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Breast Cancer™ UPDATE

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

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DR JOYCE O'SHAUGHNESSY SUPPLEMENT

DR NEIL LOVE: Welcome to Breast Cancer Update. This is medical oncologist Dr Neil Love. The June 15th issue of the Journal of Clinical Oncology contains the formal report of a data set that has been widely discussed since its first presentation at the December 2000 San Antonio Breast Cancer Symposium. The paper, in the metastatic setting, by Joyce O'Shaughnessy et al, reports a survival advantage to the combination of capecitabine and docetaxel compared to docetaxel alone. Major randomized trials in metastatic disease reporting a survival advantage to a chemotherapeutic regimen have been rare to non-existent. On the last issue of Breast Cancer Update, Dr Terry Mamounas noted that based on these encouraging data, the NSABP is considering a new neoadjuvant trial incorporating the so called XT or Xeloda-Taxotere regimen, and also, a new adjuvant study of XT in breast cancer patients with local tumor recurrence. Last year, when I interviewed Dr O'Shaughnessy about the XT study, she noted that her group, US Oncology was planning a new trial looking at capecitabine-docetaxel as adjuvant therapy and I met with her to obtain an update on reactions to these findings by oncologists. She began by reviewing the current data set.

DR JOYCE O'SHAUGHNESSY: The event rate now is very, very mature. The median survival on Taxotere alone is 11.5 months, and for the XT it is 14.5 months, so a median difference of three months. At the 12-month mark, 57% of women were alive with XT compared to 47% with Taxotere alone.

So, basically, the results are mature, and it is a real deal. There are low treatment-related deaths, very similar serious adverse events, very similar hospitalization rates, and etcetera. So, XT is no worse in terms of major toxicities than Taxotere alone, and it is definitely superior in terms of overall survival.

If you look at the women who got Taxotere versus XT and the number of people who got chemotherapy at some point after their study therapy after their disease had progressed, it was pretty high. About two-thirds on both arms of the study, got chemotherapy, so these women were still aggressively treated, and there was no major imbalance. Patients were treated appropriately; some got Herceptin, a lot got Navelbine and some got additional taxanes, a third got more hormonal therapy. So, it was good aggressive therapy and really no imbalances.

But of the patients, of the total number of patients who got Taxotere, everybody – 256 patients – 18 percent went on to get Xeloda at some other point in their therapy. But if you look at the denominator as those who got any chemotherapy, which was about 60-65%, 27% of those got Xeloda. So, one point to be made is that not everybody is able to get additional therapy. 35-40% of people did not get any more therapy afterwards, likely because their disease was quite advanced and they just really couldn't tolerate any more and it wasn't appropriate to give them any more.

So, one of the controversial areas is should you give sequential single agents, or could you give XT? One point is that if you've got 35 percent or 40 percent of people not getting any additional therapy, that means there isn't going to be the opportunity to give everybody sequential. So, for 60-65 percent, there was the opportunity to give them additional therapy. I think the number was around 50 patients, who got the Taxotere and later went on to get Xeloda. If you look at the hazard ratio for mortality in the patients who got Xeloda after the Taxotere, compared to any other chemotherapy agent – so, the othe comparative group is any other chemotherapy – the hazard ratio for mortality was 0.5.

So, there was a 50-percent reduced risk of dying after your Taxotere, if you got Xeloda, compared to any other chemotherapy agent. The actual survival figures, as I recall in terms of median survival, were something like 14.5 months with the Xeloda versus 11 months or something like that. Now, this was just a subset analysis, but it still reached statistical significance because it was a 50-percent reduction.

If you do a similar analysis on the group who got Taxotere alone in the study, who later went on to get Navelbine, if you look at that group compared to any other chemotherapy, excluding Xeloda, the hazard ratio was 1.0. It didn't make any difference whether you got Navelbine or whether you got any other chemotherapy drug. There was no difference in your mortality. So, that's very interesting.

DR LOVE: What do you think it means?

DR O'SHAUGHNESSY: It give us some data to say after Taxotere fails the patient and you're going on to your next agent, if you are using, in fact, sequential single agents, it would be very reasonable to choose Xeloda. You get a 50-percent reduction in the risk of dying, at least based on these data, compared to other chemotherapy agents, suggesting that Xeloda is one heck of an active agent in these patients and is associated with improved survival, compared to any other chemotherapy agent such as Navelbine. Now, these are small subset analyses, but it's very, very interesting. I can't think of any other reason that should be, because it makes no difference. If you lump all other chemos together, if you take Navelbine out and look at that separately, the hazard ratio for mortality is all the same.

Actually, it gives some credence to the folks who have been saying all along that it's okay to give Taxotere single-agent followed by Xeloda single-agent, that your survival is going to be no different, if you compared the sequence to the XT combination. So, it gives, certainly, some credence to that argument. The way I interpret the data from a conservative standpoint, which I certainly think is very fair, is that, if you have a patient with indolent disease – not particularly symptomatic – I think it's very reasonable to give Taxotere sequentially with Xeloda. And the Miles data would suggest that they do quite well with that.

Conversely, given the early separation of those survival curves and the early death rate with Taxotere alone, there's certainly going to be a subgroup of patients who are not going to have the opportunity to cross over. Those patients, it seems very fair to me, to say, "Give those the combination of XT," you know, the more aggressive, more symptomatic, the folks who you've got to have a response on.

There is, however, still a hypothesis on the table, which we really cannot confirm or refute at this time. It still is possible that, if you did a randomized trial of XT versus single-agent Taxotere followed by single-agent Xeloda, there would be a survival advantage. That is based on the fact that the XT has very clear biochemical and preclinical synergy, which is very different than most of the doublets we have. So, the hypothesis on the table is that XT is not just any doublet.

DR LOVE: You're talking about thymidine phosphorylase.

DR O'SHAUGHNESSY: Right. Upregulation of thymidine phosphorylase by Taxotere, leading to greater conversion of the capecitabine prodrug to 5FU at the tumor site. This combination has very, very clear preclinical synergy, which very few of our doublets, empirically chosen, do. So, it still may be, at the end of the day that giving the doublet is best for all patients, but we certainly can't say that based on the data.

DR LOVE: The other thing that I've been thinking about for a while – and I actually talked to David Miles and interviewed him in San Antonio – was I don't think there's any head-to-head, randomized comparison to Taxotere and Xeloda. Correct?

DR O'SHAUGHNESSY: Correct.

DR LOVE: So the question is if there had been a third arm, XT versus Taxotere versus Xeloda alone, with crossovers what would you have seen in terms of response rate and maybe even more interestingly in terms of survival.

DR O'SHAUGHNESSY: Well, I think, it's an interesting point because I think people are really taking a second look at Xeloda. I know I am. It's quite an active compound. There was a small randomized Phase II trial comparing Xeloda to Taxol, 175 per meter every three weeks. It was a very tiny study, 20-24 patients on each arm. It was stopped prematurely, because at that time – started several years ago – it was very difficult to randomize people to a pill versus an IV. That's why the numbers are so small. But the response rate with the Xeloda was 36 percent compared to 26 percent with Taxol, widely overlapping confidence intervals. So, you could say, basic equivalence is that you would probably say from those data.

So, the small amount of data we have using Xeloda earlier in metastatic breast cancer, when we compared it to IV CMF in larger numbers, 67 patients receiving front-line Xeloda, elderly patients, median age 70, the response rate was 30 percent. And about half of those had some adjuvant therapy so, not all anthracycline pre-treated. We know Taxotere has a solid 30-percent response rate in the anthracycline pre-treated patients, so it's possible Xeloda could be close to equivalent to Taxotere.

DR LOVE: It's kind of interesting, when you think about the psychology of giving an oral drug versus intravenous, both on the prescribing physician and the patient. I've heard all different viewpoints on that. There's the strong medicine for a serious situation thing that maybe made you lean towards intravenous therapy. But the other issue is that if you have a patient who is relapsing for the first time after having intravenous adjuvant therapy, it's a tremendous disappointment for a patient. Just emotionally having to go back to intravenous therapy versus a pill, I've heard that point brought up, also.

DR O'SHAUGHNESSY: Yes. I think that's right. I think that women want effective therapy. What I find, Neil, is that for women who relapse, they're scared to death. Most of them are still in fight mode at that point. When you go through the laundry list of options in metastatic breast cancer, I've had several look me in the eye and say, "I want the most effective one." And so, I'll lean them towards combination chemotherapy.

On the other hand, there are many women who have very, very indolent disease. They're older. They know they've been at this a long time. They know they've got time, and they want quality of life. So the idea of a pill, and an effective pill, is very, very good for them.

DR LOVE: Although it's interesting you mentioned quality of life, because I saw at the Chemotherapy Foundation Meeting some quality-of-life data on the XT study.

DR O'SHAUGHNESSY: Yes. That's a good point because a careful quality-of-life analysis was done in the big Phase III trial, and the curves are absolutely overlapping for the first four-five months of the study. Then they start to split, with XT being superior, for the clear reason that there was better tumor control. The deterioration in the Taxotere arm is undoubtedly due to tumor progression. The Phase III trial was pretty much heavily tumor burdened, heavily pre-treated patients. Two-thirds were getting the study therapy as second- or third-line therapy. So, these were sicker patients.

So, you're right. XT was, if anything, somewhat superior – although not statistically significant, but still somewhat superior quality of life, particularly towards the latter part of treatment. But, still, from an acute toxicity standpoint, there is no question that the XT has more toxicity than Taxotere alone. Taxotere has a little bit more febrile neutropenia associated with it because it's more myelosuppressive. But you don't get the diarrhea and the hand-foot syndrome that you can get from the XT combination.

DR LOVE: I think it really gets back to what you were saying about looking at the patient in terms of how long you have to wait for a response, what kind of condition they're in. But, when I first saw those quality-of-life data, Dan Budman was talking about the fact that in the long run, tumor control and tumor itself is really the issue in terms of metastatic breast cancer and quality of life.

DR O'SHAUGHNESSY: That's right. I would agree with that. And not only from a physiologic standpoint, but also from a psychological standpoint. Tumor control is king for us.

DR LOVE: When I first talked to you about this trial, which has generated a lot of interest, one of the obvious questions, I think, that came up immediately is where is this going to head in terms of the adjuvant and neoadjuvant setting? What's happened since then, and where are you with that?

DR O'SHAUGHNESSY: A lot has really happened since then. It's amazing how quickly this has come about, actually. I guess we all stand up and salute when there's a survival advantage in metastatic breast cancer because we can count on just a couple of fingers any clinical trial that has given us that. So, I guess that's why it's happened so quickly.

Probably the most important thing is that the NSABP is going to take this into their next neoadjuvant clinical trial. In the B-27 study that they presented at San Antonio, which was the preoperative three-arm randomization for operable breast cancer, either clinically node-negative or node-positive, three way randomization to AC preoperatively followed by surgery versus AC preoperatively followed by Taxotere, 100 per meter every three weeks for four cycles preoperatively followed by surgery, or AC preoperatively, surgery, and then Taxotere postoperatively, what they showed was a doubling of the pathologic

CR rate in the breast when you added the Taxotere preoperatively compared to just AC alone. So, they don't have any disease-free or overall survival data yet, but impressive doubling of pathologic response rate in both ER-PR-negative and ER-PR-positive, which is a key point for us, clinicians. So, they are going to make that the standard arm of their next clinical trial; AC for four, followed by Taxotere for four, preoperatively, will be their next standard arm. They've decided that the investigational arm will be AC for four, followed by Taxotere-Xeloda for four. And that's really cool.

Now, U.S. Oncology is going to do that exact clinical trial design, except in the adjuvant setting. So, our patient eligibility will be any node-positive or high-risk node-negative, and they'll either receive AC followed by Taxotere or AC followed by Taxotere-Xeloda. Our doses will be Taxotere, 75 per meter, with Xeloda, 950 per meter BID, which is 1,900. And that represents a 25-percent dose reduction, down from the 2,500 milligrams per meter squared. That is okay because all of our analyses – and there's been extensive analyses done now – looking at the effectiveness of either Xeloda alone or XT combination in the patients who got a 25-percent dose reduction in Xeloda, it's interesting. In the XT arm – and I just saw this analysis – the median delivered dose intensity of Xeloda on the XT was 75 percent of the intended dose. Interestingly, that took place by Cycle 2.

So, in fact, that survival advantage really, for all intents and purposes, took place with a 25-percent dose reduction in the Xeloda dose. So, the delivered dose intensity – and that was a combination of dose reduction, as well as some interruptions – was by Cycle 2. You were down to a delivered dose intensity of 1,900 per meter, and that maintained. That did not drop during the rest of the study, it maintained. So, I think that's very persuasive evidence that you're going to still have your effectiveness with 75 percent of the full dose Xeloda.

DR LOVE: Now, both of these new trials are going to include both ER-positive and ER-negative patients?

DR O'SHAUGHNESSY: Yes. Ours for sure is, and I believe the NSABP's will as well.

DR LOVE: So, you're not too persuaded by the subset analyses in terms of ER and taxanes?

DR O'SHAUGHNESSY: Well, we are all kind of watching that one with interest and trying to scratch our heads there. As you know, with the AC followed by Taxol, the subset analysis, both in the B-28 and the CALGB 9344, all show a very interesting and clinically significant trend towards an improved hazard ratio for mortality in the ER-PR-negative subset. But it's very unimpressive in the ER-PR-positive. It's virtually nothing in the ER-PR-positive group. So, here comes the B-27 then, and looks at pathologic CR rates in the breast. But what's interesting is, if you look at the ER-PR-negative subset, the pathologic CR rate with AC was about 13 percent, and it doubled to 25 percent with the AC followed by Taxotere. So, it went from 13 to 25 in the ER-PR-negative. In the ER-PR-positive, I've heard two separate numbers. One was six percent with the AC alone, going to 13 percent, also a doubling, but much smaller to start off with. The other number I heard was five percent going to 14 percent. But in that, about half of the effectiveness in terms of pathologic CR rate in the breast as your end point, half the effectiveness of chemotherapy in the ER-PR-positive group compared to the ER-PR-negative group.

DR LOVE: But still a benefit?

DR O'SHAUGHNESSY: Still a definite benefit and still a doubling. We don't have disease-free and overall survival data, so we have to be careful not to make too much of that, but I personally am taking that as a reason to use AC followed by Taxotere in the higher-risk patient even if she's ER-PR-positive.

DR LOVE: I like the pre-op studies, too, because you have the tumor right there. You really know exactly what you're dealing with, and you know it very quickly. Aman Buzdar has discussed the work at M.D. Anderson, where they've done pre-op Taxol. He says there's no difference in what they see in ER-positive and ER-negative. So, maybe that's a better testing ground. I'm sure the NSABP is going to see things way before you will in the adjuvant setting in terms of response within the tumor.

DR O'SHAUGHNESSY: Absolutely. Yes.

DR LOVE: So, they'll be able to report what's going on inside the tumor before you start to see or they start to see the disease-free and overall survival. But it's great how these neoadjuvant studies give us a clue that we can just jump right on.

DR O'SHAUGHNESSY: Yes. It really does. It really does. And I think it'll be very neat to see, because I predict that XT will make an improvement in the pathologic CR rate over Taxotere alone.

DR LOVE: Unless there's something not translating into the neoadjuvant setting, you would expect that to be the case.

DR O'SHAUGHNESSY: Exactly, because the objective response rate is higher with the doublet.

DR LOVE: You recently presented an interesting study on the use of Gemzar and Herceptin. Can you talk a little bit about that and where you see that combination heading?

DR O'SHAUGHNESSY: Yes. Yes. That was interesting, as well. We started a Phase II trial of gemcitabine and Herceptin back in '99, before we knew that FISH was critically important in the 2+ overexpressers. It was for women – they could have been pretreated with other chemotherapies – they had to have measurable metastatic breast cancer, but they could not have had prior Gemzar or Herceptin. They had to be 2+ or 3+ overexpressers by immunohistochemistry, done at their local pathology lab, because we wanted to do a real wide community study. But all of the blocks and the slides were sent for central review by a study pathologist, to make sure that they were, in fact, HER2-positive. 64 patients were entered on the study, 61 were eligible, and 59 were actually evaluated for response.

It was interesting, back in 1999-2000 these women had not had prior Herceptin. The doctors chose to put on patients who had had quite a bit of chemotherapy because back in those days, we weren't using Herceptin routinely for front-line metastatic treatment in the HER2 overexpressers. I don't think it was quite so clear that that's where your survival advantage was and you didn't have as robust a survival advantage if you gave the Herceptin later. So, it's interesting, because the patients had a median of three prior chemotherapy regimens – one in the adjuvant setting and two for metastatic disease. So, they were really receiving this as fourth-line therapy, or third-line metastatic therapy.

The Gemzar was 1,200 milligrams per meter squared, day one and day eight on a 21-day cycle, and the Herceptin was standard Herceptin weekly. The overall response rate was 37 percent. But if you look at the subset, most of the women were 3+ overexpressers. About two-thirds were 3+ overexpressers. The response rate in the 3+ overexpressers was 45 percent. That's quite interesting because in Melody Cobleigh's big Phase II trial of Herceptin as a single agent, the patients were receiving that as third-line therapy, second- or third-line therapy, but most, later line. And that was a 15 percent response rate with Herceptin. Gemzar as a single agent after anthracyclines and taxanes – and almost all the women had had prior anthracyclines and taxanes – very little data on Gemzar in that patient population, but it ranges from a low of about 12 percent up to a high of about 20 percent in one study.

So, the response rate of 45 percent – now, again, the confidence intervals are wide, so you've got to be careful here. But at least it would suggest additive effects, putting the Herceptin together with the Gemzar. It raises the hypothesis that perhaps there might even be some synergy, with a response rate of 45 percent in a very heavily pretreated, late-line group of patients where you might think Gemzar might be a 15-percent drug and Herceptin's a 15-percent drug. You might 30 percent. This was 45 percent. Is something else going on there?

That would be considered strictly hypothesis generating, and I think what you want to do is you want to move it up. Kevin Fox at Fox Chase is doing a front-line study of Gemzar and Herceptin for first-line treatment of metastatic breast cancer to see if you're going to come in with these response rates that Navelbine came in with. Taxotere and weekly Taxol are all coming in around the 70- or 80-percent response rate in front-line treatment. So, that was interesting. That was interesting. It was very well tolerated with no unexpected cardiac effects and no unexpected toxicities.

DR LOVE: We did a patterns-of-care study with 100 oncologists and 100 surgeons. We basically presented cases to them and asked them what they would do. Relevant to the two things that you just talked about, we presented metastatic cases to them. We did this for education purposes, not to prove a point about what people are doing in practice. One of the things that I thought was interesting about this Miami Meeting patterns-of-care study is relevant to what you were saying about the use of Herceptin. We presented a bunch of first relapse cases of HER2-positive, 3+ overexpressers. For example, 43-year-old woman with bone mets who received prior ACT, IHC is 3+. Guess what percent would include trastuzumab as part of their therapy, whether alone or with chemotherapy?

DR O'SHAUGHNESSY: Assuming she's ER-PR-negative?

DR LOVE: Right. Would you be surprised if I said 65 percent?

DR O'SHAUGHNESSY: Yes.

DR LOVE: I thought you would be, and if you look through the various scenarios it varies from 65 to 85 percent. So, what it suggests is 10-20 percent of oncologists are not routinely using Herceptin as first-line therapy in IHC 3+ patients. Does that surprise you?

DR O'SHAUGHNESSY: It doesn't, Neil, because in the Slamon paper, you'd have to read it closely to understand that the survival advantage was quite large using Herceptin up front, in spite of the fact that two-thirds of the patients later on got Herceptin. So, the implications of that are – this was essentially a crossover study. Everybody got Herceptin – not everybody – two-thirds of women got Herceptin eventually. But there was still a big survival advantage strongly suggesting you want to be using it up front for your maximum survival advantage. But that's a bit of a fine point. I think people say, "Okay. Herceptin's great. It's associated with a survival benefit." I think the message that you really should be using it up front from these data to get your maximum survival advantage, I think that's a finer point. I'm not sure that that is as widely appreciated.

DR LOVE: What I found, if you look at the NCCN practice guidelines, if you talk to 20 or 100 people who focus all their attention on breast cancer, you find almost uniformly that people use Herceptin up front, in general. Is that your take, also?

DR O'SHAUGHNESSY: Yes. I think so. Some folks will use it by itself, particularly in the women that you're talking about.

DR LOVE: Sure. Sure.

DR O'SHAUGHNESSY: I think it's certainly possible, for example, that if you had someone where intravenous therapy was going to be a real problem for them, it's certainly possible somebody might give that person oral Xeloda, for example, because we still have little data combining Herceptin with Xeloda. What we have looks quite good, but it's really not out there yet in any major way, because the Phase II studies are still ongoing. So, that might be an occasional consideration. But, sure, breast cancer doctors who think about breast cancer all the time, I will agree with you, they really will use Herceptin up front pretty consistently. I know myself, I think of it as a given when I'm trying to decide what chemotherapy to give up front for HER2 overexpressers. I mean, it's like you're going down a divergent pathway. It's divergent. HER2 overexpresser, you've got to do something where you're going to have Herceptin in there. HER2 non-overexpresser, that's a different decision pathway.

DR LOVE: The way I've heard it expressed in the metastatic setting was, for the HER2 over-expresser, they're going to get Herceptin up front. The question is – are you going to give chemotherapy or just give it alone? Is that the way you think it through?

DR O'SHAUGHNESSY: Yes. Yes, I sure do. That's exactly right.

DR LOVE: The other interesting question, that I know there's been a lot of controversy is what do you do with a patient who you started on Herceptin for metastatic disease once they progress? Basically, what is your practice?

DR O'SHAUGHNESSY: That is a situation you face every day. It's a really good question, because patients always ask you that. I was really impressed with the original pivotal trial. There were some patients out there years in stable remissions on Taxol and Herceptin. I hold that one dear. So, what I say to women, if they're doing well on Taxol and Herceptin, or anything else with Herceptin, I say, "Look. Let's see how you're doing. If you're doing well on it, I won't stop it." I really don't stop it, because on Melody Cobleigh's study with single-agent Herceptin, too, she had some patients out, again, for years, as I recall.

DR LOVE: Well, the other question is, what do you do once the patient progresses?

DR O'SHAUGHNESSY: Right.

DR LOVE: Do you continue beyond? Or at least continue the Herceptin?

DR O'SHAUGHNESSY: Right. Well, of course, there's no data there, really, at all, in my opinion, to guide us. So, what we can only do is talk about what we're doing. What I usually do is, when I get around to using an agent that has shown remarkable activity in combination with Herceptin, I use Herceptin. So, Navelbine, Taxotere, and probably, now, Gemzar. I will give the Herceptin, because the levels of effectiveness that you're seeing with these combinations are much higher than we're used to seeing, albeit most of them are small Phase II trials. We have to bear that in mind, although the corroborative study that was done in Florida from Palm Beach for Navelbine-Herceptin, it was presented at San Antonio, came in with excellent Phase II results, just like the Dana-Farber study had shown. So, consistently, we're seeing very, very high anti-tumor activity with Taxol, Taxotere and Navelbine. Now some suggestion with gemcitabine.

Neil, I think that most doctors are trying to milk all the activity we can get out of these. Herceptin's very well tolerated. It's almost like you're not really causing harm to the patient. Many of our chemotherapy agents are given very frequently anyway, either weekly or – now we're getting more comfortable with every-three-week Herceptin. So, you don't feel like you're disadvantaging the patient and you're really hoping to get more mileage out of these chemotherapy agents, particularly when you get in the taxane-refractory patients. You're down now to response rates that are not very big. So we want to get all the mileage we can out of them.

I'll give you an anecdote. I am caring for a women now who Dr Bob Livingston had treated with Taxotere, Navelbine and Herceptin on a Phase II clinical trial. She had a fantastic response, and a long, durable response – lung disease, only. Then she moved to Dallas, and I inherited her. And she had progressed, unfortunately, slow, progressive disease. I treated her with Xeloda, and she responded, not quite as long. Then we went on to Alimta, an investigational drug that is an antifolate. We went onto that, and she did not respond to Alimta and was progressing. She had never had Taxol, so I decided to give her weekly Taxol with Herceptin. She's been in remission two and a half years even though she had already had Herceptin. Perhaps she would have done that with Taxol

alone. We don't know. But my gut is that's a darn effective combination for her. So, we all have these anecdotes, and I think that keeps us going. We use our clinical intuition on these things.

DR LOVE: Do you want to hear what these clinicians had to say about metastatic disease with chemotherapy and where XT fit in?

DR O'SHAUGHNESSY: Yes. (Laughter)

DR LOVE: We'll see if you can guess. I'll just pull a couple of numbers out here for you. For example, we had a case we presented, 43-year-old woman with bone mets who received prior AC, ER-negative, HER2-negative. Generally speaking, what would you do with a patient like that?

DR O'SHAUGHNESSY: Well, I'm thinking of a woman right now in my mind, precisely like her. And it depends, Neil, on how extensive her disease was and whether she was hurting. It depends on her disease-free interval.

DR LOVE: Asymptomatic bone mets.

DR O'SHAUGHNESSY: Asymptomatic bone mets. It probably would depend a little bit on her disease-free interval, as well. But I think, in that particular case, I would individualize to be honest with you. If she had a quick relapse and a lot of bony disease, even though it was asymptomatic, I would give her XT in combination. Conversely, if she really just had minimal disease, I might treat her with Xeloda by itself or I might treat her with weekly Taxol or weekly Taxotere by itself.

DR LOVE: Well, what was interesting was, about 45 percent of these docs said either Taxotere or Taxol, but about 20 percent said XT. We presented the same case in a 63-year-old woman. The exact same case and you have only a third of them saying one of the taxanes, and nobody saying XT. I thought it was interesting, because, to me, 63 is not that old for there to be that big of a difference in the perception. It seems like it was the age that was driving things.

DR O'SHAUGHNESSY: Mm-hmm. That's interesting. I think that's probably true, Neil. I think breast cancer in the forties is probably pretty different than breast cancer in the sixties, by and large. Of course, there's overlap, certainly. But, by and large, cancer in the forties is, I don't know, perceived as more of a significant life-threatening disease than metastatic breast cancer in the sixties.

DR LOVE: We had a 78-year-old woman who was ER-negative, HER2-negative, with bone mets, who's asymptomatic.

DR O'SHAUGHNESSY: Mm-hmm.

DR LOVE: Okay. 78-year-old woman, asymptomatic, ER-negative, HER2-negative, with bone mets with no prior adjuvant therapy chemotherapy. What we saw there was 20 percent vinorelbine, 30 percent Taxotere, and 15 percent capecitabine, and the rest sort of a smattering of others. What would you do with a patient like that?

DR O'SHAUGHNESSY: I will often pick either Navelbine or a low dose of Xeloda in those patients. There, you've got a wide variety of single agents to choose from, clearly single agents. Effectiveness is probably pretty close with the agents. And so you're looking for effectiveness and quality of life and if you can avoid hair loss, why not? So, I would either go with Navelbine or Xeloda. Because the only single agent that has a survival advantage as a single agent is Taxotere in the anthracycline pre-treated, and she's not anthracycline pre-treated. So, we really don't have those data pushing us there.

DR LOVE: We presented that same woman with ER-negative, HER2-positive. What do you generally do with that woman?

DR O'SHAUGHNESSY: I would give her Herceptin alone if she was totally asymptomatic.

DR LOVE: That was a common choice.

DR O'SHAUGHNESSY: Good. Yeah. That's neat.

DR LOVE: One more I want to throw out at you, which was – and we did this in the end of December, and what we did was, we also sent the physicians the summary slides from the ATAC trial, in case they hadn't seen it. We said, "What adjuvant endocrine therapy would you recommend for the following patients with ER-positive, HER2-negative breast cancer?" We started out with a 65-year-old woman with a 2.2-centimeter tumor and ten positive nodes. What endocrine therapy would you use for a woman like that now?

DR O'SHAUGHNESSY: I have been choosing Arimidex in the very high-risk woman, where her risk of death from breast cancer far outweighs any concerns about long-term effects. I want short-term benefit, and you want the best you can get. So, the data from the ATAC trial would certainly suggest that short-term, at least, Arimidex is better.

DR LOVE: It's interesting when you look at the numbers. I would have thought that people would have leaned earlier towards node-positive, very high risk, also. We didn't actually see that. It looks like about a third of physician who have just basically switched over in postmenopausal woman at this point, based on what they've seen, to Arimidex. And it doesn't seem to change that much. I mean, we presented the same woman with a 0.8 centimeter, node-negative tumor, and the percent saying Arimidex is basically the same.

DR O'SHAUGHNESSY: We've had to address this issue because of the adjuvant trial I was talking to you about. We had to really come to grips with this on the Breast Committee. And we're finding the same thing, about a third of physicians have gone over to Arimidex at this time. The others are either in the tamoxifen camp or wanting docs to have a choice. What we decided to do in this adjuvant chemotherapy trial I was talking about, is that we

are going to allow the doctors the choice, but stratify up front, for whether the patients are going to get tamoxifen or Arimidex. So, the docs are going to have to put their nickel down, if they have a postmenopausal woman that they're going to be randomizing on AC followed by Taxotere versus AC followed by Taxotere-Xeloda. They're going to have to decide up front if the patient's going to get tamoxifen or Arimidex.

DR LOVE: That's very interesting. I've heard that people are really struggling with that.

DR O'SHAUGHNESSY: Oh, we've been struggling. I wrote to the cooperative group chairs to get some input. It's a tough one, Neil, because if you are going to get just two or three more absolute percentage points out of your XT, compared to your T, which is all we usually ever get with an effective regimen. If it turns out, we've got an absolutely difference in the ATAC now of 2 percentage points, that, in my opinion, could easily be five points in five to eight years of follow-up. It could easily get better.

DR LOVE: Hmm. Interesting.

DR O'SHAUGHNESSY: So I've been very concerned that if we didn't stratify for tamoxifen versus Arimidex up front, that we were going to have uninterpretable data.

DR LOVE: Well, either that, or just focus on ER-negatives.

DR O'SHAUGHNESSY: Right. But, you're going to leave out 60 percent of your patients there. And we want to beat the NSABP in accrual.

DR LOVE: That's fascinating.

DR O'SHAUGHNESSY: We want to be first. We will be first. (Laughter)

DR LOVE: Well, that's really going to be a dilemma, because usually it's sort of a given that, in these chemotherapy randomizations, the people are going to give tamoxifen. And, as you mentioned the doc's got to give what they feel comfortable with.

DR O'SHAUGHNESSY: Absolutely, and one-third has gone over to Arimidex.

DR LOVE: Now, you talked about Arimidex. What about the issue of the adjuvant use of either letrozole or exemestane in a non-protocol setting. How do you feel about that?

DR O'SHAUGHNESSY: I am not using those out of the non-protocol setting. I'm using Arimidex in the adjuvant setting, because I try to stay as data-driven as I can.

DR LOVE: Yeah. One of the things that's relevant to the last question, we asked these docs in terms of which AI they would use, just what you addressed in terms of the fact that you're using Arimidex right now. And most of them pretty much said the same thing you did.

DR O'SHAUGHNESSY: At the end of the day, Neil, I think from an effectiveness standpoint, from an anti-breast cancer standpoint, my guess is that they will be very similar in effectiveness. At the end of the day it's going to be a balance of anti-breast cancer effects and other important effects for our breast cancer survivors, who, as you know, we cure most of them. They live a long time. It's going to be a balance of side effects, in terms of how they feel, bones, lipids, and, of course, anti-tumor activity, which we'd never sacrifice. But it may well be that they have very similar anti-tumor effectiveness. There may be an irony here – it may not be, at the end of the day, that you want the strongest aromatase inhibitor. It may be that you want a good strong one, but maybe not completely sucking the body dry of every estrogen molecule at the microenvironment level. It may be that that gives you a balance there of maintaining some bone density and some lipids, cardiovascular. What about the brain, etcetera? But I think the bone story is going to be very important.

DR LOVE: Do you have the sense that we're going to be able to follow bone density and just react to that without the patients getting in much trouble in terms of a non-protocol setting?

DR O'SHAUGHNESSY: I do, Neil. I think that what's going to probably happen – and I know I've been doing this myself ever since hearing the ATAC data – I've been thinking of bisphosphonates hand-in-hand with Arimidex in the adjuvant setting. If somebody is already known to have a little osteopenia – a lot of women will come in and they will have had a bone density and they'll know where they're at. If they've already got a little osteopenia, if I start them on Arimidex, I'm going to start them on weekly Fosamax or Actonel at the same time. I don't think that's a big deal.

DR LOVE: Well, plus, there's also the hint, although it was with clodronate, that maybe it's going to have an effect on the tumor.

DR O'SHAUGHNESSY: Correct. Correct. That's right. That would be interesting. I wouldn't be surprised at that. So, I think that's going to be an interesting story, as well. So, that doesn't really bother me, particularly the weekly bisphosphonates are quite well tolerated.

DR NEIL LOVE: If there is one buzz word that repeatedly comes up in interviews with breast research leaders, it's the concept of targeted and rationally derived systemic therapy. The capecitabine-docetaxel biochemical synergy is an example of how this strategy can be translated into improved patient outcomes. Targeted biologic interventions have been yielding benefits in breast cancer for more than a century since Sir George Beatson's discovery in the 1890's of objective tumor regression in women treated with oophorectomy. The biologic mechanisms involved in endocrine therapy have been the subject of considerable study, beginning with the discovery of the estrogen receptor, and our knowledge of the complexity of these systems is rapidly increasing. This year's Miami Breast Cancer Conference included a number of presentations reviewing the current state of the art, and I met with faculty member Dr Dan Hayes for his take on what this means to clinical practice today. He began by commenting on the rapid pace of research in this area.

DR DANIEL HAYES: One of the things that's come out at this meeting, but also in general in the last five years, is how much we thought we knew about the estrogen receptor by 1990 and how little we actually knew. The knowledge that we've learned about the biology of the estrogen receptor, how it works, how it interacts with the other growth factor pathways like EGFR and HER2, how those play out clinically and how complex that play-out is in the last five years is just mind-boggling

Every time I think I understand, if you're HER2-positive, you might not respond to hormone therapy as well, then another clinical trial comes out and says nope, that's not the answer. It's completely different. The complexity of this disease really is staggering, and that's why it's so hard to treat.

DR LOVE: That's funny. Yesterday, I saw Tony Howell put up this really complex schema and I'm sitting there thinking about the ones we had in the mid-'80s where there was the little estrogen flowing into the cell. But from the point of view of a clinician in practice, what are the things that really mean something in terms of the biology of the estrogen receptor?

DR HAYES: Well, it depends on precisely what you want to do. I think, if you're just giving pills to people, maybe not much. But most of us went into oncology – even, I think, most of people in private practice, for whom I have a lot of respect – because of the fundamental interest in the biology of the disease. I interview a lot of young people who want to go into oncology, and rarely do they say, "I want to go into oncology to make a lot of money," or "to make people's hair fall out." It's usually, "Jeez, as a med student and resident, I noticed that the biology of cancer is really fascinating, and even though I may not ever want to go in the lab, that's why I'm here."

So, I would say there really are important things to know. One of the conundrums of endocrine therapy is why multiple endocrine therapies work sequentially. You would think that, if they all work the same way, then one ought to work and then it stops. And that appears to be what happens in prostate cancer. Right? We don't have serial treatments in prostate cancer.

But in breast cancer, I think one of the concepts that has gelled in my mind in the last five years, that honestly maybe I thought of but never really had in a concrete fashion, is the concept of hormone dependence rather than hormone sensitivity. We think of sensitivity and resistance in terms of treatment, but I think now, more in terms of biology, that a cell starts out hormone dependent or hormone resistant – or hormone independent is probably a better word. And that the cell may stay, or the cancer may stay, hormone-dependent for many, many years, but become resistant to specific endocrine therapies. That's because these therapies work differently.

So, for example, we know you can treat a patient with tamoxifen; she can be sensitive to tamoxifen and then become resistant to it. Then we know that patient will respond to another endocrine manipulation, like an aromatase inhibitor. So, fundamentally, you would think that cell would be hormone independent if it is resistant to tamoxifen, but it's not. It's still hormone-dependent. So, the next therapy coming in works again by changing the hormonal milieu that that cell resides in.

DR LOVE: I think we've always gone off the antibiotic-resistant model in terms of how we view resistance to systemic agents in cancer. What I think I hear you saying is it's not like that.

DR HAYES: I think that's the wrong model, especially for endocrine therapy because our antibiotics all work differently. But in terms of endocrine therapy, I think we've learned so much. We now know about the complexity of a ligand, and it can be estrogen, tamoxifen, raloxifene, droloxifene or phytoestrogens that bind to an ER. Then we know that that changes the confirmation so that it's prone to phosphorylation, and the phosphorylation comes via the peptide growth factor signaling pathways. With phosphorylation, then one gets two ERs together and they dimerize, and then they go down and bind to the promoter of estrogen-sensitive genes, and then that calls for a piling on of coactivators and corepressors. And we know that there's then estrogen receptor alpha, which is the one we've always thought of. Now there's an estrogen receptor beta. We know that the estrogen receptor actually can bind to a different part of the DNA that doesn't have an estrogen response element in it, called AP-1. We always thought the AP-1 site was where the peptide growth factors were working with.

We're beginning to understand now why tamoxifen has this funny duality, being anti-estrogenic in some cells and estrogen; we could never understand that before. To me, it's fascinating, and, again, I'm a clinician. And this is playing out in the clinic. It's starting to explain why five years of tamoxifen might be preferable to longer. It begins to explain now why serial hormone therapies might work. It begins to explain the unexplainable observation of hormone withdrawal response. We've known about this for 50 years, but no one could ever really explain it. Now we're beginning to understand why that happens.

DR LOVE: Can you dissect out some of the major hormonal therapies in terms of what we understand right now in terms of mechanism of action using modern biologic understanding of the ER and, also, what happens when the cells become resistant? You would say they become resistant?

DR HAYES: Yeah, they become resistant to specific strategies. One thing I'm actually fond of saying it's always interesting to me how little history we remember. As we see Gleevec come on board, there's so much excitement about Gleevec being the first rationally designed drug that works that's targeted. That's baloney. In 1892, George Beatson

removed a growth factor from its receptor by doing oophorectomies and saw responses in two out of three women with locally advanced disease. In my opinion, that was the beginning of true designer-drug molecular medicine, if you will. We've been doing targeted medicine in breast and prostate cancer for 100 years.

It's just that we didn't entirely understand what we were doing. But for the last 30 years, we have with Jensen's discovery of the estrogen receptor, and then McGuire's discovery of the correlation between estrogen receptor and response, and so on and so forth. Again, this is just another step forward, in my opinion. So, I'm a little off your question, but I think the good news of endocrine therapy for breast and prostate cancer is we've known for 100 years that we can do target-directed therapy. We just needed to find the targets.

For years and years, people said, "Why are we doing this basic research? Why are spending all this money on this?" It's because ultimately, this has got to pay out. You get smart guys like Brian Drucker, who is a clinician and a lab guy, who starts to say, "Jeez, I can put two and two together and come up with four." I think Iressa is another example of that. Looks like it's going to be an active drug in lung cancer. There is a whole host of these coming down the pike.

Okay. Having said that, let's go back to breast cancer a little bit. We know that the so-called SERMs – tamoxifen, toremifene, raloxifene, droloxifene, and idoxifene – all bind to the ER just like estrogen does. They all induce phosphorylation. They all induce dimerization. They all induce binding to the ERE in the promoter of the specific genes. But what they then do is that they call for a different piling on, if you will, of different coactivators and corepressors that are already in the cell. So, how a specific cell responds to a specific ligand depends on a number of things – how much estrogen receptor alpha it has and how much estrogen receptor beta it has. That balance seems to be important, as well as what kinds of coactivators and corepressors it has sitting around. So, the cell is primed to see these things as estrogens or anti-estrogens. In fact, it's probably not even a specific cell. It may be even related to more the genes that are already turned on one cell versus another.

And so these ligands then have very different effects, even though they fundamentally do the same thing – induce dimerization, induce phosphorylation, and induce binding to ERE of the genes. But then you get different effects, and so not only is it the pre-existing state of the cell, it's then the way the ligand – and Craig Jordan, for example, has shown us a lot of this – it's the way the ligand itself fits into the conformational structure of the dimer. And that allows a different infrastructure for the same balance of coactivators and repressors to pile on and give you different downstream effects for the same gene.

So, the question is can we actually design new SERMs that really do exactly what we want to do; there are anti-estrogens in one place and estrogens in another, and the way we want them?

DR LOVE: We've been hearing Craig talk about that for a long time. Do you think we're ever going to get to a point where we get to that ideal SERM that he's been talking about?

DR HAYES: So, this is speculation, because it's just too complex for me to fully understand. But I said 15 years ago that I wouldn't spend any more time on endocrine

therapy, because I couldn't believe you could squeeze anymore effect out of the ER. "We've gotten all we could with tamoxifen" And I was absolutely wrong there, it appears. I've been wrong sufficiently in my life that I'm willing to have smart people like Craig Jordan prove me wrong.

The other one then is fulvestrant, Faslodex, coming down the pike. This is exactly the question you're asking, which is that, unlike the SERMs, in which you induce some biological response – and what the response is depends on the ligand – with fulvestrant it binds to the ER and completely shuts the system down. It stops phosphorylation, or prevents it. It keeps the ERs from dimerizing. It prevents binding to the ERE. It's truly an anti-estrogen. It was developed as a rationally designed drug to do just that. And it looks like it's going to be, again, a step forward. At least, it looks like it's going to be as active as the aromatase inhibitors, another set of designer drugs, rationally designed drugs.

Now I think it's almost an embarrassment of riches. The issue is how do we use these? When do we use these? In what order? As they're beginning to hit the clinic now, I'm getting phone calls from my colleagues in practice asking, "What order do I use these in?" Well, I don't think we know. I think that's the challenge for the major cooperative groups and the companies, is to start doing trials of serial therapy and combination therapies to see where we're going. Then, even more – I know this is a long-winded answer to your question – but now I think the real challenge is to start to figure out the other pathways that modulate these. I'm convinced what we're going to find – this is right down the alley to your answer to your question – that different subgroups of patients will actually respond differently to the different endocrine therapies.

So, just like we used to use ER to pick who gets endocrine therapy, I believe in the future we'll start using not only progesterone receptor and HER1, 2, 3, 4, and actually begin to start measuring some of the coactivators and corepressors, the amplified in breast cancer 1, which came out of the NCI with Paul Meltzer and now Kent Osborne, his group are looking at. Looks like they're going to start telling us, "Jeez, this patient should get tamoxifen or a SERM, this patient should get an aromatase inhibitor, this patient should get fulvestrant." We're a ways from that, but I think we're going to see that happen.

DR LOVE: Going back to the overall model of the estrogen receptor that you were talking about and the model that you described with SERMs and fulvestrant, a couple of questions. One is, going back to that model with the corepressors/coactivators, etcetera, in your mind, what happens to that system when the patient or the tumor becomes resistant to the SERM?

DR HAYES: Again, let's be very careful. Let's assume that the cancer is still hormone-dependent, but has now become resistant to the SERM. So, what's the mechanism of that resistance? We don't know for sure, but this, again, is where people like Craig Jordan, Kent Osborne and Suzanne Fuqua have been working very hard, also Rob Nicholson, to try to explain it. One possibility is that they begin to upregulate things like HER2 and epidermal growth factor receptor, and they get constitutive phosphorylation of the estrogen receptor, so that you get constitutive dimerization and then activation independent of the ligand. So, now you can throw all the ligand in you want. It doesn't matter. The ER's already doing what it wants to do.

DR LOVE: But it is a genetic, evolutionary change?

DR HAYES: I think all of these are going to be so-called genetic, evolutionary changes. The hallmark of cancer, of course, is replication and chromosomal instability, and genomic instability. These cancers keep changing on the basis of the fact that they can't control the stability of their genome, and you get all kinds of weird mutations. Coldman and Goldie predicted years ago – what's it been? Twenty-five years ago now – that you would get, based on this – they didn't know about P-53. They didn't know about the keepers of the genome – but they predicted that the hallmark of a cancer would be genetic instability, because they knew there were a lot of chromosomal abnormalities, and that you'd get mutations to and away from sensitivity and resistance. So, it's not like the cancer cell is thinking up ways to become resistant. The cancer cell is just genetically unstable. Every time it divides, it makes mistakes. Some of those mistakes are prone to sensitivity; some of those mistakes are prone to resistance. The sensitivity allows us to treat it, but, of course, the resistance is what gives us problems.

DR LOVE: So, you're saying one possible mechanism for that resistance, would be activation of the HER system?

DR HAYES: So, one possibility is activation of the HER.

DR LOVE: What's the relationship between the HER system and the ER system?

DR HAYES: It looks like, as far as we can tell, the peptide growth factors, in general – and the HER system is probably the best example of this – are responsible for this phosphorylation. They're the things that lead to a cascade of phosphorylating events down through a signal transduction pathway, and ultimately the ER is one of the targets. So, the ER is sitting around waiting to be activated. The way it's activated in the wild type is it has to have a ligand, estrogen, and when the ligand binds to the ER, it then seems to be conformationally susceptible to phosphorylation. When it's not bound to its ligand, it doesn't seem to be. But one way of getting resistance, therefore, is to figure out, teleologically speaking, how to become phosphorylated in the absence of ligand. Because then you're off to the races, if you're an estrogen receptor.

DR LOVE: And then once it becomes phosphorylated it activates the gene?

DR HAYES: It's not going to be this easy. It's like we were 15 years ago.

DR LOVE: You've got to make it easy. (Laughter)

DR HAYES: We thought it was going to be easy 15 years ago, and every time I'm at a meeting like this, I learn five more things. But it looks like phosphorylation and dimerization are the keys to binding to the DNA, to the estrogen response element in the DNA in the promoter region of the gene of interest. So one way to get there might be to figure out how to be phosphorylated and dimerized without a ligand.

DR LOVE: But then, if that were the case, you would think that, then, for example, if you lowered the level of ligands, say, with an aromatase inhibitor or an LHRH agonist, that it wouldn't have any effect if the HER2 system bypassed it.

DR HAYES: So that may not be an effect.

DR LOVE: So, how would you explain?

DR HAYES: I'm speculating now.

DR LOVE: Okay.

DR HAYES: So, that's one. Another might be mutating your ER so that it now becomes hypersensitive to individual ligands. If that's the case, then what you said would be precisely what you'd expect, which is that ligand-based therapy, the SERMs, might suddenly start acting like estrogens; whereas, ligand-annihilating or depleting therapy, like oophorectomy or LHRH agonist or antagonist and the aromatase inhibitors might still be affective. Again, you've still got a hormone-dependent cell, and it's now, if you will, searching even more for its ligand, than it used to. So smaller doses of the ligand or maybe even a ligand that used to be anti-estrogenic now are super-estrogenic, so, depletion would completely remove it.

The other is perhaps that phosphorylation makes the receptor super-responsive to the ligand. So, again, in that case ligand-depletion might be just what you want to do. This brings in when do you use fulvestrant? Because it's neither A nor B. It's ligand therapy that essentially is a suicide ligand, if you will. It binds to the ER and keeps all the downstream stuff from happening.

DR LOVE: You mentioned suicide because the ER is lost from the cell?

DR HAYES: Yeah. I guess suicide is a bad word.

DR LOVE: Well, but the bottom line is, the ER goes away, so to speak. Why does that happen?

DR HAYES: Well, because there's a constant turnover in the estrogen receptor. I guess it's not so much that it disappears, per se. That's probably part of the natural process of the turnover, but that, while it's there, it's completely inactivated, because it can't dimerize.

DR LOVE: But it is kind of weird that you actually lose it from the cell, at least the way we measure it.

DR HAYES: Yeah, it looks like it. I think Craig Allred might be able to give you a better answer than I can on that.

DR LOVE: Speaking of Craig Allred, another question I had as you were talking about

this biology is, what is the current thinking in terms of to what extent this whole system is altered in the basic development of breast cancer? I mean, is it an alteration in the estrogen receptor system and all these coactivators that really is the essential defect that you see in breast cancer? Craig has shown that you see, I think, actually more ER in early stages of carcinogenesis than in the normal development.

DR HAYES: Well, I think one of the things that's evolving – I guess a fundamental question is – are all breast cancers estrogen-receptor-positive from the get-go, and then estrogen-receptor-negative cancers evolve out of those? Or, are there fundamentally two kinds of breast cancers from the get-go, and one is estrogen-dependent and the other one's estrogen-independent?

I think it's sort of a mixture of those, but I believe, from the get-go, there are fundamentally two cells that become malignant. Again, this is where some of the work from Craig Allred and others are beginning to tell us, of course, that not every epithelial cell in the breast is endocrine-dependent in the wild-type breast. In the normal breast, some are, some aren't. We really don't know what the stem cell is for the development of any epithelial cancer, let alone breast cancer, but I think another area of really active research is trying to find the epithelial stem cell. I believe, in the next five years, you're going to see that area explode. There are laboratory studies going on now, some of which are published, some of which are not, that are going to tell us what actually becomes cancer, what the cell is that becomes cancer.

I think what we're going to find is that from long before we call it cancer, when it's ADH or even before we call it ADH, there are cells dedicated to becoming cancer, that are estrogen-independent, and cells dedicated to becoming cancer that are estrogen-dependent. And I think that's where the two flavors of cancer grow out from, those that are ER-independent and those that are ER-dependent.

Now, I think the ones that are estrogen-dependent, ultimately, the patients we don't cure unfortunately, do become estrogen-independent. But I think that's probably actually much farther down the road, as you get more and more genetic instability and finally you begin to get clones growing out that no longer need hormones to grow and divide and do all the things they want to do. But I think that's actually a pretty late event.

Early on, I think there are two cancers to start with, and this raises, I think, issues of preventive strategies and treatment strategies. We focus an awful lot on the hormone-dependent cancers, which we should. Clearly, breast cancer has something to do with estrogen. I'm fond of telling my patients that when I was 17, I began to realize that the female hormone system confused me, as I was dating, and now that I'm 50, it really confuses me. It's very complex. And clearly, breast cancer has something to do with the estrogen and the female endocrine system, but we don't understand it entirely. In fact, we don't understand a lot of it. We don't know does estrogen really cause breast cancer? We know it's associated with an increased risk of breast cancer, but we don't know that it exogenous estrogen causes breast cancer.

DR LOVE: Looking at Craig Allred's work, sometimes I've had the thought that maybe what the problem is, is the estrogen receptor itself, like more estrogen receptor or being more sensitive to estrogen.

DR HAYES: Well, people have tried to call estrogen receptor an oncogene. Are there fundamental defects in the estrogen receptor that lead to the oncogenic process? And that's been hard to do. We've not found – Suzanne Fuqua may be the closest to that now, with these mutations, and the estrogen receptor becomes hypersensitive to estrogen. But I think that we need a lot of work on that.

DR LOVE: Well, maybe part of this co-repressor/activator mix?

DR HAYES: What we've not found are amplifications or activating mutations, the classic things we think of as oncogenic steps, like we have with HER2 amplification or go back to the real oncogenes, myc and ras – mutations that are clearly oncogenic. You can't transfect cells normal cells with estrogen receptor, multiple copies, and make them become cancer, to my knowledge. I don't believe Suzanne has been able to do that with this mutated ER. What I do believe, it's probably a secondary phenomenon. I think there are other hits in the cell that produce genomic instability, P-53 mutations, and a variety of things like that. Then, in the right milieu, that's where you begin to get cancer. So, in the right milieu, you've got difference in coactivators, you begin to get changes in the way they're expressed because of some upstream change in P-53 or BCL-2 or BCL-X, or whatever. And that begins to result in downstream effects that, in and of themselves, aren't oncogenic, but set the cell up to be more responsive to external stimuli like estrogen.

DR LOVE: Getting back to your basic model of the endocrine-dependent breast cancer cell, you talked about SERMs, Faslodex. You would assume that aromatase inhibitors and LHRH agonists, that's fairly straightforward. You're just taking the ligand away, correct?

DR HAYES: Well, it's straightforward except I think we're going to find the mechanisms of resistance to these things are going to be complex.

DR LOVE: Do you want to talk about that?

DR HAYES: Well, again, I think it has to do with the biology of the cell. In theory, for example, if the aromatase inhibitors are blocking peripheral conversion of DHEA and testosterone to estradiol, which is what we think they do, then one shouldn't get resistance to those, because those are sematic enzymes out in the fat. So, they're not prone to the genetic instability that cancer cells are. But we know that resistance develops to these things. Is my point clear?

DR LOVE: Yeah. But, I mean, my understanding was that cells just become sensitive to a lower level of ligand or estrogen.

DR HAYES: So, then we have to start saying, why is the cancer cell figuring out how to get around this, because it's obviously not the target of the drug that's getting around it? One explanation actually is, perhaps the cancer cells themselves are making aromatase. And they're making an abnormal aromatase that's just happy as a clam turning DHEA and testosterone into estradiol, because they have mutated or some other reason, because they are prone to the sematic changes relative to the instability of the malignant genotype, as opposed to the normal fat cells, which are not. So, that's one explanation. And, again,

Tony Howell and others have looked very hard at the aromatase in the cancer cells themselves. That's still an ongoing question, but that's one mechanism of resistance that's possible. Again, this is all speculation.

Another is, of course, that the cell ultimately becomes hormone-independent. So now, no matter what you do, that cell's being driven. I tell my patients it's like taking a car that drives on gasoline – so, if the estrogen receptor is the gas tank and estrogen is the gasoline – now you retrofit it with solar panel. So, it might still have an estrogen receptor, but it's running on solar power. And, so maybe the HER2 or insulin-like growth factor, we don't know – some other factor starts pushing the cell and driving the cell, and it becomes hormone independent.

A third is, it's still hormone-dependent, but there are things that have happened that make it, for example, hypersensitive to really small amounts of estrogen. In that case, you would expect that a drug like fulvestrant might work when those drugs quit working. In fact it hasn't been published yet, but Kent Osborne has been talking about the results of the Faslodex versus Arimidex trials, especially the U.S. trial, in which responses are longer with fulvestrant than they are with Arimidex. His explanation for that is precisely this, that Arimidex may be shutting down estrogen levels by 99 percent, but that the cell has become super-sensitive to that one percent of estrogen; whereas, fulvestrant just doesn't let the estrogen get there in the first place. So, again, there are a variety of explanations. I think, probably, there are more that we don't know.

I believe, first of all, this is why most oncologists went into the business, because of this fascinating biology. I think, if you're in the field, it's important to understand this, because I think it's going to dictate how we use these drugs in the next five years. We don't know what to do yet, but I think we will.

DR LOVE: It is great stuff, and this conversation reminds me of some of the conversations I've had with Craig Jordan. When we start talking about mechanisms of action, mechanisms of resistance, and go down these kinds of topics, one of the things I like asking him is what his thoughts are about the additive hormonal therapy, such as high-dose DES, progestins, and particularly the high-dose androgens, which he has made the analogy to of eye of newt and that he has no clue. Do you have any clue? (Laughter)

DR HAYES: Well, I was going to start out and say, of course, none of these are my ideas. They're all Craig's and Kent's and Tony Howell and John Robertson – and it goes back to the real giants in the field, long before any of us were even born. But, anyway, I think we're beginning to understand this. It's always been counter-intuitive that the treatment of choice for breast cancer prior to the time we had tamoxifen and all these fancy things, and even chemotherapy, was, of course, pharmacological doses of estrogenic-like therapies, like DES. This has been forgotten. But I think we can now begin to go back and say, "Oh, I get it. Now I understand why pharmacologic doses of estrogen..." And we saw a very interesting slide yesterday from Tony Howell, showing this sort of biphasic response of MCF-7 cells to pharmacologic doses of estrogen. In fact, I think those were Rob Nicholson's data, as I recall he said. I hadn't seen the slide – showing that with no estrogen, these cells won't grow, because they're hormone-dependent. This is cell culture work, at modest doses of estrogen, they grow quite nicely. Just what you'd expect. And at high doses of estrogen, they quit growing again.

DR LOVE: But that's kind of an empiric observation. What do you think is happening in that system?

DR HAYES: So, that's consistent with the clinical observation. But then he also showed that if you precondition those cells in different levels of estrogen to start with – so, now they've set their reset button, and I don't know what the reset button is.

DR LOVE: Well, that's what I want to know.

DR HAYES: Yeah. Well, me, too. And there are people with a lot more money than you and me who want to know. But, if you precondition those cells, then you still see this biphasic response, but it's shifted to the right or left in regards to the estrogen concentration that's in the soup. That may be really critically important. That may actually begin to explain all this, that is that the cell, for example, may have different coactivators and different corepressors under one estrogenic condition, and then you slam it. You change the hormonal milieu and suddenly that cell says, "Oh, I can't do that." And then, after a while, it starts to reset its coactivators. Again, this is the eye of newt. I'm making this up, but I think this is what we're going to find with people smarter than you and me, who are going to do all this in the lab.

So, what's that got to do with the clinician? I think what we're going to learn is that a patient, for example, who was on hormone replacement therapy, might have a very different hormonal milieu when they're diagnosed, than a patient who was not. And we might want to treat them differently. Now, that's not ready for prime time in the year 2002, but I think it may be in the year 2010. I think we're beginning to understand the molecular basis of hormone dependence and, therefore, hormone treatment and, therefore, hormone resistance.

DR LOVE: That's interesting. I wonder if people have looked at response to different hormonal therapies based on whether the woman was diagnosed on HRT.

DR HAYES: Not to my knowledge, but I'm not the first guy to think of this. So, I think you're going to see stuff. But you almost wonder whether just, boom, stop the estrogen, and that alone is probably hormone adjuvant therapy, endocrine adjuvant therapy. Nobody's every done that. I don't think they ever will, but, you get a hormone withdrawal response, essentially.

DR LOVE: You referred to adjuvant aromatase inhibitors and, of course, now we're all looking at the ATAC trial data.

DR HAYES: Yeah, I'd like to talk about that. All of us, I think, are very enthusiastic over the potential of the aromatase inhibitors. But I think we need to be very cautious about over-interpretation of the ATAC data as they stand, and especially about implementing their therapy in the adjuvant setting. And why be cautious? I'll take a step back. Why be enthusiastic? It's because of preclinical data and because of the data in the metastatic setting, we believe that the aromatase inhibitors are at least as effective and probably more effective than tamoxifen, especially in the long run. And so these data fit our bias.

The downside is the real concern about potential major complications with these drugs. The obvious one is osteoporosis. This is not the only aromatase inhibitor versus tamoxifen trial going on. There are at least two others that are similar in design, and then there are two others in which women have got to five years or are randomly assigned to aromatase inhibitor versus placebo. I think we need to see those data, as well as more mature ATAC data before we routinely offer all our patients aromatase inhibitors in the adjuvant setting in the postmenopausal patient.

I will say, though, that for the occasional patient for whom tamoxifen appears to be inappropriate – she has a past history of deep venous thrombosis, she's an older woman who's had a stroke or a TIA, she clearly has an allergic reaction to tamoxifen with a rash that won't go away – those are patients I have already been using aromatase inhibitors in, and I think it's appropriate, now.

DR NEIL LOVE: Another important targeted treatment strategy in breast cancer involves the HER2 and EGFR systems. The June 5 issue of the Journal of the National Cancer Institute contains two important new reports on quality control of HER2 testing based on data from ongoing Intergroup and NSABP adjuvant trastuzumab trials. I met with Dr Melody Cobleigh, a key clinical research leader in trials of Herceptin, to learn of her take on these and other recent research developments in biologic therapy. However, like most recent interviews with breast cancer investigators, our discussion began with the big research news story of the year, the ATAC trial.

DR MELODY COBLEIGH: I was surprised by the results mainly because the combination was equivalent to tamoxifen and anastrozole was better. There are theoretical reasons for that, but at any rate we are faced with these results of an aromatase inhibitor being better than tamoxifen. They are very early results and most of the patients were node negative. So while it looks impressive in terms of the p values, I would be delighted to see more long-term information, and particularly more information on toxicity. I would say that the results are provocative. I certainly don't plan on switching people who have been on tamoxifen thus far. For high-risk patients, for example, node-positive patients I would tilt toward using Arimidex. I'm not sure about the node-negative patients yet.

DR LOVE: De novo?

DR COBLEIGH: Right, de novo.

DR LOVE: I guess another question would be, is it just going to be Arimidex or you are going to look at letrozole and exemestane in terms of adjuvant therapy?

DR COBLEIGH: That's a wonderful question, and right now, I would just consider Arimidex because that's the drug that has been proven. There isn't any information on these other aromatase inhibitors. On the other hand, are we going to have to do prospective randomize trials in the adjuvant setting in every single one of these drugs? But in terms of the bottom line, if I were going to pick an aromatase inhibitor to use in the adjuvant setting it would be anastrozole.

DR LOVE: What about the patient, let's say a node-positive patient who is ER-positive, who starts out adjuvant chemotherapy menstruating and finishes chemotherapy amenorrheic and is proven by endocrinologic profiles to be postmenopausal?

DR COBLEIGH: I think you have to be very careful there because while chemotherapy can induce amenorrhea quickly, that is reversible. The World Health Organization definition for menopause is a year since your last period. So, for the patient who was premenopausal prechemotherapy who is now, not menstruating postchemotherapy, I would not put that patient in an aromatase inhibitor.

DR LOVE: 43-year-old woman who has 5 positive nodes, strongly ER-positive, finishes chemotherapy and she's still menstruating.

DR COBLEIGH: Tamoxifen.

DR LOVE: Do you use ovarian ablation in that situation at all?

DR COBLEIGH: No. There is still not a trial that has shown that chemotherapy plus tamoxifen in an ER-positive premenopausal patient is inferior to chemotherapy plus ovarian ablation.

The other thing that I think is of practical importance is this business about using neoadjuvant endocrine therapy. The initial paper using letrozole produced phenomenal results, and there was a poster looking at anastrozole in the neoadjuvant setting that produced the same pathologic complete remission rates as chemotherapy. That's amazing to me because you see 3A or 3B breast cancer and immediately you reach for your chemotherapy prescription pad. Thank God for the Europeans because they had the courage to give them hormones and it looks like it's just as effective as chemotherapy. It's obviously a much more benign thing to do. So, I think I'm going to be trying that.

DR LOVE: Haven't done it yet?

DR COBLEIGH: No, I haven't done it yet. The Ellis paper impressed me, but now that I've seen this in the anastrozole paper, I'm going to do it particularly in an older ER-positive patient who presents with advanced disease.

DR LOVE: Maybe this is getting a little bit ahead of the game, but if we are going to start moving towards using adjuvant anastrozole maybe we'll start to get into the same mode of chemotherapy. We know if they have a 2-centimeter tumor, they are going to get the chemotherapy anyhow, so why not give it to them upfront, shrink it down, maybe make it more likely for best conserving surgery and see what happens in vivo with the tumor? Maybe that's where this will all come together and that they know there are going to get anastrozole post-op anyhow, maybe give it to them pre-op.

DR COBLEIGH: Right.

DR LOVE: I mean not just for locally advanced breast cancer.

DR COBLEIGH: Well if it makes sense in locally advanced breast cancer, it would make sense to give it earlier if you are going to use neoadjuvant therapy.

DR LOVE: Yeah, I'm thinking of a woman who has a 3-centimeter tumor who is not going to be amenable to lumpectomy because she has a small breast.

DR COBLEIGH: The problem there is that since we have these survival advantages that have been shown for doing chemotherapy plus hormonal therapy, I think you have a little bit more difficulty.

DR LOVE: You mean as adjuvant post-op?

DR COBLEIGH: Right.

DR LOVE: Well there's no reason you can't give anastrozole pre-op and then anastrozole and chemo post-op, is there?

DR COBLEIGH: No, but when you're dealing with a curable situation I think you would need a trial to pop to that.

DR LOVE: I think actually, the Europeans are thinking about that kind of a trial.

DR COBLEIGH: That makes a lot of sense.

DR LOVE: Yeah, I'm thinking so what they're talking about is a 2 x 2 design, randomized pre-op and then randomized post-op.

DR COBLEIGH: This makes sense.

DR LOVE: So what kind of patient would you be thinking about in terms of using neoadjuvant aromatase inhibitors?

DR COBLEIGH: I would say particularly a postmenopausal patient who had 3B breast cancer, where the knee-jerk reaction is to go to chemotherapy and maybe that hormonal therapy is more effective. Certainly, from that anastrozole paper, anastrozole produced the same pathologic complete remission rate as was presented in the NSABP study of AC followed by Taxotere. That was astounding.

DR LOVE: You been involved in some of the key trials of Herceptin. One of the issues that has gotten a lot of attention is HER2 testing. Where do you see that right now?

DR COBLEIGH: I feel very strongly that if you're going to get Herceptin, you ought to have your tumor FISHed. There's all of this argument going on about how it's more expensive to do the FISH testing than it is to do the IHC. Well it costs about $50 to do a FISH test and it costs about $5 to do an IHC test. But it costs an awful lot of money to get Herceptin. So I think we really need to get it right, in terms of thinking about treating a patient with Herceptin. I would even go one step further and say I think we ought to get it right from the standpoint of adjuvant therapy. Women who have the HER2 alteration tend to benefit from anthracyclines, and probably shouldn't be denied anthracyclines as long as they have a healthy heart. So, I'm for FISH testing.

DR LOVE: Does that mean if a patient comes to you who has an IHC of 3, for example, you are going to FISH them before they get the Herceptin?

DR COBLEIGH: I will FISH them because they may not have the amplification.

DR LOVE: What about patients with a zero or 1 by IHC?

DR COBLEIGH: I'll FISH them too, because 3% of the zeros are amplified and 7% of the ones are amplified. So, again it's a matter of getting it right, and it's a matter of life and death.

DR LOVE: I've heard people say they will FISH patients that are zero and 1 if they have a clinically aggressive course, is that what you do?

DR COBLEIGH: I just FISH them all.

DR LOVE: So every single patient with metastatic breast cancer gets a FISH in your practice.

DR COBLEIGH: Yes.

DR LOVE: Makes sense to me. I think there's been a lot emphasis on false positives and people being treated unnecessarily. I agree with you and it bothers me because we know that breast cancer and all cancer patients for that matter are interested in even minor chances if they can benefit. You're talking about spending $50 dollars to find that out.

DR COBLEIGH: Right.

DR LOVE: How do you approach the patient with metastatic breast cancer who is HER2-positive, and let's start first with ER-negative?

DR COBLEIGH: That patient, if she does not have life threatening disease, I would treat her with Herceptin as a single agent. If you look at the trial that was done by Chuck Vogel — the front-line Herceptin trial — and look at the disease characteristics of that group versus the group that went into the chemotherapy with or without Herceptin trial, you see that they are a very, very similar patient population. And the longevity, the time-to-tumor progression and so on, was the same in the Herceptin alone versus the Herceptin plus chemotherapy. Now that's not a direct comparison, but the model that we have always used in breast cancer is that, we can't cure metastatic breast cancer and so you use the treatment that will be most likely to put the patient in remission with the fewest side effects. Clearly, Herceptin as a single agent is a more benign treatment than Herceptin plus chemotherapy. So that's my algorithm.

DR LOVE: Of course we don't have the comparison and then I hear people saying, "we know that there is a survival advantage by combining it with chemotherapy, and we don't know that for a single agent."

DR COBLEIGH: That's correct. We do not have a prospective, randomized trial, but this is one of those situations where I think I would like to use my best clinical judgment. I certainly have never lost a patient whom I started on Herceptin as a single agent. If the patient is progressing, you can always add the chemotherapy. The difference between Herceptin and hormonal treatment is you don't have to wait six weeks or eight weeks to find out if it works. When Herceptin works, it works very, very quickly, often within a couple of weeks. So if it's a patient who does not have life-threatening disease, I don't think you'd lose anything by giving them a month of Herceptin and see how things are going.

DR LOVE: That's interesting. When you talk about not having life-threatening disease is that the same kind of criteria you're looking at in the ER-positive patient?

DR COBLEIGH: Exactly the same criteria. In other words, if you've got some time, take it slowly, do it the benign way, and see what you get.

DR LOVE: When you do start Herceptin whether it's alone or with chemotherapy, first of all, I assume you continue at least until the patient progresses?

DR COBLEIGH: Yes.

DR LOVE: And, what about beyond that?

DR COBLEIGH: In terms of using Herceptin, as long as it works.

DR LOVE: Let's say you start the patient on Herceptin and chemotherapy and then they are progressing, do you stop both or do you just switch the chemotherapy?

DR COBLEIGH: So if a patient's on combination chemotherapy plus Herceptin, what do I do when a patient progresses? As you know, there isn't any information on this in terms of clinical trials, but one of the things that has consistently been true in the Herceptin story is that the laboratory models have predicted what was happening in the clinic. And what the laboratory models show us is that Herceptin when combined with most chemotherapeutic agents is more effective than when a chemotherapeutic agent is used alone. So I err on the side of expense because I believe the laboratory information. Until I see a trial that shows me that this is not true, I do continue the Herceptin along with the chemotherapy.

DR LOVE: Do you continue it indefinitely as long as you are actively treating the patient, or do you stop at some point?

DR COBLEIGH: I continue it indefinitely.

DR LOVE: In the patient who has life-threatening disease and you want to use chemotherapy, what drug do you tend to use?

DR COBLEIGH: If the patient hasn't seen a taxane previously, I would use Taxol plus Herceptin.

DR LOVE: And the next chemotherapeutic agent you would use?

DR COBLEIGH: Navelbine.

DR LOVE: There is a trial now that's going to compare the two? Any gut feeling about the relative efficacy?

DR COBLEIGH: They probably will be identical.

DR LOVE: Let's go over to the ER-positive side of the equation. ER-positive, HER2-positive, how do you approach those patients granted there aren't that many?

DR COBLEIGH: Again, if you have time, you can take the benign path. I would start that patient, if she was premenopausal on tamoxifen, and if she was postmenopausal on an aromatase inhibitor. If she progressed, then I would add Herceptin.

DR LOVE: And continue the hormonal therapy?

DR COBLEIGH: Yes.

DR LOVE: Let's say she responded to the hormone and then progressed, and you wanted to use another hormone, would you keep the Herceptin going?

DR COBLEIGH: Yes.

DR LOVE: One of the things that always comes up is the 43-year-old, ten-node-positive, HER2-positive patient. There's the question of using adjuvant Herceptin off protocol in a situation like that, any thoughts?

DR COBLEIGH: I haven't done it. Since the clinical trials started I've only been putting patients on the clinical trials, and I certainly have had patients go elsewhere to get Herceptin off protocol. I think that the bone marrow transplant situation taught us a lot, and we really need to get this answer quickly. We had preconceived notions about how transplant would work and now we know. So that's my policy.

DR LOVE: Inflammatory breast cancer?

DR COBLEIGH: We have a clinical trial that uses Herceptin with inflammatory breast cancer, so in the context of that clinical trial, we do use it.

DR LOVE: What is the trial? Who's doing it? What phase is the trial?

DR COBLEIGH: It's uses induction Herceptin plus Taxol for 12 weeks followed by AC for 4 cycles, followed by definitive therapy, followed by Herceptin plus radiation therapy.

DR LOVE: So it's a Phase II?

DR COBLEIGH: It's a Phase II study.

DR LOVE: What about Stage IV NED, a patient who has her mets taken out and they are HER2-positive?

DR COBLEIGH: (Pause) I would not treat that patient. Again, because it's tough to improve upon the asymptomatic patient. The reason why I hesitated is because I have seen a couple of patients with local-regional recurrences who were HER2 amplified, and in that situation the standard of care would be to remove the node and radiate. Nobody knows what to do after that, whether to give them chemotherapy or not. In those patients I have used Herceptin plus chemotherapy followed by Herceptin plus radiation, and then stopped the Herceptin. In other words, I've thrown the book at them. One of them I met about two years ago and she's doing fine. The other one I met about a year ago and she's doing fine.

DR LOVE: Any thoughts in terms of the optimal schedule of delivering Herceptin?

DR COBLEIGH: Every three weeks.

DR LOVE: That's it, end of sentence.

DR COBLEIGH: End of sentence. It's not FDA approved, but the data are there, and I think it will be eventually approved by ODAC (Oncologic Drugs Advisory Committee). It's so much easier on patients and it just makes so much sense.

DR LOVE: Any other issues about Herceptin that you'd like to bring up, mistakes to see being made in the community or things you disagree with?

DR COBLEIGH: Well, I like to call this Larry Einhorn phenomenon. Larry was the one who basically came up with the regimen that cured testicular cancer. What happened after that was he rarely saw a de novo testicular cancer anymore; he just saw the failures. I think that there are some very important questions that are about to be asked in HER2-positive patients. The trials are designed such that these patients have to have been Herceptin naïve. It would be a real shame if this resource were not placed in the clinical trials. For example it looks like there is a connection between the HER1 and HER2 pathways and there is a study that is being initiated by ECOG that's looking at the combination of Iressa and Herceptin. It's a very important study. But we see very few untreated HER2-positive patients anymore.

Another concept that is extremely important is the idea that there appears to be a connection between the HER2 pathway and the angiogenesis pathway. So a trial that is about to be initiated is looking at the combination of Herceptin and anti-VEGF. Again, these people have to be naïve to Herceptin. So, I guess my hope is that patients will become aware of these trials, the doctors will become aware of these trials. It's such a small percentage of patients and that they will enter them into these clinical trials or if they are not available, physicians will refer them specifically for that trial. Not that you would send the patient forever, but just for the purposes of these trials that are asking novel questions.

DR LOVE: Last time I saw you one of the things that I remember very clearly that you mentioned to me is how vexing it was to you why people don't respond to Herceptin and what the mechanism might be. Have you any clues to that since we last talked?

DR COBLEIGH: Well, no. But let me tell you about the MASH Unit. MASH stands for Molecular Assessment of Sensitivity to Herceptin. We have established collaboration with the original Herceptin investigators and we have retrieved blocks from the people who were treated with Herceptin as a single agent. The problem with addressing that question is, you can't look at people who've gotten Herceptin plus chemo because the molecular alterations that occur you don't know if they are from the chemo or from the Herceptin. So we are up to 70 blocks and, protocol has been IRB approved for this, both clinical and tissue repository, and hopefully I'll have an answer for you in another year.

But the idea is that this MASH Unit will create tissue arrays from these tumor specimens, and then anybody who has an interesting question about sensitivity or resistance to Herceptin, will have sections from those arrays made available for testing whatever novel idea that that individual wants to test. This is for not just for private or academic institutions, but even for companies who have an interesting idea about a diagnostic they would like to investigate.

DR LOVE: So the idea is that you might be able to empirically just find something that correlates with response, sort of to further refine down HER2 so to speak?

DR COBLEIGH: Right, but there's more known about the pathway now and so, a rational thing to do would be to look at downstream elements in the pathway to see if they're somehow modified, so that doing something upstream doesn't even make any sense.

DR LOVE: I guess the other thing would be, it might be interesting to do the same thing, and I don't know if it's going to be done in the Iressa-Herceptin trial that you mentioned, but to do it in that kind of trial.

DR COBLEIGH: Right. And, I think everybody has gotten the message now that if you do a trial with a novel biologic you better get the blocks. The problem with the original Herceptin trials is the blocks were not obtained and so now we need to ask that question in a difficult situation. Many people are using Herceptin with chemotherapy, that's the way it's FDA approved in terms of front line therapy. So we need to get these old blocks and we are also accruing patients to this archive or this repository who are receiving Herceptin as a single agent who were not on those original trials.

DR LOVE: Any pet theory about what the problem is or where the point is where there is a problem?

DR COBLEIGH: My guess is that it's downstream of the receptor and people have their pet molecules. AKT is probably a good bet. But it maybe multiple hits or maybe different hits in different patients.

DR LOVE: You went through your algorithm for the HER2-positive patient, what about the HER2-negative patient? And let's start with ER-negative in the metastatic setting?

DR COBLEIGH: That is the most depressing patient to meet. You're waiting for the markers, you're hoping you have something to work with, and everything that's benign is negative. The only option is chemotherapy, so I would give that patient chemotherapy.

DR LOVE: What kind?

DR COBLEIGH: Depends on what kind of chemotherapy she's had in the past.

DR LOVE: Let's start with no chemotherapy in the past.

DR COBLEIGH: Well, there is an old fashion regimen called M'F, which was described by the NSABP and was one of the forerunners to their B-13 trial. You don't lose your hair; you don't vomit; you don't end up in the hospital with a neutropenic fever; and you don't become postmenopausal. It's given day one, day eight, every 4 weeks. It's easy, so that's probably the one that I would use.

DR LOVE: Interesting. You like to be different, don't you?

DR COBLEIGH: You can give it forever. There are no cumulative neurotoxicities

DR LOVE: Interesting. So do you do that much?

DR COBLEIGH: Yeah

DR LOVE: No kidding. Wow.

DR COBLEIGH: It's cheap!

DR LOVE: What about the patient who has had prior AC recently and relapsed? Don't tell me you're going to use M'F again?

DR COBLEIGH: (Laughter). I do actually think that M'F is an option in that patient. Ok so let's move beyond M'F. Let's say that that's the only thing she's had, I would probably use a taxane. I think that weekly Taxol is very easily tolerated, except for the visits. So that's the direction in which I would move.

DR LOVE: Patient has prior ACT.

DR COBLEIGH: There are a number of options, but I think one of the easier ones for the patient is Xeloda. It is oral. It is a visit to the doctor once every 3 weeks. I'm extremely impressed by the activity of Xeloda. We've used it a lot because we've been participating in the Xeloda with or without anti-VEGF trial, and I'm impressed with two things. One the response rate to Xeloda, on its own, but secondly the fact that they can tolerate very large dosages. Many people can tolerate the doses that were described in the original trial of 2500 per meter squared. We had to start with that in this trial, normally I would have given a lower dose, but anyway it works.

DR LOVE: Off protocol what dose are you usually using at this point?

DR COBLEIGH: I would start with them at 2500 per meter squared, but I think the patient education piece is really important. At the first sign of anything in the hands or the first sign of diarrhea, we have a call in program. If you monitor the toxicity carefully many patients can tolerate the higher doses amazingly well. At the first sign of toxicity you drop back with a 25% dose reduction, and so on.

DR LOVE: When you take that type of aggressive patient education approach, how often do you see a problem that really is bothersome in terms of hand-foot?

DR COBLEIGH: Only when the patient decides not to listen to you. Some patients have this idea that "if I hit this really hard, I'll be cured or that I can take this." That's a really bad strategy.

DR LOVE: Are there patients that you'll use Xeloda before a taxane?

DR COBLEIGH: I haven't done that yet, it may just be because that's what I'm used to doing, but I don't think there's anything wrong with that necessarily. The drug is approved by the FDA for people who have progressed after an anthracycline and a taxane. But I don't frankly think there's anything wrong with using it any sooner.

DR LOVE: Any gut feeling about what the relative activity of Xeloda versus the taxanes?

DR COBLEIGH: No.

DR LOVE: What about combination chemotherapy, do you use that at all?

DR COBLEIGH: Nope.

DR LOVE: Life threatening disease?

DR COBLEIGH: (Pause) OK (Laughter). If it's really life threatening.

DR LOVE: What kinds of combinations are you using in that situation?

DR COBLEIGH: Again it has to depend upon what the patient has had before, but AT for someone who's not had an anthracycline or a taxane recently. Xeloda-Taxotere is another possibility for someone who's recently progressed on an anthracycline. But that's the rare patient, and I think it's really unfortunate that patients with metastatic breast cancer who are not curable are routinely getting combination chemotherapy, when single sequential agent treatment is just as effective in terms of survival. I think that the model for a clinical trial in terms of comparing regimen A with regimen B, is E-1193 of the ECOG study that looked at adriamycin versus Taxol with a crossover at progression versus the combination of the two. Here you have two of the most active drugs in the world for breast cancer and there was no difference in survival.

DR LOVE: Most people site that study as why not to use combination therapy, but I've heard it cited as a reason to use it because there's more responses, maybe better tumor control, better quality of life.

DR COBLEIGH: Well, you'd have to prove it in terms of a quality of life instrument. I can tell you that people who have AT have a lower quality of life than people who get sequential single-agent therapy do. They have more side effects. The bottom line is people want to live to see their grandchild or their child graduate from high school or whatever, and loading on these combinations of drugs when single sequential treatment is just as effective, I think is unfortunate.

DR NEIL LOVE: Earlier in the program, Dr Hayes, in reviewing our current understanding of the mechanism of action of endocrine therapy, mentioned the newest addition to our armamentarium, the estrogen receptor downregulator, fulvestrant. In a previous Breast Cancer Update program, Dr Kent Osborne reviewed the initial results of two major Phase III randomized clinical trials comparing fulvestrant to anastrozole. The North American trial, first presented by Dr Osborne at the 2000 San Antonio Breast Cancer Symposium, demonstrated that while the response rates in the two arms of the study were equal, the duration of response was greater in women receiving fulvestrant. A European trial, with a slightly different design revealed equivalent durations of response. Fulvestrant is now available for clinical use and to learn more about where we are in clinical research on this interesting agent, I met with Professor John Robertson, a key figure in these studies. He began by commenting on a recent analysis combining the data from the two major trials of fulvestrant versus anastrozole in an attempt to learn more about duration of response.

DR JOHN ROBERTSON: One of the issues to look at was duration of control in the patients who do respond. In any study, that's always been problematic, because you are selecting a population of patients who've responded, and you couldn't identify those pre-randomization. So a statistical method has been proposed for doing that, whereby you allocate those who have never responded a time of zero, so that all non-responders get a duration of response of zero. When you look at that, in fact what that shows us is that in the patients who do respond, you see a longer duration of response on Faslodex than Arimidex. So that's, I think, a new finding since that time.

DR LOVE: Now, is that in the combined two trials?

DR ROBERTSON: That's combining them.

DR LOVE: Interesting because the separate trials, it was just the North American trial that you saw an increased duration of response.

DR ROBERTSON: And that was by the historical method of measuring duration of response, which is only taking the responders. That method has always, as I say, been regarded as slightly less statistically secure, because of the fact that you're only taking a subpopulation of patients; i.e., the responders. This method takes note of all the patients and allocates the non-responders a time of zero for the response, zero months.

DR LOVE: So, basically, it looks at the whole population in one arm versus the other arm in terms of how much time patients spent in response?

DR ROBERTSON: Yeah. Absolutely.

DR LOVE: That's interesting. So when you combined both studies it was statistically significant?

DR ROBERTSON: Yeah. It was significant in favor of Faslodex.

DR LOVE: You're a researcher. I'm trying to represent the docs out there in practice, figuring out what this means. What they want to know is, looking at all this data and having worked with it and lived with it all this time, do you have the feeling that there's an overall greater anti-tumor benefit from Faslodex than Arimidex?

DR ROBERTSON: I would describe myself as a doctor as well in the sense that I treat patients all of the time. I would not say that categorically it was better, because it's a retrospectively derived analysis and you've got to be statistically rigorous in your interpretation. But I think what it does do is it emphasizes that there is at least equivalence of these drugs in the second-line setting, and gives you even more confidence to use Faslodex if that was your preference.

DR LOVE: How do you think it's going to be used?

DR ROBERTSON: I hope that people are going to embrace it, because it's a good drug. It's got a very good side-effect profile. I think what you see is that it's equivalent in side effects with anastrozole, and anastrozole was better than tamoxifen in the comparisons. So, it just shows this is a very safe drug in that sense. And from the data we have in second-line, I would really hope people would embrace it, but it's difficult to choose between two very good drugs.

I think that the other questions will be – what should the sequence be? Is there any information to say that, if you have Faslodex, will you respond to an aromatase inhibitor? Or, if you have an aromatase inhibitor first, will you respond to Faslodex? I think that the data is coming through, that after you have had Faslodex, you still can see responses to aromatase inhibitors. And vice versa.

DR LOVE: One of the concerns had been that if you treat with Faslodex and you "deplete" the cells of estrogen receptor then patients wouldn't respond to other hormones.

DR ROBERTSON: Yes. I've heard that said, too, that Faslodex resistance is hormone insensitivity. That's not true. There are two things to say. One is that we have seen responses post-Faslodex. We have seen good examples of that, even in our own center. We had a lady who'd been on Faslodex for six years – she was on the very first Phase II study we ever ran – she went on to get an aromatase inhibitor, and showed a partial response in her metastases.

The other thing to say about that – and this is why I think that the question you asked – is Faslodex resistance hormone insensitivity? It isn't. I published a paper called "Estrogen Response: A Stable Phenotype" to show that the estrogen receptor is stable between primary and metastasis. But we don't know if it will work in sequential biopsies. In some of those patients we have biopsied the cancer at progression. In fact, one of the ladies who we biopsied them, was this lady who had a response to Arimidex after Faslodex. And, at the time of her resistance to Faslodex, her tumor was still expressing some estrogen receptor.

DR LOVE: That's fascinating.

DR ROBERTSON: That's six years later.

DR LOVE: Interesting. I've heard it described as the fact that, basically, by using Faslodex, you're changing the phenotype in terms of expression of estrogen receptor, but the genotype is still there so when you remove the Faslodex, that gets expressed. Do you go along with that?

DR ROBERTSON: Well, this was actually at resistance, when the patient was on Faslodex. She still had some expression. This is six and a half years later and clearly we need to know a bit more about what happens over that time period in terms of the expression of estrogen receptor.

DR LOVE: So, does that suggest that maybe part of the resistance to Faslodex is developing the ability to make estrogen receptor?

DR ROBERTSON: Well that may be part of it. If you look at the presurgical studies, we saw a greater downregulation with Faslodex than with tamoxifen. But in a number of cancers, we've still not wiped out; there's still some expression. And so I think that also may be an issue, which is that there is still receptor there, and what is the mechanism by which the cancer becomes resistant to Faslodex in that setting? And we don't know that yet.

The second reason is that in some of these tumors which have got low expression, it may be that, in fact, more of the cells are expressing ER, but it's below the level of detection of the assay. So these are really more positive than you think, but it's simply that the assays that we have available don't detect that, as well.

DR LOVE: You've been one of the leaders in defining the mechanism of action of Faslodex. Can you review what we know about that, and has anything new developed over the last year or so in understanding what's going on?

DR ROBERTSON: No, I think there's not been much more. Essentially, with Faslodex the mechanism is that, first of all it prevents dimerization of the receptor, and second of all it increases degradation of the receptor's dimerized complex, so that you reduce the half-life of the protein. The mRNA levels are the same, but the protein levels are less because the half-life is reduced. By that method, what you find is that you get less of the dimerized complex and, secondly, when it then goes along to attach to the estrogen response elements and genes, you don't get translation because it switches off both the activator functions, AF-1 and AF-2. And I think that's not changed.

The second question, I think, for the future is – what is the mechanism of resistance to the pure anti-estrogen? We don't think it's an agonistic property. And I mentioned to you a moment ago that you can see ER expression on treatment, and even at time of resistance. I think that that's going to be one of the major questions to ask in the future. We are

addressing some of those by sequential biopsies in patients to try and take pieces of the cancer out to look at that both when they're responding, but also when they become resistant.

DR LOVE: Faslodex has been looked at primarily in postmenopausal women. What do we know about it in premenopausal women?

DR ROBERTSON: There is one ongoing study. It's now actually completed, which was, again, a pre-surgical study that I was the PI for. What it was looking at was Faslodex or placebo, pre-surgically, in women who were awaiting primary surgery. So, they had their biopsy for diagnosis and then, in the two to three weeks before the operation, they were given either a placebo injection or they were given Faslodex, 250 milligrams, and then a piece of the cancer was taken out again at the time of surgery. We're looking at, obviously, downregulation of ER and PGR to see first of all whether we are seeing downregulation? But even perhaps more significant, are we seeing the same degree of downregulation, as we see in a postmenopausal patient?

The reason, obviously, for the interest is that Faslodex has an affinity for the estrogen receptor, which is roughly equivalent to that of estradiol. And premenopausal women have got a logarithmically higher level of E-2 than postmenopausal women. So the question is – with such a high level of estradiol, will this reduce the degree of downregulation of the estrogen receptor? I'm sorry to say, today, I don't know. I can't give you the answer to that. But it should be available, again, hopefully in publications and in presentations by the end of the year.

DR LOVE: Any thoughts about what you think you are going to see? There have been some studies done in premenopausal women, I guess, mainly for safety purposes. Do we know anything about its anti-tumor effect?

DR ROBERTSON: Not in premenopausal patients. If you were to make a guess, it's one of two things. You're either going to see the same as postmenopausal patients or the other issue you may see is slightly less downregulation. You can make arguments either way. I'd rather not speculate, but those would be my two most expected results.

DR LOVE: Is there any reason that a higher dose hasn't been tried? It's a fairly non-toxic drug. It would be an extra injection, but it seems like it might be something that could have been looked at?

DR ROBERTSON: No. I think that it mainly was about patient acceptability particularly, in the U.S. Initially, when Study 20 and 21 were being run – those being the North American and the European, South African, Austral-Asian studies – it was acceptable to give a 5 ml injection in Europe. In North America, it was thought that you couldn't give 5 ml. If you remember, they had two 2.5 ml injections, one in each buttock. So, at that point, it would have meant giving four injections.

When it came to the global first-line study, Study 25, comparing Faslodex versus tamoxifen, that was a single protocol. In fact, it was a 5-ml injection that was used, and patients entered from America did get a 5-ml injection. So now that we've got over that hurdle, there would be no reason to think that we couldn't consider giving a higher dose,

5-ml in both buttocks. I think that is something to be looked at. Clearly, 250 milligrams is an effective agent, no question about it. We can see that. I think the point you're raising is a scope for higher dose, and that's certainly something that one would want to consider and investigate.

DR LOVE: Any reason to think that there would be a toxicity problem if you went up on the dose?

DR ROBERTSON: Apart from the fact that you're giving two injections and, therefore, you may get double the number of injection site reactions. Although we know from Study 20-21 that those are a pretty small, few in percentage and not serious injection site reactions at all. In fact, what we know from the fact that these were placebo-controlled, is that the injection site reactions are the same in the placebo arm, as they are in the active treatment arm. So, these are clearly injection site problems and not drug problems, as such. It may be the base carrier that takes it, but they're not Faslodex problems, because it was exactly the same in both arms, placebo and active treatment injections. So, that would be one. But in terms of other side effects, I don't envisage any real side effects,

DR LOVE: How about hot flashes? What are you thoughts on that, globally, after having treated a lot of patients?

DR ROBERTSON: I think that it's not a drug that causes hot flashes, both in terms of its proposed mechanism of action and the fact it's doesn't cross the blood-brain barrier, as far as we can see. I think the problem is – and this would be an issue even for the first-line study when we see the data – is that when you see postmenopausal women, a lot of women get hot flashes for many years after they enter their menopause. The problem with some of these studies is that they measure hot flashes, but they don't tell you, first of all, what there was at the beginning of the study, and how many people had hot flashes on no study treatment. I think it would be important to know how many people had hot flashes before they started and how many people get either new symptoms or get an increased severity of the symptoms.

DR LOVE: The reason I've heard described that it doesn't cause hot flashes is it doesn't penetrate the blood-brain barrier. Is that correct?

DR ROBERTSON: Yes. It doesn't, so that's why we think it won't cause them. But the point I'm making is, in the first-line study, you may actually see some hot flashes in the Faslodex-treated arm, but it may not be the drug that's causing them. Because of the way in which you report these things, which is you report a symptom if a patient gets it at any time on the drug, but it may be that they had those symptoms before they even started the treatment.

DR LOVE: Any thoughts on combining Faslodex with any other agent, whether endocrine, biologic, chemotherapy, any sort of natural combinations there?

DR ROBERTSON: There are one or two natural combinations. The first natural combination is with Faslodex and anastrozole – and we can come back to that in a second. The second would be Faslodex and perhaps Iressa. First of all, there's some good cell

culture work, in vitro work, to suggest that Faslodex and Iressa would be a good combination, and that you can prevent resistance and get longer control of the cells in vitro by the combination.

In terms of Faslodex and Arimidex, or anastrozole, I think that the rationale for that is that, if you reduce the level of estradiol to a very low level, then Faslodex is maybe even more potent at inhibiting the receptor. And I think that's a natural combination, and I suspect that some of those studies are going to start pretty soon.

DR LOVE: Is there any more biologic basis for either one of those combinations? I'm trying to think mechanistically why, for example, Iressa and Faslodex would be more potent than, say, either one alone.

DR ROBERTSON: I think that there are mechanistically potentially differences. The reason for using, as I say, Faslodex and anastrozole is that, by reducing the estradiol level, you would then have a more potent, pure anti-estrogen, which would in a sense block any remaining stimulation of the receptor.

DR LOVE: I guess that goes along with what you were saying before in terms of the dose effect.

DR ROBERTSON: Mm-hmm.

DR LOVE: So, that one makes sense.

DR ROBERTSON: That would make sense, and there's some support for that, too, from the premenopausal studies looking at Zoladex plus tamoxifen. If you reduce estradiol levels, you can perhaps get a better initial response and a better time to progression on the combination, than a single agent. Although, when you put the second agent in, you get a second response with the sequential tamoxifen, right? But we're talking first treatment. So, there's some support for that combination from premenopausal studies.

The Faslodex and Iressa has, I think, a separate rationale, which is that we know that one of the blocks to endocrine sensitivity in terms of interaction and cross-talk is the Type 1 growth factors, HER2/neu and EGFR. We also know from the cell culture work that, if you give cells tamoxifen and then they become resistant, and you then come in with Iressa, you can reverse that resistance.

We also know from some of that cell culture work – this is Professor Rob Nicholson's work in Tenovus Institute in Cardiff – that if you give tamoxifen and Iressa, you can actually delay the outgrowth of resistance to tamoxifen. And so I think that the combination of an anti-estrogen and Iressa is different from the combination of an aromatase inhibitor and Iressa, and biologically they're different.

DR LOVE: I guess another combination might be an LHRH agonist plus Faslodex if you find that it's not as effective in premenopausal women?

DR ROBERTSON: Absolutely. I think that there's an attraction of looking to see if we can get a single monotherapy that's effective. But I agree that, if you didn't, then that would be another way around, which would be effectively making women postmenopausal and then treating her as a postmenopausal patient.

DR LOVE: This kind of reminds me a little bit of the report you had at ASCO a couple of years ago, looking at I guess it was goserelin and anastrozole making the woman postmenopausal.

DR ROBERTSON: Yeah. And, in fact, since then, we have actually done the endocrinology in that.

DR LOVE: Oh, really?

DR ROBERTSON: What you can see is that you do see a logarithmic fall in estradiol when you give them Zoladex and tamoxifen. Then when you change from tamoxifen to Arimidex in combination with Zoladex, you see a further logarithmic fall that's statistically significant in terms of the estradiol levels.

DR LOVE: So, it's pretty much what you'd expect?

DR ROBERTSON: It is. It is. So I think that the responses that we saw clinically are supported by the endocrinological data there.

DR LOVE: That's interesting. When we first started talking about that trial of metastatic disease, of anastrozole and goserelin, the question I had for you was – suppose the ATAC trial shows an advantage for the anastrozole arm? Obviously, there are trials now looking at anastrozole and goserelin in the adjuvant setting. But then the other question comes in – what about using that combination off study? That kind of leads into the issue of the ATAC trial. So, let me start out first, before we get into the issue of the premenopausal, let me get your take on the early ATAC results.

DR ROBERTSON: I think, first of all, they are interesting. If you were to ask me is it what I would have expected, then the answer is no. I mean, just for people in the audience to know, who have not seen the data, the ATAC data shows that anastrozole gives you a significantly improved recurrent-free survival over either tamoxifen alone, or the third arm of the study, which was the combination of anastrozole plus tamoxifen. And that's statistically significant.

It also shows, in terms of side-effect profile that anastrozole was statistically better tolerated in terms of hot flashes, cerebrovascular accidents, DVTs, and also in terms of vaginal dryness, discharge, and endometrial cancer. It showed that tamoxifen was better tolerated than anastrozole in terms of musculoskeletal symptoms, such as joint pains, and also in terms of bone fractures. So, that's the summary of the data. And if I'd been asked to predict what I thought the trial would have shown, I would have said that after this time period, it would have shown no difference, that it was perhaps a non-significant

separation of the curves. But, in fact, we do see a therapeutic efficacy in favor of anastrozole.

People ask the question – is that something that we can put any security on? I think that there are some reasons to think that this is a true result. First of all, this study had 9,366 patients. It's the largest adjuvant endocrine study that's ever been done. When this study started out, the largest two studies previous to this were the CRC study, and the NSABP B-14 tamoxifen study, which had around 2,200-2,600 patients. So, this was a huge study. I think the possibility that this is a chance event from the size of the study is unlikely.

A second thing, I think, that gives us some security is that there appears to be some internal consistency within the data. By that, I mean, if you look at the number of local recurrences, the number of distance recurrences, number of contralaterals, each of those three measures of breast cancer disease control are better on anastrozole than on tamoxifen. So, it's not that one area of control seems to be better than another and it overrides the whole analysis. All three show consistency that anastrozole gives you less recurrences, distant metastatic, contralateral, than tamoxifen.

The third thing that is reassuring about the data is that it's consistent with what we know previously about aromatase inhibitors. If you look at the anastrozole versus tamoxifen data in first-line metastatic disease, we know that in hormone-receptor-positive patients, you've got a benefit. The benefit was 10 months versus six months in terms of time to progression. If you looked at the Spanish study of first-line therapy, Milla-Santos, it was 10 months versus six months. If you looked at the letrozole versus tamoxifen study, the benefit in terms of time to progression, it was something like 9.8, I think, versus 5.3-5.5 something. It was roughly four months. And if you looked at the exemestane study, with which I put less store by, because it was a small Phase II, 30 patients per arm, but also mostly because it was an open-label study. But, even that, the TTP, the difference is around four months as well.

So we're beginning to pick up in first-line metastatic disease that the aromatase inhibitors as a class of agents are better than tamoxifen. And you can define what that benefit was. It was around four months, 10 versus six, for all of the studies, suggesting that, in that setting, the aromatase inhibitors were roughly equivalent, but that we knew that they were better than tamoxifen. Now we're seeing an additional benefit in the adjuvant setting. So it tends to suggest, again, that if you look at this external data to the ATAC study, it suggests that the aromatase inhibitors are a better class of agent, and that this shows through in the adjuvant setting. So, I think all of those things are supportive of the efficacy data.

Should patients be placed on anastrozole immediately? I'm sure that's your next question. I think that there are two things to say. One is I think that the data is pretty secure in terms of efficacy. I think the other thing to note about efficacy is those curves are diverging. And if you look at the tamoxifen data, there is quite a lot large carry-over effect, even after the drug was stopped. If you were to ask me, I suspect those curves will continue to diverge. The second thing is, I suspect, too, although we need to wait for this data to show through, that that will eventually transfer into a survival benefit.

However, I think that there is one point to raise, which is the safety issue. With this large number of patients, I think what it does do is it gives us confidence that there are not any really serious but very uncommon side effects from anastrozole. Otherwise, I think you may have picked those up in this number of patients. But the second things is that,

because it's a large study and it's based on event numbers, you get the data quite soon after starting the trial. This is now, 30-odd months after the trial. So people may say, "Well, have we seen the full extent of bone-mineral density loss or fracture rates?" And there's more data to come on that, no question. I mean, there's a bone-mineral density sub-protocol, which will start to show us what the rate of loss is and how long that may be – takes before we see recovery of bone mineral density. So, I think that while we know that efficaciously anastrozole is better, there is still some more data to get on the longer-term side effects in terms of bone mineral density.

So, my take on whether we prescribe it is, I think there are two types of people to think about. People who are very cautious and say, "I'm going to stick with tamoxifen until we get more data, longer-term data." For those clinicians or patients, I think what it does tell us is that, if you had a patient who had some reason that you were uncomfortable putting them on tamoxifen; i.e., that they had a history of thromboembolic disease or cerebrovascular accident, this data suggests that we could put them onto anastrozole with a very low threshold. I know a number of clinicians that have already been doing that off label. But I think this data gives us even more confidence, maybe to lower that threshold. So, if you say, "Well, I'm sticking with tamoxifen as my standard treatment," you may be prepared to, as I say, give anastrozole with a low threshold to patients who have some reason to think that they may have a side-effect profile that you would not wish to start them on tamoxifen.

Then I think there'll be people who will look at the data and say, "The efficacy data here is sufficient for us to start somebody on anastrozole." By the time patients are one, two, three, five years on anastrozole, we'll have far more data to make decisions.

Secondly, we look at the side-effect profile of the two drugs and there are things that you can weigh up in favor of either of the drugs. In fact, in many cases, anastrozole has got a better side-effect profile than tamoxifen. Okay, there are more fractures, but there are fewer DVTs, there are fewer cerebrovascular accidents, there are fewer hot flashes, there's less endometrial cancer. And the other argument that you could put is that, in fact, the tamoxifen side-effect profile, where it may be treatable, is usually not preventable. You know, how do you prevent DVTs? How do you prevent the cerebrovascular accidents? How do you prevent endometrial cancer? So, as the main side effect of anastrozole, the bone fractures, is something that potentially one could treat with bisphosphonates, calcium supplements, exercise. And so some clinicians and patients may look and say, "Well, there is better efficacy here, and we are prepared to take the risk," if you put it that way, of the lack of long-term follow-up data, and in fact we would be prepared to start them on a bisphosphonate, knowing that this should hopefully deal with some of the bone-mineral density loss."

So, I think for clinicians across the country there'll be a spectrum of response is to this data. Some clinicians will be more conservative, use it in selected patients whom they see side-effect profiles from tamoxifen that they feel would have risk factors for them. And I think there'll be other clinicians and patients who will embrace the efficacy data and take the possibility of unknown long-term side effects in terms of bone mineral density or treat them prospectively by giving them bisphosphonates.

DR LOVE: Do you think that it's an issue that should be raised with any postmenopausal woman starting on tamoxifen, as an option?

DR ROBERTSON: Yeah, I think the data should be discussed with them. If the issues are explained clearly, I think most women are able to voice their opinion about these matters, and I would certainly think that it's something that should be raised. Remember that this is a large study. It's one of the largest adjuvant studies ever done. And I think that to ignore that data is doing a disservice to women, I think.

DR LOVE: I've heard people say that they may be more willing to think about using anastrozole in a high-risk woman, in a multiple node-positive woman, as opposed to a woman who maybe has a lower risk for recurrence, node-negative, small tumor. Does that kind of approach make sense to you or not really?

DR ROBERTSON: I don't think it really makes sense to me. I suspect what they're saying is that the up-sort benefit is greater. And that's true. But the side-effect profile is the same. I don't think there's really any real rationale for that. I think if you're going to use it as your standard adjuvant therapy for node-positive patients then there's no reason not to use it for node-negative patients.

DR LOVE: What about using one of the other aromatase inhibitors – letrozole, exemestane – as adjuvant therapy? Do you think that that also should be something that's considered in a non-protocol setting at this point?

DR ROBERTSON: I don't think that. One has to look and see what the studies that come out show. I don't necessarily think that you can extrapolate to say that because drugs are efficaciously the same in the advanced-disease setting that they will be exactly the same in the adjuvant setting, either in terms of efficacy or in terms of side-effect profile.

For example, we know that the degree of inhibition of aromatization is slightly different. There have been some claims with regard to letrozole that they may reduce, not estradiol, which is the main estrogen, E-2, but E-1, fractionally more than the other aromatase inhibitors. Now, does that translate into an efficacy difference? I'm not sure if it does. Let's wait and see.

But the other side of that is that there are always two sides to a sword, and it may translate into an efficacy benefit, or may not. Particularly, it may translate into a higher side-effect profile, or may not. For example, if you have a little bit of estrogen left in the woman's system that may give her some protection in terms of bone mineral density loss and bone fractures. Whereas, if you completely take estrogen out of her system, even a small amount of estrogen remaining may make a big difference in terms of the bone mineral density loss and the fracture rate. So I don't think that we can assume that the efficacy and the side-effect profiles are exactly the same. In fact, I've been on record to say before that if you were to ask me, I think that the difference between the aromatase inhibitors in the adjuvant setting will not be in terms of efficacy, but it's most likely to be in terms of the side-effect profile. That's what will distinguish between the aromatase inhibitors in the adjuvant setting. But, that's a personal view.

DR LOVE: What about the ER-positive, premenopausal woman? First, let's talk about the women that's, let's say, very high risk, although I hear what you're saying about that, 10 positive nodes. She's going to get some kind of chemotherapy. Normally, she would receive tamoxifen. Maybe some people would give her tamoxifen plus an LHRH agonist,

if she hasn't stopped menstruating after the chemotherapy. What about the issue of the non-protocol use of an LHRH agonist plus anastrozole in that kind of a woman?

DR ROBERTSON: There is some data, as you say, to add in an LHRH analog after chemotherapy if they're still menstruating, you're referring obviously to the INT 0101 study. And that did show a benefit of the combination.

Should you substitute anastrozole for tamoxifen? I've got to say that being evidence based in terms of the medicine that we carry out in our own center, I would not do that at this point in time. Unless there was, again, an issue about the tolerability of tamoxifen; a history of DVT or some other reason, cerebrovascular accidents in the past, where you would, I think wouldn't do it without some rationale for substituting anastrozole for tamoxifen. But, as a general statement, I would go with the known and proven treatment, standard treatment, I think.

I think the thing to see here with the ATAC data is that it doesn't answer all the questions. It tells us that a drug, which appears to be efficacious than tamoxifen – but it doesn't answer all the questions. It doesn't answer the question of combination with chemotherapy. It doesn't necessarily answer the question of sequencing of tamoxifen or an aromatase inhibitor. Should you give one, sequence them, two years-three years/ three years-two years? It doesn't answer those questions. It simply tells us that we've got a very active drug that, on its own, appears to be more active than tamoxifen. Clinicians are going to have to with patients weight out the unknowns in terms of some of the longer term bone mineral density questions, sequencing, and interactions with chemotherapy, and make decisions based on those as to whether they're going to use the drug or not.