

## Inflammatory Breast Cancer: Issues and Updates

Edith A. Perez, MD

**MODERATOR:** Good afternoon. I'm [Rhonya O'Neill], and I'm from Little Rock, Arkansas. ... I'm going to introduce our key speaker today, Dr. Edith Perez. She's a professor of medicine at the Mayo Clinic in Rochester, Minnesota, and the director of the breast cancer clinic at Mayo Clinic [inaudible]. She's a member of the Mayo Clinic Women's Cancer Program Steering Committee, the director of the Cancer [Clinical Study Unit at] Mayo Clinic [in Jacksonville, Florida] and a [chairwoman of the North Central Cancer Treatment Group's Breast Committee].

She also serves on [the Scientific Program] Committee and the Cancer Communications Committee of the American Society of Clinical Oncology and is a co-chair of the [inaudible] task force. Dr. Perez is involved in a range of [clinical trials] of new therapeutic agents [for] the treatment and prevention [of] breast cancer. She also developed studies to evaluate [inaudible] and genetic markers in the development of aggressive breast cancer.

After our presentation, we're going to ask her some questions, one person at a time.

**EDITH A. PEREZ, MD:** Hello, good afternoon. Welcome to Jacksonville. I am glad the rain stopped, but I guess there are still some clouds. I came back from a trip last night just to participate in your meeting today after being away for a few days, and it's really my pleasure to be able to share with you some information related to inflammatory breast cancer and to welcome you to our

town. This is the outline of the presentation I put together for you. It's quite different from the handout I submitted to the organizers about two weeks ago, as I just put together what I think is a better talk this morning.

I will first address some general concepts related to the presentation and biology of inflammatory breast cancer. Then I'll talk a bit about our recommendations for pre-therapy evaluation. What kinds of tests should patients have? Then I'll address systemic selection of therapy for patients, then talk a bit about patient monitoring while receiving preoperative therapy. I'll do that in the first nine slides.

Then, for the subsequent six slides, I will talk about the type of surgery and radiation we recommend, then talk about the management of patients after surgery is performed. In the last 17 slides, I will discuss the two topics of long-term safety issues as well as new futures and how I see the future. ...

... Inflammatory breast cancer, in terms of diagnosis, tends to be rapidly progressive, increasing size of the breast associated with redness of the breast and this concept of what is called peau d'orange, which is this redness, kind of orangey look. This can be associated with induration and tenderness and then a pathological report with what we call dermal lymphatic invasion. In addition to the clinical manifestations of inflammatory breast cancer – which unfortunately in some situations is misdiagnosed for many months with the idea that if the patient presents with

redness of the breast, this might be associated with an infection, which delays biopsy and then therapy – there are some specific pathological markers that are important for all of us to be aware of in the setting of inflammatory breast cancer.

I think it's critical that when a biopsy is performed and a tumor is found that the pathologist performs an evaluation for estrogen receptor, progesterone receptor as well as HER2, because finding out the results of these biological tests helps us make decisions related to therapy for our patients. It has been reported that HER2, which is sometimes referred to as ERBB2, is overexpressed or increased in 38 percent or even up to 70 percent of patients with inflammatory breast cancer. One of the changes that have occurred in the management of patients with this disease is that since the introduction of trastuzumab, but now lapatinib, patients have newer options compared with the options that were available ten years ago.

These options are critically important, because they are available based on the biology of the breast cancer, and they are allowing patients to have a better outcome compared with what has been thought for a long time, which was that patients with inflammatory breast cancer have a horrible prognosis. I think it's time to move from that concept. I think, first of all, it's no good that anybody develops breast cancer. That's pretty clear to all of us. But it's important also to realize that many of the statistics that we utilize are based on patients who were diagnosed with this disease 20 years ago, because they are the only

patients for which we have 20-year data. But based on patient participation, awareness of this disease, and the introduction of these novel modalities, it is clear to me that these statistics are really not that valid in a patient who is diagnosed with this disease in 2008.

However, it's important to think about what else is being done in terms of the understanding of the biology of this disease that will lead to better therapies, even compared with what we have today. There are markers that have been identified as being present in patients with inflammatory breast cancer – things such as RhoC, cadherin and p53, which are being used by many persons to devise strategies to have drugs directly against those targets that may eventually be introduced into clinical trials and potentially ultimately lead to approval that is specific for the management of patients with inflammatory breast cancer.

At this time we manage patients with inflammatory breast cancer essentially the same way we manage patients with breast cancer in general, because there is not a specific marker that says, "Okay, we have to use this specific drug for this specific patient with inflammatory breast cancer," except that we do take advantage of the understanding of, as I mentioned before, estrogen, progesterone or hormonal receptors, as well as HER2, to make decisions on therapy. People are looking at these different markers – RhoC, cadherin, p53 and EGFR1 – as potential targets for clinical trials for patients with this disease.

You may wonder, well, you have

these clinical manifestations of inflammatory breast cancer. There are some particular pathological findings that are being evaluated, but how do you really manage patients with inflammatory breast cancer? In general, patients with inflammatory breast cancer are not surgical candidates to begin with because this disease tends to be kind of diffuse in terms of the redness and the edema and the higher weight of that breast. So patients need to be treated with what we call neoadjuvant therapy, which typically includes chemotherapy.

The most commonly used chemotherapy regimens include anthracyclines and taxanes, but in addition to the classic chemotherapy drugs, we use targeted therapies, such as biological therapies, and I mentioned before that a lot of research studies continue to be developed trying to harness the biology in terms of leading to better patient outcome. In addition to chemotherapy, biological therapies, surgery, radiation or hormonal therapy still form very important parts of the treatment of a patient with inflammatory breast cancer, so let's go over some of that information.

Before we make a decision on treatment, we need to do a good physical examination of the patient, and then we need to determine the extent of the cancer. The physical examination includes evaluating the clinical size of the tumor. We look at skin changes, and we should document these findings. Erythema or redness, edema may be present; ulceration and dimpling are pretty characteristic of inflammatory breast cancer. We look

at lymph node status in terms of clinical breast examination. Then we do some pretty routine blood work that includes evaluation of the complete blood count, hemoglobin, hematocrit, platelet count. We look at the chemistry group, mainly to evaluate liver enzymes. I mentioned that a core biopsy is critically important, but besides physical examination and routine blood work, there is some breast imaging that we recommend as part of the presurgical evaluation of a patient with inflammatory breast cancer.

Certainly bilateral mammograms are important to look at the extent of microcalcifications, the evidence of multifocal disease. We use ultrasounds as indicated. Everybody should have bilateral MRIs at an appropriate facility. The role of PET scan is controversial, but it's increasingly being done in the setting of inflammatory breast cancer because of the propensity of inflammatory breast cancer of not only presenting in a localized fashion but also presenting with some metastasis. The PET scan has become a very useful tool to utilize in this setting.

Another potential test we can consider ordering in some patients – actually, in the majority of patients – is evaluation of cardiac function with either a MUGA or an echocardiogram. The reason for that is that anthracyclines remain a very important part of the management of patients with inflammatory breast cancer, and we need to be sure that the patient's cardiac function is adequate before we administer any drug that may exacerbate cardiac dysfunction.

I mentioned to you that neoadjuvant, or presurgical, therapies are very important in the setting of inflammatory breast cancer. The goals of administering these therapies are many. We want this initially inoperable tumor to potentially become operable, so we want to shrink the size of this tumor so that surgery can be performed. We want to potentially create the ability to perform breast-conserving surgery. However, this has to be done with extreme caution in the setting of inflammatory breast cancer, again, because these tumors tend to present in a more diffuse fashion. In spite of our ability to administer very good neoadjuvant therapy, mastectomy still is the primary surgical technique in the setting of inflammatory breast cancer. But our goal one day is going to be to not have to do breast surgery in any patient, including patients with inflammatory breast cancer.

I mentioned to you that research remains a very important part of our approach. One of the main areas of research – and I will address that toward the latter part of my talk – is to figure out whether we can find some early predictors of the outcome of the patients. Can we do some biopsies early on? Can we do some blood tests that will tell us whether a patient will respond to one therapy versus another, so we can advise the patient in a better way compared with what we do today? Right now, the outcome data that we can provide to a patient is based on hundreds of patients who have already been diagnosed with this disease, and our goal is to be able to identify the specific therapy that will help that particular patient in front of us. Again, I will talk about that some more toward the latter part of my

presentation.

I mentioned already the issue of how we do the clinical breast exam, blood tests, some radiological tests that we recommend – and the fact that the management of patients with inflammatory breast cancer is multidisciplinary. Now let's talk about some more specifics of the therapies we may consider. There are many regimens available, so there is not a single best therapy that applies to all patients diagnosed with inflammatory breast cancer. The standard regimens, as I mentioned before, utilize anthracyclines and taxanes. The most commonly used anthracycline is doxorubicin, but there are other agents, such as epirubicin, as well as liposomal preparations of doxorubicin. In terms of the taxanes, the two most classically used are paclitaxel and docetaxel. There is a novel preparation of paclitaxel called nanoparticle albumin-bound paclitaxel, which can also be considered in this setting.

Chemotherapy is usually administered for a period of three to four months. You might wonder, well, is it three months or four months? The decision related to the duration of chemotherapy depends on the schedule of chemotherapy that we utilize, as well as how the patient is doing when the chemotherapy is administering. We're going to go over how we make that decision, utilizing clinical basic examination or radiologic tests.

Two things related to therapy already: First, there is no single therapy for all patients; we have various options. Second, the duration of therapy is also based on the patient's tolerability as well as the ability of the chemotherapy

to decrease the tumor size. In addition to these standard chemotherapy drugs, newer protocols evaluate biologic therapy. So, for patients whose tumors are HER2 positive, where HER2 testing is performed by evaluating the HER2 protein or the HER2 gene, we have lapatinib and trastuzumab. Please note that neither one of these two drugs have been approved by the FDA specifically for patients with inflammatory breast cancer.

Trastuzumab, also known to some of you as Herceptin, received regulatory agency approval in 1998 for patients with metastatic breast cancer and eventually received approval in the adjuvant setting about a year ago based on studies that many of us participated in. Lapatinib received approval by the FDA for patients with advanced HER2 positive breast cancer who had already been exposed to anthracyclines, taxanes and trastuzumab. Many of you may be aware that we just activated an adjuvant trial that incorporates lapatinib called the ALTTO study [<http://www.cancer.gov/clinicaltrials/digestpage/ALTTO>]. How many of you are aware of ALTTO?

Well, it's good that we're going to have a news release in New York on Friday to talk about the activation of this trial here in North America, as this trial has already been activated in other parts of the world, and I'm having the honor to be the co-principal investigator for this study. Essentially what we're doing is incorporating lapatinib in the adjuvant setting. The study has four arms. Two of the arms are single agent, but every patient gets chemotherapy. Every patient receives hormonal therapy, if indicated. But the patients are

randomized to four potential ways to receive anti-HER2 therapy – either trastuzumab or lapatinib, or the sequence of trastuzumab followed by lapatinib, or the combination of the two drugs. Again, we're incorporating the knowledge of biology into earlier settings of breast cancer with the goal of optimizing the cure rate and minimizing toxicity for our patients. Again, this is called the ALTO study, and you will hear more and more about it after the news release Friday.

In addition to anti-HER2 therapy, which is based on the finding of the tumor having too much HER2, there is a lot of interest to incorporate antiangiogenic therapy. As you see, there are many agents. This is only a partial list of the different antiangiogenesis agents currently under evaluation in the setting of breast cancer, including inflammatory disease. They include antibodies such as bevacizumab or VEGF Trap. These are two different drugs. Bevacizumab, as you may be aware, received what we call an accelerated approval by the FDA just yesterday, around 4 in the afternoon.

When we hear "accelerated approval," you may hear that the data are so good, the FDA sped up the approval. That's not really what it means. What it means is that there is no full approval. It's kind of a "conditional" approval because the initial data look good, and the company has to submit additional data to solidify whether full approval is warranted. This word "accelerated" may confuse a lot of people related to the standing of a particular drug for patient management.

Really, we are very gratified that the

FDA at least allowed a partial approval of this drug until further data become available. Further data will become available at the ASCO meeting this year.

[<http://www.asco.org>]. Bevacizumab is one, and it received approval for patients with advanced breast cancer, first line in combination with paclitaxel. The other agents currently being evaluated for breast cancer that you should be aware of include VEGF Trap. This is also a monoclonal antibody, but it binds in a different place compared with bevacizumab. We're doing some trials within NCCTG looking at VEGF Trap in the setting of breast cancer.

There are two other drugs that are also antiangiogenic, but they have a different mechanism of action compared with bevacizumab and VEGF Trap, as these two drugs come in tablet form. Bevacizumab and VEGF Trap are intravenous. Sorafenib and sunitinib are tablets. Studies are being done related to the potential use of these agents, in the setting of inflammatory breast cancer as well as advanced breast cancer. You see a lot of options here: traditional drugs, newer biological agents.

How do we manage patients whom we've already decided have inflammatory breast cancer? We have a series of options. We decide that's the therapy we're going to start. Clinical and radiological evaluations are performed. Certainly every time we evaluate the patient, whether the patient is due to receive chemotherapy, we perform a physical examination. We do talk to the patients. It's amazing – patients sometimes feel that even after one dose of therapy, the swelling of the

breast starts to decrease; the hardness of the breast starts to change. So, listening to the patient remains a very important part of what we do.

The sensitivity and specificity of radiological tests are not that great for predicting what we call pathological complete response – and that includes ultrasound, MRI and PET – so we do not routinely recommend interim radiologic tests to predict pathological complete response or whether the patient will have a good disease-free survival. Studies continue being done, but they're not 100 percent. The best we can do is to do physical examinations, listen to patients.

Then, after we complete the planned chemotherapy – which, again, can be three to four months, depending on the patient's response and tolerability – then we may do, let's say, MRI, which may help the surgeons with the right decision related to the extent of surgery. But, really, MRI is not a great predictor of what will happen to the axillary lymph nodes. We cannot rely on the MRI to know whether the patient has achieved a complete or a partial response to any neoadjuvant therapy we administer.

In addition to the tests I mention here – physical examination, radiologic tests – there is a significant amount of interest to look at what we call CTCs, or circulating tumor cells, in the setting of inflammatory breast cancer. What I mean by that is that before the patient receives any therapy, we can do a blood test to determine whether there are circulating tumor cells. Then, after a couple of cycles of therapy, we can really do the test to see if there has been a change in the number of circulating tumor cells. This is

investigational at this time and not something that we recommend on a routine basis. It's just another test, another expense, and it, at this time, should be part of clinical trials, but I wanted to let you know that there are many people interested in finding this kind of marker. Again, we would like to be able to see a patient and tell that patient, "Yes, this is working and this is not working," early on, because if the therapy is not working early on, then we have other choices to go to.

I've covered nine slides, but I've discussed already a lot of information: presentation biology, pretherapy evaluation, selection of systemic therapy and patient monitoring while receiving preoperative therapy. Now let's go over the latter part of the talk – unless you want to ask me some questions related to the topics I have covered already. Yes, go ahead.

**WOMAN:** Hi...I'm with the Inflammatory Breast Cancer Research Foundation [<http://www.ibcresearch.org>]. I have a question on circulating tumor cells. After all the treatments have ceased, we all have this fear of the elephant in the living room that's going to [rear] its ugly head again. Would that be of any help to us presently?

**EDITH A. PEREZ, MD:** We don't know yet. This is another aspect of research, and that's why when we write [new] clinical studies, we are essentially mandating that patients contribute tissue specimens and blood. This is something we need your help with, because if we do not have the appropriate material to do these correlative studies, I don't think we'll ever find a complete cure for this disease.

**WOMAN:** We have a bio bank.

**EDITH A. PEREZ, MD:** But this has to be part of all clinical studies. I'm very happy that you have taken such a serious approach to inflammatory breast cancer, but many patients still are reluctant to contribute tissues, thinking that somehow we're going to do something mean with the tissue. I can tell you I'm doing this because I want to help and figure out how to conquer this disease. I'm not going to be selling tumor blocks. Some people may – but that would be illegal, actually. But we need your help, because everybody wants us to find better things, and we need to be able to do these collaborative studies.

In many of the trials, this is exactly what is being done. Circulating tumor cells – we look at much more than that. We look, certainly, at the tumor specimens, and we do these things periodically to figure out whether these things can predict the ultimate tumor redevelopment. That applies not only to circulating tumor cells but also to some of the blood markers that are commercially available such, as CA 27.29 and CA 15.3. But right now none of these things are officially recommended, because they have not been associated with an improved survival.

Every time I order a test, it's because either the result of the test will modify the management of the patient or knowing the results of the test will change the survival of the patient. Information for the sake of information sometimes is not that helpful. It just creates a lot of worry.

**WOMAN:** On another note, what about COX-2?

**EDITH A. PEREZ, MD:** COX-2 is another one of the markers that has been felt to potentially be involved in breast cancer as well as many other malignancies. People have talked about targeted COX-2 in many, many ways as a potential way to reverse HER2 resistance, and it didn't work. People have talked about targeting COX-2 to ameliorate the hand/foot syndrome associated with capecitabine, COX-2 as a way to potentially decrease the risk of developing cancer – but all of this is very theoretical at this time, and because of the association of COX-2 inhibitors with cardiovascular mortality, there has been a reluctance to do large trials.

**WOMAN:** Weren't you involved with a study with Celebrex and the COX-2 and the HER2?

**EDITH A. PEREZ, MD:** We are involved in many, many things these days. We've been looking at this for a long time, but right now we are not doing any studies with COX-2 inhibitors in the setting of breast cancer – again, because of the risk of cardiovascular mortality. On the other hand, we are trying to look back at the initial studies we conducted with trastuzumab. We're going to go over some of this cardiac data, because we just published it.

**WOMAN:** One more question, and then I'll sit down. Adriamycin: I just read something recently where they were saying that we shouldn't be using Adriamycin anymore.

**EDITH A. PEREZ, MD:** I am so glad that you are at the meeting today, because I'll give you the real data, okay? In a few minutes.

**WOMAN:** Thank you. Most all of us get the Adriamycin. I thought, what if someone reads that and they say you can't give the Adriamycin?

**EDITH A. PEREZ, MD:** We'll talk about this. One of the issues that she brings up very well – and it's a very important reason for all of you to be here today – is that breast cancer is such a common disease. It's feared by everybody. There are a lot of well-meaning people, but a lot of people with a lot of opinions. Sometimes it's hard to figure out if opinions are really based on a little bit of data and just a belief, or a lot of data and belief. Sometimes opinions are not really the truth. You need to be discriminating of what people tell you, including what I say.

The good thing is that – I probably should have mentioned this to you before – I do not accept any money from any pharmaceutical company, because it's prohibited by our own beliefs and it's prohibited by Mayo Clinic. Not even when I do advisory boards – all of this money goes to Mayo Clinic, and the money is reinvested so we can do research. I don't have any stock in any pharmaceutical company, either. This allows me the opportunity to assess data and be able to talk to everybody about the data and be able to do studies with all drug companies, because there is no particular alliance to any company, which is the way we should all practice medicine. (Applause)

Now let's talk about the rest, unless there are any questions related to the four topics in the first four bullets. Yes, please?

**WOMAN:** Just a general question about when you biopsy a breast with inflammatory breast disease. I'm a nurse, and I've never seen a patient with inflammatory. The biopsy methods I know are stereotactic and ultrasound. Can you go anywhere in a breast that presents with these symptoms?

**EDITH A. PEREZ, MD:** Yeah, typically patients have redness, so it's just a skin biopsy. That's all that's needed. Just a very small biopsy, and that's all that's required. Any other questions related ... yes, please?

**WOMAN:** Can you expand a little bit on the controversy with PET scans?

**EDITH A. PEREZ, MD:** Yeah, PET scans.

**WOMAN:** I've had a second opinion, so I've had an experience with one person saying no and the other person saying absolutely. Can you get a little bit deeper into what is the controversy?

**EDITH A. PEREZ, MD:** First of all, PET scans are, I think, a fascinating technology because they look at metabolism, which is classically associated with really increased uptake of glucose. The challenge with PET scan is that for a lesion to be seen by PET scan, it has to be more than about 7 millimeters. The PET scan is not perfect, first of all. Second: Large studies related to the value of PET scan in breast cancer have not been done compared to whether it really helps save lives. PET scans are very expensive, so people who run insurance companies, even our government, have to question us doing

tests. It's not a matter of us doing any test available. It's what is the significance of doing tests for that patient's life, or for the public health of this nation? That's why it's controversial, because we don't have any proof that it helps in population studies.

**WOMAN:** You made the comment about inflammatory being a little bit more [inaudible].

**EDITH A. PEREZ, MD:** A little more [inaudible] because these patients do have more aggressive breast cancer. Typically, they have not been diagnosed quickly, so there is more time for these breast tumors to be very large and have the opportunity to metastasize. In that situation, because there may be higher than a 30 percent chance that there is metastatic involvement, we can justify ordering a PET scan. But insurance companies may balk at this a little, again, because there is not a lot of information to back this up. Usually, working with your physician, this is something that should be reimbursed.

**WOMAN:** Backing up, can you do something in the future then? If you were dealing with somebody who didn't think you had inflammatory. Later you found out that you did have inflammatory, so you didn't get any of that testing. Later in the process, can you go back in? Would there be any beneficial advantage to doing a PET scan later? Or is it because you've had so much chemo, so much treatment, that a PET scan is not going to do you any benefit?

**EDITH A. PEREZ, MD:** Sometimes we do these later on. If it wasn't done before, and I think it's appropriate for

that particular patient at this time, that would be fine. The situation in which this tends to be done is someone who had therapy, and then the patient has another abnormality, and we just don't know what's happening – or a patient who, for some reason, got a blood test that may give us a clue that there may be an abnormality. Then a PET scan can be very helpful, instead of submitting the patient to CAT scans of the chest, abdomen and pelvis, and bone scans. It can be much quicker to do one test than to order three tests. Yes?

**WOMAN:** But not proactive for recurrence, not looking for recurrence.

**EDITH A. PEREZ, MD:** No, there is no reason at this time to recommend PET scans every three to four months in a patient who has been diagnosed with inflammatory breast cancer. That applies to blood tests. In spite of how we think about this, we think, "My gosh, this tumor tends to be aggressive, thus I need to monitor it very closely." But we don't really have any studies truly saying that doing any of these things improves outcome. That's why they're not done routinely.

Let me give you an example that is awfully important to think about. In this country today, as you know, there are [millions of] people without health insurance. In some way, we could offer health insurance to everybody, but if we do that, even now, we cannot afford to get PET scans every three months, because it would bankrupt the system and then we would not have money to do mammograms. It's the complex of medicine and the complexity of public health versus the life of that particular patient in front of

us. That's one of the difficulties that insurance companies have, because they are companies that need to create money for their stakeholders. Somebody has to pay for them. Then they have to be responsible to patients.

I've never worked for an insurance company. It would be a little hard for me, I think. At the same time, I could probably help, because I wouldn't deny many things. (Laughter) But we need to create this balance against ordering many tests versus participating in clinical trials to figure out whether things make sense so they can then be recommended for everybody.

As a physician, and probably you as patients or knowing somebody with this disease, you understand the dilemma that we have. I see many patients – actually, the only patients I see are patients who are referred to see me because of the type of practice I have at Mayo. I've seen all kinds of things happen. I've seen patients who have bone scans every six months, and then I'm appalled because I think getting bone scans every six months will eventually lead to leukemia because of all of the radiation patients are exposed to.

I always think of short-term benefits versus potential long-term adverse effects of any test I order. Every big test I order that is radiologic, unless it's an MRI, has some radiation. Again, it's all a matter of balance. It's not just ordering test after test after test. Some people say, well, get blood tests every month. Why not every two weeks? Why not every week? In general, the approach we take is that patients receive neoadjuvant therapy, then they're monitored, and then they

go over these other therapies. Then the monitoring is that we see the patients about every three months for the first year. Again, it varies from patient to patient, but that's pretty standard. We see patients every three months. The patients get radiologic tests, usually in the form of MRI, depending on the situation, or mammograms in six months.

But we don't have the specific follow up for each patient. Some patients want to come every month after they finish therapy, and we listen to the patients, because for some patients it's really tough. We finish this therapy, the tumor is gone, and then the anxiety really kicks in. The patient says, "My gosh, I'm no longer getting any therapy for my cancer," so they need this kind of reassurance.

It's pretty amazing, because another thing that occurs is that when patients are receiving chemotherapy, they're seeing the chemotherapy nurses every week sometimes, every couple of weeks. There's a bond that's created between the patient and that medical person that is really severed when we finish the treatment. This bond occurs with the nurses. It's not with the physicians, because you guys don't see us that much. You see the chemotherapy nurses much more than you see us. We need to be responsive to that need after these intensive therapies are given. That's why the follow-up can be very individualized, also, depending on the needs of the patient. But, if I was going to make a general recommendation for follow-up, it's about every three months. Yes?

**WOMAN:** Just to follow up on that, for PET scans, is that also for stage

IV? Like, if we had a PET scan, it didn't show stuff and now we're in NED [no evidence of disease]. Do we need to follow up with them because of that?

**EDITH A. PEREZ, MD:** There are no specific national guidelines for how often a PET scan should be done in the setting of metastatic breast cancer. We tend to have more frequent follow-up, perhaps every three months for the first year – because that's when there is the increased likelihood that the tumor will return. We tend to be a little bit more vigilant during that first year; then we start spreading things out.

**WOMAN:** Just a note, because I think the nurse mentioned and you mentioned the redness. I was diagnosed at stage IV. I had no redness, no swelling, no peaudo orange.

**EDITH A. PEREZ, MD:** That's fascinating.

**WOMAN:** I had nothing but one breast larger than the other. That's already stage IV. So I think even within this inflammatory breast cancer –

**EDITH A. PEREZ, MD:** That's T4.

**WOMAN:** T4, whatever, yes.

**EDITH A. PEREZ, MD:** It's different from stage IV.

**WOMAN:** I had mets to my lungs, liver and bone, and that's without anything other than a larger breast. So I think even if I had looked at an inflammatory breast cancer site, I might not have thought I had it

because I wasn't red and everything.

**EDITH A. PEREZ, MD:** Good point. Thank you. Thank you.

**WOMAN:** So, for people who are diagnosing or looking at women's breasts with this, you don't need that.

**EDITH A. PEREZ, MD:** Actually, I really appreciate you sharing this information with us, because in that list we provided, as in any list, any one of those things can occur. It's not that everything on that list has to be present first to make a diagnosis. Vigilance and awareness are particularly important. You're going to see that word twice toward the end of my talk. Yes? Somebody else had a question.

**WOMAN:** On November 30 – I don't know if you're aware of it – M.D. Anderson [Cancer Center] released a news release [<http://www.mdanderson.org/departments/newsroom/display.cfm?id=4867C12A-F413-4D7B-A1F6B84AD1F337AF&method=displayFull&pn=00c8a30f-c468-11d4-80fb00508b603a14>] stating that subsequent to finishing chemotherapy within – I remember reading somewhere – three to four months, a PET scan is recommended. And part of standard treatment at the Inflammatory Breast Clinic at MD Anderson is a PET scan as part of the routine test that goes on in the initial diagnosis, just FYI. I don't know if you're – a PET/CT.

**EDITH A. PEREZ, MD:** Just because they decided that at their institution that was done does not mean that insurance companies will pay or that it's done anywhere else.

It's something that they decided to do, which is reasonable. It's fine. I have no problem.

**WOMAN:** Because, as you know, inflammatory is not your average breast cancer. It's a much different animal.

**EDITH A. PEREZ, MD:** Yeah, I do know. (Laughter)

**WOMAN:** I'm here to tell you that I had no redness; I had no swelling. I had the tiniest thickening, and it encompassed 10 percent of a very small boob to begin with. It was very slight. Six months after treatment with a complete clinical response, fabulous – my tumors were less than a millimeter – mine went from HER2 negative to HER2/neu positive, and it went to my bones and my liver.

**EDITH A. PEREZ, MD:** The challenges that occur ...

**WOMAN:** The day I was told I had no evidence of disease was the day MD Anderson said you should follow these women a lot closer with PET/CT scans for inflammatory.

**EDITH A. PEREZ, MD:** The problem with all of this – and your stories are really so important – is that doing tests is not preventing recurrent disease. The reason we do tests is to try to find the disease at a stage that is not really causing symptoms so we can institute therapy. The idea behind this is that then that will be related to an improvement in survival. That's what has not been demonstrated. Many studies have been done looking at blood tests, looking at chest X-rays. Over two years, there is no difference if we just order tests, because ordering

the tests does not prevent the disease from coming back. It's what we do to prevent the tumor from returning to begin with or what we do after diagnosis that will have an impact on the patients. If you are logical about it, you want to know, get a PET scan every month – my gosh. Why do it every month?

**WOMAN:** No, no.

**EDITH A. PEREZ, MD:** No, this is an example of the challenge, because studies that have been done looking at these tests every three months, they have not shown an improvement in survival. People say, "Well, perhaps you should have done them every month." Then, if you think about this, if we're going to spend \$4,000 every month or every three months in a patient, it's just the reality of how we have to deal with this. Essentially what we have to do is be aware, be aggressive, be involved like you guys are so that we can figure out what really is needed to save lives. Yes?

**MAN:** Thank you for letting me ask a question or make a statement. I'm a cancer patient and survivor at M.D. Anderson Houston and Orlando. My morning started off – I shouldn't be standing here. I had surgery last August and radiation and chemo in September and October. I moved to Houston for two-and-a-half months. I live in Jacksonville, and I saw [woman's] picture on the front page of the business section. I have a rare and aggressive cancer that pathologists identified as a breast cancer, HER2 positive.... I have a year of chemo treatment ahead of me. One, I want to thank you, because I met you through printing out your research on early-stage metastatic breast cancer

treatments for Herceptin.

Mine is here and here in the duct glands and my salivary gland – carcinoma ex pleomorphic adenoma. When [my doctor] sent me back and said get your chemo treatment for a year, Taxotere, carboplatin and Herceptin, in Jacksonville, the first small group I went to said, "We don't want to treat you." I said, "Doctor, have you ever treated anybody with what I have?" She said no. I talked to her about Edith Perez, Dr. Perez – she said, "You won't be able to get to meet her." (Laughter) I went to Starbucks this morning and I only attempted to come down here to write them a small check to this organization. I haven't worked since last July. Thank you. Thank you. (Applause)

I went home in January from that meeting, and I said to my wife, "What are we going to do?" They told me that I have to either go to Mayo or back to M.D. I'd have to go out there. I'll go out there. She said, "Why don't we go to Orlando? It's only two hours away." So Dr. Sang, who's a breast cancer specialist and a head- and neck-cancer specialist, saw me in early January. Tuesday, Genentech gave me the green light for the \$100,000 worth of Herceptin I need. (Applause)

I'll close with one other thing – thank you very much. I'm doing extremely well, for what I have. I was in San Francisco around Christmas, and there was a 32-year-old patient. Because of insurance, she was sent by Kaiser. For a year, her inflammatory – you know, she looked 65. Of course M.D. and UCSF said, "You need surgery, then the other adjuvant therapy after that. We've got to get the tumor away from

the blood source." I am so thankful for everybody in this room. It's insane how unusual – only through humor can my friends tell me, "You've got breast cancer of the mouth – nice going." (Laughter)

**EDITH A. PEREZ, MD:** I think after that I'm going to have to move on.

**MAN:** I'm 57. My treatment is for a year now, and my white blood count was 1.2 this week. I'm going for my next three chemo treatments. I've got three chemos to take up until June, and then nine more Herceptin. Do you think some day – five years, ten years out – instead of saying the site of where the cancer is, the line of what the cancer is, because my cancer is HER2 plus three.

**EDITH A. PEREZ, MD:** We're looking at the biology of breast cancer – and I want to talk a bit about this later – to optimize therapy for each individual patient. It may be that in the future, instead of talking about breast cancer, we're going to talk about HER2 positive disease, or we're going to talk about pathways that are abnormal, and then devise therapies based on that pathway. That's the theory we have. Sometimes the theory just has to be subjected to the appropriate studies. It has to.

Trastuzumab was tried in lung cancer, because some cancers have HER2 positive disease, and it didn't work. It was tried in ovarian cancer, and it really didn't work that well, whereas it works very well in the setting of breast cancer. The same is happening with lapatinib. It's being looked at in other tumor types. Again, it's great to have ideas. Then we have to develop the

clinical trials, and then we have to get the cooperation of people involved to realize that unless we fight for research money for meetings like this to occur and for clinical trials, we're just going to stay the way we were ten years ago.

Let me go on. There is much more. Let's talk about surgery. We want things to get better, and then we do surgery. That's really, in essence, the way we approach this. Essentially we look at resolution of the skin edema. We look at the tumor size being smaller than 5 centimeters, absence of extensive breast lymphatic invasion. The calcification is no longer there. No evidence of multicentricity. As I mentioned before, for breast-conserving surgery, it's very selectively used in the setting of inflammatory breast cancer.

How about axillary nodal surgery? That is really part of management. The way we manage this is, for patients in general, we administer neoadjuvant therapy, then we evaluate for the sentinel node. Then, if the sentinel node is positive, then we proceed with the full axillary node dissection. The reason we do this is because we cannot rely on the MRI or PET to determine whether there is a complete response in the lymph nodes. It helps with local control. It's part of our assessment of efficacy of any neoadjuvant therapy, and the absolute number of positive nodes after therapy affects prognosis.

This is the way we typically do it, because the outcome of patients with inflammatory disease or patients with locally advanced breast cancer is mostly dependent on what happens after we administer the neoadjuvant

therapy. If patients respond well, then the patients will do better. That's why we don't do evaluation of the lymph nodes before, because what I want to know about is how the patient tolerated the initial therapy. It's controversial in some settings, but it is the approach we take at Mayo.

Postmastectomy radiation therapy, standard – we usually administer locoregional radiation, not only radiation to the breast. That's why partial breast irradiation is not classic for inflammatory breast cancer. Again, this tends to be a more diffuse disease, and more extensive radiation is classically indicated. How about postsurgical adjuvant therapy? We've made a decision, and the patient has inflammatory breast cancer. We administer chemotherapy with or without biological therapy. The patient undergoes surgery. Then we need to make a decision about adjuvant hormonal therapy. That is administered only for patients with estrogen and/or progesterone receptor-positive breast cancer, defined usually as having more than 10 percent of the cells being positive, more than 10 percent of the tumor cells being positive.

The type is based on menopausal status, and we're going to talk about type and duration in the next two or three slides. Recommended type of hormonal therapy in inflammatory breast cancer for premenopausal patients: tamoxifen or toremifene. These are very similar drugs, standard. Another standard could be participation in the SOFT study [<http://clinicaltrials.gov/ct2/show/NCT00066690>], the trial that is comparing tamoxifen versus ovarian function suppression with either tamoxifen or

exemestane. You, as a group, have been very helpful to increase awareness of the importance of this clinical trial, which I really have to thank you about. As a physician, I want to figure out some day what the best therapy is. The only way we're going to do it is if we finish the accrual to SOFT.

There are other studies worth mentioning, and they are here. Enrollment to one of them, the TEXT study [<http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=316458&version=patient>], was completed, but the study may be reactivated if additional funding is obtained. This is the trial that looked at ovarian function suppression followed by either tamoxifen or exemestane. We completed accrual to this study about six months ago. Data, of course, will take a while to be available. Additionally, data from the ABCSG-12, a trial that looked at ovarian function suppression with either tamoxifen or anastrozole, are expected at ASCO 2008 [[http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmmview=abst\\_detail\\_view&confID=55&abstractID=35897](http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmmview=abst_detail_view&confID=55&abstractID=35897)]. This is a trial very similar to TEXT, except that the aromatase inhibitor was anastrozole instead of exemestane.

In these two studies, everybody underwent ovarian function suppression because they thought, mainly in Europe and in some parts of the U.S., that ovarian function suppression should be standard for premenopausal women. We are not certain that that's the case, but because some people felt like that, these two studies were developed. Again, data

are expected at ASCO 2008.

You may wonder, “Well, Perez, how is it that you know what will be presented at ASCO 2008?” I know because we are involved with people, and I am in charge of the metastatic track for the ASCO program this year. We’ve had a chance to look at all of the abstracts submitted to ASCO, and we pretty much know what will come out in June. This is one of the presentations that will be eagerly awaited by everybody.

One of the things people ask me is, “Well, Edith, ovarian function suppression is not a [inaudible] thing. Why don’t we do it on everybody?” We don’t do it on everybody because we don’t know if it’s any better, first of all. Second, if we do ovarian function suppression on everybody, there may be a couple of important risks to think about: number one, significant osteoporosis; number two, there was a report saying that ovarian function suppression may be associated with Alzheimer’s disease and dementia. Again, there are pluses and minuses to any approach; that’s why it’s critical that we do the right studies to find the answers instead of having all of these opinions forever.

For postmenopausal women, our recommended strategy for hormonal manipulation is aromatase inhibitors. They’re listed here in alphabetical order, not the preference of any company: anastrozole, exemestane and letrozole. Essentially, we administer these hormonal therapies for about five to ten years, and the time keeps being expanded based on our clinical trials.

Let me now go over the last two very

important issues, which are long-term safety issues and new studies in the future, because now you know pretty much how we approach this disease. There are two safety issues that are of most interest to a lot of patients and to us as physicians: cardiac issues and bone health. As you see, I don’t have chemo brain here, and that’s because we don’t know whether chemo brain really exists. Many studies need to be properly done. I see some smiles. I completely lost my credibility.

**WOMAN:** If you [inaudible] you’ll see it exists.

**EDITH A. PEREZ, MD:** It does exist, huh? Actually, this is being taken tremendously seriously to try to figure this out. Let me address two more defined issues. Two papers that were published [online in *the Journal of Clinical Oncology*] on [January 28] address this cardiac issue. Again, I’m not going to talk about opinions; I’m going to talk about data. One of them was a paper by Patti Ganz from UCLA [<http://jco.ascopubs.org/cgi/content/abstract/26/8/1223>] that looked at the issue of anthracycline versus non-anthracycline in the adjuvant setting. I’m going to show you two slides of her study. Essentially, what they found was a slight difference in left ventricular ejection fraction at five to eight years but no difference at ten to 13 years for patients who were randomized to six cycles of CAF versus six cycles of CMF – so, an anthracycline versus a methotrexate-based regimen. Very important study – I’m going to go over some of the details of this study.

If you talk to people in general, they’re going to tell you that anthracyclines are the worst things

since moldy bread. But, I’ll tell you – I don’t know if another one of the speakers here at this meeting addressed the Oxford meta-analysis presentation at the San Antonio [Breast Cancer Symposium] meeting this year clearly demonstrating that anthracyclines have been part of the therapy that have ultimately led to an improved survival for breast cancer. We need to be very cautious, because when we’ve had success, success, success, we cannot just go completely berserk or start eliminating things without proving that eliminating them is good for patients. However, we want also to be cautious, always be cautious. Let’s look at data.

Additionally, we had a chance to publish our paper related to the cardiac safety of the three arms of the N9831 adjuvant trastuzumab trial, in which we found this risk of congestive heart failure at four years: 0.3, 2.8, 3.3 percent [[http://lungca.asco.org/ASCO/Abstracts+&+Virtual+Meeting/Abstracts?&vmview=abst\\_detail\\_view&confID=34&abstractID=31075](http://lungca.asco.org/ASCO/Abstracts+&+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=34&abstractID=31075)]. No increase in congestive heart failure after patients completed the trastuzumab. Most patients were covered. Let’s go over a few slides from each one of the studies addressing the very important issue of cardiac safety in the setting of breast cancer.

Here is the schema of the study published by Patti Ganz. The reference is eliminated from the bottom here; it’s not seen. One of the reasons I wanted to spend a few minutes with your group addressing these two studies is that we need your continued help to address this very important issue of long-term safety of all of the treatments we administer. If patients

do not participate in studies, we'll never have the answer. We all want the answers, but if people don't participate, how are we going to get the answers?

A study that Southwest Oncology Group did, called 8897, had 1,176 women enrolled. Out of those women, 996 decided not to register in the new study. This new study was going to look at the long-term cardiac safety. The reasons that were given for patients not participating in the long-term cardiac safety study: In 59 percent of the instances, nobody really even tried to contact the patient. Although Southwest Oncology Group sent a new protocol to the sites, the sites said, "We don't have enough people to really try to find out where these patients are." In some situations, they don't know how to find the patients because patients participate in clinical trials and then say, "I don't want to be followed anymore."

It almost breaks my heart when I see this. This is happening in the adjuvant trastuzumab trial that we're doing. Every patient who says, "I don't want to be followed," is hurting probably herself and thousands of others. If we do not have long-term follow-up, how are we going to be able to counsel others in the future? We need your help to counsel other patients, first of all, to consider clinical trials, and second, don't get lost to follow-up. If people don't treat you right at your facility, go to another facility. But continue being followed by the system so that everybody can gain knowledge.

Seven percent of the patients refused, which was also very interesting to me. They found the patients, and 7 percent said, "I received this therapy, but I

don't want to participate in any other study looking at cardiac safety." Again, every patient has the right also to make decisions. It's critically important. We have to respect that.

Essentially, 880 patients were ultimately registered; 863 were registered after they had had chemotherapy at least eight years previously; 17 ten [years] to 13 years after they finished chemotherapy, so very long-term follow-up. What these investigators did is look at cardiac function of the patients. These are the data. I'm going to guide you through the graphs. Here we have resting left ventricular ejection fraction, which is a measurement of cardiac pumping ability. This is for the group of patients who finished chemotherapy five to eight years before; you have the median left ventricular ejection fraction at 61 percent or so. For the patients who had received the non-anthracycline regimen, CMF, it was about 64 percent. So there was statistical diminution of cardiac function in terms of the test that was done for the patients who received anthracycline.

Then, when they looked at the patients who had been followed for more than ten years, there was absolutely no difference between the two arms. More important than that, in this study, they looked at the groups of patients who had left ventricular ejection fraction that had dropped below normal, less than 50 percent, and there were no differences between the two arms. So whether or not the patients had received anthracyclines, there was no difference in the number of patients who had abnormal left ventricular ejection fraction.

How do you interpret this study? You can say, "We're pretty reassured here; we are not causing horrible damage to the heart." But another potential way to look at it is, unfortunately, not too many patients had the test. There is a bit of an unknown, but, again, we can try to speculate what the unknown is all we want. The data are the data.

Based on what we know related to anthracyclines, they can cause some cardiac dysfunction. However, because there is a problem, we limited the amount of anthracyclines that all patients receive, so essentially no patients are getting six cycles of CAF anymore, because studies have been done showing that four followed by a taxane is better. We're limiting the amount of anthracycline. But even if we look at these long-term studies that use the higher doses of anthracyclines, we see a bit of problem; it's really not an overwhelming problem that would prevent me from using anthracyclines. Again, we still continue looking for alternatives. We're not going to stay in the dark ages forever. But we cannot just eliminate something that works because we're fearsome. We, again, need to look at the data.

The second paper was related to N9831, and I'm going to go over the schema of the study so you can understand where the data come from. Many of you are aware of this study; perhaps others are not. We randomized 3,500 women with HER2 positive breast cancer to three arms: A, B and C – AC followed by paclitaxel; AC followed by paclitaxel followed by a year of trastuzumab, what we called the sequential arm; and the concurrent arm of AC followed by paclitaxel concurrent with trastuzumab for 12 weeks, then subsequent

trastuzumab. This is one of the studies that led to the approval of trastuzumab, or Herceptin, as part of adjuvant therapy by the FDA as well as many regulatory agencies throughout the world.

We started writing the study in 1998. The study was ultimately activated in the year 2000, and, as many of you are aware, we completed the accrual in 2005 when we released the data at ASCO. As part of this clinical trial, we incorporated very stringent evaluation of cardiac function, including an evaluation of left ventricular ejection fraction, before the AC chemotherapy. We're talking about doxorubicin/cyclophosphamide, or anthracycline/cyclophosphamide. We ordered a left ventricular ejection fraction at three months or post-AC, at the time of the completion of the paclitaxel portion of the chemotherapy, with or without trastuzumab, nine months and 18 to 21 months. This study allowed us to get the important data.

These are the results of the long-term cardiac safety in the context of this pivotal clinical study. Here we have the cumulative incidence of cardiac events, percent here, time since start of post-AC – so, after the chemotherapy was given. Here we have the congestive heart failure rate for patients who received chemotherapy alone, 0.3 percent. For the patients who received sequential chemotherapy followed by trastuzumab, it was 2.8 percent. For the patients who received AC followed by paclitaxel concurrent with trastuzumab, it was 3.3 percent. That's one way to look at the data.

Certainly, the way we could have drawn this figure is to draw from zero

to 100, and if I had done that, then you wouldn't have seen practically any differences between the three arms, because the differences are very, very small. However, because this Y-axis is from zero to five, you can see that there appears to be a huge difference between 0.3 and 2.8, but it's really very small.

Another way to look at the data from our study was to look at the follow-up based on the time the patients completed the AC. What happens at a half month, a sixth month, one year, two years, three years in terms of the incidence of congestive heart failure? We can look here at the three-year data, or you can look from the beginning out to three years. You see what happens – especially in arm C, which is what we use now for clinical practice, based on the data from our studies showing the huge improvement in disease-free survival and overall survival – that the incidence of congestive heart failure within six months was 2.5 percent, 3.3 percent at year one and year three, and actually the same at year four. This congestive heart failure appears to occur while the patients are receiving the trastuzumab. We stop the trastuzumab, and no more congestive heart failure, as far as we see today.

Another piece of information that is also in the manuscript is that we've looked at what happens to the few patients who develop congestive heart failure in arm C of the study, which were actually 19. We looked at the ejection fraction at the time, at the beginning of their enrollment into the study, and then when they developed CHF. Then, what happens, and you see from these curves – and each line represents one patient – is that, like in

this patient, the ejection fraction went down to 10 percent, and we don't have follow-up for some reason. We had only one patient in this study who died of congestive heart failure – one.

The reason the death was associated with this situation – it's a very unfortunate situation, as you may imagine. It's a 33-year-old woman who developed congestive heart failure, and the patient went to the operating room to get a cardiac pump. She died of intracranial bleed as she was having surgery. Otherwise, what has happened in these studies, as you can see – what happens with the majority of the patients who develop congestive heart failure – is the ejection fraction drops and then comes back to normal.

**WOMAN:** Is that with medication?

**EDITH A. PEREZ, MD:** With medication, yes. We stop the trastuzumab, and in the majority of patients, there is significant improvement of cardiac function. It does not mean that every patient gets back to normal, but the great majority of patients get back to normal or dramatically improve, which is obviously very reassuring. And it's critically important for us to put this in the balance of how we can save lives using trastuzumab. These patients were included in the survival curves.

We, as physicians – you have to trust me. I want to help you guys, all of my patients. We do take side effects very seriously. However, I cannot forget that if my patient does not survive breast cancer, then I don't really care that much about the bones. If the patient is not alive – that's my first goal, working with the patient, of

course. It's not that I want the patient to be alive and not functioning; we always balance both things. But the fear of cardiac toxicity is not going to keep me away from recommending this lifesaving therapy for our patients. However, my duty as a physician is to do the clinical trials, to get the data that you need and that your friends will need, to be able to make decisions related to their lives.

But these data are reassuring. Congestive heart failure can occur. The majority of patients get better. Not only that, but we did this analysis, which can also be very helpful to all of you. We looked at the changes in LVEF during post-AC therapy for the patients in the three arms: chemotherapy; chemotherapy followed by H, which is trastuzumab; or the concurrent administration. What you see at the 18 months evaluation – look at the differences in left ventricular ejection fraction, from 63 to 61, 63 to 60, 63 to 60. There are really no major differences in median left ventricular ejection fraction. Again, this is published in [the *Journal of Clinical Oncology*], and the material is available for all of you to review independently [[http://jco.ascopubs.org/cgi/content/abstract/26/8/1231?ijkey=497887821b4e2b3508b50d712c9f9c7e32f002b2&keytype=tf\\_ipsecsha](http://jco.ascopubs.org/cgi/content/abstract/26/8/1231?ijkey=497887821b4e2b3508b50d712c9f9c7e32f002b2&keytype=tf_ipsecsha)].

The second safety issue that we think about is bone health. In terms of premenopausal women getting chemotherapy, trastuzumab, lapatinib – all of the drugs that we can think of – there will be data related to the effect of chemotherapy on bone health and the results of using zoledronic acid or risedronate – two bisphosphonates – available at ASCO

2008. For postmenopausal women, we recommend monitoring bone density, and we use bisphosphonates for all patients, depending on the bone density. We are not routinely recommending that all patients who receive therapy for breast cancer receive drugs to protect their bones at this time.

Progress, increased awareness – we're going to go back to this in about five slides. Management based on biology. I'm recapping some of the things we've talked about. We administer neoadjuvant therapy, then surgery. We use radiation, then subsequent therapy that may include chemotherapy, biological therapy or hormones. We want more effective therapeutic regimens and novel methods for patient selection. And we want to identify appropriate candidates for particular biologically based therapies. That will address, then, the last topic of my presentation, which is ... studies in the future. We have eight slides for that. Actually, we have six plus two. It still makes eight. (Laughter)

Modern study objectives – how are we dealing with all of this for the future? I want patients to be better, to get better. That's my main objective with any study I do. We want to identify a tumor profile that may predict for increased likelihood of response and disease-free overall survival and overall survival for our patients. Why do we do this?

I'm going to show you two examples of the typical study that is done in the setting of inflammatory breast cancer. We have a group A; we have a group B. We can do a pretreatment tumor biopsy. We can look at some

biological markers, we can give a little bit of therapy, and we can do a tumor biopsy at 14 days or 21 days or whatever time we select. Then we give more therapy, and then we do surgery, and then we try to correlate the findings on the [pretreatment tumor] biopsy or the 14-day tumor biopsy with pathological complete response and long-term patient outcome. That's what we address in this situation.

Another situation to think about in terms of studies for patients with inflammatory breast cancer is depicted on this slide. We have to think of the patients who receive the best therapies that we have but still have tumor when surgery is performed. We typically have mentioned that based on the poor prognosis, additional therapy is considered by most physicians. Let's say I have a patient with inflammatory breast cancer. Other therapies are administered, surgery – ten positive nodes. Typically we recommend more treatment, different from what the patient received before. The new therapy may include chemotherapy, hormones, biological therapy. And new studies are in development. This is an example of the type of study that can be done in that setting.

We have a patient who has persistent disease after neoadjuvant chemotherapy. This kind of study can be done for both groups of patients: patients who do have disease after neoadjuvant therapy or even patients who have a complete response. The patients can be randomized to nothing versus some novel biological therapy to see if the novel biological therapy can help. The chemotherapy decision is usually left at the investigator's discretion, [because] it's impossible to randomize to chemotherapy versus

non-chemotherapy. This is a way in which we are thinking about addressing the challenges we face with inflammatory breast cancer, where the biological therapy may be given for three months, six months, 12 months. It depends on the study.

We have two potential ideas of how to address this for future study: number one, [pretreatment tumor] biopsy, give a little bit of the therapy, get an early biopsy and try to correlate markers with outcome. Another study is to treat the patient the best way we can, then figure out what happens at surgery, then do randomization to some novel therapy versus nothing, because nothing is the standard, although we allow the physicians and the patients to make the decision of whether chemotherapy should be used. This is being done a lot. There is a plan to do this with antiangiogenesis drugs.

This is the schema. I thought instead of telling you the true studies that are available, that would give you the principles of this disease in terms of diagnosis, therapy studies. The studies change all the time, and with your help, people are aware of the studies available.

Over here, therapeutic individualization: Who doesn't need treatment? Who doesn't need a specific treatment? Who needs a specific therapy? We do gene analysis of tumors, and then we need to explore pharmacogenetics, which really means we need to look at how patients metabolize drugs so that we can make decisions on what therapy each individual patient should receive. Simple and complex, because we have 25,000 genes; we have about a million

proteins. There is a lot that we need to look at.

How do I see the actual management of patients with inflammatory breast cancer as well as the future? Awareness is number one. People need to think about this disease and be aware that it can exist. The answers to questions will come from good research, and good research is translational clinical trials combined with collaboration of all of us with patients. That is the only way we're going to do this.

I view our fight against breast cancer as a path that we all need to take in our lives. This is a series of balloons here in Jacksonville that was created as we were launching the first National Marathon to Fight Breast Cancer. I see kind of a road ahead. We need to have a plan of action to be able to fight this disease. That's why we developed – with the help of my tremendous patient, Donna – this breast cancer marathon. Many people have thought about having 5Ks to deal with this disease, and we thought, well, let's do something extra. So we came up with this idea to do a marathon and a half marathon, which we held for the first time last Sunday.

As you see, I am walking pretty well, and I ran the marathon, the full marathon, on Sunday. (Applause) It was pretty amazing. I don't know how many of you were here. We also had a half marathon, and many patients participated. We had persons from the 50 states and nine countries participating in this first inaugural national breast cancer marathon to fight this disease.

We were so touched at not only the

participation of many people but also how everybody was welcomed by the community of Jacksonville. For some of you who participated, it was amazing to see the thousands of people along the sides with their cowbells and their pompons. So many patients and medical people walked the half marathon. It was just a matter of walking four hours. When I talked to people about this, people said, "Oh, my gosh – a half marathon or a marathon. I cannot do this." I thought, how many of us go to the mall for four hours walking? People did this. This is an example of what we can accomplish.

I view this exactly as I view the fight against breast cancer. Sometimes it looks like an impossible goal to reach – just running a marathon. But you have an idea; you develop a plan of action; you get together a team, and you get a group of people who want to work with you, and you can get to your goal. The fight against breast cancer is simplified here, and we're going to get to our goal, working together.

I thank you for your attention today, and I certainly welcome you to participate with us Sunday, February 15, 2009, and that's going to be the second year. Thank you very much. (Applause) Questions?

**MODERATOR:** Any more questions?

**WOMAN:** I, too, want to thank you for further enlightening me today. Last August, August of 2006, I had my third daughter on August 22. August 25, I went into congestive heart failure. Doctors still don't know why I went into congestive heart failure –

just one of those flukes. By the time I got to the hospital, I had a 15 percent ejection fraction rate.

**EDITH A. PEREZ, MD:** That was in August?

**WOMAN:** That was last August, August 2006. October 6, when I went for my six-week checkup for my daughter, I showed my doctor, my OBGYN, a milk duct that wouldn't go away. To his credit, he urged that I went and got a mammogram and went to a surgeon. The mammogram came back inconclusive; follow up in six months. I called him and said, "I'm tired. I just had this baby. Do I really need to go to the surgeon?" He said, yes, go to the surgeon. At that time, they did a fine needle biopsy then a core biopsy – came back as aggressive triple-negative breast cancer. I'm the baby of six girls.

I went through Adriamycin, Cytoxan and Taxol and the lumpectomy. And April 28 of 2006, I went into remission, no cancer. June, July, August, went through extensive radiation therapy and was cleared. But the middle of September of this year, I kept telling my radiation oncologist, something is not right. Something is not right with my breast. Come to find out, October 4 of this year, which wasn't even a year from my first diagnosis, it came back as inflammatory breast cancer. But through all this, the reason I'm standing and asking you is, I have no one really tracking me. I hear you talk about chemo brain. See, it is a real phenomenon. (Laughter)

I hear you talk about congestive heart failure. Although there may not be a direct correlation between my – it was

only a six-week time frame in which I was actually diagnosed, so I don't know if there was a direct correlation. But for someone like myself who stays – I stay on the Internet but don't stay on the Internet. You know what I mean? Sometimes you can overeducate yourself. I've gone to the Mayo Clinic and I've gone to NCI and everywhere else just trying to find – because of course I don't qualify for a lot of ...

**EDITH A. PEREZ, MD:** The trials? Yes.

**WOMAN:** Thank you. The trials. Because of the congestive heart failure; because of the onset. But I know because of the congestive heart failure, because of the aggressive triple negative and because of the inflammatory all coming back-to-back within a year, and my doctor, my oncologist, whom I greatly admire, asking himself if you were cancer free but in the middle of a chemical warfare – you're going through radiation and dose-dense Adriamycin, Cytoxan and Taxol – how did inflammatory breast cancer get through? I do get PET scans done, and I just had a PET scan done two weeks ago that cleared me, again, as being in remission and not having any active cancer cells.

But, again, I don't have anybody that I could be – I am a willing participant to track me as far as the congestive heart failure, because African-American women are not tracked. We know that 2 percent of women that are diagnosed with cancer get inflammatory breast cancer, but 10 percent of African-American women, they get diagnosed. But we die. We have a higher [death] rate, because we

aren't diagnosed soon enough and early enough. But I just can't walk up to the Mayo Clinic and say, okay, I'm a candidate. I have nobody tracking that. My question is for people like myself who have nobody tracking – again, everybody knows what I'm saying, chemo brain – where would I go?

**EDITH A. PEREZ, MD:** Participating at these meetings is critically important, so you have access to the websites, such as the one she mentioned, that will provide you with information related to new trials that become available. Certainly the National Cancer Institute now mandates that all clinical trials are listed at [clinicaltrials.gov](http://clinicaltrials.gov) [http://clinicaltrials.gov/], so this has been a major improvement for everybody, because we must list our trials. We must list all of the results of the studies. This is a major improvement compared with the way it used to be, when some people were not as careful with data, would keep the results of studies and not publish them, although this tended not to occur in oncology. Now everybody is obligated to share the information, so you as a patient should have more confidence that you have ways to find out whether new studies are available.

It's interesting, because what you mentioned related to congestive heart failure is very different from the situation I talked about, which is congestive heart failure that could be associated with treatment. This occurred even before any therapy. Congestive heart failure can occur – a viral infection, or some people have inherited disorders that are associated with congestive heart failure. In the African-American population,

hypertension is very common, and that is associated with congestive heart failure. This is very important when we do studies, because if I do studies of only ten patients, and one of them develops a problem, it may be secondary to 20 other things. That's why we do these randomized trials – to compare one thing versus another. There are some questions here on this side. Yes?

**WOMAN:** I don't know if this is a very general question, but is there an alternative to the bisphosphonates?

**EDITH A. PEREZ, MD:** In terms of bone health?

**WOMAN:** The only reason why I'm asking is because I have osteopenia due to ovarian suppression and those type of things, but I have been getting severe, severe bone pain because of Fosamax. She just found an article, something that happened a couple of weeks ago that they published, saying it could be related to that. I stopped taking it, and my pain is gone. So I am wondering if there is an alternative to that kind of thing, or if stopping the ovarian suppression would help.

**EDITH A. PEREZ, MD:** The bisphosphonates are the best drugs that we have in terms of bone density, but there are other drugs available. Additionally, some people have correlated the bone pain associated with these drugs with low levels of vitamin D, so this is something that has been done in many cases. This is something you may want to talk to your physician about, because if you are deficient in vitamin D, sometimes vitamin D supplementation can help with the bone pain. This is actively under study, but this is something I

certainly would evaluate in your case. There are, indeed, other drugs besides bisphosphonates. There are alternatives. I would look at vitamin D and try to figure this out.

**WOMAN:** Vitamin D – you take that for calcium absorption, correct?

**EDITH A. PEREZ, MD:** Yes.

**WOMAN:** I already take more than I'm supposed to.

**EDITH A. PEREZ, MD:** There is no reason to take more than you're supposed to. Let me clarify this point. This is one of the challenges that we worry about a lot. When we do studies in which we find deficiencies of something associated with something, it's a different thing to supplement to normal than to take extra. We worry about this, because everything has potential for side effects. Get the level. Who knows? Maybe you are not absorbing the vitamin D. That's a possibility. It would be nice to do the test. It's a blood test.

**WOMAN:** What about osteonecrosis?

**EDITH A. PEREZ, MD:** Osteonecrosis of the jaw can occur. It's rare, but it can occur associated with bisphosphonates. That's one of the reasons I am worried about ovarian function suppression in young women, because a significant number of them will develop osteoporosis, which will mean that they need to be on bisphosphonates for a long time, and it will increase their risk of developing osteonecrosis of the jaw. There is a new drug under development called denosumab. It's a monoclonal antibody against RANK ligand. That

may be a great drug for bone health, and it may not be associated with osteonecrosis of the jaw, but it's currently investigational. Yes?

**WOMAN:** In patients who are triple negative and there is not a biological therapy, what do you feel about stem cell transplant?

**EDITH A. PEREZ, MD:** Stem cell transplant does not work, so we're not going to do it again.

**WOMAN:** I'm in a clinical trial for it.

**EDITH A. PEREZ, MD:** Yeah, we would not recommend it. There have been so many studies done of high-dose therapy and transplant that the answer is given. There are some people – it's like the story of hormone replacement therapy associated with breast cancer. We spend millions of dollars every year looking for a cause for cancer. We find it, and it's hormone replacement therapy, and people refuse to believe it and keep recommending these drugs to patients. It's like, how many studies do we need?

The problem with triple negative is that chemotherapy works initially, and then the tumors go back. That's the challenge. The way this has been approached is to look in the molecular profiles in terms of gene expression, proteins and triple negative and deriving newer therapies. They're not currently available. ASCO will provide some additional information. But giving the same drugs in higher doses is not going to change the outcome. It's a matter of looking at the biology. But studies are being done.

**WOMAN:** What about with a complete response to the previous drugs and then a stem cell transplant for recurrence purposes? No?

**EDITH A. PEREZ, MD:** I would not do a high-dose therapy and transplant with the current drugs; it's not something I would get involved in in terms of clinical research. We've done that. Move on. We need to think of the biology. It's not giving more of the higher doses of the drugs that we already have. Yes?

**WOMAN:** All of the studies I've read regarding inflammatory breast cancer give a five-year survival rate of 20 percent, 25 percent. I know one of the copyrights was 2002. Is there anything more recent that shows we have a better survival rate? I should retire in about that five-year mark.

**EDITH A. PEREZ, MD:** Just keep beating it; keep beating it. Keep beating it. Again, we have new therapies. This is evolving. I know looking at these figures is important, but I am so hopeful that people are doing better today and they're continuing to do better by awareness. You guys are part of the awareness, and you're helping others to be aware and be involved. With inflammatory breast cancer, one of the challenges is that it's fairly rare. There is no institution that can do a study just at that institution, so they have to be multi-institutional studies. More and more data are coming. I tell you; they are coming. Numbers are looking better.

**WOMAN:** So it's better than five years?

**EDITH A. PEREZ, MD:** All of my

patients are doing well. The numbers of 40 percent, 50 percent – things are getting better. I wouldn't focus on the studies that were done. Again, we have newer therapies. Lapatinib was approved just a few months ago. Trastuzumab was approved essentially just a few months ago in the adjuvant setting, and we do not have any long-term data with these new drugs.

**WOMAN:** I'm a three-year survivor of metastatic IBC. I was diagnosed with IBC in both breasts. Do you see a higher incidence of inflammatory breast cancer in both breasts versus regular breast cancer?

**EDITH A. PEREZ, MD:** Yeah, what we typically see is that it starts in one area, and it starts creeping up. We see the redness of the skin. There are some patients who have some very amazing disease. We administer one dose of chemotherapy, and then by the time they come back, the redness returns. We see this waxing and waning of the redness associated with inflammatory breast cancer. Yeah, we see that.

**WOMAN:** Can you tell me if there have been any new studies – I know there are studies that are ongoing, but I don't know if the results are out yet – regarding administering the Herceptin for longer than one year?

**EDITH A. PEREZ, MD:** There is an ongoing study that has been performed called HERA. But we don't have any data yet, and the data have not been submitted to ASCO, so we don't have that ...

**WOMAN:** Coming soon, do you think?

**EDITH A. PEREZ, MD:** It depends

on the number of events. It's like in my study N9831, where we compare sequential versus concurrent, we don't have enough events to be able to report it to ASCO. We had to withdraw our late-breaking abstract. For HERA, it depends on the number of events, so maybe in 2009.

**WOMAN:** Do you have a feeling about it, about your own experiences with that?

**EDITH A. PEREZ, MD:** We never use it beyond one year, because we don't have any data. Studies are also ongoing looking at three months, looking at nine weeks and looking at six weeks. We're looking at shorter duration and longer duration. Right now we use one year. Yes?

**WOMAN:** I had heard of some very early studies suggesting that IBC is particularly sensitive to insulin. Do you know any information about that?

**EDITH A. PEREZ, MD:** In one of the first slides I showed, there may be some abnormality of the insulin growth factor receptor pathway in the setting of inflammatory breast cancer. Inhibitors of the IGFR1, the insulin growth receptor or growth factor 1, are ongoing, and we're going to start a study at Mayo. But none of these drugs are commercially available; the safety is currently under evaluation. It's one of the pathways that we are looking at. Yes?

**WOMAN:** In terms of awareness and early diagnosis ...

**EDITH A. PEREZ, MD:** Awareness and early diagnosis?

**WOMAN:** Yes. Do changes show up

on mammogram for ...

**EDITH A. PEREZ, MD:** Oh, very good question. Yeah. That's one of the challenges with inflammatory breast cancer, and I apologize for not mentioning it earlier. Women can have a bit of swelling of that breast, and then they have a mammogram and the mammogram "doesn't show anything." What typically happens is that there is some thickness that can be seen on the skin on the mammogram, but you have to be really astute to compare both sides.

The challenge is that if inflammatory breast cancer shows up on both sides at the same time, then they cannot compare one versus another. That's why awareness and looking – you have to be proactive. Physicians, they do it proactively. We cannot just rely on you guys to tell us something is wrong. That's why we go to medical school. But if you feel something, go. And if the physician doesn't spend time to go over things with you, then go to someone else and get a second opinion.

**WOMAN:** I think I saw on one of your slides that if you don't respond to your initial – I did almost six months of initial chemotherapy, thought that I had responded, until I got into surgery and still had a 10-centimeter tumor, a 4-centimeter tumor, everything was still there, lymph nodes, so I did not respond. But they didn't know until I went into surgery.

**EDITH A. PEREZ, MD:** Before you go any further, you could have had 20 positive nodes before you started and had ten nodes at the time of surgery. It's a very important issue to realize.

**WOMAN:** It's worthwhile to come just for that. No evidence of prior disease.

**EDITH A. PEREZ, MD:** Because nothing would have felt [hard].

**WOMAN:** There wasn't even anything left over, dead cells or anything, so that's what I was told. I literally was told, "Get through radiation, and go spend time with your family." I got an impression from your slide that if you don't respond, you're talking about in the future doing some targeted therapies or looking at targeted therapies.

**EDITH A. PEREZ, MD:** I'm not as pessimistic as a lot of people out there, it seems. I have great hope that we'll continue doing better. For each one patient I see, we can help every single patient.

**WOMAN:** Currently do you see options for people who don't respond after radiation?

**EDITH A. PEREZ, MD:** Absolutely.

**WOMAN:** All right, well, this was a Mayo Clinic physician in Rochester, so I'll come to you.

**EDITH A. PEREZ, MD:** Let me know who that person is. I'll have to call him or her.

**WOMAN:** I won't say names, because I think at any institution you can have a good doctor or a bad doctor. But that's exactly what I was told. And I came back after doing a lot of my own research and was told, "Well, you obviously know more than I do, because you've been doing a lot

of reading." She particularly, obviously, had not seen much for inflammatory. Yes, Mayo Clinic, Rochester.

**EDITH A. PEREZ, MD:** The opinions are quite varied in this situation, because some people completely feel like that physician saying if you don't have a pathological complete response with initial chemotherapy, then you've lost the battle. My opinion is different. My opinion is you didn't respond maybe to that initial therapy, but we have therapy that works differently. If you talk, let's say, to George Sledge, George Sledge feels that there is nothing else to do. I don't know, that's his opinion – it's like the biology has manifested itself; you didn't respond to chemotherapy. He's from Indiana.

I view this completely differently. I say I have to give that patient the opportunity to receive what we call non-cross-resistant therapy, because that therapy didn't work, well, this other may work. I want to give this patient a chance. I don't just say, "Go home." ... There is more. I think there is life after breast cancer. We have to seize it and do the best we can. On this note, I do thank you tremendously for your attention, and have a good afternoon. (Applause)

[END OF TRANSCRIPT]