[MUSIC PLAYING]

ADAM BRUFSKY: I'm going to talk today about the best of ASCO, in terms of the adjuvant, and local regional abstracts. Apology to the surgeons here, because there's so many things we could talk about here, I'm going to focus mostly on some of the adjuvant medical oncology-based studies. So the first thing, I think, and probably one of the most important breast abstracts to come out in the last several years, really, is TAILORx. I think people have heard about that, to some degree.

Really, I think it's one of the first of two trials we're going to talk about in the last two or three years that have come out that now provide prospective evidence for molecularly guided avoidance of chemo in early stage breast cancer. So again, these are the authors here, and I'm proud to say our group got part of this, because we accrued I think, we're number two or three in the entire world, in terms of accruals.

I think we're about 200, 220 patients we put on the TAYLORx trial as it was conducted. So this is the idea behind TAILORx. Between April 2006 and October 2010, approximately 11,000 women with early stage breast cancer were pre-registered. Now, when you register people at another 100, about 1,000 of them decided they didn't want to be randomized during the registration. So they came out of the trial, that left about 10,000 women.

They all had a recurrent score. And the recurrence scores are shown here. If they had a recurrent score from 0 to 10, and that was about 16%, 17%. 1,629 patients that were given endocrine therapy. If, however, they had a recurrent score of 25 or above, that's about 13% of the patients, they were assigned to chemotherapy and endocrine therapy. Really, where it was important were the women between 11 and 25, and that was approximately 65% of the entire group.

They were randomized, actually, to chemo. As you can see down there about, 3,300 women randomized chemo, followed by endocrine therapy, and another 3,400 got endocrine therapy alone. The interesting thing here is why they chose, and something people always ask, is why they chose 10, or why we chose 10, 11, and 25. Where 11 and 25 is the intermediate range, it has to do with the 95% confidence intervals.

So, the typical Oncotype DX test was 18, is actually the cutoff between low and intermediate. And it was felt that this was the 95% confidence interval, the lower end of it was 11. The lower end of the 31 was actually 25. So that's kind of how they chose those numbers. So again, it was one with invasive breast cancer, ages 18 to 75. No negative ERP or positive HER2 negative, which is important.

Because other tests, such as a 70 gene assay actually you start in positive patients. The tumor size had to be between 1 and 5 centimeters. You could have T1b disease if you had intermediate or high grade disease. And again, the most important one was on the bottom. You had to be willing to be randomized.

And women would often do this, we know from our own experience. Women would try to do this trial, and we'd say, well, you'd have to be randomized, Mrs. X. Oh no, I don't want to go in the study. So we lost people that way when we did the trial. This just shows you in the randomized arm, the arm that actually was intermediate, the median age was about 55, although about a third were under 50.

About 63% had T1 disease. 57% had intermediate to grade high histology. And again, by clinical risk criteria, about 74% were low risk. Everybody got the typical endocrine therapy we would give. AI in 90% of postmenopausal women, ovarian suppression in about probably 15% of premenopausal women. And those common chemos we usually give, TC times four, AC times four, what we normally give.

And again, these just the various endpoints they use. It's important, though, when we look at these sort of trials, that we really look at this endpoint here. A distant recurrence-free survival. That's what kills women with breast cancer. I think one of the things that we're learning I think in the breast cancer business is that yeah, it's important to have a local recurrence. It is, I think significant in many ways.

But a local recurrence generally doesn't kill somebody with breast cancer. A distant recurrence does. And I think that all of us tend to look at those now in the trials. And then here is actually the result of this study. You can see here absolutely no difference between chemo and endocrine therapy, and endocrine therapy alone in women overall with a recurrence score of less than 25.

And you can see here, distant relapse free survival, pretty much the same. And the nice thing about this trial is that if you look at this, the distant relapse-free survival is in excess of 90%. I'm going to show you are the actual number in a minute. Relapse-free survival, overall survival, all the same. So basically, in general, any woman who has a recurrent score of 25 or less, pretty much gets no benefit from chemotherapy in a prospective, randomized clinical trial.

Interestingly enough, they looked at all of the data here. You can see here the women with a current score of 10 or less, and even 25 or less, even with endocrine therapy. As long as you got endocrine therapy, you had a really very nice overall, invasive disease-free survival. Women who have recurrence score of 26 to 100, even with endocrine chemotherapy still had about a 10%, or actually now at a nine year median follow up, about a 15% to 20% relapse rate.

And I think that this is important, meaning that we should probably try to find other things, other than simply chemo and endocrine therapy, in this population. That just shows you the actual numbers here. I mean, the important thing is this incurrance free interval, which is about 95%. If you get endocrine therapy alone, and have a recurrent score of 25 or less. The interesting thing is there were pre specified endpoints in this trial.

There were about 2,200 women who were less than 50 years old in the recurrent-- in that intermediate arm of the study. And you can see here, if you had a recurrent score of 16 to 20, and were under 50, you had 2% fewer distant recurrences. Which is OK, but I think even more importantly, if you had recurrence score between 21 and 25, you had 6% fewer distant recurrences. That, to me, is clinically significant. The 16 to 20 personally is not.

Everybody under 15, whether they were under 50 or not, had a good prognosis. And this just shows you this data. These hazard ratios and these confidence intervals you can see here, the blue bar, kind of overlap over each other. And I think the breast cancer specialists who kind of say, well, this should be done for everybody, I think need to really understand the fact that these intervals really cross each other. And they're not quite statistically significant.

And they really weren't designed for statistical significance. This is kind of like a post hoc analysis. But nonetheless, I think it makes sense to really consider for someone under 50 a cutoff of 21, and not 25 based on this data. So again, this just shows you there was some interaction. I think everybody under 25 should probably not get chemotherapy. Women under 50, if you're under 21, probably not get chemotherapy.

And this just shows you the impact on care that Joe Sporano, when he presented, just showed you. That basically, really, you now have really taken women and probably gone chemo sparing in about 70% of women with no negative or positive breast cancer. And probably has now saved us probably at least 20% to 30% of women who ordinarily get chemo, really don't need chemo at all.

Now, what I want to do is kind of compare and contrast that to the other large trial, prospective trial, that was done, and published in the *New England Journal of Medicine* about two years ago now. And this is the MINDACT study. Again, a prospective trial using the 70 gene assay, instead of the 21 gene assay to kind of decide whether women need chemotherapy or not.

A very similar trial, a smaller study of about 6,700 women, of which 41% did not get chemotherapy because they had a clinical risk, which was determined by adjuvant online. And a genomic risk, determined by the 70 gene assey. If they were both low, about 40% of the women did not get chemo. If they're both high, 27% of the women got chemo, and endocrine therapy. But again, if they were discordant, and in particular, this area here, clinically high, that would give him chemo.

But genomically low, we shouldn't. About 23% of the patients. These patients were randomized to chemo or no chemo. Let's get through this in a second. And there is differences in this. And again, I think that the important thing to understand is that this is a slightly higher risk population. 58% of the patients were over two centimeters. 93% were high grade.

Half were lymph node positive. One to three lymph nodes, most of them hormone receptor positive. In face, the other thing that people don't talk about is probably 8% to 10% were HER2 positive as well. Now, it's important that if you look just at the node negative subgroups, this does match the TAILORx, acts and think people from Genomic Health are very specific to let me know that, when I talk about this.

But nonetheless, at least overall, this is a slightly higher risk population. And the most important thing about this trial is that there is no difference with chemo, and no chemo in the randomized studies. Now, these were not as powered as high. There were fewer patients, but still in this trial both lymph node negative and lymph node positive, there was no difference.

And in T1 and T2 disease, there was no difference in chemo or no chemo. And again, just like with TAILORx, if you do use the staylor instead of the oncotype, if you use the Agendia 70 gene assay, you can save chemo in about half of the patients who ordinarily would have received chemotherapy. And so, looking at this, and just comparing the two, and this is the important slide, clearly the risk profiles were different in randomized populations.

TAILORx was all node negative, predominantly T1. 74% intermediate grade. MINDACT which was much smaller, was 50% node positive. About the same, about 60% T2, and about 93% intermediate to high grade. But TAILORx was much larger in the randomized group, about 6,700 versus 5,500. TAILORx had nine years of follow versus eight for MINDACT, or five for MINDACT.

MINDACT was 8% HER2 positive. Both trials were non inferiority with a benefit to chemotherapy set at 3%, so they couldn't rule out a 3% benefit to chemotherapy in TAILORx. They couldn't rule out a 2% benefit for chemotherapy in MINDACT. But the bottom line is that clearly both trials showed that women with a low genomic risk, whether by Oncotype DX, or the MammaPrint had a five-year, or actually nine-year in the case of TAILORx distant disease free survival in excess of 94% to 95%.

What I think is fabulous prognostically for women with breast cancer. And I think it's really-- I think this just tells you that we now have two large randomized trials that have shown enough, identified a population, even a population that's node positive, that does not benefit from chemotherapy. And I think saving women chemotherapy, yet giving them a good prognosis, is something we've tried to do in breast cancer for many years.

And I think we're probably there. So again, one last thing, just to kind of toot our own horn, as we have in the equations. You can put in the Nottingham score, the ERPR, the tumor size, and the KX67 percentage. And if this turns out to be 18 or less, with the mitosis portion of the Nottingham score. And I'm [INAUDIBLE] mitosis tubules and nuclei. If the mitosis score is 1, with a McGee score of 18 or less, the Oncotype is never over 25.

Never. And we just published a paper on that a few months ago, about a month and a half ago. So, the thing is that this is important data. I think if you don't want to use Oncotype, now we all Onca and MammaPrint here. But again, if you're in a low-resource area, I think it's most important. You know, if I go talk around the world, you go to Vietnam, you go to India, you go to parts of China, they don't have $3,000 or $4,000 to spend per assey.

You know you may be able to use these sort of things, to avoid doing a genomic test if you have to. The other two things I want to talk about is another topic near and dear to my heart, this is breast cancer recurrence prevented by bone-targeted agents. And the most recent one we have is now Denosumab. So the idea here is that, again, you have osteoclasts, and you have potentially micro metastatic disease in the bone marrow.

The osteoclasts, if you're osteoperotic, tend to secrete a lot of growth factors. They stimulate the metastatic tumor cells to grow, and therefore you get macro metastatic disease. That's the idea and the theory behind using either a bisphosphonate to kind of cause apoptosis of osteoclasts, or using Denosumab, which is basically a mimic of the RANK Ligand, which interferes with RANK binding to its receptor on osteoclast, and therefore stops the osteoclast from growing.

That's the simple kind of handwaving explanation. So we have a bunch two trials, large trials of the test of this hypothesis with Denosumab. And the first one is ABCSG 18. The idea behind ABCSG 18 was that we took women-- actually I'll get back here, is kind of out of the order here. But there it is.

We took about 3,500 women with postmenopausal breast cancer, early stage breast cancer. All had ER positive disease. All got the standard of care, which could have been chemo, which is in a few women. But mostly endocrine therapy, with an aromatase inhibitor. They were simply randomized to Denosumab. 60 milligram sub Q, every six months for five years versus placebo.

It was a one to one randomization. And the primary endpoint of this trial is shown here. Did it prevent fractures in women getting aromatase inhibitor? The answer is clearly yes. You can see here, obviously, and this is all women. These women not with a T-score less than two, or even at risk for breast cancer bone fracture from aromatase inhibitors. But what you can see here is clearly you reduce the risk of fractures by half in women receiving aromatase inhibitors.

So this is women who are postmenopausal. This actually was the clinically significant endpoint. The trial was actually unblinded when this happened, because ethically Michael Gannot and the ABSCG is could not continue it because of the fracture difference. And so what they decided to do is actually look at the disease-free survival of these women, who got it.

And basically, the first thing is that there were very few adverse events. In particular, on the one thing we worry about in giving these agents is osteoperosis of the jaw. There was no adjudicated. I mean, there were some that people thought it was a jaw problem. But the bottom line is that this was adjudicated, most of the osteonecrosis was adjudicated, and found not to be.

As you can see here, there were supposedly 31 cases that were suspect in this entire trial. So 31, is about 1%, were suspected to have ONJ. But when they were adjudicated by an expert panel, not a single case had ONJ. The other thing we worry about with long-term bone suppression is atypical femoral fracture. And there were four candidates, but only one after adjudication was felt to be related to the drug.

So again, the side effect profile of this was well, was good. And in fact, if you look at invasive disease-free survival here, you can see it actually reduced it by about 20% in relative terms. In absolute terms, out here now, at about seven to eight years of follow up, it's about 3% or 4% improvement in invasive disease-free survival, which is actually a benefit, consistent I think, in these sort of agents with chemotherapy.

If you take women with ER positive disease, or postmenopausal, give them endocrine therapy, in absolute terms, they probably get a 3% to 5% benefit from chemo. All right, I think in this case, the bone target agent gave them roughly the same benefit. But what was kind of weird and interesting in here, it really was yes, there were distant metastases as you can see here. Probably 11 fewer.

There's also a little bit of other things going on here. Contralateral breast cancer, second primaries, which I think is the big one, really is what really drove this is second primaries. And I think a lot of us can't quite understand why that is. But really, it wasn't preventing distant disease-free survival that much. And most of the people who got the benefit were those who aromatase inhibitors naive as well in this trial.

So putting that in context, we then look at a large clinical trial, which took everybody, not just postmenopausal women receiving aromatase inhibitors. But all women with early stage breast cancer, and actually randomized them as you can see here and DeCare. This took all women, whether ER positive, ER negative, premenopausal, postmenopausal, on endocrine therapy, not.

Got the standard therapy for their disease. Then were randomized one to one at a fairly intensive regimen Denosumab. So Denosumab was every month for six months, followed by every three months for 2 and 1/2 years, followed by every six months to complete five years. So got Denosumab or got placebo in this trial. And again, these are the typical patients you would see.

I think what's important here-- I've got to kind of look at it, because it's small up here. But the bottom line is that you can see here there were substantial numbers of ER negative and HER2 positive patients at this trial. And there were substantial numbers of lymph node positive women in one. And some even in two and in three. Actually, women with over 10 lymph nodes in this particular study.

And you can see here, the vast majority of these patients, because they did have a worse prognosis than the patients and ABCSG 18, almost all of them got chemotherapy, taxing the anthracycline base. Almost all of them got hormonal therapy. And when appropriate, women who needed HER2 positive, HER2-based therapy got HER2-based therapy. But this is the bottom line.

The end result was this bone metastasis-free survival. No difference whatsoever, 0 to this. Which is actually quite surprising for all of us. When I initially saw this data, actually, before it was presented, no difference in distance disease free survival of any kind. And really, when you look at the events, when you start to look at this, you do have a reduction in bone metastases from the women getting Denosumab.

35 fewer events, which is kind of interesting. But that was overcome by an increase in non-bone distant recurrence. So this is actually kind of counteracting each other, resulting in an overall survival that pretty much was the same. Looking at some exploratory endpoints, not a single one of them really. I mean, really the time the first bone metastasis was both borderline significant. Time to bone metastasis, first sign of recurrence was borderline significant.

Time to symptomatic bone metastasis, but basically that was overcome. I think the theory here is this increase, or improvement in bone metastatic disease was actually counteracted in actually distant non-bone disease in women receiving Denosumab. So again, in this case also, because you're getting a more intensive regimen for bone-targeting, you actually did have significant osteoporosis of the jaw.

Adjudicated ONJ in this and the Denosumab was 5%, which is clearly a lot higher than giving the drug every six months. So clearly, you have no benefit, in terms of disease free and overall survival. But more ONJ with the intensive regimen. So this is clearly not a regimen I think that we do want to use.

And you just see here the time that ONJ kept increasing. It didn't ever plateau during the time of the trial. Up to here, about 4% to 5% during the trial. So it really did not improve bone metastasis survival. And it really was well tolerated with the exception of ONJ at 5%. So really, where are we going to go with this?

I mean, I think we're all bone headed. I mean this is yet another problem. I remember from 2003 when we had oral bisphosphonates. this is now almost 15, 20 years ago, a single negative trial just made us abandon the field. We then had zoledronic acid, which in a zoledronic acid clearly in a meta analysis of all trials, shows a 3% overall survival improvement in postmenopausal women.

So clearly, why didn't work? One, because they're more non bone metastases. And mostly, I mean, I didn't really show this in higher, in premenopausal women. And so I think that right now, we should use these drugs to prevent fracture. Either one works. I think that the only-- if I'm trying to give someone drugs, though, to prevent disease free overall survival, based on this data, I really, at this point in time would tell you that I would use bisphosphonates.

And we don't know why. We have no idea why this is. I just want to show you. I tihnk we have the MAF, yeah. So we don't know why. And I think that it's important though, is trying to look for biomarkers of response. And I think we may have found one, actually. There's a marker called MAF. It's on chromosome 14. It's an avian myelo blastoma virus factor, transcription factor.

We're not sure quite what it does. But it turns out that if you have less than 2.5 copies of this amplified in your primary breast tumor, you have a better progression and overall survival on zoledronic acid, whether you are pre- or postmenopausal. So we may actually now have a biomarker that determines who should get this. I think prospective trials are currently, or retrospective analysis of large trials is currently ongoing.

In fact, I just reviewed a paper on this. And I think this is something that's going to be important. We may actually have a biomarker to tell us who should get these bone-targeted agents for disease free and overall survival. I think that's going to help us out a lot. OK? And I think this really may push this field forward, despite the disappointing data from DeCare.

So I think the last thing I think I'm talking about Persephone. And Persephone asked the question, how much Trastuzumab is enough? That's really an important question, I think, for all of us. We have two trials that have been presented over the last several years that are non-inferiority trials. These are simple designs. Basically, they take women who are getting her two-based therapy with Trastuzumab.

And they're randomized them to 12 months or six months of therapy. So fair, which is a huge trial, as you can see here, was lacked. I hate to say not non-inferior. I don't know how to say that any better. But the bottom line is that it did not meet the non-inferiority boundary. That means that you couldn't be guaranteed that if you give six months versus 12 months of Trastuzumab, in the fair trial, that the outcome would be the same.

Same thing in Hor, which is a slightly smaller trial, the same thing. Really, it didn't meet the non-inferiority boundary. So the bottom line is that 12 months, based on these two studies, was still superior to six months. So on this, then we have Persephone, presented at ASCO, an oral presentation. This took HER2 positive invasive early stage breast cancer, which is either 3 plus or 2 plus and fish amplified.

No metastatic disease, and a clear indication for chemotherapy. The women got their standard therapy, and then as they approached their sixth month of Trastuzumab, they were to sign an informed consent to be randomized to six months or 12 months. As it shows the design of the trial, fairly simple.

I mean, it's is basically, this is the Trastuzumab six months versus 12 months at a standard dose that we always get. The primary endpoint was disease-free survival, the secondary endpoint was overall survival. So it is a very large trial, 4,000 patients. The four year disease-free survival, with 12 months of Trastuzumab, was estimated at 80%.

I think it was kind of low, to be honest with you. But it was a non-inferiority trial. They would accept, and this is important to understand, they would accept that if six months of Trastuzumab gave a DFS 3% worse, that was still considered non-inferior. That's important to understand.

So even though it may say they're non-inferior, that's within a 3% benefit. So if you think a woman should get that 3% extra benefit, then maybe you should think about giving her that 12 months of Trastuzumab. There were three interim analyses of this trial. And you can just see how it was done. They did this as kind of interesting way of doing it.

They had all these landmark analyses after you had each kind of percentage of events done. 25% 50%, 75%, 100%. And these are the number of events that were required. And again, they met them quite like they should. And this is after 500 disease-free survival events.

After about five years of follow up, this was the ratio 1.85. No difference whatsoever you can see here. I mean, it has a ratio of six versus 12 is one. So there's no difference, and they presented the results. And so the median follow up was 5.4 years. 8% had died, 13% had relapsed or died.

So think about that. That's 87% five year disease-free survival. They predicted 80%, they got 87%. Which is consistent, actually, with some of the modern trials that we're doing now. It just shows you here, there it is, 90% disease-free survival with no difference in either arm. You can see here this is a non-inferiority boundary.

Clearly it does not cross it, so therefore it is non-inferior, and it the thing, is I think the discussant, Martin Picard, really focused on this. And what she said was well, what about people who only got taxane-based therapy. They seem to do pretty well. What about people who had concurrent therapy?

They seem to need 12 months. And so this does introduce a few questions into this, these subgroups. Although, these were predefined subgroups. But again, they're small. They aren't huge subgroups. So I'm not sure what to make of this, although it is potentially something to think about, as you're deciding between six months and 12 months, based on this data.

The top line says we should only give six. But on the other hand, you've got to think number is still have a potential 3% difference. Number two, there were women who on taxane-only therapy, which is what we give a lot, TCHP is tane only. Maybe they still have a benefit there, and maybe if you got concurrent Trastuzumab with it, also had a benefit from 12 months.

So these are things to think about in this particular trial. Overall survival, not surprisingly is unchanged at about 94%. And again, this is really important. This is overall HER2 positive patients that walk in the door, that the vast majority of them are going to live. I think this just says that speaks of the fact that therapy works really well.

And again, the overall survival, the same thing. There's these benefits here. For the ER negative, it looks like maybe some overall survival benefit to 12. In the taxane-only therapy, maybe a little bit of benefit. Concurrent maybe a little bit of OS benefit. Again, not huge differences. But nonetheless, things that you need to think about when you think about between six and 12.

Again, the interesting thing not surprisingly, you had double the cardiac toxicity, which is defined as EF. This is in congestive heart failure. This is a drop in EF at a certain percentage in most of these patients. It wasn't symptomatic, but it was 4% in six months, 8% with the 12 months. The majority of cases were covered in this trial. And again, other toxicities or as expected.

So again, I think it basically showed that there is really no difference overall in six versus 12. But I think we need to think about the fact that taxane-only patients may have had a benefit, and the concurrent patients may have only had a benefit. And you still can't rule out a 3% benefit from an additional four months, or six months, of Trastuzumab. So again, that's what I said.

You can't exclude the possible 3% benefit. I think for women with low risk HER2 positive disease, a typical woman comes in with T1c ER positive, HER2 positive, even T1c ER negative, HER2 positive. Gets TH times 12. Our typical therapy, the APT regimen.

I think a lot of us are really going to think about giving those women six versus 12. I think that, to me, is where this is going to be. But what is low risk disease? Is it less than T2? Less than T3? No negative? What is low risk disease? And I think that in the US, we have no problem giving these drugs. So that's not the issue. It's really for resource-constrained countries like India, China et cetera.

I think that I'm not sure is going to change practice in our group. Or actually our group, or even in the US, it may. But I think that it likely will help out with practice in resource-constrained countries, especially now when you piggy back on that, the fact that we're going to have biosimilars in the next year or two for Trastuzumab. So with that kind, I'll kind of end. Thank you very much.