profiling to subtype breast cancers. There are four or five recognized subtypes: luminal As that are very hormone responsive; and luminal Bs, which are also from the lumen or lining of the duct, but they're not so hormone responsive, even though they're ER positive. And then the basals, which come, as the name implies, from the base of the duct. They are often similar to the triple-negative name but not identical. Basal-type breast cancers and triple negatives are overlapping but not identical subsets. People are starting to think about how to use these technologies, but in many ways they are complementary. If you just do ER, PR and HER2, the triple negatives, to a large degree, overlap what you would call basals. Indeed, the clinical trials are then being driven by those subtypes. I hope that answer makes some sense to you.

CALLER:

It does. Thank you.

ELYSE S. CAPLAN, MA:

Thank you so much.

OPERATOR:

Your next question is from Castleberry, Florida.

CALLER:

Hello. Thank you for having this lovely conversation. I have been on Herceptin, and I had to go off because of the ejection fraction going so low. I am now on Arimidex. The CA27.29 and the PET scan are about the only things they use to detect how it's going. What other tests are there to make sure it's not – I'm in remission, but what

other ones are there besides the PET scan and the blood test?

CLIFFORD A. HUDIS, MD:

I assume the caller is asking about the management of established metastatic breast cancer. The question is once you have that disease, how do you best track it? The truth is that there are 1,000 ways to do that, all individualized by doctors and patients. If you have a skin nodule, you don't need any fancy test. You just want to measure it by hand. But often, for deeper organs, you need, as the caller describes, to have PET scans or CT scans or whatever.

Simply stated, there is a bit of a technology push here, but it's not crystal clear that there is any best technology. What I always advocate is the simplest and easiest test that lets the patient see what's going on, and consistent use of that same test over time so that you are comparing apples with apples always and not apples with oranges.

OPERATOR:

Your next question is from New York, New York.

CALLER:

Thank you very much, Dr. Hudis, for the conference and for taking this call. My question refers to PARP and to the stem cell theory that I've been hearing more about. I've been also hearing that these would be effective for triple negative and also for brain mets. Can you talk a little bit about those two theories?

CLIFFORD A. HUDIS, MD:

Sure. Let's start with the stem cell one, because that's sort of less specific. That theory is sort of, again, a resurgence of a very old view of breast cancer, or all cancers, for that matter, which was that there are some self-regenerating cells that, even though they spin off the cells that act badly, they continue to essentially duplicate themselves. They're like a storehouse of new, young cancer cells. There is a theory that the reason we don't cure more patients with breast and other cancers is that even though our treatments are effective, they're being effective against the more well-matured – is, I guess, the best way to say it – cancer cells, and doing less of an effective job against the immature stem cells.

That's leading, therefore, to parallel efforts to do a better job of naming and identifying stem cells – that's not a clinically possible task right now – and, once that's accomplished, to then develop therapies that are specifically killing stem cells so

that if you eradicate a tumor, there is no chance that you've left behind its roots, as it were. That's really the state-of-the-art now. It's an interesting science discussion, but in all fairness, it has zero clinical relevance at the moment.

The PARP inhibitor story is a completely separate issue. In BRCA1-mutated breast and ovary cancers, there is already a defect in those cells in the way they repair the normal chromosomal damage of living. That's why you will hear the phrase "DNA repair gene" associated with BRCA1. A PARP inhibitor essentially inhibits something called PARP – which is a long word, but essentially it's another DNA repair mechanism. And it's [inaudible] an old idea that two hits on a vulnerable pathway will be useful. What's been exciting about this is that the preclinical data suggest that a second drug of this type would be effective in the BRCA-mutated cancers, and in phase I and II studies, there is clear evidence that the PARP inhibitors can shrink some advanced ovary and breast cancers, when the patients have the BRCA mutation. That's being pursued very actively right now.

CALLER:

I see. Thank you very much, Dr. Hudis.

ELYSE S. CAPLAN, MA:

I think that's a great place for us to wrap up today's program, with hope for the future and the subject of PARP inhibitors, etcetera. And all of the other novel approaches you've been able to cover today, Dr. Hudis, really give us insights into the future. While we've covered a lot of territory in terms of new treatments and new ways to use old treatments, etcetera, I'm hopeful that folks listening in will continue to follow the research and know that there is a lot going on, a lot more to get done. That gives us a good spot to end by keeping that door open, keeping our ears and eyes open for new research findings.

On that note, I want to remind everyone to complete your evaluations. We will definitely read all of your evaluation forms. Stay in touch with us through our Web site [<http://lbcc.org/>]. As I mentioned, we do have recordings and transcripts of past programs available. For peer emotional support, we have volunteers who have been treated for breast cancer, breast cancer survivors, answering calls on our toll-free Survivors' Helpline at (888) 753-LBBC (5222). With that, Dr. Hudis, any closing remarks? We so much appreciate your time and expertise today.



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CLIFFORD A. HUDIS, MD:

I just want to thank everybody for joining. It may sound cliché, but I often feel after I do these kinds of things, be it on the phone or in person, that I get more out of it than the audience, because their questions refocus our attention where it needs to be but also often highlight areas of research that we should be thinking about. Your active participation really means a lot to me. Thanks very much.

ELYSE S. CAPLAN, MA:

Thank you. Thanks, everyone. We hope you have a good rest of your day, and please stay in touch with Living Beyond Breast Cancer.

[END OF TRANSCRIPT]