Finding the Positives in Triple-Negative Breast Cancer:

A Three-Part Live CME Webcast Series

Seminar III
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SEMINAR 3: New pathways, novel agents and recent reports on triple-negative breast cancer (TNBC) in the neoadjuvant, adjuvant and metastatic settings

DR LOVE: Welcome to *Finding the Positives in Triple-Negative Breast Cancer*. This is Neil Love from Research To Practice in Miami, Florida, and it has been a long time for patients with triple-negative breast cancer and the physicians in looking for new developments. But as we've seen in this series, in our two prior webcasts over the last couple of weeks, there's a lot of encouraging news coming out in the field and we're going to talk more about that tonight.

Joining me for this webcast is, first, Kathy Miller from Indiana University. And Kathy, I've been telling the listeners and viewers on the prior two series that actually the title of this series, you actually came up with. We had a preconference meeting and I said, "Well, we're thinking about calling this Triple-Negative 101, but I'm not sure that's appropriate since I don't understand about 80 percent of it," and you came up with this title, which, I think, really there's a message in.

I'm curious, just before we start rocking down the translational road here, what you've been hearing from patients and their families and referring physicians over the past year, and when they come in and ask you about having triple-negative breast cancer, what have they been telling you?

Recent developments in the management of TNBC

DR MILLER: That is actually where the title came from. So many of my patients with triple-negative disease come in and say, quite frankly, "I'm tired of hearing about Herceptin®. I'm tired of hearing about hormone therapy. What have you got for me?" And until very recently what we had for those patients with triple-negative disease was chemotherapy — the good news being chemotherapy, in general, has been more effective for patients with triple-negative disease than other subsets, the bad news being chemotherapy isn't what anybody wants.

So, more recently, there's been huge enthusiasm about the PARP inhibitors — so much so that it starts to feel like we have to kind of talk patients back from the ledge who sort of assume that if they can't get a PARP inhibitor they'll be dead by Friday and that there aren't any other options for them. And that also is certainly not true.

DR LOVE: And also joining us tonight for this webcast from UCSF is Hope Rugo. And Hope, we were mentioning last week that we did a satellite meeting at San Antonio and we covered five topics, and one of them was triple-negative disease. And we polled the audience ahead of time on "What's the thing you want to hear most about?" and like, way up, number one, was triple-negative disease.

What are you seeing, again, and docs in the community that are referring to you and in patients as they come in over this past year with triple-negative disease?

DR RUGO: I think obviously there's a larger awareness now that we, by understanding the biology of not just HER2-positive and ER-positive disease, that we can potentially break some of the huge barriers that we've had in achieving good outcome for this high-risk subset of breast cancer. But I also think that there's — to echo what Kathy said, there's a misconception that exists about this being a universally horrible diagnosis

with a terrible outcome and that when the patients start their neoadjuvant therapy, that they should get something different.

And in fact, as we'll talk about some today, we recognize that, as Kathy mentioned also, these patients do pretty well with standard chemotherapy, a subset of them, and what we really need to understand is what the right therapy is for individual cancers. And that's what docs in the community are really looking for, like, "How do I know this is the right treatment for this cancer, for this patient?"

DR LOVE: So I'm going to try to set the stage for what we're going to try to accomplish tonight. We're going to talk a lot about managing patients today in practice, but also, what's coming up for the future.

Here are my disclosures and I just want to briefly set up the stage for what we're going to talk about tonight.

As part of this three-part series, we have six different faculty people who are giving talks. Tonight, Kathy's going to talk about some of the new pathways that are being looked at in triple-negative disease. Hope's going to do kind of a journal club kind of thing, and go through a bunch of papers that have been published recently and presentations on the disease. But all slides from the speakers will be posted on the website as an integrated educational resource, along with the webcast and the transcript.

So just kind of try to sit back tonight, don't worry about every single detail in the slides, and just kind of maybe focus on the global issues that we're going to talk about tonight. If you have a question you'd like to see us address, in the lower left-hand corner of the module you can type it and we'll try to get to as many as we can. And actually, before we start with the presentations we're going to go through a bunch of questions that we've already received about this, in these three meetings.

BRCA, PARP DNA repair pathways and synthetic lethality with PARP inhibitors

And before we go through some of the specific questions that we got, I want to just take a minute and give you two a shot at explaining something that our prior faculty of Cliff Hudis and Lisa Carey, on number one, and then last week, Jenny Chang and Joyce O'Shaughnessy, where they all took a shot at, which is to explain this concept of the new biology of triple-negative disease. And Kathy, we had a journal club kind of thing at San Antonio in triple-negative disease. One of the best papers — review papers — we found that got into this issue of BRCA-ness and Chuck Perou's Classification and PARP inhibitors actually came out of Indiana. Your bud Bryan Schneider was the first author. You were involved, Hope — you were actually there. And really there were some fantastic graphics in there trying to explain the new biology.

Kathy, maybe you can take a crack at how you explain to, I mean maybe one of your fellows starting out, this basic stuff about what we're learning about BRCA-ness, triple-negative, and the basal subtype?

DR MILLER: I'll take a crack at it using a car analogy. If you understand the concept of synthetic lethality, then understanding the PARP inhibitors becomes actually relatively simple.

So think of it this way: Cars need an engine in order to be able to run. I have a hybrid car. It can run on gasoline or it can run on the battery. It runs slightly better in some circumstances on one or the other, and depending on the driving conditions, it will switch between one or the other. If one of those sources of power stops working, the car still runs. In some conditions, it might be slightly less efficient, but it still runs — you can get where you're going quite safely. But if now the second one stops running, the car's dead. You're going nowhere.

So take this to the cells. DNA gets damaged and the damage has to be fixed. Think of two major ways of fixing the damage. They're preferentially used in different circumstances, but if one stops working, the other can take over. It might not be quite as efficient and quite as reliable, but it still gets the job done and the cell runs perfectly fine. That's BRCA-ness. BRCA tumors have lost the BRCA repair pathway, otherwise called homologous combination. PARP is the other major pathway, or is an enzyme in the other major pathway, otherwise called base excision repair, as the method of repairing DNA.

So if you've lost BRCA, either because of an inherited mutation or you have a triple-negative tumor that is like BRCA, and you now inhibit PARP, you've lost both sources of power — both sources of repair — you're dead.

DR LOVE: So and that's tumor that's dead, which is what we're trying to accomplish. And —

DR MILLER: Not the patient, just the tumor.

Understanding BRCA1 mutations in TNBC

DR LOVE: Right. So, Hope, last week — I love the different analogies people come up — Jenny Chang showed a table with one leg coming off and then two legs coming off, kind of similar to the car thing. I think at the

roundtable you were at, somebody drew an analogy to something that Nietzsche said, which is always interesting to include. What about the issue of the basal subtype and triple-negative disease? What's the overlap there, Hope?

DR RUGO: It's actually really interesting, and I think it's taught us so much about how to understand that basal subtype, but the idea being that we understand that BRCA-associated cancers — so what does that mean? Patients who inherit a BRCA mutation and then develop a cancer have to do so because they no longer have that BRCA pathway intact, so as Kathy was saying, you're actually born with — you still have function in that pathway. So there has to be something else that occurs that allows you develop a cancer.

So, interestingly, patients who have BRCA1 mutations mostly get triple-negative breast cancers. So then there was a lot of interest in trying to understand the similarities between the so-called sporadic triple-negative breast cancers and BRCA1-associated tumors, which, of course, represent a really significant minority of the patients we see. So being able to understand triple-negative breast cancer relatively is more important for the population than BRCA1-only associated disease.

So actually, just looking at the biology of these cancers you see that many of the features that are true for BRCA1 mutant-associated cancers are similar for sporadic triple-negative cancers, and specifically that basal subtype — so p53 mutations, certain cytokeratins are seen, the biology, high-grade, rapidly proliferating. These cancers tend to have a better pathologic complete response rate, for example, than hormone receptor-positive disease. So that's led us to believe that maybe some of the treatments that worked for one might work for the other, and it also has helped us to understand that the triple-negative cancers also have almost an upregulation, the ability to repair DNA damage, which then helps us to figure out ways to overcome that.

Neoadjuvant and adjuvant treatment regimens for TNBC

DR LOVE: So in a minute, Kathy, we're going to ask you to go through your slides, looking at maybe other pathways that might be exploitable or are being looked at in triple-negative disease. We're going to also begin with your case. But first, we are getting a lot of questions from people in the field and a lot of them are just basic management. We don't have PARP inhibitors or new — of course, they could put people on trials, but what about actually taking care of patients?

So I'm just going to kind of run through a few of these. We could probably spend the whole night talking about these, but maybe just to kind of get your quick take. So, Kathy, we've got a lot of questions about adjuvant therapy. We've had cases already presented with adjuvant triple-negative disease. One question, in general: How do you approach the neoadjuvant and adjuvant therapy of triple-negative breast cancer? And what about the case, as you see here in the bottom, of a patient with triple-negative disease who needs neoadjuvant therapy? Most people have heard about platinums. Is that something you do in a nonprotocol setting?

Just briefly, how do you approach neoadjuvant and adjuvant therapy?

Standard neoadjuvant therapy for TNBC

DR MILLER: So in patients with sporadic triple-negative disease, we actually have very good evidence that they have an excellent response to neoadjuvant therapy with higher pathologic complete response rates with standard regimens. So while the platinum data is very interesting, it's still based on a very small number of patients, so the confidence intervals around those response rates are quite high. Outside of a protocol setting, I'm actually a bit worried about abandoning things that we know have been successful and that have led to more women being alive.

So while at this point I would fully support focused clinical trials of platinum-based or other DNA-damaging-based regimens in the neoadjuvant setting, outside of those protocols, I would still give those patients an aggressive standard regimen. In my clinic, that's going to be dose-dense AC followed by paclitaxel. Whether that was TAC or AC followed by a weekly taxane, I think all of those third-generations would be very reasonable options as standard treatment.

Adjuvant therapy for TNBC in elderly patients with no major comorbidities

DR LOVE: And Kathy, actually one of the cases that you submitted and we're going to chat about briefly is a neoadjuvant question. Before we get to that, Hope, we had a couple of other specific questions about adjuvant. And of course, there's the 80-plus-year-old question that always come up — in this case, a patient who's 83 with a two-centimeter, node-negative triple-negative tumor. On our audio series, we had an 86-year-old with six positive nodes. How to approach the octogenarian with triple-negative disease in the adjuvant setting? And then the second case, vexing for all subtypes, but particularly triple-negative,

the patient who has significant residual disease — in this case, 35 positive nodes — after neoadjuvant therapy.

What about those two clinical scenarios, the older adjuvant situation and the postneoadjuvant situation, Hope?

DR RUGO: I think both of them obviously are excellent questions of which there is no right answer. But I would say that for the 83-year-old, you're kind of making a risk-versus-benefit analysis, and it's a lot easier with triple-negative disease than it is with ER-positive disease. So this is a patient who doesn't have major medical problems except for hypertension, presumably well controlled. So from a triple-negative breast cancer, her risk of mortality over the first three years is recurrence and then rapid death with chemotherapy is very high. And also her potential benefit from chemotherapy is also possibly high.

So what I would do is try for a regimen with less intensive up-front toxicity, like docetaxel and cyclophosphamide maybe every three weeks for four cycles or even a weekly Taxol®-type approach to see how she tolerated chemotherapy, and that would allow you, if she was interested, to try and reduce her risk of recurrence, because these cancers may indeed derive benefit from a fairly short course of chemotherapy. And most 83-year-olds will tolerate that treatment. And I say that as "most" because some people just don't metabolize these drugs as well, and you have to be very cognizant of that when you start, embark on this course of therapy — you can always stop.

Adjuvant therapy for a 52-year-old woman with significant residual disease after neoadjuvant therapy of AC x 3 → paclitaxel x 5 for TNBC

For the 52-year-old, I mean this is a really difficult situation because this is a younger woman with a long potential survival and she has gotten — presumably she only got three cycles of AC because of concern that she wasn't responding — then she gets some paclitaxel, there's still concern she's not responding. She goes to surgery — has a lot of cancer left.

So the one question, I think, is should you give more treatment? She's only gotten five treatments. Presumably — now we don't know this for sure — weekly paclitaxel rather than dose-dense. And I think that in past we would have said, "Well, this woman's chance of dying of cancer is very, very high, so you should stop now, do your radiation therapy. If there's a clinical trial the patient can go on, great. But otherwise, why give more treatment that you don't think will be effective?"

I think — my thinking at least has changed a little bit, and although I do definitely follow the evidence-based medicine approach, in this case we don't have it. So I might give her a paclitaxel and a platinum or some combination therapy postoperatively, maybe even gemcitabine and a platinum, although if she got only five cycles of weekly taxane I might try the platinum approach for some course of therapy and then stop. You do radiation therapy and figure you've done the best you can, unless you have a clinical trial available.

That having been said, there will be a bevacizumab trial open in the near future that will randomize patients to receive bevacizumab or not in this type of setting. And then there will also be PARP inhibitor trials as well.

DR LOVE: So, again, before we get into a little bit more biology, we'll bring up your case, Kathy. And I might say, in terms of the 52-year-old, Hope, last week one of the things we were talking about with Jenny and Joyce were the new trials. You mentioned trial — of course, I think the issue of looking at PARP inhibitors in either the adjuvant or neoadjuvant setting is going to be of interest, particularly after we see the Phase III, first-line metastatic setting.

Case discussion (Dr Miller): A 56-year-old woman with a 15-cm Grade III TNBC responds to treatment with cisplatin after the identification of a BRCA1 mutation

But, Kathy, let's just talk briefly about this patient. I know she kind of came to you in midstream when things were looking pretty bad. Maybe you can just briefly go through what happened with her?

DR MILLER: Sure. So this is a 56-year-old woman who initially presented elsewhere with a very large mass, with inflammatory disease. The mass itself was measured to be about 15 centimeters with associated axillary adenopathy. Biopsy found triple-negative disease, confirmed actually by two pathologists, and despite the extensive local disease, she did not have any evidence of invasive disease elsewhere.

She was treated on the Phase II protocol with the combination of docetaxel/capecitabine and bevacizumab. After her first cycle she had a profound toxicity with between Grade III and IV diarrhea — greater than 10 stools a day — profound neutropenia and a neutropenic fever, which landed her in hospital. She got her second cycle of therapy one week late, but without dose modifications, and had exactly the same problems with fever and neutropenia and diarrhea, even earlier in her course of treat-

ment. Back in hospital now with two perirectal abscesses, which required incision and drainage, and quickly developed persistent fistulas tracts.

It was at that point that I met her. She left her hospital room and came to see me in a wheelchair, still on IV antibiotics, still with draining fistula tracts, still not eating, still recovering from hand and foot syndrome and with, at best, a modest response. At the time I saw her, I was not impressed with inflammatory changes. She still had palpable axillary adenopathy and she still had a mass that measured between 10 and 12 centimeters. So she'd had some response, but it was not particularly robust.

Based on her presentation and her family history, genetic testing had been recommended. And about a week after I met her, her results came back with a deleterious mutation of BRCA1 identified.

She took almost a month, after I first met her, to recover and be able to even contemplate additional chemotherapy. With still the draining fistula tracts and all of the problems before, we particularly wanted to avoid chemotherapy that might cause myelosuppression. And with the knowledge of the still-early data, but very intriguing data, of cisplatin responses in patients not with sporadic triple-negative disease but with known BRCA mutations, we thought that was an, honestly, nonstandard option but a reasonable option in her situation.

She tolerated the cisplatin extremely well, and after two cycles of therapy all clinical evidence of her disease had completely resolved. Imaging was completely negative after four cycles of therapy. She proceeded to bilateral mastectomy, and that confirmed a pathologic complete response. She is now about finished with her radiation and then will, within the next month or so, proceed to oophorectomy and excision of the fistulas tracts, which are still present.

DR LOVE: So, Hope, when I — we ask people to present cases, sometimes they present these unbelievable cases like this one, and I don't know, should we present or not present them — they're anecdotal, et cetera. But what do you think about this case?

Pathologic complete response (pCR) in TNBC with neoadjuvant cisplatin

DR RUGO: I actually think it's really fascinating, because there are Polish investigators — and I'm going to talk about it in a little bit — but that have looked specifically at patients who had BRCA1 mutations in the neoadjuvant setting and used exactly this regimen — and presumably that gave some thought of further treatment that Kathy selected here — and showed a really remarkable pathologic complete response rate. And their data — actually, one of the patients I saw recently had been communicating by email with the investigators in Poland and some investigators they've collaborated with in Russia, where they have identified a fair number of patients with BRCA1 mutations that they've treated, and their preclinical — they suggested to this patient that taxanes were relatively ineffective in cancers associated with BRCA1 mutations.

Now we don't have that clinical data, but I think that they have seen, on the other side, that cisplatin, in particular, maybe, and probably carboplatin — we just don't have that data — may be particularly effective for these cancers.

So I actually think it's a very clever idea. You have a patient who can't tolerate the therapy she's getting, she's gotten a good slug of a taxane and has terrible infections. She can't tolerate more drug that's going to cause bone marrow suppression, like an anthracycline or additional taxane, and then we have this data on the other hand. So I actually think that giving cisplatin was a very clever idea, and the proof is in the pudding — she's had a great response. I think, then, with this patient having so much toxicity, you're not going to then have a conversation of, "Oh, let's give her a few cycles of AC afterwards just to be sure." You're just happy you got her through it.

New pathways in TNBC

DR LOVE: So, Kathy, we're going to talk a little bit now — we're going to kind of go back to the biology. And remember, these people have had a long day. They're kind of sitting there probably half dazed after some of the things you go through in medical oncology, so just kind of take it easy in terms of some of the pathways and the biology here, but maybe just kind of paint a broad picture about some of the pathways, in addition to PARP and BRCA, that are being looked at in triple-negative tumors. And you were telling me about a couple of new initiatives that I think are fascinating.

So, Kathy...

DR MILLER: Thank you, Neil, and I promise I'll go gentle on the audience. My disclosures are here for you and they'll be available on the slides on their website as well.

We're going to focus initially on some efforts to identify novel pathways, and then a little bit about C-

MET, where I find the data particularly compelling, and finally, think about efforts to restore the metastasis suppressor genes and how that might be useful as therapy.

So this really is where the title, *Finding the Positive*, comes from. I've explained to many patients with triple-negative disease, this is very hard to develop a therapy for something your tumor doesn't have. What we need is to identify what does it have, what is that positive for that drives your tumor, and then develop a therapy that will block that. So I'll show you just briefly two efforts, looking at that sort of process.

Heterogeneity of gene amplification in triple-negative breast tumors

Now in this first study they essentially were looking for the HER2 equivalent — genes that were consistently overexpressed if they were amplified. Now the good news is that in all of the triple-negative tumors that they looked at, they found at least one amplification in nearly 80 percent of those tumors. But in total, they identified 40 genes and no individual amplification was seen there at high frequency. So the hope that we would be able to break down triple-negative disease into maybe a third that had BRCA-ness and another third that had something else and another third that had something else and it would become three groups is probably not realistic.

And to give you an idea of how small some of the subsets might be, of the genes they identified, one was the fiber blast growth factor receptor. They found that activated in two triple-negative breast cancer cell lines, as well, and those cell lines responded to inhibition of that receptor. So the next reasonable question was, how common is this — how frequently might this be a real target?

So they looked at 165 other triple-negative tumors, found out amplification in only four percent. So in that four percent this might be very fruitful, but that's a tiny number of our patients. Now they did find some commonalities that could find ways forward. So while the individual genes were very different, you could group them into several very common pathways, suggesting that maybe inhibiting those pathways at a very basic level could still be helpful.

Association of high expression of immune-related genes with better prognosis in TNBC

Now the second effort looked not at new gene array data but a meta-analysis of a bunch of previously published series, and it found similar pathways, I think giving us confidence that these pathways are really important in triple-negative disease but also suggesting that patients who have upregulation or expression of immune-related genes tended to do a bit better. So perhaps there's a way to identify the subset of triple-negative patients for whom all is not such doom and gloom — and perhaps suggesting that strategies to enhance immune response in other patients could be fruitful.

Significance of MET receptor overexpression in breast cancer development

Now all of these gene expression studies have identified either the MET receptor, which is one of the many cell surface tyrosine kinase receptors, or its ligand to hepatocyte growth factors being commonly expressed in triple-negative disease. The MET receptor's involved in lots of different things, but they're all bad if you're a patient. They make cells grow more rapidly, they make them more invasive and more likely to survive.

Now MET has been looked at — its overexpression has been looked at in a lot of different pathology series. You find it more commonly in tumors that involve the lymph nodes. Patients who have MET expression tend to have a decreased overall survival. So this is all starting to sound a bit like the early days of the HER2 story, and perhaps the basal subset are the group where this is particularly important — or at least we find overexpression much more commonly in the basal subtype of tumors than in the nonbasal breast cancers.

Now expression does not necessarily mean that this is a key factor. It might be commonly expressed, but inhibition might not do much. But there are two recent reports that suggest, to me at least, that MET might actually be more important. So these use transgenic models, but the simple way of thinking about this is you create a mouse that has a particular defect in all of those mouse's cells. So in this case the defect is a constitutively active MET mutation, so MET is always turned on in these mice. They are otherwise healthy — they develop normally — but they consistently develop breast cancers and they consistently develop breast cancers that look exactly like basal tumors by gene expression and immunohistochemistry. And this has been done by two different groups using two different MET mutations, both of which stick MET in the on position, and that suggests, to me at least, that this might really be a more crucial driving factor than something that's merely frequently present.

Now this has not escaped the attention of the drug companies as well. There are many MET inhibitors that are just making the move into clinical trials, and I suspect you will be hearing more about their early

clinical data and that many of their early clinical trials will try to capture patients with triple-negative disease to see if this pans out in the clinic.

Elevation of metastasis suppressor gene expression with medroxyprogesterone acetate (MPA)

Now, finally, an area that we've done some work in is looking at the metastasis suppressor genes. Now these are a bit different than classical tumor suppressors in that they inhibit the growth at distant sites but not at the site of the primary tumor. Their expression is frequently lost in aggressive tumors that metastasize, and therefore, if you could turn them back on, that might decrease the growth at sites of metastatic disease.

Now I mentioned early that turning things on is a whole lot more difficult therapeutically than turning them off, but some of our colleagues at the National Cancer Institute have found that a very old drug, hydroxyprogesterone acetate, commonly used for breast cancer therapy in the days before tamoxifen, tends to turn on the metastasis suppressor genes. And it does so by mechanisms that have absolutely nothing to do with ER, so the other glucocorticoid receptor.

They've also found that it inhibits angiogenesis, so it has potentially a couple of different actions that could be important in triple-negative tumors. And in a mouse model of triple-negative disease, mice treated with MPA had fewer lung metastases, and they were able to see upregulation of the NM23, one of the metastasis suppressor genes, in both the tumors in the lungs and in skin biopsies, as a potential surrogate for the biologic activity. They were also able to measure the levels of the drug and find that those levels should be clinically achievable.

TBCRC 007: A clinical trial of MPA alone or with metronomic chemotherapy for ER/PR-negative breast cancer

Now that led to the first clinical trial of MPA specifically for patients with ER- and PR-negative disease. Now, based on how this would work, we didn't expect it to shrink established tumors. We hoped that it would prevent metastases from growing or would slow their growth. So we looked at prolonged stable disease as the primary outcome of this study. We escalated the doses based on the PK data to try to make sure we had achieved the levels that we predicted we would need, based on those mouse studies.

So the first cohort enrolled 15 patients. They were all very heavily pretreated. Now overall there was not a lot of activity here, which is probably not surprising. But what was striking is the one patient who was on this therapy without progression for over 500 days. We did look at some angiogenic factors and saw some changes there as well, suggesting that this agent might actually have biologic activity in female humans, as opposed to female mice, that we had seen before. So this trial is continuing to follow patients now in a second cohort of patients, where we've combined this therapy with very low-dose chemotherapy in hopes of amplifying this activity.

So this is certainly not a therapy widely available or that we would recommend outside of a protocol setting. So I've included this merely as an example of how understanding the biology of triple-negative disease could lead not just to new therapies but to reconsidering other therapies and how we might take advantage of some of the tools available.

Identification of potential therapeutic targets in TNBC with genomic profiling

So I think the thing I want our listeners to take away is that those profiling efforts have really identified many potential therapeutic targets — some might actually say too many — that the heterogeneity is greater than we had expected. We need to be very aware that expression alone might not be sufficient and that there are, perhaps, other models that could be more compelling in identifying which things are not just expressed but might really be driving factors where we might hope to see greater activity in the clinic.

Besides the PARP inhibitors that I know have been a huge focus, I think you'll see many of these therapies coming into the clinic in the very near future, and we hope that this will allow us to keep whittling away at the sort of undefined triple-negative population.

DR LOVE: Awesome. Yes! That was good. That was great. Really understandable. And we're kind of going back and forth between translational stuff and practical stuff. We'll get to a couple of more clinical questions that came in, but — and Hope, when I was listening to Kathy talk about Megace® for triple-negative, I was thinking: Cliff Hudis was talking about antiandrogen therapy and androgen receptors in triple-negative.

Phase III, multi-center, open-label, randomized trial of gemcitabine/carboplatin with or without BSI-201 in patients with ER/PR/HER2-negative metastatic breast cancer

But let's get back to this issue of BRCA-ness. Last week, Jenny Chang was talking about genomic predictors, of maybe moving towards that in terms of PARP inhibitors and trying to be able to identify the BRCA-like triple-negative tumors. Where are we right now, Hope, in that whole process?

DR RUGO: I think we're really still very, very much at the beginning, and it's an important question. And I think that where we're going to learn more about that is actually from this Phase III BSI-201 trial that just completed accrual. Because some of the triple-negative patients really have different histology, not just looking at gene expression by getting these fancy tests done in a research laboratory, but actually the metaplastic cancers, the more sarcomatous-type cancers, the neuroendocrines — they don't really fit into the basal subtype. And there's another group that is referred to as claudin-low — I'm sure you might have talked about that too — where a lot of these cancers fit into, an expression category.

So maybe what we'll be doing in the future — my take on it is that we haven't figured out the right treatment for those cancers. They don't do very well, and it'll be fascinating to see whether those subtypes benefit from the addition of BSI-201, the PARP inhibitor. But I think that what we need to do, as we move forward, is actually to subtype these tumors so that we can better understand when we go forward in trials which subtype is benefitting, much as Don Berry, Dan Hayes, and others have done looking at our big brush stroke subtypes and how patients respond to standard chemotherapy based on ER, HER2, triple-negative, et cetera. Now what we need to do is break down the triple-negative group — and, of course, the ER-positive group, too.

Management of de novo metastatic TNBC

DR LOVE: So yes, of course, we had to talk about claudin-low just because I like the name of it — I'm not sure I really understand it at this point. We're not going to talk about it tonight. We actually want to swing back and talk about more pragmatics, and Hope, we're going to have you talk about your case in a second. But one of the questions we've got a lot, and you can see a couple of examples here, from the field, Kathy, is current management of metastatic, first-line triple-negative breast cancer and where does getting patients on a trial, if there is a trial — for example, the PARP inhibitor — fit in?

So, first question: In general, how are you approaching these patients off study? And what kind of studies are out there for patients like that — again, the second case here — this patient's relapsed within six months of getting neoadjuvant therapy. What about a PARP inhibitor? How did — what about management of these patients, Kathy, on and off study, right now?

DR MILLER: For the de novo patient with metastatic triple-negative disease, outside of a clinical trial — and PARP inhibitor's not currently available outside of a trial — I would think about something like the paclitaxel/bevacizumab regimen as in the E-2100 trial. It's still a very effective regimen in this subset of patients with triple-negative disease. Their hazard ratio was very similar to the overall group, so it's not something we can say is specific to triple-negative patients, but they certainly derived the same benefit as the whole population, which was a very important finding and a very important question.

For those patients very soon after adjuvant or neoadjuvant therapy, I would actually have similar thoughts. And my modified answer is a bit — depending on exactly what their neoadjuvant therapy consisted of — if they had anthracycline- and taxane-based therapy and they progressed within just a few months, that actually is the patient that I would think about a platinum-based regimen as my initial chemotherapy, outside of a clinical trial setting. Of course, if PARP inhibitor was available, I would be delighted to include that with their platinum-based chemotherapy.

If there was a PARP inhibitor trial available to this woman, I would fully support her enrolling. And actually I would say if there was a clinical trial of any novel agent, for someone who progresses within six months of adjuvant or neoadjuvant anthracycline- and taxane-based therapy, this is someone for whom our best chemotherapy currently available has a very low likelihood of having any meaningful response. So I would not be at all reluctant to enroll this woman on a clinical trial of a completely novel agent as her first therapy.

DR LOVE: So, Hope, we're going to talk about your patient, but it's really tricky, being a CME, to get into this issue of where does a new and exciting agent fit it into nonprotocol management or the management in the community? So often we see agents and trials out there that really aren't that exciting — ABC versus DEF, or whatever. But then you see something like Joyce presented at ASCO last year, with chemo plus BSI-201.

Another that I think a lot about is T-DM1 and HER2-positive disease that you can only get on study. And it's kind of tricky, in terms of where does a new agent that's not even available, kind of — when do you want to try to get it for your patient? And why don't we talk a little bit about your lady, as an example of where experimental therapy can maybe help people. Can you talk about this woman?

DR RUGO: Absolutely. It's a really challenging patient. But I'll just say in comment to what you just were talking about, which I think is really important, is that, for example, if that patient had bone-only disease and it was nonmeasurable and they couldn't go on a trial because they didn't have measurable disease, of course, as Kathy was saying, our standard chemotherapy might work — even capecitabine might not be a

bad choice for that patient, just to see how it works. So you don't want to abandon the baby for the bath water, I guess is the saying.

Case discussion (Dr Rugo): A 29-year-old woman with a 4.5-cm node-negative TNBC with DCIS and pulmonary metastases develops brain metastases after treatment with paclitaxel and bevacizumab. Subsequent treatment with BSI-201/gemcitabine/carboplatin results in a significant response

So this is a 29-year-old woman — she's now 30 — and she presented with a four and a half centimeter, high-grade tumor of the right breast, node-negative on sentinel node and then a few additional nodes were removed. The tumor was triple-negative, and she had a little bit of DCIS associated as well. Interestingly, this woman whose whole family comes with her to the appointments — no one had any history of breast cancer or any other malignancy that they knew about, except for a few relatives with lung cancer who smoked a lot. So there was absolutely no family history.

And she was treated locally with AC followed by paclitaxel, given every three weeks for unclear reasons. But unfortunately, during her chemotherapy, the oncologist didn't use growth factors, and she also had a lot of things going on with transportation and child care, so she got her treatment over eight months, which is probably not the right way to treat a triple-negative breast cancer.

So then she went back to work in August of 2008, having finished her treatment in January of '08, and immediately when she went back to work she started having all these symptoms, and eventually what was diagnosed was extensive pulmonary metastases. So she actually was asymptomatic when she saw us, although she had huge tumors in her lung and also triple-negative on biopsy. And so she enrolled on a clinical trial at that time, and this was two years ago, with paclitaxel and an oral tyrosine kinase inhibitor, VEGF. So like bevacizumab but an experimental agent.

And she had an excellent response, but she got a lot of toxicity from the experimental agent, so we dose reduced her and eventually stopped the paclitaxel. And she was on that, and then she developed — she had a seizure and had brain metastases, so she got whole brain radiation and went off the study drug. And at the end of recovering from this wild experience with the big brain metastases, she had growth of the pulmonary disease and was hypoxic and really, really sick.

So we actually got her well enough to be able to be treated on the BSI-201 Phase III trial. So she received gemcitabine and carboplatin and the BSI-201 agent. And although the going has been quite difficult, she's had an excellent response. She just had a scan recently. She's not hypoxic, she's not on oxygen and her performance status is significantly better than it was when we started her treatment. Although I have to say the treatment is challenging in that there's a lot of bone marrow suppression, so these patients require very close monitoring.

DR LOVE: But also, just to clarify, you had told me that she was actually randomized to the control arm, so she got the gem/carbo. And the, I guess there's a crossover built in and she got the PARP inhibitor on the crossover.

DR RUGO: Yes, and it was a little traumatic, and it has been with all of these patients, because you put your heart and soul into treating these women. They sign up to do a new-agent clinical trial and so we treat them and then their scan shows progression, and you want to get them right on to the PARP inhibitor, but in order to make this as clean as possible you actually have to submit the scans on a CD to Rad Pharm, so you have to mail them overnight and get them to read the scans and tell you you can put the patient on a PARP inhibitor. So it takes a few days and you're getting the patient back and forth.

So she went on a PARP inhibitor. It took us about five days through a weekend, and then her first scan actually was just last week and showed a significant response, which I think is great in a crossover arm, to show a significant response with the addition of the PARP inhibitor.

DR LOVE: So, Kathy, again, it's kind of tough. You hear cases like this. Joyce presented a case last week of people — a person who was treated on the trial. We had a think tank recently and Hy Muss, always the realist, said, "We're seeing a lot of almost hysteria about trying to get these agents or this agent," but it doesn't look like they're getting cured.

How do you deal with this issue clinically, Kathy? Do you always have access to a PARP inhibitor or a trial for these patients?

Patient enrollment in clinical trials as a treatment option for palliative therapy

DR MILLER: That would be a lovely thing, but I'm not nearly that powerful. So I do think that the very real and legitimate and well-founded excitement about this area has been hyped a bit too much to the detriment of our patients. This is not curing women with advanced metastatic disease. It certainly increased response rates. It added to the progression-free survival by about three to four months. And it added to overall

survival in the one, small trial that we had, with a regimen that I share Hope's comments, is actually quite tough. We've been struck by the degree of myelosuppression, even in patients on the control arm, because really nobody at IU gets randomized to the BSI arm up front.

So I do sometimes feel like we need to keep reminding patients that if the trial's closed or they're not eligible, that there are other options for them that have real potential benefit. This is not the only option and it's still palliative therapy. So we still make these decisions based on all the usual clinical grounds: What have they had before? How symptomatic are they? What toxicities are of concern for them? What schedules are suitable? What schedules are not suitable? And for me, the clinical trials become a huge part of that. I think the time to think about a clinical trial is any time a clinical trial is available that meets the need for that patient.

Phase II clinical trials are typically very early. There's no way to know which drugs will totally bomb out and never be heard from again and which will be the next Herceptin or the next BSI-201.

So the reality is, most of our patients get lots of different therapies. It probably makes very little, if any, difference about the order of those therapies. As long as you're following patients closely — so if there're clear signs that whatever therapy they are on now isn't working, they've got the opportunity to switch, to try something else.

So for many of my patients, clinical trials come into play pretty early, because we've always got the option to switch them immediately to standard therapy. I don't always have the option to switch them immediately to investigational therapy, even if I've got a trial available. Sometimes the washout period just isn't matching the pace of the patient's disease.

DR LOVE: I mean, I think it's worth thinking about. Those early patients who went on the BSI trial, they didn't know that this was going to happen — they were just going into another study — and a lot of them did benefit.

We're going to finish out here. We're going to kind of go back to the practical again and talk about some issues related to chemotherapy, related to bevacizumab, related to platinums. And we actually asked Hope to do a mini journal club, and actually her talk — and the whole talk will be posted on the web — has 11 papers and four trials in it. She's only going to go through about half of that tonight, but, again, when we post this on the web in a few weeks, they'll all be available.

So, Hope, can you talk about some of the papers that we pulled out over — that have been presented or published over the last year, relating to treatment of patients with the agents that we do have available?

DR RUGO: Yes, I will. And I will say that just in responding to that case, we have had patients on the trial, randomized to the BSI-201, who had absolutely no response — progressed at the first scan. So no hysteria at the moment.

Anyway, here're my disclosures and they're also going to be posted, of course. So what we're doing to do, actually, if we just think about — because the slides will be available, regardless of what we get to cover right now — is thinking about three main topics. So the first is what does standard chemotherapy do for patients with triple-negative breast cancer? And we can look at that in the neoadjuvant setting in two different studies, and I think that's very helpful.

The second thing is does bevacizumab help patients with triple-negative breast cancer? Kathy alluded to this earlier, and we'll talk about some summary data that's been presented — and you'll see more of it coming up at ASCO — based on looking at subsets.

And then the third is what new chemotherapy approaches might benefit our patients who have the highest-risk cancers? So you might look at, for example, platinums. We've talked about that. I'll show a little bit of that. And then what we won't get to is talking about new chemotherapy agents that might benefit patients with triple-negative breast cancer, like the epothilone ixabepilone. There's a slide in there from a study, as well.

Retrospective study of response to neoadjuvant therapy in patients with TNBC

So let's talk about the neoadjuvant therapy. There was a study that's published in the *JCO* that looked at this huge database at MD Anderson — and they always have the ability to go back and do these database studies, starting back in 1985, which the rest of us really don't have the databases to study. And they looked at patients who received neoadjuvant chemotherapy — and most of their patients are on clinical trials, so they received anthracyclines and then, more recently, taxanes. They had over a thousand women who got neoadjuvant treatment. And then 23 percent had triple-negative breast cancer, so about 250.

So what they did was actually look at the difference in pathologic complete response rate, and then they've divided it up by regimen, but I don't think that's particularly important, between the triple-

negative and the nontriple-negatives. So remember, this is all before trastuzumab, but the HER2-positive represents a smaller population.

So you can see, if you just look at the bottom line of the total patients, that 22 percent had a pathologic CR in the triple-negative versus about half that in the nontriple-negative. And overall, if you look at the taxane-containing and anthracycline regimens, it's actually getting close to 30 percent. So that suggests what other people have shown in smaller databases, that patients with triple-negative breast cancer, who have very highly proliferative tumors, actually can have a very good clinical and pathologic response in the neoadjuvant setting to standard anthracycline- and taxane-based chemotherapy regimens. And that's pretty good. So you remember that, overall, for the taxane/anthracycline combinations, there was about 28 percent in this single-institution retrospective trial.

Long-term survival in patients with pCRs from neoadjuvant therapy for TNBC

The other thing that they looked at was what the outcome was of these patients — again, they have the ability to do that. We know from the NSABP studies that looked at neoadjuvant therapy, the patients who have pathologic complete response rates, regardless of subset, appear to have an excellent survival compared to a group of patients with the same stage of disease, where you don't know what the PCR would be in the adjuvant setting. And indeed, the triple-negative patients who had a PCR had a very good outcome, and others have now shown this. And that's really important because it means that PCR is an important endpoint for patients who have triple-negative breast cancer in clinical trials and does correlate with a better outcome that we would expect from the group as a whole.

I-SPY trial: Molecular profiles predict tumor response of neoadjuvant doxorubicin and paclitaxel

Now Laura Esserman, on behalf of the ISPY investigators, presented data looking at both immunohistochemistry and, basically, expression subset characterization, looking at what happened to pathologic CR in patients receiving taxane- and anthracycline-based neoadjuvant chemotherapy regimens. Now this multicenter trial didn't look at the chemotherapy, so everybody got a taxane and anthracycline, and looked at MRIs serially, and then patients had biopsies to try and look at predictors of response.

This is just the biopsies from the initial time — so before they started treatment — and then looking at pathologic CR. And if you look at the patients in the bottom line of the IHC category who have hormone receptor-negative, HER2-negative disease, 53 patients, the path CR rate is 33 percent, identical to patients who had hormone receptor-positive and HER2-positive disease or just HER2-positive disease overall.

Now they also looked at gene profiling because, of course, there was fresh tissue and they were working with Chuck Perou and he looked at the gene profiling. In the basal-like subgroup, 48 patients, the pathologic CR rate was 34 percent. That's much higher than if we look at a group as a whole with taxane- and anthracycline-based chemo.

So very impressive, and it does go along with the idea that these highly proliferative tumors do respond well to our standard treatment, and when patients get diagnosed with triple-negative breast cancer, it's not a death sentence by any means. These patients who achieved pathologic CRs and even patients who had a near PCR, so just a little bit of residual disease left — those patients did extraordinarily well.

So we know that in contrast, patients who have ER-positive luminal A disease don't have much pathologic CR rates and maybe they don't need chemo. That's a whole other question.

Randomized trials of bevacizumab with chemotherapy: AVADO, ECOG-E2100 and RIBBON 1 — Subgroup analysis of HER2-negative metastatic breast cancer

So then, what about using new drugs to treat these patients? So where can look to, to see what the benefit of bevacizumab might be? Joyce O'Shaughnessy actually did an analysis of the three large randomized trials looking at the addition of bevacizumab to standard chemotherapy as treatment of metastatic breast cancer in the first-line setting. Of course, all these patients had HER2-normal disease, and the three trials that were evaluated, including ECOG-2100 — Kathy's Cooperative Group trial — the AVADO trial in Europe and the RIBBON 1, recently presented data last year looking at patients receiving capecitabine or a taxane and anthracycline grouped together. Very few patients were in the anthracycline group.

Improvement in progression-free survival with the addition of bevacizumab to chemotherapy in patients with metastatic TNBC (mTNBC)

So this summarizes the data and actually looks at it by an interesting way. Just to understand it, it's the absolute improvement in progression-free survival seen by adding bevacizumab to the standard chemotherapy arm. And then if you look at the overall group and then the line below it, which is the triple-

negative group, you can see that that group looks like it benefits as much as the group as a whole, in almost all groups — a little bit different in RIBBON 1, a more heterogeneous group of patients and a much larger — relatively larger — trial.

It's interesting, also, that there was a lot of benefit in patients who received neoadjuvant or adjuvant taxanes, a curious finding that's been observed before and suggests that bevacizumab may play a role in being able to reverse resistance to taxane-based chemotherapy.

So this data suggests that bevacizumab does benefit patients who have triple-negative disease as well as the group as a whole.

ATHENA trial (MO19391): First-line bevacizumab with chemotherapy in triple-negative, locally recurrent or metastatic BC

So then there's another, actually large trial, a community-based trial, nonrandomized, in more than 2,000 patients, called the ATHENA trial, done in Europe, primarily, where patients were treated with bevacizumab and chemotherapy of choice. It was mostly a taxane alone or in combination or another standard chemotherapy if the patient couldn't get a taxane — a standard of care-type treatment. In other countries it might be something different.

So the patients were HER2-negative, hadn't received prior chemotherapy. And if you look at the data here of triple-negative versus nontriple-negative — very large trial — again, not well controlled for what kind of chemotherapy patients receive. The time to progression rate was 7.2 months for the triple-negative breast cancer patients, which is quite reasonable, looking at historical groups — longer than what we would expect from this type of treatment. You can see that the patients who had nontriple-negative breast cancer did better, but the response rate is quite similar, almost 50 percent. So again, it suggests that bevacizumab may help these patients.

Clinical trials with neoadjuvant and adjuvant bevacizumab and chemotherapy for TNBC

We're now looking at that specific question in a number of different clinical trials in the neoadjuvant and adjuvant setting, and some of these trials are specifically directed towards the patients with triple-negative disease — a trial in the CALGB in the neoadjuvant setting and a randomized trial in a network setting, called the TRITON trial, looking at bevacizumab.

pCR rates after neoadjuvant cisplatin for BRCA1-positive breast cancer

So if we move on to what we might use in terms of new chemotherapy treatments, of course one group that we might want to look at that we know might benefit from DNA-damaging treatment because they can't do DNA repair — as Kathy talked about earlier, that DNA repair pathway is defective — there are patients who have BRCA1-associated cancers.

So a group in Poland actually was able to identify over 100 patients who had BRCA1 mutations, and most of them had triple-negative disease. And they looked to see what happened to these women when they got a variety of different neoadjuvant regimens. And if you look at the last line, cisplatin, that what's got the most interest. Twelve patients treated, 10 had pathologic complete responses — much greater than the other regimens where the PCR rates were very low, actually abysmal — so 83 percent pathologic CR rate. So they presented at ASCO last year a bigger group of 25 patients with a pathologic CR rate of 75 percent. Really intriguing, and is being studied again in a neoadjuvant regimen in all-comers, triple-negative breast cancer patients, randomized to carboplatin or not with standard chemotherapy.

And then, lastly, what happens with patients who have sporadic triple-negative breast cancer, who are treated with cisplatin? Same regimen — 75 mg/m^2 every three weeks times four — same regimen Kathy used in her BRCA1-associated tumor patient in the preoperative setting. And then they give other standard chemotherapy postoperatively. And you can see here that the pathologic complete response rate in this data set, recently published in the *JCO*, was 14 percent. So not as good as what we saw with standard chemotherapy, but it indicates that cisplatin has effective — has a potential effective use in this group of sporadic triple-negative breast cancer patients.

So now, adding that agent to standard therapy is the next approach, and again, as I mentioned, it's being studied in a couple of randomized trials in the neoadjuvant/adjuvant setting.

Subset analysis from randomized trials of ixabepilone with capecitabine versus capecitabine in patients with TNBC

DR LOVE: So we're going to finish out in a second and Kathy, here are a few questions that we got, again related to PARP inhibitors. And you can look these over while I ask you, Hope: One other paper that's in your series that you didn't get to is your own work looking at ixabepilone in triple-negative disease. Can you kind of summarize what we know about that?

DR RUGO: Ixabepilone is a novel antimicrotubule, targeted agent in a class of drugs called epothilones, and it can

overcome, we know, some of the resistance mechanisms that tumors have to standard taxanes. And the randomized trial that led to approval of ixabepilone looked at ixabepilone and capecitabine versus capecitabine alone, capitalizing on the synergy that's been previously demonstrated in the clinic and in preclinical studies.

And what they showed, obviously, was ixabepilone and capecitabine was better than capecitabine alone and met their endpoints. But what we did was look at the subset of patients who had triple-negative breast cancer in the two large randomized trials, the one in the US and the one in Europe. So we have a large number of patients who had triple-negative breast cancer and we saw a significant improvement with the combination therapy versus capecitabine alone. And even more strikingly, we saw that capecitabine alone in these sporadic anthracycline- and taxane-pretreated patients with triple-negative breast cancer was not a great drug, with a PFS of only about two and a half months. We could double that with the combination.

So it suggests that we should be looking at these patients who have triple-negative breast cancer to understand what the right chemotherapy regimens are for them, whether they should receive combinations with these novel agents, platinum-based therapy, bevacizumab-based therapy, or maybe they should — most of them — should receive PARP inhibitors as well.

DR LOVE: So let's close out with some of the many, many questions. Clearly, the most common question that we got in this series so far, which is the issue of PARP inhibitors — Kathy, here are three typical questions we got. Maybe you can breeze through them.

As far as I know, I think BSI-201 is the only one that's been looked at in triple-negative, or at least reported, but we did talk about olaparib last week in BRCA tumors, and there are other PARP inhibitors being developed. What do we know about them? What about PARP inhibitors in HER2-positive or ER-positive disease? And is there any way to get any of these PARP inhibitors outside of a trial right now?

Access to PARP inhibitors through clinical trials or expanded-access protocols

DR MILLER: So I'll take your last question first. As far as I know, there is no way to get any of them outside of a clinical trial. BSI does plan an expanded access protocol — it will still be a protocol, it will still be very similar to their registration trial — that will be available in the next month or two, we're told. And that will still require a protocol, though perhaps a little bit easier for people to access.

Most of the others that your questioner has listed are in earlier stages of development. Some have just moved into the clinic into just Phase I, all-comer studies, though they certainly hope that there will be more triple-negative and breast cancer patients enrolling. But we have very little, if any, clinical data to guide us.

PARP inhibitors in HER2-positive or hormone-positive disease

And the question about other hormone-positive or HER2-positive disease is one that we give a lot of thought to. And I think what you will see is as we get closer to defining a signature of BRCA-ness or DNA repair defect that could identify this subset of patients with triple-negative disease most likely to benefit from PARP inhibition, we will rapidly be looking at breast cancer with other phenotypes. Because it's quite possible that a subset of patients with ER-positive disease have similar defects in DNA repair, and they might also benefit. And so that will be the next step in the studies.

I think for right now, most of these agents are focusing either on patients with known BRCA mutations or triple-negative patients. There's also interest in other tumor types. I might not care much about lung cancer, but other folks do, and many lung cancers have DNA repair defects as well. So I think you'll see PARP inhibitors fairly rapidly leaving just the realm of BRCA in triple-negative breast cancers.

DR LOVE: So, Kathy and Hope, thanks so much for joining us tonight. And to our audience, thank you for tuning in. We hope that you've seen there is a lot of positive research and developments in triple-negative breast cancer to talk about. And thank you for tuning in.