

## Triple Negative Breast Cancer: Research and Treatment Update

Clifford A. Hudis, MD

**CINDY GEOGHEGAN:** Welcome, everyone. My name is Cindy Geoghegan, and I work with Susan G. Komen for the Cure [<http://www.komen.org>]. I am especially privileged to be here this year, because this is the first year that Susan G. Komen is cosponsoring this event with Living Beyond Breast Cancer [<http://www.lbbc.org>] and the Young Survival Coalition [<http://www.youngsurvival.org>]. I'm also an old young survivor. I was diagnosed 12 years ago when I was 35. So I'm kind of grown up and old, and it's really cool to be here, because 12 years ago there was nothing like this. It's an extreme privilege to be here with you and to share this with you. Our first event is going to be quite the event, and I think it will be great. ... With that, I would like to introduce you to Dr. Cliff Hudis.

**CLIFFORD A. HUDIS, MD:** Thank you. What I'm going to do is spend about 45–55 minutes talking about the topic at hand, which is triple-negative breast cancer. That will leave us the better part of 40 minutes to have a discussion about the topics that I've covered and the ones that I haven't that are important to you. I'm sure that there will be plenty [of questions], because I can't cover [everything]. ... We can't do consults in an open room, so [please phrase] any question you ask [with words such as] "my friend has ..."; "I've heard about somebody with ..."; [or] "what in general do you do for this kind of situation?"

Triple-negative breast cancer has become a hot topic and, as I imagined how to approach the discussion today, I thought that it would pay to [first] explain how we got here [and] what it is that we're talking about when we talk about triple-negative breast cancer; then I will focus on a little bit of the research that's been done here — and I will be biased [in] showing you some of the work that my team is doing. But by no means is that the only work; quite the opposite. Then that will

leave us time for questions.

What is triple-negative breast cancer? To answer that, you have to go back into the history of medicine. Probably the first effective systemic therapy for cancer ever reported was by a Scottish surgeon by the name of Beatson. He published, in 1896, the effects of removing the ovaries in young women with locally advanced breast cancer. That's 112 years ago. He didn't know from the estrogen receptor. All he knew was that women, as opposed to men, tended to get breast cancer. In those days it was virtually always locally advanced. He described [the findings of] what would nowadays be called a phase II study — that some of these patients without ovaries had regression of their cancers. [The study marked] the beginning of the recognition of hormone-responsive breast cancer and [it] is, therefore, an important foundation for our discussion about what is not hormone responsive.

It's also worth pointing out that, after Beatson — Hadow, actually, in 1944, first described the use of synthetic estrogens. You know with decades of follow-up, DES actually looks at least equivalent to tamoxifen in the long-term survival of people with metastatic breast cancer, which undermines one of those simple rules everybody thinks they understand: that estrogens are always bad. It's a much more complicated story. The first randomized clinical trial in medical oncology, maybe in most of medicine, was the first adjuvant trial that tested oophorectomy in 1952. By the way, that same year Huggins described adrenalectomy. He won the Nobel Prize in 1966 in part for his description and discovery of the estrogen receptor. It's all a little bit of interesting, to me, background.

Because there is an understanding of the estrogen receptor and its linked receptor, the progesterone receptor, we have a whole bevy

of interventions for hormone-responsive breast cancer. We can remove ovaries. We can block ovarian output. We can give selective estrogen receptor modulators. We can give, in postmenopausal women, aromatase inhibitors. We can give progestins. We can give testosterone. We can give selective estrogen receptor downregulators, and we can give estrogens themselves. All of that is a way of interfering with a signaling system: the estrogen receptor. There is a part of breast cancer that is driven in some way by hormonal influences. We can treat it by interfering with those. And we are done talking about that today. We're going to carve that out of our discussion of triple-negative breast cancer.

This is an ER negative tumor. Actually, stained a little bit of brown — you see, [there] is some estrogen receptor staining in a few cells. It makes a point about this discussion, which is that estrogen receptor testing is not a yes/no question the way you think it might be. It's much more subtle. This is data generated from the Oncotype [DX] test. Some of you may be familiar with that test. I have a conflict of interest. I helped to develop it, and I was given equity in the company when it was developed. You always have to recognize the speaker's potential conflict.

Having said that, in ER positive breast cancer — which they have been processing out in California for a couple of years now — when you actually look at the ER results by immunohistochemistry staining and by real-time quantitative PCR, you see something interesting. On your left is B14, and on your right is a follow-up data set from the Kaiser Permanente people. These are several hundreds and hundreds of specimens, as you can see. What you notice is that there's a range of expression across the bottom for the estrogen receptor and up the y-axis for the progesterone receptor. The

overall range of expression for the progesterone receptor is over 1,000 fold, meaning if you put raw numbers on it, it goes from one to 1,000 or more in terms of the expression. Much more than that, actually.

Similarly, when you look at estrogen receptor, there's a 3,000-fold range of expression. The range that you call positive, in the smaller arrow I just showed you, covers about a 200-fold difference in expression. So the point is that, when we talk about ER positive breast cancer, we're talking about a wide range of the expression of the receptor and, one presumes, sensitivity to hormone therapies. Conversely, when we talk about estrogen receptor- and progesterone receptor-negative breast cancer, we're talking about a range of expression. It's at the low end. But this notion of black/white, yes/no, on/off is really too simple for the biology here. This will have some bearing on how we think about the disease.

The third receptor we have to think about for a minute to identify triple-negative breast cancer, of course, is the HER family. HER stands for human epidermal growth factor receptor family. HER2 is the one that defines this group here, but the other members of the receptor family should be known to you. Everybody in [the United States], I think, knows HER1, although most people don't realize they do. Why does everybody know HER1? Its synonym is the epidermal growth factor receptor, EGFR. If you're scientifically and oncologically inclined, you know it because you know it's an important target in lung cancer. There is a small number of patients with mutated HER1/EGFR. And those patients are sensitive to erlotinib, the tyrosine kinase inhibitor Tarceva that you hear about a little bit.

But the better reason that you know about it is that people like to read *People* magazine, and why is HER1 a subject of

*People* magazine? Because Martha Stewart went to jail, and the reason she went to jail was that she supposedly lied about a phone call [in which she engaged in insider trading] related to the approval of a drug, an antibody, that targeted HER1. That's the ImClone monoclonal antibody cetuximab [that was not approved by the U.S. Food and Drug Administration]. It will come back to haunt us in this room in about 15 minutes in terms of triple-negative breast cancer. I think it's worthwhile describing this little side tour because it makes everything hang together in a way that makes sense. So HER1/EGFR, ImClone, scandal. HER2, trastuzumab, Genentech. You're all familiar with that. HER3 and [HER]4 are less well known to all of us because they are not directly targeting drugs for those two receptors. So it is the absence of ER, PR and HER2 [positivity], using the conventionally available tests, that describe triple-negative breast cancer. This is really all I wanted to say.

I am not a Virginian, and I am not a Floridian. Does that make me a Californian? I am not ER positive, I am not PR positive and I am not HER2 positive. Therefore I'm triple negative? Well, yes, but what I am is not ER, PR and HER2 positive. The important question that then arises is whether triple-negative breast cancer is a distinct entity, like ER positive or HER2 positive disease, or a collection of diseases, plural, that share three out of 1,000 features — just the three we happen to know and use. This is a pet peeve of mine, because my suspicion is that it's a collection. Not everybody agrees. I'm going to show you evidence in both directions. But it's important because if you think it's one disease, then it seems awfully simple to go about tackling. If you see it as a collection of diseases, it gets a whole lot more frustrating, potentially.

One way to tackle this, which we can now do using technology that was just a dream years ago, is to look at which genes out of

the 30,000 are turned on or turned off and to group tumors according to those and try and figure out what's going on here. It turns out that this, to some degree, closely recapitulates the simple dichotomy that I described for ER, PR and HER2 already. This is called tissue microarray. A bunch of tumors are placed on a tray, and a whole bunch of these tumors can be processed at once. In this case, they're processed [to indicate] whether genes are turned on or turned off. If they're turned on, they're red. If they're turned off, they're green. What you can't see in this slide, because it's too fine, is that the column on the right is a listing of selected particular genes, not all 30,000. You could [list them all], but it would just be a gigantic slide; hard to read. These are selected groups of genes.

Across the y-axis here, with those colored lines identifying them, are individual tumor specimens. For each tumor specimen, as you go down — C, D, E, F, and G — you see green, black and red, which indicates relatively whether or not those genes have been turned on. Then what we use is either the eye or some kind of artificial intelligence [to] cluster tumors that look similar based on which genes are turned on or off. You see these big areas of red. If you look just at the E panel and you look on the left there, you see an area of red. The machine has kind of clustered those tumors together because they have those genes turned on — not in every case, but fairly consistently. This is called supervised, or it can be unsupervised, clustering.

When we do that with the computer — look at all of these genes — what we end up with is a relatively consistent grouping. On your left [you see an example of] what's called "basal like." Those tumors, if you go back and stain them, are ER negative, PR negative and HER2 negative mostly, most of the time. Speakers like me interchangeably use this term basaloid, or basal-like, breast cancers or triple

negative, and the purists take us to task. Basal breast cancers are identified this way, based on these genes. Triple-negative breast cancers are identified by conventional pathology. There is a good bit of overlap there, but it is imperfect. Basal cancer won't necessarily, always, 100 percent of the time be ER negative. Maybe the staining isn't right. You can make up stories for why this happens, but it does.

If you go across the right there, the next group is a HER2 positive group. The next group is a so-called normal breast cancer-like. That is, it looks like normal gene pattern, but it's a cancer. We know the specimens were malignant. Then there are the luminals, which are gradations of hormone responsiveness. The ones that have stuck out there — and you've heard this term — is luminal A, which is very hormone responsive; luminal B, which is ER positive, but they don't do so well. They look more like hormone nonresponsive breast cancers. I hope this illuminates this for you because these are terms that get thrown around a lot, and I want you to understand that there is an incomplete overlap of what the gene profiling describes as basal cancers and what we describe as triple negatives from the conventional pathology processing. It's close. It's just not perfect.

I asked this question before: is all triple-negative breast cancer the same entity or not? Now I am going to be — I forget the right word here, but I'm going to focus on our work, just because it's illuminating [in terms of] the problem. About four years ago a fellow in my program named Michael Danso and a kid out of college with bad grades who couldn't get into med school decided to work on a project. The kid's name is Ashley Doane. He decided to work in William Gerald's lab. William Gerald is a pathologist at our place, and he has a collection of these tissue microarrays that I described a minute ago, trays of tumor specimens from hundreds of patients [that can all be processed] simultaneously [in order to] figure out

various biological properties in the specimens.

What Ashley did, with William Gerald's guidance and Michael Danso's clinical guidance — he took a panel of just about 100 breast cancers, shown here, and he focused on the hormone receptor-positive gene profile. That's not the same as saying they had the estrogen receptor. What he focused on is the fact that on the right were ER negative breast cancers. You see the red lines clustered and all the green. In the middle were ER positive breast cancers. You see the blue lines indicating the specimens and all the red. But if you go to the left, those are some red lines there. Those are ER negative breast cancers, but they have the gene profile of an ER positive tumor. So he was flummoxed. Why are these tumor types that are straining ER negative giving an indication that ER is nevertheless active?

He gave [this phenomenon] a name of [inaudible], which is a fancy way of saying it's as if they were ER positive, but [that] the ER had been removed. So everything downstream of ER was turned on, but you didn't see ER in the specimens. He dived further into this. He proved that they were really ER negative. These are the same specimens; on your right is the estrogen receptor signal by messenger RNA, and in red is actually the staining score, which [is] the conventional estrogen receptor staining. You see that they correlate. So those specimens that he thought were ER negative really were. Still, they had signaling properties of ER positive breast cancer. This just shows that he [replicated the results] in a separate set of specimens, so it wasn't just a fluke [that showed up on] this one set.

The reason to point this out is that one of the queries everybody has is how we will develop targeted therapies for estrogen receptor-[negative breast cancer], progesterone receptor-[negative breast cancer], HER2 negative breast cancer. I'm getting to an answer to that question. What Ashley described, [in an article] published

in *Oncogene*

[<http://www.nature.com/onc/>], he gave a talk at San Antonio about as a premedical student, is that these tumors had the androgen — the male hormone receptor. The reason that they were signaling like ER is that the androgen receptor, if you will, was stepping in and playing that role. They're what you could call triple negative: ER, PR, HER2 negative. But they're behaving a little bit like ER positives, and they're doing it because of androgen, not estrogen, receptor signaling. The reason to go through this exercise is this: what you want to do [is] ... find those tumors in the clinic and treat them.

We have a research protocol now whereby we find patients with ER and PR negative breast cancers [and] stain [the cancers] for the androgen receptor. When we find a positive, if the patient has metastatic disease, we offer [him or her] enrollment ... in a research study using a prostate cancer drug, bicalutamide, [which is] an androgen receptor blocker. It probably won't work. You have to know that going in, unfortunately. The odds are against us. But it is important to try. If we don't try, we'll never know. If there is a small number of patients who can benefit from a relatively nontoxic hormone therapy, despite having been labeled hormone nonresponsive, this would be an important breakthrough for us.

I will tell you, we're having trouble. We've stained 13 patient specimens since we opened the study. We've only had two actually stain positive for the androgen receptor. So the frequency of this may be low. That's a drug development problem across the board. It speaks to my earlier editorial: If triple-negative breast cancer is not one disease, but instead is a collection of diseases, we could have two, five, 10, 20, I don't know how many biologically distinct subtypes in there. But it will make therapy for triple-negative breast cancer a bit of a challenge to develop.

Now, more recently there has been a tremendous interest — and I think it's

appropriate — in identifying triple-negative breast cancers for the testing of a new class of drugs called PARP inhibitors. I'm going to talk about this in a little detail for a minute. This is important on two related levels. The first is [that] it probably is most relevant for a subset of triple-negative breast cancers, and those are the cancers, by the way, more typically seen in women who have BRCA1 mutations — typically young patients; typically [patients who are] ER, PR and, often, HER2 negative. So you can use triple-negative status as an indicator of potential gene mutations BRCA1 and 2.

And the reason that's important [has to do with] the way the PARP inhibitors work: they inhibit one DNA repair mechanism. Most cells have redundant repair mechanisms, so inhibiting one repair mechanism won't bother the cell much. But BRCA1 heterozygotes — people who [get] breast cancer because they [have] a BRCA mutation — have several DNA repair abnormalities. People believe, at this point, that BRCA plays a role in maintaining the normal structure of your DNA [by] repairing it when it's damaged. It's a housekeeper, in a sense. So if you have a BRCA1 mutation and you've got, as shown on the right, a defect in one of the DNA repair processes, which is labeled HR here, by giving a PARP inhibitor, which picks off another one, labeled BER, you increase the potential for a therapeutic benefit.

So KuDOS [Pharmaceuticals] — which has been, I think, acquired or managed by AstraZeneca [<http://www.astrazeneca-us.com>] — has a drug [labeled] KU-005943 .... This drug is orally available. It's in phase I, and it's given for two weeks by mouth, with a one-week rest. That's a practical issue. It doesn't sound like a particularly difficult drug to give. In the phase I study the drug was relatively well tolerated. This list [of potential side effects] doesn't look pleasant, but any of you who have had significant therapy for cancer know that [the] frequency of these types of side effects, not so bad. If you

look at the right, grade 3 is the stuff that really gets your doctor's attention; it's not so common. The drug looks to be reasonably well tolerated.

They've enrolled a whole list of patients, shown here. It's hard to do a clinical trial that insists on having a mutation in BRCA1, for complicated medical and legal reasons. In breast cancer [trials,] what we do is select for patients who report a family history [of breast cancer] and who have triple-negative disease, because they're more likely to have a BRCA mutation, even if we haven't recorded that mutation to put them to the side. Let me back up for a half-second. Imagine a clinical trial that requires you to have the BRCA mutation. Imagine your concerns about privacy and keeping mutation analysis secret. To participate in the trial is to declare your status. It becomes a little bit of a conundrum, which you don't necessarily want to [have happen]. Now, it varies by people. It varies by state. There are all kinds of issues here. But that's been a bit of a stumbling block for developing drugs narrowly for BRCA mutations.

So what you see here is [that] they accrued a large number of ovary patients — 16; a reasonable number — [and] eight breast [patients]. [Shown] in blue are patients who don't have known BRCA status or who are known to be normal for BRCA1. What you see in black are the BRCA1s; in green, the BRCA2 mutations. They did a good job — at least in breast and ovary cancer — of loading, [or] stacking the deck, with mutation carriers without having insisted that [participants carry the mutations in order to be part of] the study. This is what's interesting: There is actually activity for this oral PARP inhibitor in phase I. You can see this here. There's a list of patients, individual patients, with ovarian [at the] top and some breast at the bottom. You can see that their mutation status is reported there, and you can see that some of them have had reasonably long durations of treatment, meaning they probably

[experienced] stable disease from this relatively well-tolerated pill.

That was the push [that was] needed to take the drug forward. If you focus narrowly on the ovary cancer patients who [tested positive for a] BRCA mutation [and had a] history, shown here, [of] a significant amount of prior therapy, you see that about half of them are still having an ongoing response right now. This bodes well for triple-negative breast cancer. So we have a phase II study. It's at Dana Farber. It's at Memorial. It's in England. It's at any number of centers around the country .... The point is that we are optimistic that, because we have identified triple-negative breast cancer [and] enriched the study population [with participants who have a pertinent] family history, we may be able to carve out another subtype of breast cancer that will be responsive to a PARP inhibitor. This is very preliminary, but it gives you a sense of where we're going.

This is the eligibility requirement for the study, which I won't belabor. People have to have a decent performance status. This is the "get you excited" shot, [although it] may not be obvious to all of you right away. On the left is a pretreatment scan. This is cancer, these nodules here, and this is [that cancer] after — I'm trying to remember how long — not forever; a period of weeks on this study. You can see that the nodules — one is gone and one is smaller. It's not a home run. This doesn't cure anybody. But this is biologic activity. This is the kind of thing, especially when you see it in early phase trials, that gets you excited as an investigator. It means that your drug is not inert; it actually could do something good. This is what we aim for.

Stepping back from the two examples of ... cutting-edge research that I just showed you, the androgen receptor work and the PARP inhibitor, a question you can reasonably ask is, "Why does my doctor care, and why do I care so much, about identifying triple-negative breast cancer?"

What good does it do me to know this? What good does it do me to focus on this particular aspect of this disease?" One [reason is that] it identifies you very quickly in terms of where you'll end up in treatment. This is a typical, standard algorithm for treating metastatic breast cancer. What it means to a medical oncologist is that you look for hormone responsiveness; you use hormone therapy as long as you can, as repeatedly as you can, until you can't justify it anymore. Then you go to the right, which I've just circled, and you use sequential chemotherapy. Triple-negative breast cancer picks off right there at the beginning. There is no earlier chapter.

From a practical point of view, in the clinic, triple-negative breast cancer is really no different from hormone-responsive breast cancer that is hormone refractory. So from your doctor's point of view, [on a] day-to-day [basis], maybe it doesn't matter so much. There is any number of therapies that have been developed for hormone-insensitive breast cancer, and only a few of them are actually FDA approved. This list is not complete. I'm not going to dwell on this. It's just to make the point that triple-negative breast cancer is the same as any number of other epithelial malignancies, frankly, like lung cancer or esophageal cancer [or] anything else. There are no targeted therapies for them. It's chemotherapy or nothing, pretty much.

This brings me back to my HER1 and [HER]2 story. What this slide shows you, on the right, is trastuzumab — that's Herceptin — attaching, binding, to the part of HER2 that sticks out of the cell. On your left what you see is cetuximab. That's C225. That's the ImClone antibody, and it does the same thing, except that its target is HER1/EGFR. There are, in addition to these antibodies, tyrosine kinase inhibitors. They do what their names suggest. They shut off tyrosine kinase. Tyrosine kinases live on these receptors, but they live on the part of the receptor inside this cell. These tyrosine

kinase inhibitors, Iressa and Tarceva, which have had some play in lung cancer, turn off the tyrosine kinase associated with HER1. Recently you've heard about lapatinib, which turns off the tyrosine kinase associated with HER2.

The difference, though, is that the antibodies to HER1 and [HER]2 are very specific. They bind exactly where they're supposed to bind. Cetuximab does not bind to HER2. It only binds to HER1. Conversely, trastuzumab does not bind to anything but HER2. These tyrosine kinase inhibitors are what we call dirty drugs. They're promiscuous. They bind to all of these tyrosine kinases. When we say that they're HER2 inhibiting, [we mean that as] a relative term. They do a better job against HER2 than HER1, HER4, BCR-ABL [or] any other tyrosine kinase, but they have activity in a broad pattern. This has had some impact on how they're developed. Here's an example of what happens when you're focusing, for example, on your market.

This is a clinical trial that GSK [GlaxoSmithKline; <http://www.gsk.com>] reported last year at ASCO — [the] ASCO Breast [Cancer Symposium; <http://www.asco.org>], actually, I think. In this trial, patients [were] HER2 negative, hormone refractory, but mostly ER/PR negative breast cancer, and they were getting paclitaxel; standard chemotherapy. They were randomized to add to that lapatinib. Now you say, "I've heard about lapatinib. It's FDA approved for HER2 positive disease. What was going on here?" What was going on here is [reflective of the fact that] many people want to develop a tyrosine kinase inhibitor for HER1. They want to believe that targeting HER1 will be effective as a strategy.

We've done, with colleagues, a single-agent trial with Iressa — gefitinib, the HER1 inhibitor from AstraZeneca. It didn't work. We've done erlotinib — Tarceva — it didn't work. But these folks with lapatinib wanted to suppress, if you

will, the notion of a drug as an HER2 drug, because, after all, that's a small market. And they wanted to focus on the possibility that they could go after a big market. It didn't work. Here's where the story gets delicious, though.

You had to have HER2 negative breast cancer [or be] HER2 unknown to get on the trial. A small number of patients with HER2 unknown disease were included in the trial, and when they tested them, [they discovered that] some of them actually had HER2 positive disease, and there was a robust signal for activity [of the HER2 gene]. Lapatinib and paclitaxel was great for those patients compared to paclitaxel alone. And there was nothing in the larger population that they were actually trying to develop the drug for, so it makes the point that targeting matters — and it frankly, from my point of view, suggests that HER1/EGFR may not be a great target in breast cancer. But before we knew that result, and for good reasons, other clinical trials were developed specifically for triple-negative breast cancer, specifically to target HER1/EGFR.

This is work that Lisa Carey presented at San Antonio. This is the first report of a clinical trial from the Translational Breast Cancer Research Consortium, [or] TBCRC. This clinical trial looks like it's randomized, but it's a little more subtle than that. There was a cohort of patients who got cetuximab, the antibody to HER1. They also then got carboplatin, a drug that has been associated with activity in triple-negative disease. But take it from me; it's been overhyped in that regard. It's not clear that there's anything special about platinum and triple-negative disease. They work there as well as they work in other breast cancers. There was another cohort that [initially] just got cetuximab, the antibody alone, and then, when the disease got worse, they [were given] the carboplatin as well. [This trial provided] a chance to see, in a controlled setting, whether [or not] one could get any mileage out of narrowly inhibiting HER1/EGFR using an antibody.

Here's the data. For cetuximab alone, there were two patients who might have had a partial response and none who had a complete response. This was below the threshold to call this promising. On the right [you can see that], when carboplatin was given, there was activity. But of course it's confounded. You don't know whether the activity is 100 percent due to the chemo or due to the combination. A randomized trial of platinum with or without the antibody would be the only way to answer that question. Indeed, that was reported this year by Joyce O'Shaughnessy. [That trial is also] a little bit confounded because it [involved the use of] a second chemotherapy drug, irinotecan. It's not a drug [that's] approved for breast cancer. It is used sometimes. Joyce likes it for triple-negative breast cancer. So they did the study this way.

[The trial is] carboplatin and irinotecan alone or, on the bottom, the same two drugs with the addition of the antibody. And here's the data. On the left are all comers for the trial. In the middle are the triple negatives. It's hard to interpret this kind of result. Overall there's no difference [in] the patients who got the antibody [and those who] didn't. In the subset of triple negatives, there is a numerical advantage for those who got the erlotinib. It looks like it's about a 50-percent response proportion instead of 30 [percent], and that can seem exciting. But I have to caution you: these are small numbers.

When you have a negative trial [finding] overall, finding a subset [that indicates] a difference is [such] a frequent source of confusion as to be misleading. Indeed, the authors did not call this a positive trial. They actually called it negative [trial finding, meaning the study did not find an advantage to the primary treatment under study], but they thought this [triple-negative subset finding] was interesting. I would say that the story of cetuximab for triple-negative breast cancer is not over

yet. It is still going to be explored. I would not suggest that anybody go out and beg their doctor for this drug. It's not clear that it matters very much. What you can see as well, if you see the curves, is that there was really no difference in the duration of the benefit.

These are all of the drugs and drug combinations that are actually formally approved for breast cancer. I only put this up [as a] contrast to that slide with all the names that I had before, to show you how limited it really is in terms of the FDA. In the adjuvant setting there are the anthracyclines: that's epirubicin and, historically, Adriamycin. And there are the taxanes. In the first-line metastatic setting it is the taxanes and it is capecitabine. Then there are some combinations, which are hard to interpret, but you see them listed there. After that, again, you have the taxanes, capecitabine and, very recently, ixabepilone and so on. That's a pretty limited list of drugs. Doctors are very free, and it is appropriate for them to give what they want, in my opinion, because there is activity for any number of drugs not filed with the FDA. ...

That brings me to what we can do here. In the quest for targeted therapy ... maybe we should look beyond the tumor itself. That brings me to the VEGF story. [VEGF is] targeted therapy, because there's a biology here. There's a target. But I'm going to [make] a really stark distinction between this [VEGF] kind of targeted therapy and estrogen receptor or the HER2 or the androgen receptor, or HER1, which I've been talking about so far. [In the VEGF situation,] the target is not exactly tumor specific. The target is VEGF — vascular endothelial growth factor. It circulates. It's in the bloodstream. It attaches to the VEGF receptor, VEGFR. When it attaches to VEGFR it tells VEGFR to tell the cell to grow. But the cell in this case is a blood vessel cell. This is called angiogenesis.

When we block VEGF, we are indirectly starving the cancer. We're shutting off the

supply lines; the blood supply to the cancer. But it's not narrowly tumor specific. It's not specific to ER/PR/HER2 negative breast cancers. In fact, this science has been proven to work in head and neck cancer; in lung cancer; in GI cancer. It should work everywhere, because all cancers need new blood vessels. Neovascularization, new blood vessel formation, is the target in this case, [the treatment is globally targeted VEGF], so it's targeted therapy. The biology can be elegant. But it's not really tumor specific, and the truth is that [VEGF is] important in triple-negative breast cancer because of the limited number of approved drugs. But it should be important in ER positive breast cancer. It is important in HER2 positive breast cancer as well. There's nothing unique about triple negative [and the use of VEGF].

There are antibodies to VEGF. I've described that already. There are also tyrosine kinase inhibitors. And the same biology that I reviewed for HER1 and [HER]2 [applies] here [in] that tyrosine kinase inhibitors do work directly on the receptor in the cell. They turn off the tyrosine kinase. The drugs you may know are sunitinib and sorafenib, the latter being a drug that just got approval to treat liver cancer. It was a big news story at ASCO the last time we were together. This is the pivotal clinical trial: E2100. This is a trial that Kathy Miller conducted for ECOG, the Eastern Cooperative Oncology Group [<http://ecog.dfci.harvard.edu>]. This is not a directly drug company-sponsored trial. This is a trial that we in the cooperative groups wanted to do, and we actually wanted to do it in part despite what had been [observed in] a first negative study [finding] in breast cancer.

Many of you will recall that there was a randomized trial [that focused on the] second-line setting in metastatic breast cancer. [A second-line study is] for patients who have already had a taxane and [whose] cancer grew. They got capecitabine or capecitabine plus bevacizumab, the antibody to VEGF, and

that trial [had a] negative [finding]. The only other large trial that was actually launched following that [study] was this one, and Kathy Miller was the principal investigator for both of these trials. We participated in this through the cooperative group system. Patients in this trial were getting their first chemotherapy for metastatic breast cancer. HER2 positive tumors were excluded because those patients would go off to get Herceptin, trastuzumab. So [the study is] not exactly triple-negative breast cancer, because [participants] could be hormone refractory. But functionally it's kind of the same thing. [The participants were] no longer candidates for hormone therapy. They need chemo. There are a disproportionate number of triple negatives in a trial like this, but it's not exclusively that.

They got [either] paclitaxel alone or [paclitaxel plus] the antibody, bevacizumab. This is the curve for progression-free survival. There is a lot of value judgment in this [study], because what was demonstrated here was a near doubling of the time of benefit [in the] first treatment [of paclitaxel plus bevacizumab]. If paclitaxel lasts, on average, six months, [the addition of bevacizumab] made it last almost 12. [What's] very frustrating is [that] this trial failed to demonstrate a significant improvement in overall survival. How do you double, as these two curves show, the duration of benefit, yet not improve survival? This raises all kinds of questions. It led to that ODAC [the U.S. Food and Drug Administration's Oncology Drugs Advisory Committee] five-to-four vote for nonapproval. The note that Cindy just showed me [indicates] that, as promised today, the FDA made the decision ... to approve it.

This is controversial. I have to tell you guys that among the loudest cheers when the ODAC vote went against it [were those] from a patient advocacy group. This is a very loaded issue. It's an expensive drug. It is not clear that it improves

survival. And arguing vehemently about the importance of this is tough in some quarters. My bet is that it does improve survival. My bet is that the trial, by fluke, underestimated the survival advantage. That's just a bet. I'm thrilled that it's been approved. But I can understand — and I'm sure you can, too, when you really think about it — why this would be controversial, unlike trastuzumab, which, out of the starting block, improved survival 25 percent. If somebody can't get bevacizumab, Avastin, it's not clear that there's a long-term sacrifice [because a survival advantage has not been proved]. It's not as clear as it would be if there was a [demonstrated] survival advantage. Later, when we look back and say, "This trial was not so positive, but others are more so," then I'll eat more words. And that's okay. That's why we do more studies. Anyway, that's how this played out.

The problem, of course, is that most people do progress, and [that's one reason that] we're going to continue to study new drugs. I'm showing you here a trial that I'm doing with Lee Schwarzbach, [in which] patients who have [experienced] progressive disease after [taking] bevacizumab can get gemcitabine or gemcitabine and sorafenib, one of the tyrosine kinase inhibitors for VEGFR. This is exactly the way lapatinib was developed in HER2 positive disease. It's parallel. And the question is really the same: if a tumor grows despite [the use of] Avastin, is it resistant to [all] antiangiogenic treatments or [to] just that one? That's what [we hope] this study will answer.

I want to end on a little more of an up note because there is a sense that, gee, hormones don't work and chemotherapies have limited value. And that canard is repeated out there all of the time. In fact, triple-negative breast cancer, at least in the adjuvant setting, is a tumor type that benefits the most from chemotherapy. That is lost on a lot of people. This is a retrospective analysis that Eric Winer and

I did with Don Berry. And what we did here — it was published in *JAMA* [*Journal of the American Medical Association*; <http://jama.ama-assn.org>] — was to go back through three sequential adjuvant therapy trials [conducted by] the CALGB, the Cancer and Leukemia Group B [<http://www.calbg.org>]. Eric and I cochair [that group's] breast committee.

In these trials, [we] asked chemotherapy questions dating back to 1985. In [the CALGB trial] 8541 we asked about low-, intermediate- or high-dose CAF, for an old regimen. Ignore the 5FU, the F, for now; it's just AC chemo at a low, intermediate or high dose. The second study, CALGB 9344, is a famous trial. It was the first study that reported a paclitaxel benefit in the adjuvant setting. The third trial is the dose-dense trial, [in] which [we] took our AC/paclitaxel regimen and squeezed it, shortening the time between treatments. But when you look at [this study] graphically, those two arms are actually the same and those two arms are the same. So we could go across three clinical trials and basically do an indirect comparison of the benefits of treatment in various subgroups without belaboring this [point].

What Don Berry showed is [that,] fundamentally, the benefits of each chemotherapy step are larger in the ER/PR negatives than in the positives. In fact, remembering that there is no untreated control — the control arm here got chemo, from the baseline of getting modest chemo [benefit] — there's a 63 percent, meaning two-thirds, risk reduction in getting the best version of chemo if you have an ER negative breast cancer. This has been widely misunderstood to mean that [chemotherapy] doesn't work [in ER/PR positives], as shown in blue ... That is wrong. [Chemotherapy] just doesn't work to the same degree. But you have to pause and focus on that for a moment. In the ER/PR negatives, the magnitude of the chemo benefit is the same or larger as the magnitude of chemo and hormone therapy for hormone receptor-positive breast cancers. So there is a lot to be gained from

conventional chemotherapy.

How does this relate to triple negative? This is a slide from an extremely controversial paper that we just published in the *New England Journal [of Medicine]*; <http://www.nejm.org>. Dan Hayes did this. What many people took from that last slide I had up was that you don't need to worry about which chemo you give in ER/PR positive breast cancer. We went back and looked at HER2, the third factor. On your upper left are the triple negatives: in red, paclitaxel; in blue, no paclitaxel. So the triple negatives get a profound benefit from AC/paclitaxel compared to AC alone. What we also showed here is that HER2 status gives you a big benefit. On the bottom panels, C and D, you see [that] the red is better than the blue, and that's independent of ER status. That's all about HER2. So the only group [that does not seem to have benefited is] the group that was estrogen receptor positive and also HER2 negative or normal. That's not the focus of my talk today, but I wanted you to recognize that the triple-negative cohort, while lacking in targeted therapies, gains the largest [advantage] of any of the cohorts from conventional chemo. So there is a whole lot of upside in that regard.

Where is this all going? We're bringing bevacizumab, Avastin, into the adjuvant setting, and the focus will be on triple-negative breast cancer. This is a pilot study, [which the] ECOG just reported this year, that used our dose-dense, every-two-week chemo regimen. They asked whether or not it was safe to give Avastin with that regimen, and it seemed to be. This has led to E5103, a trial that is supposed to be opening — I think it is open in a few centers now. In the post-op setting, mostly [people with] triple-negative breast cancers will go in, and these patients will be randomized to get standard AC/paclitaxel, the same thing with bevacizumab while they're on chemo, or the same thing with bevacizumab on chemo and [continuing bevacizumab every three weeks for 30 weeks]. It's a

three-arm trial that will answer two questions: Does bevacizumab — Avastin — help? And if it helps, how long do you have to be on it? Questions, you all know, that we struggle with in the HER2 positive group. We're also doing this in the pre-op setting; this is Bill Sikov's trial for the CALGB. Here we are focusing on triple negatives, but remember my introductory comments about definitions. We know that labs vary; we know that the quality of testing varies. We say that ER can't be too positive [to be on this clinical trial]. But low positives can go on this [study], because we think that these distinctions may not be so black and white.

These patients will be randomized [so that some will] get carboplatin [and others will] not. We're going to answer the question: does carboplatin have a special value here? Second, they'll be randomized separately for the use of bevacizumab, [with the question being,] again, whether [or not] it has a general value here. My suspicion is that carboplatin will be of some value here. I don't think it's unique to the triple negatives, but we'll demonstrate it anyway. Conversely, my suspicion is that bevacizumab will be of value, but I don't think it has anything to do with being triple negative. I think it just has to do with augmenting any anticancer therapy.

These are slightly tired slides at this point, this graph, but it is worth pointing out to everybody [that] the dark blue line is the age-adjusted mortality of women aged 35 to 70, roughly, in a collection of Western countries. On the upper left is the United Kingdom. On the upper right is the United States. The bottom left is Netherlands, and the bottom right is France. In all cases — to the greatest degree in the United Kingdom, but in all cases — you have a continued downward trend in terms of mortality for breast cancer since 1990. The raw numbers are improved. In the United States in 1990 there were about 46,000 deaths, last year [there were] about 40,000. While 6,000 fewer is nowhere near enough, you do have to recognize

that that's in the context of an older, more overweight population with more absolute incidence of breast cancer.

So I think that, despite what seems like mixed news here, there really is something happening. We're pushing out survival. I do think separating out breast cancers, like I've described, will help. I am optimistic that we will further divide the so-called triple negatives. I think we will come up with targeted therapies for some of them. In other cases, we'll figure out better ways to apply the tools that we already have, which I've gone through.

That is everything I wanted to say formally. I will be really happy to answer those questions that I have not addressed, which are, I think, innumerable. Thank you. (Applause)

**WOMAN:** With all of these trials and everything that's being done, how much of this is specifically geared toward and includes the 40-and-younger population with breast cancer?

**CLIFFORD A. HUDIS, MD:** That's a great question. There are really two ways to answer it. It is illegal for us to do age restriction in clinical trials. If you have NCI funding, you can't have age discrimination. That's one issue. The second issue that you bring up is the potential for age, independent of other factors, to be important, meaning that age would affect the biology of the tumor or the response to therapy. There is a reasonable likelihood that that's the case in some ways.

**WOMAN:** Absolutely.

**CLIFFORD A. HUDIS, MD:** But it's not as proven as you think. The third thing, to be fair about this: the global problem with breast cancer trials is [that] they are biased to young people. The median age of accrual in American patients who go on trial, at least in big centers, is in the late 40s. The real dilemma is that the median age of breast

cancer is 63. So, as much as we may fail to do a good job in the young people with breast cancer — who are more rare but who are still of concern — we get, of course, criticized at the other end for doing massive clinical trials [that are] of no relevance to the largest cohort of people, [who are] in their 60s, 70s and 80s. It's a tough issue. Young people are more likely to go on clinical trials than older patients.

**WOMAN:** I understand that. But it's known that breast cancer in women under 40 is much different than what you hear about [in] the major population.

**CLIFFORD A. HUDIS, MD:** Yeah, it is. But let me answer that.

**WOMAN:** It's [disconcerting] to hear that we don't have the numbers to really count. I would wonder, out of all those studies that you put up there, what kind of numbers on women that were included in that trial were ...

**CLIFFORD A. HUDIS, MD:** Small numbers. I showed you small numbers for all the trials. The issue is that young women have typically more aggressive breast cancer. [This is] frequently conflated with ... a higher frequency of BRCA heterozygosity and these triple-negative subtypes. Triple-negative breast cancer has a similar natural history in different age groups. It is more likely to occur in the young person. Do you see? So it's a difficult issue to nail down. If we insist, for example, on doing drug development in women [aged] 30 to 40, if we narrowly did that, we'd actually slow things down a lot, because we wouldn't accrue enough patients in a short order. It's a frustrating problem.

**WOMAN:** I was trying to absorb all that.

**CLIFFORD A. HUDIS, MD:** I spoke slowly for a New Yorker. (Laughter)

**WOMAN:** I'm from Canada, though, so it takes me a little bit longer. I kind of got

that with the PARP trial — that women who are known to be BRCA1 and [BRCA]2 negative aren't benefiting as much. Did I get that?

**CLIFFORD A. HUDIS, MD:** No, I don't think we know that yet. We have preliminary evidence of activity. We have a theory that the drug will work best in the BRCA1 heterozygotes. And we're enriching the trial for them. That's all we can say so far. But we're going to have a lot of people in those trials who describe a family history [that is] consistent with the gene when, in fact, the gene is not abnormal, but they have triple-negative breast cancers. Maybe the gene is abnormal, and the limits of our testing are being exceeded right now. There are all kinds of ways that ... science never gets more simple with the passing of time. Some of you who are familiar with this will know that, about three years ago, it became clear that about 10 percent of BRCA abnormalities were being missed by conventional testing. So it's possible that something like that will still happen. You have to have a very open mind.

**WOMAN:** I noticed you didn't mention Abraxane; I know that's just starting. I'm about to start a trial with Avastin and Abraxane. It had a similar trend [in other trials] of doubling the tumor response rate but not having an increased survival rate. Is that similar to the Avastin story, then?

**CLIFFORD A. HUDIS, MD:** What we're drifting toward is a *Wall Street Journal* kind of discussion about business. Abraxane is paclitaxel, period. It is attached to a little bit of the egg protein, albumin, and that makes it dissolve in water. That is the sum total of its difference. It turns out that using Abraxane — and giving [it], by the way, [as] a higher dose there [than you would as] paclitaxel [without the albumin] — gets you a higher response rate, like you've described, and a longer progression-free survival. The problem with first-line clinical trials in breast cancer is [that] there are enough effective

salvage therapies that whatever happens after first line confounds survival [rates, because if the cancer recurs, there are many other treatments women can try that may prolong their lives].

That's the counterargument that's always made. Yes, Abraxane was better than paclitaxel, but the people who got paclitaxel were able to go on capecitabine and, therefore, the survival difference was mitigated. That's been the back-and-forth discussion. I didn't focus on that or any drug in particular because I have yet to see clear evidence that any chemo drug actually really is specifically active in the triple negatives as opposed to other populations.

**WOMAN:** But in terms of managing your own ... like especially in the premenopausal set and looking after young kids and stuff, managing side effects is a huge deal. So taking Abraxane over Taxol or Taxotere, to me, seems really desirable.

**CLIFFORD A. HUDIS, MD:** Again, we're in a bit of a marketing thing. I am always dismissive of these differences. I think there is profound marketing pressure from the various drug companies here, and I think that there are individual patients who benefit more or less from other drugs. But I'll give you a couple of examples of the ways in which this has been twisted. Which drug causes more neuropathy — paclitaxel or docetaxel? Everybody who thinks [it's] docetaxel, raise your hands. Everybody who thinks [it's] paclitaxel, raise your hands. In the randomized trial TAX 311, [which was] run by sanofi-aventis [<http://www.sanofi-aventis.us>], of docetaxel, Taxotere, compared to paclitaxel, the rate of neuropathy was twice as high for docetaxel as it was for paclitaxel.

Abraxane causes much more neuropathy. It happens to not cause hypersensitivity reactions as often, so you're sort of picking and choosing. It causes much less myelosuppression. So many would argue

[the opposite of] what you just said. They'd say that paclitaxel is the less toxic drug because their nerves don't get shot as quickly. The company and others will say it reverses more quickly. I'm going through this in granular detail not to say that you're right or wrong, but to say [that] this is exactly the kind of thing one discusses individually with [his or her] doctor. Just be careful of drug company claims in all directions.

**WOMAN:** You often hear that AC is the big drug, the one with the punch, or the two drugs with the punch, and that the taxanes, for many, is more of a secondary — more of an “insurance policy.” Is that true in triple negative?

**CLIFFORD A. HUDIS, MD:** No. It's not true anywhere. It's just [that] doctors are ... AC is the enemy, you know. We're familiar with it. It causes a lot of acute toxicities. It's tempting to conflate the toxicity with the benefit. It's so complicated. I don't think that's one bit true.

**WOMAN:** I've heard a lot about people with triple-negative tumors — that the tumors are actually very influenced by estrogen because of the cells around them and their influence of estrogen. Given that, is there a role at all for the hormone medications, like tamoxifen and stuff like that, for people with triple negative?

**CLIFFORD A. HUDIS, MD:** It's pretty complicated. Historically, when estrogen receptor testing was not done well done, there was a high rate of false negative test results. A classic example: A woman would have surgery on Friday. The specimen would sit in the pathology lab until Monday. When tested, it would be negative for the estrogen receptor, but if [the woman were] given tamoxifen in those days, in the 1970s, there would be evidence of benefit. The test was falsely negative because the receptor degraded while the specimen sat.

That doesn't happen anymore. In the

modern era, as a practical answer to your question, truly ER and PR negative tumors do not benefit from hormone therapies. We've tried and tried again. They don't. But the noise in the system is still there because some of what you said is very true. There is estrogen receptor expression in blood vessels. There is a potential, in some ways, to capitalize on that, but one has to be practical as well as sort of abstract. I love to study this abstractly in the lab and maybe in clinical trials. [But] it is misleading to suggest that any patients benefit from that kind of approach right now. In fact, there is evidence [that] they don't.

**WOMAN:** Is there evidence, though, that ovarian removal — because of that reduction in estrogen, would [that] help in triple negative?

**CLIFFORD A. HUDIS, MD:** Again, there is really not [evidence to suggest that]. There is really not. To the degree that there's a benefit, it would relate to the fact that some of the testing is wrong, unfortunately. I wish it were more of what you said, but it's really been pretty neatly parsed out. In fact, the Oxford Overview does not report hormone therapies in the ER/PR negatives anymore, because there's no benefit.

**WOMAN:** I got in on the last end when you were talking about a prostate cancer drug. Right now I'm on Abraxane, and that has been one of the best drugs that have helped me in three months. I had tumors around my neck, like big ...

**CLIFFORD A. HUDIS, MD:** I'm just worried that you're drifting toward the story about me instead of the generalized ... you don't have to tell everybody your personal details. And I can't do a consult.

**WOMAN:** I feel like the Abraxane — my body is getting used to it.

**CLIFFORD A. HUDIS, MD:** Good.

**WOMAN:** I've been on chemo every

week for the last five years. Abraxane did not give me as much neuropathy as the Xeloda and the Tykerb. Tykerb and Xeloda together didn't do anything for me, so she took [me off of them] and put me on Abraxane. But Abraxane — I had the best results from Abraxane. The Xeloda made me like a corpse. My hands and my feet got all black and ...

**CLIFFORD A. HUDIS, MD:** So the point is that individuals vary. You have to deal with your doctor on all of these things. You're exactly right.

**WOMAN:** Yeah. But you mentioned something about the drugs for prostate. Is that something that you were ...

**CLIFFORD A. HUDIS, MD:** It's purely experimental. I'm hoping it works. What I described is that we found a small subset of breast cancer that might be sensitive to antiandrogen therapy; male hormones.

**WOMAN:** Oh, given to female patients?

**CLIFFORD A. HUDIS, MD:** Yes. That's what we're trying.

**WOMAN:** How far off is that?

**CLIFFORD A. HUDIS, MD:** It's pretty far off right now. We've gotten only two patients that have this tumor type. So we're far from being able to show that that works. I have to say: one has to always be skeptical.

**WOMAN:** What type of tumor type is it?

**CLIFFORD A. HUDIS, MD:** It's triple-negative breast cancer, but it has the androgen receptor. That's what makes it distinct.

**WOMAN:** I wanted to find out if the belief is that triple-negative breast cancer, aside from BRCA1 and BRCA2, is most likely to be genetic; [that] it's just undiscovered BRCA's.

**CLIFFORD A. HUDIS, MD:** There is

some epidemiology data. For example, triple-negative cancers are seen a little more frequently in East Africa and in African Americans. There may be other populations around the world like that. It's impossible to tease out genetics ... from, for example, environmental factors or diet, nutrition, whatever. I think that, apart from the known association with BRCA1, it is not clear that there's a higher frequency — let me say it differently. I think your question is, "If I have a triple-negative breast cancer as a sporadic breast cancer, is it more likely that my children will have inherited a trait for that kind of cancer?" Right now the evidence [indicates that the answer is] no.

**WOMAN:** I had heard that the triple negatives can start off [as] estrogen receptor positive, and then they shut down. Can you speak to that?

**CLIFFORD A. HUDIS, MD:** That's another one of these issues that gets a lot of play and traction — like the change in HER2 status or, in general, changes in ER. At the moment, again — I know I sound like a bit of a skeptic. It's not clear to me that evolution of the tumor really happens this way. It is much easier to ascribe those changes to poor quality testing along the way.

**WOMAN:** I thought that I had heard something [about] BRCA1s who ... had had oophorectomies incidentally, just earlier in life — that they tended not to get the triple-negative breast cancer, so there was some thought that, because they shut down the estrogens, the breast cancers didn't occur.

**CLIFFORD A. HUDIS, MD:** There is some data that [indicates that] people who take out their ovaries lower their risk of breast cancer, but the risk reduction actually appears to be mostly in the ER positives, like you'd predict. That's where the data is now. The numbers are small.

**WOMAN:** I was hoping you could expound a little bit more on triple-negative

breast cancer and correlation to the African-American community.

**CLIFFORD A. HUDIS, MD:** There is not a lot to say. There is epidemiology data that just says [that,] if you take the average African-American patient with breast cancer, it is more likely to be the case that [he or she has] a triple-negative tumor. But that doesn't get us very far. If the incidence is 30 percent instead of [the] 20 percent [found] in the larger Caucasian population, from an individual point of view it doesn't help very much. It is what it is, right? You have to treat it. The question is: why is that happening? It leads us back to important basic genetics questions, environment and epidemiology all mixed together. But, from a practical point of view, if it's triple negative, the choices are the same no matter what the incidence is in a population.

**WOMAN:** I was diagnosed when I was 16. That was 14 years ago.

**CLIFFORD A. HUDIS, MD:** Are you saying you had invasive breast cancer at age 16?

**WOMAN:** Yes. At age 16.

**CLIFFORD A. HUDIS, MD:** I will tell you: in 20 years — that's a record for me.

**WOMAN:** Yes. (Applause) Well, I'm glad to be here.

**CLIFFORD A. HUDIS, MD:** The applause is for being here, but that is a shockingly young age. Even among the Ashkenazi Jews with BRCA1 mutation, you almost never see [cancer in patients who are in their] early 20s. You see it every now and then, but it's really rare. [Until now, the] youngest patient I ever heard of was actually 21.

**WOMAN:** I was definitely 16. No family history. But the second question is ...

**CLIFFORD A. HUDIS, MD:** You've made my trip worthwhile yourself. I can

never cease to be humbled; I'll tell you. Sorry.

**WOMAN:** My second question [has to do with the fact] that testing was not available back then. Is there any way for me to know, at this point, whether it was triple negative or what my risk factor ...

**CLIFFORD A. HUDIS, MD:** Of course. That's easy, actually. These tests are done in what's called paraffin-embedded tissue; wax-stored tissue. If you had a breast cancer — [this applies to] anybody — and it was removed, it's actually stuck in wax and fixed there. When they want to study it they take, essentially, a knife, slice off a thin layer of the edge of the wax and the tumor and stain that using the estrogen receptor stain, the progesterone receptor stain or the HER2 [stain].

**WOMAN:** Would they still have that, [from] 14 years ago?

**CLIFFORD A. HUDIS, MD:** That's an individual thing. That's a dilemma. But one would actually think that, [because it was found in] such a young patient, they might have saved it. Generally the rules are — and I don't want to quote them, because I could get them wrong — but I think, like tax returns, it's seven years that you're supposed to keep them. But it may have been changed, right?

**WOMAN:** Actually Komen is working on a white paper that will probably go out in a couple of weeks. In the community hospitals it can be as few as two years. There's no law.

**CLIFFORD A. HUDIS, MD:** But one would think that they may have held onto this kind of a specimen.

**WOMAN:** Why would she want to know?

**CLIFFORD A. HUDIS, MD:** There's no urgent need to know today, but I can make up a scenario [in which] you'd want to. For example, you might want to have that

written down someplace in case something else happens in the future. Maybe you [were] thought to have disease but they couldn't get a biopsy, or maybe you were thought to have disease but they couldn't get enough [of a specimen to perform] that test. You just never know. While you could wait, the longer you wait the more likely it is that the specimen will have disappeared. In truth, ER/PR testing [has been] standard for decades. Don't tell me how old you are; I'm not asking. But HER2 testing has been standard in the clinic since the late 90s also. So one would actually think, unless it was really long ago, that they probably did all three tests.

**WOMAN:** It was in 1994. And I just turned 30. (Applause/cheering)

**CLIFFORD A. HUDIS, MD:** Child. (Laughter)

**WOMAN:** As a triple negative — I don't know if anybody else feels this way. I know a few of my other friends do. But I feel like I'm screwed.

**CLIFFORD A. HUDIS, MD:** I ended the way I did on purpose.

**WOMAN:** Oh, no. That did. It did. It gave me a chance. But what should we be doing? Should we be participating in th[ese] trials? Should we be going with NBCC [the National Breast Cancer Coalition; <http://www.stopbreastcancer.org>] to lobby the government? As triple negatives, what should we be doing?

**CLIFFORD A. HUDIS, MD:** You ask some really loaded questions. First, everyone should be in trials. No more than 2 percent of American adults participate in clinical research trials. To give you a sense of contrast: In pediatrics there's never been a big breakthrough for acute leukemia; no one [single] big breakthrough. Yet, over the decades, the survival rate has increased from 20 percent to 80 percent because virtually every kid with acute leukemia in America

goes on a clinical trial. The reason they do it might sound like [the work of] a monopoly, but, basically, the pediatricians say, "It's a bad disease; it's rare." It speaks to the question about age earlier. They sort of conspire, like old oil companies [did to control the behavior of consumers,] to say [that,] if the kid has leukemia, the kid is going to one of, let's say, only two dozen centers in the country. And the kid is going on a trial unless [the parents] refuse.

Coercion is the wrong word, but there is a strong effort [made] to get the kids on the trials. That is what has transformed acute leukemia. In a way, it is amazing [that] we've made the progress we've made in solid tumors of adults, where one in 50 people participate in research studies. So should you participate? You bet you [should, and at] every opportunity, always, if you can. That's my view. Editorial. Your second question brings another equally important editorial response. Cindy can almost smell this one coming from me. But the notion of lobbying because you want money for triple-negative disease — you're right. But the big problem isn't a lack of funding for *that* cancer. The big problem is a lack of funding for cancer.

**WOMAN:** Would your best guess, maybe, now be [that] triple-negative cancer is driven by the whole blood thing?

**CLIFFORD A. HUDIS, MD:** No. I was trying to be very clear not to say that. Angiogenesis is a universal requirement of tumors. It is a way to add onto chemo for triple negatives. My guess — and, in fact, something we're exploring that I didn't talk about — is that it will add on to effective therapy for HER2 positive disease, and for ER positive disease as well.

**WOMAN:** So much of what has been said here is just totally off the charts, in terms of understanding it, for me.

**CLIFFORD A. HUDIS, MD:** Then I

apologize, because my goal is to be understood.

**WOMAN:** I'm sure it's just me.

**CLIFFORD A. HUDIS, MD:** If I have to start over again, I will.

**WOMAN:** But my question is: if ER/PR negatives don't benefit from hormone therapy — it's kind of the flip side of that — should triple-negative women who are approaching menopause avoid hormone therapies that are treating ...

**CLIFFORD A. HUDIS, MD:** That's a loaded issue in so many ways. Here I'm a little bit outside the mainstream. Let's start with the basics. Hormone replacement therapy was hyped for decades through the results of non-randomized research studies. The putative advantages of hormone replacement therapy using both estrogen and progestins were virtually nonexistent. This is an object lesson in how not to interpret clinical trials. It's a painful one for doctors, because it fuels the belief that we don't know what we're talking about and that we don't know how to do science. What I mean is [that,] if you take a group of people, and the healthier, more active ones elect to take hormone replacement therapy for 30 years, and you do your research by looking back over [those] 30 years and asking, "How do people who took hormone replacement therapy do compared to those who didn't?" [the result you will come up with is that] they do better.

But it isn't because they took HRT. It's because they were better to begin with. We learned that, finally, when the Women's Health Initiative [<http://www.nhlbi.nih.gov/whi>] was reported. Remember, that was placebo controlled and randomized. And the HRT-treated patients didn't do any better for any of those endpoints that you care about. There are maybe one or two exceptions. There is no doubt that hot flashes will be better controlled for women who take HRT compared to [those who don't], and

there are some more subtle things. [There are] some bone health issues. It's not clear about cardiovascular and the other claimed advantages. The reason I'm answering the question this way is [because] the drive to take HRT is, in many cases, external and pharmaceutical industry driven.

People should be willing, in my opinion, to put up with a few months of discomfort. I am also quick to say [that] there are patients for whom nothing but estrogen will actually let them sleep and [who] take HRT — and one of the little ironies in all this is that HRT, for those patients, for a short period of time, is probably perfectly safe. This is heresy in my world, to say this. But it isn't related to ... breast cancer [being triple negative or not]. It's just [that] the whole field is so filled with hype and misleading information, I think. Was this bothering you, too, or no?

**WOMAN:** I was [diagnosed as being] double negative, because they didn't do triple negative, and I went into menopause at 36. And I couldn't find anybody ...

**CLIFFORD A. HUDIS, MD:** That's tough.

**WOMAN:** So that's why I was [inaudible] to myself. I was reliving those [inaudible].

**CLIFFORD A. HUDIS, MD:** There is this issue that young people [who are] forced into early menopause do seem to have a greater degree of suffering than people who go through a natural menopause at the median age of 53. We walk a very fine line, because we want to be sensitive. We want to do what is right. But we also know that there is some evidence of harm. There is more breast cancer in people who take these treatments for a long period of time.

**WOMAN:** Is there anything different than triple-negative women should be doing in terms of their follow-up?

**CLIFFORD A. HUDIS, MD:** No.

**WOMAN:** Diagnostics, whatever?

**CLIFFORD A. HUDIS, MD:** It's all the same.

**WOMAN:** Have you heard anything about L-glutamine being used?

**CLIFFORD A. HUDIS, MD:** That's sort of in the realm of supplements. It suffers from the same, unfortunately, weak science as the rest of them at the moment.

**WOMAN:** I have heard many anecdotal stories about women who have been diagnosed with cancer when they were either pregnant or delivered a baby, many of whom are triple negative, and I [fall] in that category [of being diagnosed with triple-negative breast cancer after a pregnancy]. Is there any research or any literature out there that is looking into that? Is it all in our heads?

**CLIFFORD A. HUDIS, MD:** Nothing is in our heads. The overlap between pregnancy and a breast cancer diagnosis, if I remember correctly — and you may remember the numbers — is one in 3,000 pregnancies. I think that's the number that is affected by breast cancer. It's a growing problem because of the good health of our society — the way we [have come to] count on having two children, and having two adult children. This is unheard of in the history of humans, that you can put off pregnancy until [age] 35 and expect to [have] two healthy children who go to college when you're 60. I'm not criticizing; I'm not making a joke of it. It's never been true before.

Women had children at 18 and 20; at 24. Women died at 45. Their husbands remarried; [by the time the men died, some had] had three wives. There is more breast cancer and pregnancy, I think, in part because we have delayed childbearing, which is appropriate for our society. I am not sure there is more to it

than that. The question in the beginning about triple negatives and young people — of course there is going to be a disproportionate number of triple-negative tumors. But you also have some strongly ER positive tumors, and they are very responsive to the high hormone levels associated with pregnancy. So that one cuts both ways.

**WOMAN:** Can you speak to the WINS study at all, or are you familiar with it?

**CLIFFORD A. HUDIS, MD:** Yeah, I can. I'm a coauthor of that trial. For everybody who doesn't know what that is, WINS is the women's health study that looked at nutrition and breast cancer. I'm going to summarize it because it's one of these trials that, again, has been hyped, and maybe too much. The conjecture, the hypothesis, that drove that trial was that ER positive breast cancers will do better in the long run with a fat-restrictive diet. The reason for that had to do with the biochemistry of the fat metabolism, what downstream metabolites are being generated and their influence on ER positive breast cancer. I'm making this point for a reason.

There were four analyses of the trial that showed no difference. For those of you that don't know the trial — approximately 2,500 women were randomized in the study after they finished their standard therapy: chemo; tamoxifen if ER positive. And they went on either a low-fat diet [in which] 30 percent of calories [came] from fat — which, remarkably represents about a one-third reduction in the average amount of calories from fat [that Americans eat] — 45 percent is the baseline — or a really restricted diet, which was originally aiming for about 15 to 18 [percent of calories coming from fat]. In reality, it was in the low 20s, as I remember. So the randomization was a healthy diet or a restrictive diet. The funding for the study was withdrawn after a while. It showed no differences. The Breast Cancer Research Foundation

[<http://www.bcrfcure.org>] actually came in and gave the American Health Foundation [<http://www.americanhealthfoundation.com>] money to finish monitoring the study, and the fifth analysis showed an advantage to the lower-fat diet.

On retrospective testing, that advantage was entirely restricted to the ER negatives. The hypothesis was the ER positives would benefit from this. The study was done for that. And in one out of five analyses over time, the other group appeared to benefit. In addition, the people on the low-fat diet lost weight, which is fine. It sounds great. But it confounds the interpretation. Was their little benefit, if it's real, due to the low-fat diet [itself] or [to] the calorie restriction that ensued and the weight loss? That's a long walk I just took you on. The short answer is [that] there's never an argument for being heavy and there's never an argument for a high-fat diet. It's terrible for your heart and your joints and your diabetes. So a low-fat diet is a good way to restrict your calories. [Editor's note: Follow the advice of your doctor or a nutritionist. Many low-fat packaged foods are high in calories!]

**WOMAN:** The way that my oncologist explained it was that the benefit for triple negatives was actually very significant in that the reduction [in recurrence rates] was, like, up to 50 percent; that, actually, the benefit [gained by following] a low-fat diet was even better than what we get with our chemo statistics.

**CLIFFORD A. HUDIS, MD:** With the caveats that I just described for you. I made you into a pseudo statistician there, which is to say [that], yes, the result is what he or she described. But there are some wrinkles that you have to keep in mind. You need another study to confirm it.

**CINDY GEOGHEGAN:** You need to take the last question.

**CLIFFORD A. HUDIS, MD:** Oh, I have to take the last question. I wanted to go on.

It's not me.

**WOMAN:** It's funny that you come to these things, and we read about clinical trials, and yes, people should be in them. But I'm willing to bet that almost everyone in this room is either in treatment or [has had] past treatment. I'm a perfect example. I'm triple negative and I'm BRCA2 positive, and I think, gosh, I could have been in a study like that. But now, however many years out of treatment — are there any studies for people who are out of treatment? I feel like I'm this healthy guinea pig now. I'm ready for someone to use me. Do we all have options to contribute toward your research in different studies, being post-treatment? Because all of your studies seem to be metastatic studies.

**CLIFFORD A. HUDIS, MD:** I showed you that on purpose. The issue is, of course, [that] if [a person is] not on treatment and is healthy, there is no motivation to treat [him or her], and there is no reason to subject [him or her] to the risk of therapy right now.

**WOMAN:** Someone like me — I'm willing to because of the family history issue. Seriously; four aunts and a daughter. I'm saying [that, even] if I'm healthy now, I'm willing to take something like a Herceptin that's not as hard on you. Are there those kinds of things that are ever ...

**CLIFFORD A. HUDIS, MD:** Not so much. There is another bit of good news here; I actually thought about showing you this, and I didn't. But now I wish I had. The interesting thing about ER [negative] and PR negative breast cancer — now I'm talking narrowly about the early stage setting — is [that,] if it is going to recur, it recurs typically — not exclusively; typically — in the first few years. By the fifth year, if you look at the yearly risk [of] something bad [happening], it's back down to just about baseline. There are occasional recurrences after five years. In contrast, people whose tumors are ER

positive do not have that early spike in recurrence, but they don't get the falloff at five years, either. It goes on forever.

I always say, it's like having a fixed-rate mortgage versus a weird adjustable-rate mortgage. So the rewards for participating as the years go past get less and less. There is virtually no possibility of a benefit, nor [is there] a possibility of demonstrating effectiveness of a therapy, because most people who are at the fifth year, for example ... don't rush me with the bad stories. I know they're out there. But most people who get to the fifth year with that kind of cancer are really done with it, luckily. So there is a little bit of a disconnect that as the dust settles you're really sort of in the clear. Which is good news, right?

**WOMAN:** I'd love to help my daughter out in some way. I don't know what kind of cancer she's going to ...

**CLIFFORD A. HUDIS, MD:** In fairness, one thing to do is to talk to the geneticist in your community. There are observational trials, serum studies and epidemiology studies that could be very helpful, just not treatment studies.

Thank you all. I have to tell you ... (Applause) Let me just say, some would ask why, in the face of a blizzard, I got up this morning, took the train to Newark and flew down here just to do this. The truth is, I get more out of it than you get. "Fun" may sound like the wrong word, but it actually is fun to come and see all of you. It is fun to hear what's on your mind. It is useful, because we take that back and think about it from a research [perspective]. It's also the uplifting experience of seeing so many interested and enthused people. It's more than you can imagine. I want to thank you for having me. (Applause)

[END OF TRANSCRIPT]