DR. JOSEPH SPARANO: And the final speaker, prior to our discussion, will be Sandra

Swain, who's a medical director at the Washington Cancer Institute at Washington

Hospital Center and Vice Chair for the NSABP Breast Committee. And she'll talk about

"Inflammatory breast cancer -- A unique pathological entity?".

DR. SANDRA SWAIN: Thank you very much. I am delighted to be here today and to give

you the last talk of the evening. I'm the last thing between you all and dinner, and it's

been a wonderful meeting. I've really enjoyed all the talks and learned so much.

First, I'm going to give an overview of inflammatory breast cancer. You've heard a lot

of what I'm going to say, so I'll make it brief, and then I'm going to talk mostly about the

therapy of inflammatory breast cancer and some future directions.

Now, inflammatory breast cancer is rare. If you actually look at one of the SEER codes

which includes only that inflammatory cancer that has a pathologic diagnosis as

lymphovascular invasion, it's 1 percent. So you have to look at that carefully when you

look at the numbers, so it is about 2 percent if you include those codes or those patients

that do not have the invasion in the lymphatics.

It has higher incidence in other countries, such as Egypt, Tunisia. And it is the most

aggressive form of breast cancer.

It's a clinical diagnosis -- obviously with an invasive breast cancer being diagnosed with

it somewhere in the breast -- with diffuse erythema, peau d'orange, and frequently --

probably more than 50 percent of the time -- no palpable mass.

So, this is data that Bill Anderson has generated and published a couple of years ago. And he also has a recent publication in breast diseases where he is really looking at locally advanced breast cancer and inflammatory breast cancer, trying to determine whether they are actually distinct entities.

And he hypothesizes that they are, based on the data I'm showing you here -- that the age-specific incidence rates for inflammatory breast cancer actually plateau, and there's no Clemenson's hook with inflammatory breast cancer as there is with other breast cancers. And also, the patients -- though it's not shown on this slide -- that have ER-positive or ER-negative disease also plateau. So you don't increase incidence or increase the amount of ER-positive disease as you get older.

So, he would suggest that they are distinct. I'm not sure that I'm quite convinced. Another hypothesis is that this is just a very aggressive end of the continuum of breast cancer.

So, there is a small, increased incidence in the U.S. over the last thirty years. That's very difficult to actually tell, because, as was mentioned by I think Dr. Byrd, it's frequently difficult to diagnose clinically, because you see all sorts of things that are said to be inflammatory breast cancer, and it's hard to figure out. It's not always rapid, though that's what the definition says.

There is a higher incidence in blacks than whites. Younger age than non-inflammatory. There's a very weak association with pregnancy, lactation, family history, and a larger BMI. And, in the Tunisian studies, they link an increased incidence with rural residence, hyperimmune response, and MMTV. So, you can see that there's very limited epidemiologic data, so we really have no idea of the cause, based on this information.

And the mammogram of a patient with IBC is very non-specific, as you can see here on the CC views -- it just shows some increased density. And, just to make a point that dermal lymphatic invasion is not required -- it's shown by the arrow here -- to make the diagnosis. It is a clinical diagnosis, and there are no increase in inflammatory cells.

I know that seems elementary to you, but I was just asked yesterday by a very prominent oncologist who does a lot of breast cancer where the inflammatory cells were and what they were in inflammatory breast cancer. Well, there really aren't an increase. It is called that because of the clinical view and the redness in the breast.

So, more frequently ER/PR-negative and HER2-positive, and it is T4d, as you've already heard, which the definition, if you look it up in this staging, is that it includes a "majority of the breast".

This is an example -- another biopsy showing to me why it's so difficult to study this disease, because you have, frequently, only a few scattered cells in the breast, as shown here, so it's often very difficult when you do the core biopsies to get a lot of tumor cells. And it also makes the point that you really do need to make the diagnosis by at least a core biopsy, that an FNA would not be adequate, and I think one of the other speakers made that point today.

So, the standard treatment is primary chemotherapy -- I don't think anyone would argue about that -- followed by mastectomy, as was so nicely laid out by Dr. Byrd, with delayed reconstruction followed by radiation and hormonal therapy. And also I would suggest trastuzumab for those patients that had HER2-positive tumors.

This is an example of a patient I actually saw as a fellow when I was at the NCI many years ago who had a classic inflammatory breast cancer. And to me, this is what is so frustrating about this disease. If you… we all know when we treat these patients with chemotherapy, they have an outstanding response, and she had such a great response, you couldn't tell which breast was involved. Unfortunately, these patients relapse.

And as you can see here, by three actually large studies -- or, not studies -- collections of patients from M.D. Anderson and from France -- that the ten-year survival is very poor -- 20-30 percent. So, even though they have very responsive disease, they relapse almost all the time.

And we updated our study in *JCO* a couple of years ago showing that only 20 percent of patients with inflammatory cancer will be alive at 18 years. And the median survival is just over 3 years in these patients, and it's clearly a decreased survival when you compare it to non-inflammatory breast cancer.

This is the… another bit of data from Bill Anderson that he just published in the last year. And if you just look in the right-hand corner, you can see the -- it's hard to see it, probably, from where you're sitting -- but the two lines are ER-positive and ER-negative, and the one with the peak are the patients that have ER-negative disease, showing that in inflammatory breast cancer, they relapse very quickly -- within the first year -- when they have ER-negative disease. And, as with many things later on, the ER-negative and ER-positive relapse at the same rate when you get out to about six or eight years.

So, there's one, very large, population-based survival analysis that was published in the last couple of years. It's the biggest group of inflammatory breast cancer patients -- almost 500 -- and it was a retrospective study from British Columbia. A third of these

patients had metastatic disease at diagnosis, which is pretty typical. If you were to do which we all do -- scans in these patients -- about 30 percent will have metastatic disease.

In about 300 of these patients, they concluded that more intensive chemo improved survival. But I would say that this data is very limited, and by "more intensive chemo", they didn't mean really high-dose chemotherapy -- it was just maybe increased dosing. And they did conclude also that mastectomy improved local control and had a decreased local-regional relapse when you used mastectomy compared to when you used radiation alone.

So, I think that that's pretty clear, as was mentioned already -- that these patients should all have mastectomy and not have breast conservation.

And I wanted to briefly mention high-dose chemotherapy in inflammatory breast cancer, because there are, I think, still investigators that are looking at this.

There are several studies -- most of them pretty small, and not all these conclusions include all of the patients -- but the pathCR rates are anywhere from 3 to 32 percent in these studies using high-dose chemotherapy, with survivals anywhere from 50-70 percent at 3 or 4 years.

And I would suggest that this should not be standard treatment. And if you were to treat patients with inflammatory breast cancer with high-dose chemotherapy, it still should be within a clinical trial. But I did include it for completeness.

Now, if you look at the molecular characteristics of inflammatory breast cancer -- Sophia Merajver at Michigan has published much data on these things, including RhoC-GTPase, and found that it's increased in inflammatory breast cancer.

And then, looking at some of the xenograft models in some of the other studies in immunohistochemistry -- E-Cadherin has been noted to be increased, MUC1 and p53. Also, Sophia's group has found that there's a loss of the LIBC protein, or it's an IGF-binding protein or tumor suppressor gene.

And some of the investigators, especially in the ones I'm going to show you later, have taken this to be pathognomonic of inflammatory breast cancer -- that is, increased RhoC and decreased IGF BP. But, these are fairly small studies, and I would say the jury is still out on the definitive pathognomonic findings.

There is an increase in angiogenic and lymphangiogenic markers, especially VEGFC and D, in some of the pre-clinical and clinical studies of this disease.

Now, in our group we looked at microvessel density in a group of Tunisian patients that had inflammatory breast cancer and found that microvessel density was really dramatically and statistically increased in those patients who had inflammatory breast cancer.

And, based on the data of angiogenesis and lymphangiogenesis and this microvessel density, we chose to do the study that Lisa Carey's already talked about, so I'll just run through briefly. And the main point of this was to really look at the molecular markers and to look at the DCE MRI.

So we did find one pathologic CR in the study, out of a 67 percent response rate, or partial response rate. And just to summarize the findings again -- you've already see this. The most interesting thing was that the activated receptor for VEGFR2 was decreased dramatically on the TUMOR cells, which was not predicted. We thought these anti-angiogenic agents would act through the vessels or on the vessels. That was the initial plan of the study -- to try to figure that out; it was very difficult -- I don't recommend that anybody do that.

But we did find that there was a lot of this activated receptor on the tumor cells and that it decreased quite markedly. And we found that apoptosis increased.

Now, none of these things correlated to response. We had the fortunate aspect of this, that almost all the patients responded, so there wasn't a big dichotomy. And, also, it was a very small study.

So, I would suggest that these small locally advanced or inflammatory studies are important to generate this pilot data, so these markers can be looked at in larger studies, because I think that's the biggest problem we have right now. Everyone would agree. We give bevacizumab. We give these other agents, and we really don't know what we're doing. I think we do know with hormonal therapy and trastuzumab or lapatinib, but not with the anti-angiogenic agents.

So we did do DCE MRI, as was nicely discussed earlier, and we found, after bevacizumab alone, that there was a decrease in permeability and flow. And then, when we added chemotherapy, it decreased even more. And, again, this did not correlate to response.

So, to summarize our study, we had a good clinical response to the combination of anti-angiogenic and chemotherapy, decrease in the phospho-VEGF receptor 2, increased apoptosis, decrease in permeability and flow, and we're doing gene expression profiling for IBC signature and also for signature of response.

So, next I wanted to talk about the SWOG trial that was mentioned, looking at conventional versus metronomic therapy. And I think it was Lisa that talked about (Unint.)'s data -- somebody did mention (Unint.)'s data -- in the pre-clinical data suggesting that metronomic therapy or lower doses was more beneficial.

So, the SWOG Group has done a lot of work in this area, and Georgiana Ellis presented this at ASCO last year. They stratified this study for IBC, giving five cycles of AC every three weeks, so the typical 60/600 followed by paclitaxel weekly versus weekly Adriamycin at 24 per meter squared and cyclophosphamide daily for 15 weeks, and then followed that with G-CSF and then followed that by paclitaxel weekly. And I just want to make a note of this -- that there were 372 patients randomized, but only 265 evaluable for primary outcome.

I feel that this is really not adequate data to make a good assessment of this trial. And it has not been published yet, but I'm going to present you what was presented at ASCO. There were about 107 patients that were excluded from the analysis that I'm going to show you. There were 81 patients who had inflammatory breast cancer. They found that the pathCR rate in the breast was increased if you used the metronomic therapy or the weekly and daily therapy, and also the node-negative rate, if you add that into the pathCR rate, was also increased.

And then the patients with the inflammatory breast cancer -- specifically for that typical AC regimen, it was 12 percent pathCR versus 32 percent with the metronomic therapy. So, I will leave you to your conclusions about that. I think it's not definitive until we see the rest of the data and why those hundred patients were excluded from that presentation.

So, next, to move on to lapatinib. And there were many phase 1 studies with lapatinib. And in these studies in breast cancer, there were inflammatory breast cancer patients. I should mention that these had secondary inflammatory breast cancer, or they had recurrences.

This is an example of a patient pre-treatment -- was treated with lapatinib for two months and then later on, at four months, basically almost had a complete response; so the investigators were very excited about this. So, the company actually, GSK, decided to do two multi-national trials in inflammatory breast cancer alone.

And this really hasn't been done. Most of the trials, as you saw with Dr. Chia and other people who've presented, have included inflammatory breast cancer, but not specifically targeted inflammatory breast cancer.

So, the first trial was in patients who had the refractory or relapsed inflammatory breast cancer. And since lapatinib does work as a tyrosine kinase inhibitor against HER2-positive and HER1-positive, there were two cohorts. And they received lapatinib for 1,500 milligrams a day and got biopsies at 28 days. Just to note that most of the patients that had anthracyclines and taxanes, 75 percent had trastuzumab; and the Tunisian patients in this study did not, because it wasn't available.

Well, the response rate was very high. It was a 50 percent response rate, and that also included skin responses, not just all RECIST responses. They found that most of the responses were in those patients that had HER2-positive tumors. In fact, only one that had HER1-positive only tumor. And they did find that those patients who had PTEN mutation or deficiency did have a very high response rate, as opposed to the data that had been presented for traztuzemab.

Now, the other study was in newly diagnosed patients, again the two cohorts, giving lapatinib monotherapy for two weeks, and then giving the paclitaxel. Now, in this study, the response rate was similar in the two groups, whether they were HER2 positive or not. However, it's interesting that there was an amazing clinical response to lapatinib monotherapy of 30 percent. And then the pathologic CR rate was 17 percent in those patients that had HER2-positive disease.

So lapatinib in inflammatory breast cancer -- this short-course had a 30 percent response rate in previously untreated patients, 50 percent in heavily pre-treated, and activity was almost exclusively in patients with HER2-positive disease. Responses were seen with PTEN deficiency or mutant p53.

So, this slide summarizes all of the data on molecular profiling of inflammatory breast cancer. There are five or six that have been… come out in the last two or three years, and I'm not going to go into detail.

There's really nothing clear right now about the signature. It looks like they may more often have the basal-like tumors -- NF Kappa B over-expression in one study, and the angiogenic- and lymphangiogenic-related genes.

To summarize this, inflammatory breast cancer is a rare disease with a very poor prognosis, and, as I said, may be just one end of the continuum. And I think we can learn a lot from this disease by trying to identify other markers that could potentially lead to theraupeutic benefit. The anti-angiogenic therapy resulted in a direct tumor effect. And the lapatinib was effective in HER2-positive inflammatory breast cancer only. And it's really important that we define the molecular signature for this disease and predictors of response, as with all of breast cancer. Thank you.