Finding the Positives in Triple-Negative Breast Cancer (TNBC)

Dr. Love:
Welcome to Finding the Positives in Triple-Negative Breast Cancer. I'm Neil Love from Research to Practice in Miami, Florida. Welcome to the many oncology clinicians out there. Undoubtedly, it's been a tough and challenging day for all of you. We appreciate you taking the time to join us tonight.

And for this first of our three-part series, we have in New York Cliff Hudis from Memorial Sloan-Kettering and Lisa Carey from the University of North Carolina. Cliff, actually, Kathy Miller, who's one of the faculty members in the last session, came up with the title of this series, Finding the Positives in Triple-Negative Breast Cancer, and I guess reflecting the fact that maybe the perception of this entity, if it is an entity, has kind of changed in the last year in terms of maybe now some things that we can kind of get excited about.

Is that what you're seeing, Cliff?

Dr. Hudis:
I agree. I think that we're starting to see an enhanced understanding of the biology of these tumors, and I think this is leading us nicely to at least the promise of some novel, less toxic and more effective therapies.

Dr. Love:
So, Lisa, actually, the working title for this series originally, because we kind of had the idea of doing this as an integrated course of these three hour-long sessions, and initially, we talked about calling this Triple-Negative 101, because of the course format, but given the sophisticated nature of the science that's involved here, it's kind of maybe not an appropriate title. But really, the science and the publications that are coming out in this field have just been overwhelming in the last year or two. Any thoughts?

Dr. Carey:
Yes. I have to say I share your enthusiasm entirely — it's interesting. Sometimes I see patients who say, “Wow! Is anybody doing any work in triple-negative disease?” And I say, “Oh my, are you kidding?” This has been a very hot topic for research for several years now. And I think that we're seeing the fruit of that labor.

Dr. Love:
Both of you participated in recent programs that — Lisa, at San Antonio, we had a roundtable discussion, specifically focused on triple-negative. Cliff, you were involved in a roundtable think tank in our studio here in Miami a few weeks ago, where we talked a lot about this. And again, just looking at the publications that have come out in this field, even over the last year, just look at some of the review articles, it's really amazing what's coming out.

We're going to try to distill this down for the clinician who's dealing with a hundred other kinds of tumors and pathways, et cetera. So just to introduce this, here are my disclosures for this program. And in terms of what we're going to be covering tonight, at the core of this three-part series, each one of these hour-long sessions will have two faculty. As part of the hour-long discussion, each faculty person will give about a 10-minute talk. And we're actually going to weave this together, all six talks, into kind of an integrated slide set at the end of this for people to access. And, of course, the total program will be available on the web to access.

Cliff is going to begin by giving kind of an overview talk and talking about the triple-negative disease entity. He has a case from his practice that we're going to talk about. We've already gotten a bunch of
cases and questions from docs out there who are interested in this, and we'll bring some of those up. And then Lisa will get into really a challenging area, I think, to understand, which is: How does triple-negative integrate in terms of the intrinsic subtypes of breast cancer, and particularly BRCA-ness, and now a new thing I just found out about in San Antonio, the claudin-low subtype? And then we'll do a case there.

If you have a case or a question that you'd like to pose to us, just type it in, in the box in the lower left hand of the screen, and we'll do our best to cover as many of these as we can. If you want to include your name and location, that's fine. If you want to be anonymous, that's fine also. And we'll try to talk about as many of these as we can.

As we mentioned, we're hoping to weave these things together into an integrated kind of curriculum when we get done, but it's going to be a little bit of an experiment, I think, as we go along. Please fill out your CME evaluation and give us some feedback on what we're trying to do here tonight.

Case discussion: A 54-year-old woman has a 1.2-cm, ER/PR-negative, HER2-negative BC with no nodal involvement and no family history of BC

And I thought before we get into the presentations and the data, we could just take a step back and begin with one of the cases that we received a couple of days ago from Dr Patricia DeFusco in Hartford, Connecticut. And, Cliff, it's not an unusual situation: a 54-year-old woman, bottom line, she's got a 1.2-centimeter, node-negative, two sentinel node-negative, triple-negative breast cancer. And one of the questions she posed in this, that we didn't actually put on the screen, is: How should she view this type of patient in terms of prognosis? Should she be thinking about aggressive chemotherapy, even though it's a node-negative tumor, small, node-negative tumor? And then what about the issue of BRCA testing? We've heard about PARP inhibitors and BRCA. Should she be thinking — and this woman doesn't have a family history, but should she be thinking about that?

How would you think through, Cliff, this kind of a case?

DR HUDIS:

Gee. I mean, this really highlights any number of important issues in clinical medicine. Let's start with the question on the screen, which is the BRCA testing. So, normally, you would think for a person in her midfifties, approaching the peak incidence of breast cancer, which is 58 to 63, that having a breast cancer is not such an unusual event, and so testing wouldn't come to your mind.

But the more you scratch the surface of this, the more subtle it becomes. Lots of people don't really know their family histories in detail. And so we would certainly probe for ethnic background and patterns of migration from Europe and so forth. All of that said, if we don't identify any other risk factors for the average 54-year-old, the mere existence of a triple-negative breast cancer does not constitute a standard indication for formal BRCA testing.

I'll go short on the question of the prognosis. This is certainly a higher-risk cancer than the equivalent tumor that would be ER-positive, and probably than the HER2-positive version of this, now that we routinely use trastuzumab. But you said one thing that I want to come back to, and that is the idea that she should get more or less aggressive therapy. Boy, I think that's a conundrum, because, for example, you would think of CMF as less aggressive than an anthracycline-containing regimen.

And yet the Canadians last summer at ASCO showed really interesting data from MA5, where the inverse of the anthracycline benefit being amplified in the HER2-positives was seen. And in fact, they may have evidence that triple-negatives, or at least the basaloid subtype of the triple-negatives, have a benefit from CMF. So I would actually separate the notion of aggressive therapy with better therapy — I think that it's really so.

Current clinical perspective of TNBC

DR LOVE:

So, Lisa, you've had interest in triple-negative for a long time. And we did a satellite meeting at San Antonio, and one of the things we asked as a poll question to the audience — we listed a whole bunch of topics and said, “What's the one you're most interested in?” And actually, triple-negative was number one on the list. I don’t think that would have been the case a year ago.

What have you seen? You've been involved with this field for quite a while in terms of interest in the entity. And what do you think is going on in terms of how people perceive it?

DR CAREY:

I think in truth, the triple-negative disease has been there all along. And the reason that it's of greater interest now is because we're having emerging ideas that we can treat it better. And I think that's when people develop greater need to know and greater interest in it, is when we actually have the sense that we can develop therapies that are specific to one kind of breast cancer.
I think the same thing happened with HER2 a few years ago, because we developed HER2-targeted therapies. The hope is we'll do the same thing here.

**DR LOVE:** Lisa, do you find that in both of these roundtable discussions, we heard from investigators that there’s tremendous concern from patients when they hear they have triple-negative disease, and also from physicians. And one of the things that I think I heard from a lot of the investigators was maybe that’s a little bit blown out of reality in terms of what the actual prognosis is. Do you find patients and physicians maybe inappropriately — or maybe overmagnifying the risk of this situation, or is it pretty appropriate? Lisa?

**DR CAREY:** No. I mean, I think like all things, there’s always a kernel of truth in it. But it has been, I think, amplified, probably inappropriately in some respects. I mean, if you think about it, we used to focus all of our attention prognostically on anatomic details — how big is the tumor? Does it involve the nodes? How many nodes? Then came the advent of biologic knowledge and profiling and things like that, and the pendulum swung entirely the other way, and now everything is all about biology. And in truth, a Grade I breast cancer is a Grade I breast cancer no matter what biology it has. And you cannot turn a very small node-negative breast cancer into a high-risk breast cancer, regardless of these features. So I think these things have to be looked at in concert, and I think that some of that gets lost when the focus comes down on these data sets that do suggest a poorer prognosis relative to, say, hormone receptor-positive breast cancer, but that doesn’t mean that all triple-negative breast cancer is going to do poorly. In fact, we know that many do quite well.

**DR LOVE:** So, Cliff, we’re going to start with you and your presentation in just a second, but one thing that I think both of your presentations sort of get into — and I just kind of want to get this out on the table before we start going through all the detail of your slides, which is: Is this really a defined entity of triple-negative breast cancer? Or is it just the people who don’t have responsiveness or ER-positive, HER2-positive? How do you, Cliff, kind of visualize this?

**DR HUDIS:** For me, and I’ll talk about this, I don’t yet believe that triple-negative breast cancer is a single entity at all. I think that it is, for sure — it reminds me of the early days of psychiatry in the sense that it’s very much a diagnosis of what it isn’t. And there are psychiatric illnesses that have been developed the same way, and then we tease them apart later, and I think that’s what’s happening here. It isn’t ER- or PR-positive, nor is it HER2-positive. So that may describe a predominant type of breast cancer, but we will see in our discussions, I think, that it also includes some others.

**Epidemiology of BC**

**DR LOVE:** All right, let’s go ahead and get started with your talk, Cliff, because this, I think, ties into one of the major points that you’re going to get into.

**DR HUDIS:** Thank you very much, and it’s really my pleasure to present this tonight. I do want to point out that I have some disclosures, which will be obviously available to you to check.

Let’s just start with the big picture. Breast cancer is one of the most common life-threatening cancers in American women. In fact, it’s the most common life-threatening cancer, with about 192,000 cases expected to totally be recorded for 2009. Interestingly, that does represent a decline. With the removal of hormone replacement therapy pretty sharply in 2003, there’s been a decline, in particular, of low-risk ER-positive breast cancer in postmenopausal women.

Interestingly, since 1990, the number of women dying of breast cancer has been falling fairly steeply in epidemiologic terms. It was 46,000 that year, and last year it’s probably about 40,000, give or take a few hundred. So there is a real success that has been unfolding slowly in front of our eyes.

The lifetime risk of breast cancer is frequently quoted as one in eight or one in nine. It’s just important for everybody to remember that that is a cumulative risk. If you remember your calculus, the yearly risk, and even the decade risk for any individual woman is actually far lower than that.

The epidemiology is important for women in the sense that lung cancer is less common — you can see about 14 percent of the 700,000 new cases last year — but it’s much more lethal. In fact, it’s responsible for almost twice as many deaths from cancer. So the thing to really do, of course, is not smoke and not get lung cancer. Breast cancer is more common, but much, much more likely to be cured.

**Intrinsic subtypes of BC**

So we’re going to circle back, I think, several times during this course to slides that look like this one. This is a description of one way of segregating breast cancer. And we’re starting again at the top-line view. This is all breast cancers, and this is the unsupervised, if you will, subtyping, based on gene expression analysis from microarrays. And what happens here is that certain sets of genes identify breast...
cancers that segregate together. In the ER-positive group, there are two subsets, the luminal As and the luminal Bs. There is also a small group of luminal C that's now been, I think, further refined. We'll hear more about that later.

And then there are the ER — I'm sorry, the HER2-positives — they represent a relatively small group — and the basal-likes. And the reason we're focused on the basal-likes is that they overlap, as you'll hear, to a large degree, but not entirely with triple negativity.

This does matter clinically, and I'll draw your attention to the left side of this slide, where the curves are plotted. These are patients from a BCIRG chemotherapy trial in the adjuvant setting, and just what clinicians have learned to expect is seen here. The luminal As, being the hormone-responsive subtype, do the best. Luminal Bs are ER-positive, but less likely to be hormone-responsive, and they don't do quite as well. And this is a pretrastuzumab-era study, so the HER2-positives do much worse, and so indeed do the triple-negatives.

**Pathologic and molecular features of TNBC**

The pathologic and molecular features of triple-negative breast cancer consist of things you'd expect to see in aggressive tumors — a high proliferative rate, pushing borders and central necrosis may be reflecting growth of the tumor that outstrips the vascular supply. And at the molecular level, this is associated with a higher Ki-67, p53 and maybe EGFR expression. There's also a statistical association with BRCA1 status. You'll hear much more about that, but one can describe it from one of two directions. Triple-negatives are more likely to be in patients with mutation status and, conversely, BRCA1 mutation carriers, when they get breast cancer, are more likely to develop triple-negative breast cancer.

The risk factors for this include, I think, several things. First, as we've already described, BRCA mutation and family history are a surrogate for mutation status. Being young and premenopausal and having African-American ancestry, that's associated with triple-negative breast cancer.

A couple of these factors, though, I think you have to watch. Younger age at first birth and high parity, they're also associated with lower socioeconomic status. And as has been pointed out in some fascinating epidemiologic studies, within controlled, tightly defined ethnic groups, lower socioeconomic status, all else being equal, associates with a higher rate of triple-negative breast cancer. So you don't know which came first, the chicken or the egg, as it were.

Some of the features of the phenotype, I think are clinically known to docs in the field. They often present as interval cancers. Yearly mammograms are done, and yet this cancer appears in between. Why? Because it's rapidly growing. It has a peak incidence of recurrence in the first, second and third years. That's a different pattern of recurrence for early-stage breast cancer as compared to ER-positives. They tend to have sort of a slow and steady rate of recurrence.

In the aggregate, although they have an increased mortality over the first five years, the overall rates of mortality — as described in the Oxford Overview for all subtypes of breast cancer — until recently appeared to be the same, if measured over decades. In this case, though, the deaths are early, typically in the first few years, because there's a rapid progression from the time of recurrence until the time of death.

**Characteristics and features of TNBC phenotype**

So, now, recapitulating the question asked overall for breast cancer and the one that Neil asked about in the introduction: Is triple-negative breast cancer itself really one disease, or in fact is it a collection? One can see that there's at least some heterogeneity in triple-negative breast cancer, because some of the biomarkers that clinicians use in the pathology lab — especially if they don't have access to tissue expression analysis — is things like EGFR expression or CK5/6. And this overlaps to a degree with triple negativity, but it doesn't overlap perfectly. Lisa will address this in greater detail later.

In one example of the way we can use modern molecular tools to try and define this, Ashley Doane, when he was a premed student at our place, took a cohort of patients who had known ER status and they segregated in an unsupervised fashion according to gene expression analysis, into the ER-positives, shown in the right, and they are largely green on your slide with red lines denoting that they're cases. And the ER — I'm sorry. Those are the ER-negatives. And on the left were the ER-positives, largely red on the bottom with green lines denoting them.

But what was interesting and key is, if you look far to the left on this slide, you'll see that there are, in fact, some ER-negative cases that segregated with the ER-positives in terms of their expression. And when he drilled down on these, an example of 41 of these, what distinguished them — and it's expanded on the right-hand side — was that a cohort of them, shown with an orange vertical line and red
highlighting, actually had features that marked them as likely hormone responsive, but they definitively
did not have the ER. What we found that they had was the AR.

**Effect of androgen receptor positivity on treatment algorithm**

Now, everything old is new again. AR has been described in breast cancer for decades. It’s not really
new. But this gave us a reason to think again that triple-negative breast cancer isn’t just one thing. And
it gave us a place to translate a finding, because we have antiandrogen receptor drugs, most notably
Casodex® — bicalutamide — which has been used for years in prostate cancer. And we have a clinical
trial currently accruing patients both at Memorial and now through the TBCRC, where we’re giving the
antiandrogen receptor to triple-negative breast cancers based on AR positivity.

There’s also the pearl described in all this. This is about 10 percent of about 15 or 20 percent of breast
cancer, so it’s a pretty small cohort of patients, and it’s a tough place to develop a drug.

Now, another avenue of study in recent years has been the role of platinums. And this is an old drug
— of course, in fact, it’s just interesting to point out that — it’s been around since the middle of the
nineteenth century, first described clinically as causing — or preclinically — as causing massive-size,
large *E coli* that fail to divide. That led ultimately to the development of cisplatin and then later carbo-
platin for testes and ovary cancers, and now there are several others.

**Activity of platinum-based chemotherapy in patients with BRCA1 deficiency**

Platinums in randomized trials have not consistently been shown to be advantageous. In fact, the Creagan
study shown at the top of the slide is a trial where, by random assignment, metastatic breast cancer
patients received platinum and doxorubicin or not, and they actually did worse in that case.

A prospective randomized trial of unselected patients given epirubicin alone or with platinum went a
little bit the other way — a small advantage in PFS for the platinum, but no impact on survival. And
recently, we’ll see in a *JCO* paper from Dana-Farber, showing the activity of single-agent cisplatin in the
preop setting. Fourteen out of 28 patients responded, six with a CR — that’s great. Two of them, though,
actually had mutations in BRCA1. If you eliminate them and you ask, “What’s the rate of PCR in just
triple-negatives?” it’s four out of 26, 15 percent, and you’ll hear again that this is very much similar to
what’s seen with lots of other single agents in metastatic disease.

We’re trying to get a handle on this with a prospective randomized trial in the preop setting in the
CALGB. Bill Sikov is the PI. The key randomization is for the use of platinum or not. There are a variety
of additional targeted therapies that our course will cover, notably PARP inhibitors, EGFR inhibitors and
many, many others. It’s an exciting and rapidly growing list.

So what am I telling you tonight? Triple-negative breast cancer, in my opinion, is clearly not one
disease. There are a variety of standard therapies. You’ll hear about some of them, including the role
of bevacizumab, but we need to develop new targets in this cohort and new therapies to match those
targets, and then rationally develop combinations.

I just want to end by pointing out that what we discover in this cohort of breast cancer patients likely will
be informative for treatments in other solid tumors.

Thanks very much.

**Use of EGFR inhibitors in combination with platinum agents as treatment for TNBC**

**DR LOVE:**

Thanks, Cliff. And we’ll follow up on that issue of the androgen receptor and antiandrogens, which I never
heard about until you brought it up at our think tank a few weeks ago — really fascinating. We actually
got a case from one of the docs asking about it from New York, so maybe she kind of heard about it
through you.

But first, just before we get to that, Lisa, we’re going to talk a lot about the issue of platinums and
EGFR and EGFR inhibitors throughout this series, and you’ll talk about it. But can you kind of give us an
overview of this? It’s been a little bit confusing. Do you think there’s a qualitative difference in terms of
the response of patients with triple-negative tumors to platinums compared to non-triple-negative tumors?
And what about EGFR and EGFR inhibitors? It kind of seems like that’s tanked out a little bit — we were
excited. You’ve done a lot of the work — what about these two issues? Can you kind of give us a global
perspective on that?

**DR CAREY:**

I think the question of platinums is one that we’re going to talk about a little bit, but I think Cliff hit the
nail on the head in that there is evidence of sensitivity to platinum agents, but frankly, in this disease,
there’s evidence of sensitivity to a variety of agents. And whether there’s a particular responsiveness to
one approach versus another within cytotoxics is an unanswered question. And that’s exactly why there
are randomized trials like the CALGB-40603 trial, which is going to directly ask the question of adding a platinum agent to a taxane.

In terms of EGFR, it’s been a very interesting arena. There are three studies that have looked at this that are quite substantial. One was a study that was limited to triple-negative breast cancer — it was done through the consortium that Cliff mentioned, the TBCRC — and looked at carboplatin and an EGFR monoclonal antibody, cetuximab, in triple-negative disease. In a pretreated setting, a modest effect was found of about 17 percent response and about 30 to 31 percent clinical benefit, meaning sustained response or stable disease.

At the same time, Joyce O’Shaughnessy’s US Oncology trial enriched for triple-negatives, and they saw a substantial improvement in response rate but no improvement in progression-free survival with the addition of the same antibody, cetuximab, to irinotecan plus carboplatin, so really raising the question of whether there’s a benefit within this group that’s substantial enough to approach pursuing it further.

I can tell you that within the TBCRC trial, we did have the benefit of serial biopsies from the target lesion in a subset of the patients, which gave us a lot of very interesting hypothesis-generating ideas in that although the majority of them had EGFR activation of the pathway, the drug only inactivated a small minority of them. And all of the clinical activity that we saw was within that small minority, where the drug actually turned the pathway off. In the other ones, even though the pathway was on and the drug was given, the pathway didn’t get turned off. So I think one of the things we’re learning about cancer is it’s smarter than we are in some respects. And one drug is unlikely to be enough to turn off a pathway in many, if not most, of the tumors that we’re treating.

So we have to get smarter, and that means we have to do more tissue-based studies of the kind that I think Cliff was highlighting, and others will also, because we need to know more about the biology. We can’t rest on the laurels we have so far.

**Role of anti-androgen therapy as treatment for AR-positive TNBC**

**DR LOVE:** That’s interesting, though.

**DR CAREY:** Just to let you know, there is one European trial that will help us know a little more about that. It’s a randomized study of a platinum with or without EGFR antibody.

**DR LOVE:** It’s interesting though in terms of what you’re saying about EGFR. So maybe that is a pathway that would be fruitful — we maybe need other agents or other ways to attack it. Is that kind of what you’re saying?

**DR CAREY:** Yes. I think as a single agent, it’s unlikely to be fruitful in all but a few.

**Endocrine therapy for patients with disease previously thought to be ER-negative**

**DR LOVE:** That was a point that we talked a lot about at the think tank. And when can you really feel comfortable that this is a triple-negative tumor? You don’t want to lose the opportunity to be able to use targeted therapy. And I remember, Cliff, you brought out a question that, for example, if you have a patient whose original tumor was ER-positive or HER2-positive, you get a biopsy and it’s triple-negative, that
maybe you’re still going to be thinking about targeted therapy, based on the original. You want to comment on that?

DR HUDIS: I mean, this is actually sort of old — I’m actually getting old enough to say this — this is just old oncologist lore, but it’s true. So, if you see a patient — to give you the extreme — who supposedly has an ER/PR-negative breast cancer in 1987 and shows up in your office in 2007 with bone metastases, you give hormone therapy. Who cares what the ER/PR result is? A nuance is the decalcification of the specimen to do ER/PR testing in the case of bone biopsies is known to have an impact on ER testing. And there’s nothing to lose. The notion that you might be hurting that patient is not really supported. You can pick the wrong chemo first-line too and not get a response. So I think we make a little too much about it.

My bigger concern is missing the chance to use hormone therapy. So if it was ever positive, certainly I think it’s worth a try. And if it is clinically consistent with a positive result, I think it’s worth a try. There are cases that are triple-negative and indolent and bone dominant. They do happen, but one has to be savvy.

I’ll give you another example that’s a classic, and that’s invasive lobular. Somewhere around 90 percent or higher invasive lobular cancer should be ER-positive anytime. I mean, 100 percent of the time that I see a so-called triple-negative invasive lobular, we get those retested. I’ve seen some that are really negative, but they are rare.

Prognosis based on molecularly defined BC subtype

DR LOVE: So, Lisa, actually, we got questions about this in terms of, quote, indolent triple-negative disease. Obviously not everybody with triple-negative tumors has recurrence or has rapidly progressive disease. Where are we in trying to identify within the triple-negative subtype maybe more indolent tumors? This apocrine thing may be an example — I don’t know.

DR CAREY: And I think you’re absolutely right. I mean, there is clearly heterogeneity in behavior within triple-negative disease or even within basal-like or however you want to categorize it, either by molecular or immunostaining. And the fact is that right now, we don’t have the tools to identify the good-prognosis/poor-prognosis subtype within the triple-negative disease. And that is a real challenge for the future.

I can tell you that I’ve spoken to many scientists who are trying to do this, but it’s not easy. I mean, this is a real challenge, and some of it has to do with the fact that these are simply more genomically unstable to begin with, so it may be that they don’t segregate easily into just two or three groups within them — there may be 100. If you have 100 tumors, they may have 100 different phenotypes, and so figuring out how to find the good-prognosis ones may not be a trivial exercise. It may be far harder than it is for some other subtypes.

CASE DISCUSSION: A 45-year-old woman has metastatic TNBC, biopsy-proven liver metastases and a family history of BC

DR LOVE: So before we dip back into the translational science of triple-negative disease, which certainly is a challenge for me to try to understand even after these recent think tanks, let’s bring up your case, Cliff, not just to get into the issue of this unusual subset and the trial that you’re looking at — I always have my ears open when I see the possibility of an endocrine therapy or something that might benefit a patient without causing a lot of toxicity. But I think also your case can kind of get into the issue of general management of patients with metastatic triple-negative disease. Again, that’s going to be a theme throughout the series. Maybe you can talk a little bit about this patient, how she presented?

DR HUDIS: First, the issue here is a young woman who’s maybe not having regular screening yet presented with a de novo Stage IV breast cancer, never presented as early-stage disease, and had a suspicious blood test. And this led to the diagnosis of liver metastases. Both the breast and the liver were biopsied. Both contained triple-negative breast cancer. This presentation, young person, it’s not shocking.

So she got a taxane and bevacizumab and did about what you’d expect — seven months of progression-free survival and then clear-cut progression. Her tumor was AR-positive, because she was willing to sign up for our study and actually get tested. And the clinical question that she actually had, scared and, of course, worried about her future, was in the face of some mild symptoms, three- to four-pound weight loss and occasional early satiety and a little bit of upper quadrant discomfort, but functioning, going to work, sleeping through the night, not on any pain medicine — her question was: Is it safe for her to enroll on this trial and actually take a chance on a drug like bicalutamide?

Role of AR testing

DR LOVE: So what have you actually seen in this study and what’s involved in getting a tumor tested for AR?

DR HUDIS: I’ll start with the last question, because it’s pretty easy. The way we do it is we get consent first, because there’s not really a standard role for AR testing yet. And we test patients at any point along their illness.
We don’t wait until there’s a problem. So we meet a new patient like this one, and we’ll get consent as we treat with first-line therapy to allow us to do the AR testing. And as I mentioned earlier, we’ve been a little frustrated that the rate of AR positivity has been lower than our TMA had predicted. We saw about 20 percent in William Gerald’s TMA that Ashley Doane processed, and we’re really running about 10 percent in the clinic.

Among those patients, then, we’re waiting for some of them to have progression and be willing to go on the trial. And obviously, this is a work in evolution. So what I can say is that we’ve enrolled a modest number of patients. We hope to actually get the study completed through the TBCRC.

On the flip side, I can say definitively there is clinical activity here, because we have some patients who’ve been on the anti-AR after having progressed through other standard therapies, for six months and 12 months and even longer. So there’s at least the clinical anecdote of potential activity here. If all we wanted to do is answer the question, “Could an anti-AR drug be effective?” we actually have that answer. The answer seems to be yes. But now we’re trying to get a point estimate for how frequently we’ll get a clinically meaningful response.

**DR LOVE:** So I’ve got to say: What’s TMA and TBCRC? Just for the record.

**DR HUDIS:** So TMA is a tissue microarray, which is a way of putting a whole lot of specimens on a piece of plastic essentially and allowing us to do rapid processing of a whole bunch of individual patients’ tumors. And TMAs are used in a variety of settings at the more macro level, IHC staining, and the more micro level, like gene expression profiling.

TBCRC is the Translational Breast Cancer Research Consortium, which is a nonfederally funded philanthropically supported translational group where the focus isn’t on big clinical trials to make estimates of activity. It’s not exactly on drug development, either. It’s really on tissue correlative — or studies that are heavy in tissue correlates. And Lisa mentioned hers, for example, where patients largely provide biopsies. And we’re trying to understand the molecular biology and the correlates with response, so that we can do the smarter large trials that are ultimately needed to get drugs out there.

**Efficacy of bicalutamide in the treatment of TNBC**

**DR LOVE:** And I take it from what you’re saying that you’ve actually seen objective tumor responses with bicalutamide?

**DR HUDIS:** I’ve seen patients who benefited, by which I mean stable disease or minor responses. Partial responses and complete responses with endocrine therapy aren’t that common to begin with, and I don’t think we’re in a different league here.

**DR LOVE:** So what happened with this lady?

**DR HUDIS:** It’s interesting. So this patient really struggled emotionally with the idea of such a nontoxic therapy, and went on, ultimately, the bicalutamide, and unfortunately had progression at her very first assessment, which was eight weeks in. So that’s not an example of a great long response.

She then actually tried to go onto the gemcitabine/carbo plus or minus PARP inhibitor trial and was actually unable to do that because of an ineligibility, a biochemical ineligibility, in the end. And she got gem/carbo after the AR inhibitor.

**Nonprotocol management of first-line treatment for metastatic disease**

**DR LOVE:** I want to talk about nonprotocol decision-making also and where protocols might fit in, but just one more thing I want to ask Lisa about this generic clinical situation. How big was the primary tumor? You said she presented with metastatic disease. Was it a large tumor you were concerned about locally, or not really? In this lady. You said she had a —

**DR HUDIS:** You’re asking me. This is my case. Yes. Yes, she didn’t have a particularly large tumor. She had a, like, 2.5-centimeter tumor, but it was palpable. And then she had a little bit of sternal discomfort and abnormal blood tests, which led to her diagnosis of metastases.

**DR LOVE:** So, Lisa, just kind of backtracking a little bit here and talking about first-line therapy of triple-negative metastatic disease, whether there’s a primary, as in this case, or recurrence afterwards, how do you think through nonprotocol management? What are some of the protocols available that you would consider in this kind of a situation?

**DR CAREY:** As Cliff was mentioning, the Phase III registration trial of the PARP inhibitor, BSI-201, only recently closed. And we did participate in that trial in the latter part of it. And that took patients in the chemotherapy-naïve setting all the way through two lines of prior therapy. So we put patients on that trial. There have been a couple of trials within the TBCRC, particularly some of the lower toxicity regimens.
The one that Cliff was mentioning, I think, highlights the idea of many of these patients come with very few symptoms and, if you can find a targeted or a low-toxicity regimen to manage them, then it’s a very worthwhile thing to do as opposed to aggressive chemotherapy, which tends to be the default position in many cases.

And I think off protocol, I think the choices are the usual chemotherapy-based approaches. And the one that Cliff used here would be quite appropriate. I tend to use single agents in these, as I do with others, unless they have symptoms or rapid progression, concerning regarding visceral crisis, for example.

**DR HUDIS:** I agree with Lisa — we actually favor single agents. But the issue was that we hoped to have this expanded access trial of the PARP inhibitor, and the setup here is by using what was the control arm, then the crossover would mirror exactly what happened in that trial. And maybe that’ll be how things play out or maybe not.

**Enrolling patients on the Phase III trial evaluating gemcitabine/carboplatin with or without BSI-201**

**DR LOVE:** And, Cliff, this also kind of brings up an interesting point in terms of how do clinical trials fit into management in a community-based setting? We’re going to get — Joyce O’Shaughnessy’s on our next program, so we’re going to be reviewing a lot of the data that she and others have presented now on the BSI-201 study. But it’s really interesting in terms of the issue of when you have a promising agent and the only way you can get it is on a clinical trial, and you have people flooding into the trial, what does it really mean?

We, at that same San Antonio satellite, we presented a case very much like yours, first-line metastatic disease. We asked people what they would do, the usual chemo or chemo/bev. And then we said, “Suppose you could get the patient on the BSI study. How would that fit into what you’d want to do?” and 85 percent of them said, “I’d try to put the patient on the study.”

Do you think — and I don’t know what both of you are seeing in terms of docs in practice and patients kind of hearing about the excitement and bringing that into kind of a clinical context. Any comments, Cliff?

**DR HUDIS:** I think we have to be careful. It is really exciting, I think, scientifically, that the randomized Phase II in an exploratory endpoint suggests that a survival, overall survival advantage that may or may not be seen in the Phase III. If it’s true, I think it’s important far beyond this particular setting, because one of the push-backs we get all the time is, “The field’s mature. We can’t really expect to change survival with new drugs.” And I personally don’t agree. I actually find that offensive as a theory, because the reason we’re doing drug development is to improve survival and maybe cure metastatic disease, as crazy as that sounds.

And so I don’t want to say that our whole careers are really measured in terms of a few months of progression-free survival. I know it’s important clinically, and you walk a fine line for this, but that’s the first thing. So it’s really existential for me that there might be an overall survival advantage.

That said, it’s important to point out that randomized trials are valuable in their context. I don’t know how weekly paclitaxel and bevacizumab compares to the PARP inhibitor with gem/carbo at all. It’s not a randomized controlled trial for that question, and so we should be careful, as excited as we are scientifically, not to overstate this. There’s a lot of disappointment about it. There are patients angry and upset that they can’t get a PARP inhibitor, and sometimes you have to tell them some bitter truths about what the results of that trial were for the good arm, still not what I think we’re aiming for.

**DR LOVE:** Yes. I think Hy Muss, always the philosopher, brought that up at our think tank, the fact, as you say, even in the PARP/chemo arm, these people don’t seem like they’re being cured. Although clearly, as a nontoxic therapy, it really has something to offer.

What are you seeing, Lisa, in terms of patients and physicians coming to you as, quote, a triple-negative expert, and wanting to get involved not just in that study, but other PARP inhibitor trials?

**DR CAREY:** Oh, I have to say my impression from our referring physicians is that they’ve been very appropriate. They tend to send the patients in and, if the patients have been appropriate and eligible for the study and go on, great. If they haven’t been, then they go on other studies, or they go on other options. And to be frank, I think there’s an acknowledgement that there’s a lot of enthusiasm, but there aren’t a lot of data yet. And that’s the point of the trials. And I think there’s also a recognition that this is real. It will play itself out rather quickly, and so we’ll know in a relatively short time.

**Unsupervised gene expression array analysis**

**DR LOVE:** All right. Let’s dip back into the translational science of triple-negative disease. And Lisa, particularly with your colleague at the University of North Carolina, Chuck Perou, having done so much really incredible
work that’s helped us begin to understand some of this, if you could go through your talk and discuss these issues?

**DR CAREY:**

I’d be happy to. I’m going to start with a talk on the intrinsic subtypes. I don’t have any relevant disclosures, so we can move directly to this slide, which is, as Cliff mentioned, the unsupervised gene expression array analysis. This is where the intrinsic subtypes came from. And I think it’s important to comment that when we say “unsupervised analyses,” that it loosely means that the tumors are analyzed regardless of their clinical outcome or behavior. It’s simply a biologic question of whether a group of tumors are different from one another in reproducible ways.

And if you do unsupervised analyses, you will find that out of thousands of genes, there are about 500 or so that will segregate breast cancer into several different definable subtypes that are highlighted by the different colors on the top of the array there. And those genes that segregate them are, as one might expect, hormone receptor-related genes are very key. HER2-related genes are key. There’s a group of genes called the basal cluster of genes, that I’ll talk about in a second, and then, of course, proliferation genes are very important.

As noted, these actually have prognostic implications, even though they weren’t designed for prognosis. And in particular, you see in the top, the two luminal subtypes, the major ones, luminal A and B, that are highlighted, have very different prognoses, even though they are both ER-positive breast cancer. So this has some clinical relevance from the very beginning.

**Heterogeneity of TNBC: luminal, claudin-low and basal-like subtypes**

Let me just sort of give an overview of the major intrinsic subtypes. The first are the luminal subtypes, of which there are at least two. These make up, of course, the majority of tumors, since these are the hormone receptor-positive breast cancers and, of course, are characterized then by high expression of the hormone receptor-related gene cluster.

The HER2 gene cluster can be either up or down, and they can be either HER2-positive or negative. They can also be either highly proliferative or not and, as you’re probably already guessing, these are, in fact, the most heterogeneous group of tumors.

The HER2-enriched subtype is a smaller component, makes up about 15 to 20 percent of the tumors. It’s characterized by a high expression of that HER2 cluster that’s on the top. It has, actually, low expression of the hormone receptor-related genes. If the HER2 genes and the hormone receptor genes are both up, and that tends to fall in a luminal subtype, they’re typically very proliferative.

As we get more information, we will be finding additional subtypes. And the most recently described one is that claudin-low subtype. It makes up a very small number of tumors, as you can see, because it’s that little teeny yellow box in the middle, five to 10 percent, no more than that. This is one of the triple-negative subtypes, and it’s characterized by some very interesting features. In addition to being triple-negative, it also has low expression of cell-cell junction and adhesion proteins, lymphocytic infiltrates. And there are some what are thought of as stem cell characteristics that seem to be found here that raise some very interesting questions that’ll be addressed in future research.

And then finally the basal-like subtype, which makes up the majority of the triple-negative subtypes. Again, these are a minority of tumors, only about 15 percent, characterized by low expression of those HER2-related genes and hormone receptor-related genes. A high expression of a unique cluster of genes called, of course, the basal cluster, and in there are EGFR, c-Kit and a number of interesting genes. They are highly proliferative, and there’s evidence of abnormal DNA repair. What has been shown by several groups in terms of copy number, gains and losses and things like that, there’s just a sense of wholesale genomic instability in these tumors.

Now, as mentioned, this is the majority of tumors that arise in BRCA1 mutation carriers, but there’s evidence of BRCA1 pathway dysfunction, regardless of whether they have a mutation. We’ll talk about that in a second.

**Challenges associated with obtaining accurate genetic profiles**

Now, how do you identify these intrinsic subtypes? And the short answer is: In the clinic at the moment, we really can’t. If you had the gene expression array analyses that produced them, were produced from frozen tissues that were in tumor banks, and that’s very accurate, but it’s also hard to do.

What we have in the clinic at the moment are these immunostaining proxies, which, of course, are easier and instantly available, but are not as accurate. And I think this is an area that’s rapidly evolving. There’s at least one assay, the PAM50, that was published in *JCO* earlier this year, that does actually make an effort at identifying the subtypes in fixed tissues, and we’ll be seeing more of this as we go forward.
Now, what about the actual overlap of triple-negative and basal-like, meaning the molecular subtype? And as is sort of shown here, it’s important to remember that there are triple-negative breast cancers, meaning ER-, PR- and HER2-negative on clinical assays, that are not basal-like on molecular analysis. And these can include not only that claudin-low subtype I mentioned before, but actually any of the subtypes can show up as triple-negative. And on the other hand, basal-like molecular subtype can have expression of ER, PR or HER2. So if you’re using triple-negative, you will introduce some misclassification of what you’re trying to get at as the basal-like biology. And it’s important to keep that in mind.

As mentioned, this is a minority, and it’s important to keep that in the front of our heads. This is only 15 percent of incident breast cancers. However, because of the poorer prognosis, they tend to be overrepresented in the metastatic population.

Clinical characteristics and risk factors associated with TNBC

Clinical characteristics are something that’s very interesting and emerging understanding. As noted, younger women and African-American women have a higher likelihood of developing triple-negative breast cancer than other groups. I’ll talk a little bit about the association with BRCA1. Interestingly, when these tumors develop, they actually don’t seem to differ much from other breast cancers in terms of their stage of nodal status at diagnosis. But at relapse, there is a sort of intriguing difference in this group.

And what’s shown on the top curves is a higher likelihood of early relapse, as you see, the green line showing the triple-negative, which falls off after about five years and, in fact, is quite rare to relapse after seven or eight years. There’s also the sites of relapse that tend to differ among the different subtypes. And as you see, triple-negative has a high likelihood of involving the viscera and a relatively low likelihood of involving the bone. And we’re starting to understand that this subtype does in fact have a predilection for going to the CNS.

Some have wondered whether or not some of the profiles that are developed in order to prognosticate in breast cancer, whether those work in all the subtypes. And the short answer is they work best in the luminal subtypes. And you see on the bottom — the luminal A in particular — the Recurrence Score® of the 70-gene profile and a wound-healing signature that are all prognostic seem to give you some difference within luminal A. Some are positive, some are negative. But when you go up to the basal-like subtype, they pretty much all give poor prognosis profiles.

So while we clearly know that some triple-negative breast cancers do well, the currently available molecular prognostic profiles are not really developed to identify them.

Prognostic significance of subtype and treatment implications

We do know, also, that triple-negative breast cancers are sensitive to chemotherapy. There’s a lot of information on this slide, but if you look in the middle at the triple-negative and the response to neoadjuvant T/FAC or a modern chemotherapy regimen, you see the pathologic complete response rate is 50 percent. And in particular, if you’re looking at the basal-like subtype two lines down, those that are triple-negative and basal-like, it was 65 percent. So, in fact, these are sensitive to the drugs we already have available to us, particularly in the adjuvant setting.

Now, I think getting to risk factors is something that we can’t forget, that in addition to having treatment implications, these also have implications in terms of risk. So what we’re starting to understand is that the same risk factor may differ in terms of its effect in luminal A and basal-like, and this is a post hoc analysis of a very well-developed epidemiologic study that just demonstrates that, in that conventional risk factors may not only vary in the magnitude of their effect in terms of risk but actually may flip-flop in the direction of effect between luminal A and basal-like breast cancer. And the reason this is important, of course, is that we may be able to come back around and look at modifiable lifestyle factors for individual subtypes.

As shown on the top, the arrows are women with BRCA1 mutations who developed breast cancer. And as you can see, they are clustering down in that red area, which is the basal-like group. So BRCA1 mutation carriers, when they get breast cancer, about 80 percent of the time it is basal-like. But of course most triple-negative or even basal-like breast cancers are not arising in mutation carriers — they’re arising in what we call they’re sporadic. And because of the shared characteristics they have, there’s a term that’s been called BRCA-ness. And some of those characteristics are in the table on the bottom. They include not only triple negativity, but several pathologic features that are shared. So there are some reasons to think that BRCA1 is important across all basal-likes.

So, of course, the question, “So what,” comes up and the reason that that’s important is because BRCA-1, among other things, is a very key mediator of DNA damage repair, and this has implications for chemosensitivity and now, of course, emergingly, for targeted agents with PARP inhibition.
Inhibition of DNA repair pathways resulting in synthetic lethality

I’m just going to highlight here two of the columns. This is a general description of DNA damage repair. If you look in the first column, these are the ones that relate to chemotherapy. Base excision repair is, of course, a very key component, which is, in fact, PARP-dependent. And in the third column, you see that those kinds of damage, including x-rays and certain chemotherapy drugs which produce double-strand break, are dependent on homologous recombination primarily and that is a BRCA1-dependent function.

So the chemotherapy implications of this is highlighted on this slide. This is theory, not fact, but the idea being that if you develop DNA damage, BRCA1 is important in cell cycle arrest, so that DNA damage can be repaired. This would confer resistance to those DNA damaging agents, of course. If you lose BRCA1, then you lose this ability. You don’t have DNA damage checkpoint induction, you don’t have DNA repair and you have sensitivity. This is the theory behind DNA damaging agents in triple-negative breast cancer.

So what about PARP inhibition? And the idea of synthetic lethality, which you’ll hear a lot more in the future, is diagramed here. And the idea is synthetic lethality is when you have cell death on the basis of loss of two pathways, either of which alone do not produce cell death. And you see here base excision repair by itself being lost, it still results in a viable cell. Homologous recombination lost by itself still results in a viable cell. But if you lose both, the cell is no longer viable. That’s synthetic lethality.

Biology of intrinsic subtypes

So the summary for the intrinsic subtypes is, of course, that these reflect biologic differences among different classes of breast cancer, but we can’t get away from the fact that this really — one of the fundamental things we have to keep in mind is hormone receptor-positive and negative on a biologic level really is different, and it is the first separation of these intrinsic subtypes.

The most difficult therapeutic challenge we have right now is this basal-like subtype — the majority of triple-negatives — but we’re getting some very interesting information. They have unique risk factor profiles, which raise questions about prevention, that we really haven’t thought about in a while. They are sensitive to modern chemotherapy, so we should not ignore conventional treatments, particularly in the adjuvant setting. But they are a poorer prognosis group than the average, so we still have therapeutic challenges.

We may be going someplace with the implications of BRCA-ness of all basal-like breast cancer, whether sporadic or mutation-based, and that right now is the biggest areas of study, are the choice of DNA-damaging chemotherapy and the role of PARP inhibition.

Thank you.

DR LOVE:

So thanks, Lisa. And we’re going to finish in a few minutes. I’m going to go through Lisa’s case and a few of the cases and comments that have come in here. Just to reassure you, I get the opportunity to interview great educators like Lisa and Cliff and have them try to explain to me, pathways and stuff. And we’re going to keep going back over this. Come back for our second and third one. We’re going to go back to these things. We’ll talk about claudin-low, whatever that is, again, and try to get into some of this translational science and mix it up with the clinical science.

I was thinking about the fact that we deliberately put Joyce as the last speaker in our San Antonio symposium, and nobody left until she got up, so we know there’s a lot of interest in this field.

CASE DISCUSSION: A patient has a 7-cm, locally advanced TNBC and a strong family history of BC

Cliff, we got an interesting case from Celebration, Florida, an interesting place, a Dr Ricardo Crisostomo. Sorry if I didn’t pronounce that. But a patient who presents with a locally-advanced, a seven-centimeter triple-negative breast cancer, and says that two months ago it was a small lump. So clinically growing quickly. Interestingly, she has a pretty strong family history of breast cancer, otherwise well. So the issue of neoadjuvant therapy and maybe BRCA testing in a patient like this — how would you be thinking through a case like this, Cliff?

DR HUDIS:

There’s the acute issue, which is how to manage this locally advanced breast cancer. Seven centimeters used to be a pretty common presentation for breast cancer in an earlier era, but nowadays, it’s extraordinarily rare. So acutely, the question is: One, does she have metastatic disease or not? And from what you presented, it sounds like clinically, hopefully, not. And the second question is: Is she primarily approachable for definitive — that is, curative — surgery or not? And again, the old standard was if you could have a mastectomy, you should. If you couldn’t have a mastectomy, then you needed preop therapy — end of discussion.
Improved surgical outcomes after neoadjuvant therapy

More recently, we've added the ability to convert patients from mastectomy to breast conservation by virtue of preop therapy, and both Lisa and I and many others are working hard to get a lot of patients treated with preop therapy who don't need it medically, but whose tissue will then inform our understanding of the biology of breast cancer.

The truth is, in this case with the strong family history and a very high likelihood of ultimate bilateral mastectomy, I don't think it would be wrong to have just done the mastectomy on this patient and then proceeded to conventional adjuvant therapy. Conversely, if she's not yet made up her mind for that or she's participating in a study or she might ultimately change her mind, giving preop therapy and shrinking this mass and facilitating an easier surgical procedure later is also perfectly reasonable.

We do know from preop studies — randomized studies — that preop chemo and then surgery is equivalent in terms of disease-free and overall survival to the more conventional surgery and then conventional adjuvant treatment.

On the BRCA testing front, sure I would test her. But here's an example where it goes the other way. It doesn't much matter what her result is. She's got a genetic risk factor for breast cancer. It's either one we can identify and name or it's a new one. And so I think her management is going to be as would be the case for anybody else with BRCA mutation.

Rationale of clinical trial designs to evaluate PARP inhibitors in the adjuvant and neoadjuvant settings

DR LOVE: So, Lisa, I ran into Chuck Geyer at San Antonio and he was telling me that the NSABP is interested, as are the cooperative groups, in looking at PARP inhibitors. He mentioned the neoadjuvant setting and the postneoadjuvant setting with people with significant residual disease. And it seems like a patient like this, it'd be really interesting to look, if you could sort of look at BRCA-ness to try to maybe assess that.

What about the issue of trials using novel agents like PARP in the neoadjuvant and adjuvant setting, Lisa?

DR CAREY: Oh, I think there is a great benefit of the neoadjuvant setting. Cliff has pointed out the truth is, if you're going to give the exact same drugs, it actually doesn't matter if you know you're going to give chemotherapy, whether you give it preoperatively or postoperatively. You can get some improved surgical outcomes in some cases, but in truth, I think one of the benefits is really from the standpoint of research, and that's because in the neoadjuvant setting you obviously can measure what's happening to the tumor. You can collect tissue, and you can monitor. And so it's a much better and richer resource for identifying predictive factors for response to even conventional therapies.

Moreover, if you have a drug that — we're in an explosive area, an arena of developing drugs, and we're faced with — we may have 20 or 30 drugs that we think are worth looking at. How are we going to decide what combinations and what drugs are going to move forward? And then truthfully, there's a limit to how many 5,000-patient adjuvant studies we can do. And the neoadjuvant setting lets you look at promising regimens and promising drugs that have some safety data already there, so they're worth giving. You can give them to patients who may well be cured and gain a great deal of knowledge. And you can do studies that take a few hundred patients, as opposed to a few thousand, and you can get an answer in a few months, and it helps us, I think, refine our direction in terms of treatments for the adjuvant setting. I don't think it will replace adjuvant studies.

Implications of the Oncotype DX® and MammaPrint® assays in TNBC

DR LOVE: Cliff, we're going to close out in a minute with Lisa's case, but before we do, we got a couple of interesting comments about Dr De Fusco's case that I'd like to throw back to you. As you'll remember, this was a patient with a triple-negative tumor that was only 1.2-centimeter, node-negative. One comment that came in from Monique Anderson was: What about Oncotype? Of course, Oncotype's been used in ER-positive tumors. What about a genomic predictor? MammaPrint's been talked about for ER-negative. Anything we could do genomically to try to figure out what to do with a patient like this? Cliff?

DR HUDIS: We don't have any prospective clinical trial data that would actually allow us to answer that question. But there are people working on this. And I'll give a couple of facets to the answer.

Of course, Oncotype DX is only really useful in ER-positives. And the question it answers is not so much prognosis, but more specifically, prediction of a chemotherapy benefit as an addition to hormone therapy. But it is interesting that they are now offering to do the test in ER-/PR-negatives. And if it's positive, they then report it. And really what they're getting at there is the issue we touched on, of false-negative testing. So that's one angle there.

The MammaPrint is a purely prognostic test at the moment, and the implication of course is if you have a good enough prognosis, then there can't be a benefit for adjuvant systemic chemotherapy. And that may
be how we end up using that test ultimately, but at present we don't have predictive value of chemo-
therapy as an interpretable endpoint of the MammaPrint or several of the other newly available tests.
So my answer for the clinicians is that you probably can't do a whole lot of molecular testing to help
decide how to treat these patients today, but you surely should be enrolling them in trials that may help
us answer the question later.

**CASE DISCUSSION: A 59-year-old woman has Stage I TNBC and 26 involved lymph nodes**

**DR LOVE:**
So we'll go to Lisa and your case. And just to mention, we've got several dozen really great questions
and cases. And we're going to actually try to integrate some of these into the next two sessions. We kind of
see these three things as an integrated program that's going to hopefully come together by the time we're
finished. And hopefully, by the time we're finished, I'll know what claudin-low is and what it really means.

But Lisa, again maybe as a — to kind of almost set the stage for where we're heading in these next two
sessions — because this is a clinical situation. There's just a huge dilemma, the patient with metastatic
disease and triple-negative breast cancer. If you could just summarize her course and we'll kind of end
discussing this patient.

**DR CAREY:**
Yes. So, this is a very healthy 59-year-old woman who, in 2008, developed a Stage I, as is generally true,
Grade III triple-negative breast cancer. The patient chose to have local therapy only, no adjuvant systemic
therapy. About a year later, she recurred as inflammatory breast cancer with involvement — basically a
locoregional relapse. It was biopsy-confirmed and was, again, triple-negative.
She then received systemic therapy with AC for three cycles. However, she progressed through it, then
was put on combination paclitaxel/bevacizumab for 12 weeks, with response, but with a complication.
She had a perforated diverticulum and quite a lengthy time off of therapy because of that.
She went to mastectomy, ultimately, with axillary dissection. She actually no longer has a mass in the
breast. She did have dermal lymphatic invasion, lymphovascular invasion and 26 involved nodes at defini-
tive surgery.
She declined radiation therapy and was placed back on paclitaxel/bevacizumab. She received this for two
months and had locoregional progression at this point, so while it worked initially, it no longer worked at
this point. And she then was eligible for, was put on the registration Phase III trial for the BSI-201 drug.
She was, in fact, randomized to the chemotherapy-only arm and received that and made it no more than
two weeks with cutaneous progression. So, I think, as we sometimes see, very rapid. The BSI-201 drug
was added to the regimen, and so far, clinically she's doing well. She's fatigued, has not reached her
restaging time, but we'll know more in a few weeks.

**Current treatment approaches for metastatic TNBC**

**DR LOVE:**
So, Cliff, one of the interesting things — and, again, we'll talk about the BSI trial next week a lot — but
— about that study — was that the control arm, as this patient was randomized to, was gem/carbo. And
that's not a typical regimen that we utilize. And of course, this patient progressed so fast that it was
maybe not even a question. How do you feel about putting a patient on that arm? And what do you think
about that as a chemo regimen in metastatic breast cancer?

**DR HUDIS:**
Certainly, as you point out, it's not a standard regimen. And it was selected for the pivotal, if you will,
Phase II randomized trial because of preclinical study suggesting that these chemotherapy drugs would
heighten the cells' sensitivity to PARP inhibition for a variety of reasons, including upregulation of PARP
as a consequence of their cytotoxicity.
I don't know the answer to where gem/carbo fits in as a standard therapy. It's not one that I think most
clinicians would use. And outside of a clinical trial setting, I would typically not reach for that or most
other two- or three-drug combinations. I favor low-dose single therapy arm or single-agent therapy,
because of the generally more favorable toxicity profile.
Having said all that, I think we have to be careful not to be too dogmatic in metastatic breast cancer.
There's nothing from a chemotherapy point of view that's going to cure her, unfortunately. There's no
therapy that's been definitively shown to be the single best way forward. This patient's already had
paclitaxel and bevacizumab, which might be a semi-uniform opinion from people that that's a reasonable
choice. So fine, go and be well. That's a perfectly reasonable from my point of view. I don't think there's
more to say.

**Therapeutic considerations after disease progression in the metastatic setting**

**DR LOVE:**
It was really interesting in our roundtable. We got into the question of, if the metastatic trials with PARP
inhibitors are, like BSI-201, are positive, what are we doing to do in the adjuvant setting? Are you going to have an adjuvant trial with a control arm of gem/carbo? A really fascinating discussion.

I’m just going to ask one final question to both of you. I’ll start with Cliff, which is: What options would a patient like this have if she develops progressive disease at your institution? Any novel agents? Anything that we can get excited about, that maybe we ought to be thinking about putting a patient like this in? Cliff?

**DR HUDIS:** There are a lot of exciting molecularly targeted therapies. And certainly, this week at my institution, because it’s ever changing, when this patient has her, unfortunately, inevitable progression, we would offer a treatment trial with a Src inhibitor combined with paclitaxel. We have a small molecule tyrosine kinase inhibitor for the VEGFR family, both sorafenib, which this patient’s no longer eligible for, but also AVF-951. There are a variety of others — there’s a transcriptional blocking agent called PTC that’s in clinical trials right now. There are, like I say, many things. And indeed, this patient, like the others we talked about, we would always test for AR and see if that target could possibly be exploited.

**DR LOVE:** And the AR testing, incidentally, can that be done locally or do they have to send it to you all?

**DR HUDIS:** It has to be done in a laboratory that does it regularly. It can be done at the study centers or at a central lab, but we would have to repeat it if it were done just in a routine laboratory setting.

**DR LOVE:** So again, Lisa, final question. Again, this patient, if she unfortunately develops progressive disease, what are some of the trials at your institution or trials elsewhere that — it’s so hard for a doc in practice to sort these things through. They hear about new agents and pathways. Is it really maybe going to help their patient? Of course, who really knows? But anything exciting that a patient like this might be able to consider, Lisa?

**Emerging data on the use of small molecule inhibitors as treatment for TNBC**

**DR CAREY:** I have to say there are a number of promising agents. And, of course, we have this great level of excitement about the PARP inhibitor trial, which was, with all of the caveats, was quite remarkable in the outcomes and in the improvement in survival. And in truth, everything else is far behind that in terms of deciding that one’s more exciting than another.

I think most of the things that we’re the most excited about and that people are promoting, particularly after PARP inhibitor failure, would be things that are targeting growth factor pathways. These are still the most promising areas of study, are various ways of targeting growth factors. These are highly proliferative tumors, so it makes sense.

And in addition, there’s certainly emerging data, as Cliff was mentioning, with many of these drugs that are small molecule inhibitors that actually affect growth factor pathways and have anti-angiogenic properties, and that’s an arena that I think many people think will be one that is more likely than not going to be one of the ways we go forward.

**DR LOVE:** So thank you so much, Lisa and Cliff, for joining us tonight. Thanks to our audience. Come back next Thursday night. We’ve got Joyce O’Shaughnessy and Jenny Chang. Jenny is one of the great pathway explainers and hopefully can talk more about some of these things that we’ve talked about tonight. And our last program the following Tuesday, again, we have two master educators. Hope Rugo and Kathy Miller are going to take a shot at explaining this. And have a great night.