Expert Insights on Triple-Negative Breast Cancer: Preparing for the Next Wave of Treatments

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JENNIFER WEBSTER Good evening, everyone. My name is Jennifer Webster. Welcome to our CE-certified symposium, "Expert Insights on Triple-Negative Breast Cancer: Preparing for the Next Wave of Treatments."

Now, it gives me great pleasure to introduce our speakers for this evening. We have Dr. Lee Schwartzberg and Heather Greene.

Dr. Schwartzberg is the medical director of the West Cancer Center in Memphis, and the chief medical officer for One Oncology. He is also professor of medicine at the University of Tennessee Health Science Center. Dr. Schwartzberg specializes in the treatment of breast cancer with a specific research focus on new therapeutic approaches, targeted therapy, and supportive care.

Ms. Greene is an oncology nurse practitioner and a subject-investigator at West Cancer Center. She currently works in the outpatient setting managing patients with gastrointestinal, genitourinary, and breast cancers. Ms. Greene is a contributing author for *JADPRO* and the Oncology Nursing Society, having most recently authored a chapter for the *Advanced Oncology Certification Review and Resource Manual*.

HEATHER GREENE Thank you for the introduction. Okay, so I believe that we're going to start, here's our disclosures listed here, and then our learning objectives.

First, we're going to evaluate the clinical significance of recent and emerging data regarding the efficacy and safety of approved therapeutic options for triple-negative breast cancer. We're going to develop strategies to identify and manage adverse events associated with PARP inhibitors and immune checkpoint inhibitors in patients with triple-negative breast cancer and identify novel therapeutic strategies being investigated for triple-negative breast cancer.

Okay, we'll turn it back over to Dr. Schwartzberg.

DR. LEE SCHWARTZBERG Okay, so good evening everyone, and thank you for spending the beginning of your evening. I know it's been a long day for all of you, and I appreciate you coming. So we're going to talk about triple-negative breast cancer tonight.

What is triple-negative breast cancer? So it's defined by what it isn't, and whenever you have a disease that's defined by what it isn't, it means we don't know a lot about it because every disease should really be defined by what it is, but of course, the convention of triple-negative breast cancer is negative for the three biomarkers that we typically look at in every breast cancer, estrogen receptor, progesterone receptor, and *HER2*, and the thresholds for ER and PR have moved around a little bit. Currently in clinical trials, they're defined as less than 1% for ER and PR, but I would say in practice, most of us use 10% as the cutoff because in general, very, very low ER-positive patients tend not to respond

like hormone receptor–positive patients. Triple-negative breast cancer accounts for about 10 to 15% or 17% of breast cancers. We do see a higher incidence in African Americans. It is the most aggressive of the molecular subtypes if we're thinking about the broad subtypes, either *HER2*-positive, hormone receptor–positive, *HER2*-negative, or triple-negative. Most of the cancers under the microscope are grade 3 histologically. Triple-negative breast cancer compared to the other subtypes of breast cancer, especially with modern therapy, tend to recur more frequently early rather than late, so most of the recurrences are in the first 5 years, actually even in the first 3 years, and by 5 years after diagnosis, actually hormone receptor–positive breast cancers are more likely to recur than triple-negative breast cancers as you go on beyond that. Unfortunately, the mortality from triple-negative breast cancer tends to be the highest and still is, both in the early-stage breast cancer setting as well as the metastatic setting, and so pretty much all my patients who come in when they learn they have triple-negative, there's a lot of awareness among the patient community, and they're very nervous about having triple-negative breast cancer, so I think an important thing when you're first seeing a patient with triple-negative breast cancer is to reassure them that we have good therapies for them and that we can manage their disease well. However, when they do become metastatic, they still have a poor prognosis as you'll see and a rapid progression from distant recurrence to death, especially as we've made greater progress in hormone receptor–positive and *HER2*-positive breast cancer. Hopefully, that will be changing.

So we would like to classify triple-negative breast cancer as something what it is as opposed to what it isn't. So there have been a number of molecular classifications that have been looked at, one of them which you may be familiar with is called the intrinsic subtype, and that's a very useful classification that sorts patients into luminal A, luminal B, so called basal cell, and normal subgroups, and *HER2* subgroups, so those five, and there's an extra small group called claudin low, and most triple-negative breast cancer is basal by gene profiling, but not all of it. Somewhere between 60 and 75% of it will actually be basal like. The reason this might be important is that although this is not clinically actionable today, if you have a patient that histologically is triple-negative but is in PAM50 or intrinsic classification is luminal, it might actually act more like a luminal cancer and maybe some of those low ones are like that. So that's a research question for the future. Trying to build on that, groups, particularly the group at Vanderbilt, has come up with another molecular classification which divides that group of patients whether they're basal or non-basal into several different subgroups, and that's been refined over the last 5 years since this genomic profiling has been evaluated into four groups, basal-like 1 and basal-like 2, which have some similar properties but different, and an immunomodulatory group has sort of come out, the M-group and the luminal AR-like group, which may be those ones in the intrinsic subtype as well. So what does that really mean? I'm just showing it to you. It's not yet of clinical utility although there is a lot of interesting trials that are ongoing now that are looking at giving specific therapies, like AR therapy,

androgen receptor therapy, which we'll talk about a little later for that LAR group or using a specific type of therapy for the other groups.

So if you think about it now, if you break it out by the intrinsic subgroup, about 20 to 30% are either luminal or AR, and the other 70 or 80% are what we normally think about, triple-negative breast cancer and phenotypically, they're very highly proliferative, they express EGFR, they may have a lot of immune cells, and so the more proliferation that triple-negative breast cancers have, the more likely they are to be chemo-sensitive.

One thing that I'm not going to talk about much tonight but is a very rapidly emerging area is the impact of TILs, or tumor-infiltrating lymphocytes in a primary tumor, and I think it's fair to say now the data is pretty solid. The more TILs you have in triple-negative breast cancer, the better the patients are going to do – not really a surprise if your body is trying to mount an immune reaction against the cancer you might do better, and that's in the absence of immunotherapy, which we're going to talk about, although it may actually help immunotherapy as well. On the other side, the AR, at least theoretically, may be the ones that are most sensitive to anti-androgen therapies, and those that are HER2 enriched might be sensitive to anti-HER2 therapy. So the whole point is, we have to do a better job classifying triple-negative breast cancer so we can find better therapies for them in the future. For right now, we still define it by ER, PR, and *HER2*, as I mentioned.

So let's talk about early-stage breast cancer for a minute. You're all familiar, I think as an experienced group, that lumpectomy radiation therapy gives

at least as good survival as mastectomy, and even for patients for triple-negative breast cancer, that should be the preferred surgical approach. For patients who have a *BRCA* mutation, many women, although not all, do opt for mastectomies, mainly for secondary prophylaxis. The early-stage treatment typically is triple therapy with an alkylating agent like cyclophosphamide, anthracycline, and taxane; however, small cancers don't necessarily need that aggressive therapy. In general, we're moving towards neoadjuvant therapy for triple-negative breast cancers unless they're a T1 lesion under 2 cm, and we strongly consider that, and we'll talk about that in a second, and then there's a possibility of giving post-neoadjuvant therapy and platinum drugs, so we'll explore all of those things. The rationale for neoadjuvant chemotherapy was originally the thought that if you gave the chemotherapy before surgery, maybe you would reduce the metastatic rate because it was known in experiments, and I actually want to acknowledge that this week, Dr. Bernie Fisher, who actually pioneered this concept as the chair of NSABP, he was a surgeon, was very far thinking, he died at age 101. He's probably done more to change our thinking in breast cancer than any single individual I can think of, and one of his concepts was the concept of neoadjuvant therapy; and we take it for granted now. When he came out with this, he was branded a heretic. People would get up at a podium and say, "You are threatening our lives." Not to mention, he also started lumpectomy, and the surgeons who did mastectomies said, "That's absolutely wrong, get off the stage, you're going to kill women." And, you know, it turned out to be correct, so I just say that because, you know, we're giving – you hear a lot of things from a lot of

speakers at this meeting, but it represents the current state of truth; it's not the absolute state of truth, and some of the things we're saying today are going to be proven wrong, and other things are going to be proven right, but keep an open mind about everything. So we'll talk about each of the concepts here.

So the current landscape for neoadjuvant chemotherapy for triple-negative breast cancer is that standard therapy many people use, sequential anthracycline cyclophosphamide, followed by taxane; about a 33% pCR rate, and about another 10 or 15% achieve a near pCR, and you can look at it by a pathologic staging system called RCB, which I recommend actually if you're a pathologist and not doing that. If your center is doing a lot of neoadjuvant therapy, it's a good thing to think about. It's being used in all the trials today, and it's a little more accurate than just giving the post-chemotherapy TNM staging. We can use carboplatin and add that to anthracycline taxane-based therapy, which improves the pCR rate; however, it also increases the toxicity, and we're awaiting further survival advantage, it may be useful in certain areas. Unfortunately, we don't have a good biomarker for platinum yet. What's most important about pCR is that it's a good surrogate marker, so in and of itself is a biomarker for event-free survival, or in other words, reducing the risk of relapse. So the lack of a pCR, you have a higher risk of relapse. With a pCR, in every subgroup, not just triple-negative, in every subgroup of breast cancer, a pCR is associated with an excellent prognosis, and we're looking at a lot of other markers as I mentioned, TILs, and other things.

So here's an analysis that was done that sort of concluded what I just said, that neoadjuvant chemotherapy across multiple trials was 1100 patients in 12 randomized trials showed about a 34% pCR rate, which is defined as no tumor in the breast, except for in situ cancer could still be there, and no tumor in the nodes, so ypT0 or IS – in situ – N0. And of those patients, you can see that the majority of them here had a good outcome, and in more modern studies at 5 years, it's about 90-plus percent, so even if you start with a big tumor and you get a pCR, that's a good thing for patients, and the overall survival is better as well. So if you add – this is showing the evolution pre-immunotherapy and where we've gone with neoadjuvant chemotherapy, so if you give three drugs, either together or sequentially, you get about 30%. Bevacizumab is the B here, it's been used in several trials, but it really doesn't extend the event-free survival, so you can ignore these, and you can see if you add platinum either, let's see in these arms here, you can get about 50% pCR rate.

So that led to the introduction of immunotherapy drugs, specifically immune checkpoint inhibitors in the neoadjuvant setting because it's a very good model to study and get an early readout of what's going to happen with patients using pCR as a surrogate endpoint, and pembrolizumab was studied in a platform trial, which is an innovative platform trial, which is ongoing called I-SPY 2 where they use an investigative therapy and then they slot in multiple investigative therapies in relatively small patient population, so they get a readout faster. All the patients get a backbone of 12 weeks of a taxane followed by AC, so in this case, they looked at it in all three subgroups of breast cancer, but as

you can see in the triple-negative – actually, it looked good in all three, they had a 20% pCR rate in this relatively small population, but it tripled in the triple-negative population, which predicted there's a mathematical model associated with this I-SPY study that in a phase 3 adjuvant trial, it should work.

So here is the KEYNOTE-522 trial that was one of the questions you were asked, and it was a bit unfair because this study was just released at ESMO about 3 weeks ago, so unless any of you were in Barcelona that week, it would be unlikely for you to know about this yet, so and I'm sorry if you weren't because it's a lovely place, but this study randomized patients. So the backbone here was they wanted to use the optimal backbone, so they added carboplatin, so I'm not saying that's necessarily standard, although some people do it, and so it was carbo, pac, followed by AC or EC, and those patients got eight treatments of that and also got pembrolizumab or a placebo, it was a 2:1 randomization. These were patients that had triple-negative breast cancer from T1c through T4. And that was the neoadjuvant phase. The primary endpoint of the trial was pCR rate, but then patients went on to receive either pembrolizumab or a placebo to complete a year of therapy, so it was a year of adjuvant therapy with the IO. So here are the results: The pathologic complete response rate was 65% in all patients. Now these patients were not selected by PD-L1 status; they were allowed to go on trial, importantly, whether they were PD-L1 positive or PD-L1 negative, and in the control group, you can see that with the addition of carboplatin about 50% response, so this looks like a standard control arm, what you would expect. In this population, it went up 14% with the addition of pembro,

and to my mind, very interestingly and not what I would have expected, both groups derived benefit, whether they were PD-L1 positive or PD-L1 negative, and the magnitude of the benefit was similar in both groups. Now, that was the primary endpoint of the trial. The next endpoint of the trial is event-free survival, which is really the important endpoint. So if the surrogate endpoint predicts it, it's great; but if it doesn't, it's not really a benefit to patients. What we want to make sure is that patients who get therapy live longer without cancer, and that would be event-free survival, so it's a very premature trial, but at 18 months of follow-up, you do see a 6% improvement in event-free survival, so this is not statistically significant yet, but it's encouraging, and we have to follow this trial a little bit further. This pembrolizumab is not approved in the adjuvant setting yet; I'm not sure this will be going to the FDA for approval, but it might be. So we'll have to wait and see, but as of now, this is the phase 3 trial that does show the pCR rate met its primary endpoint. As you see, that *P* value is very strong there, and 14% should be enough difference potentially to lead to long-term event-free survival, but we have to wait and see what happens with that.

Now for patients who don't achieve a pCR, we do have adjuvant therapy, and it's based on this trial called the CREATE-X trial, which looked at adjuvant capecitabine after preoperative chemotherapy, and you can see here in the left-hand panel, the patients who received capecitabine who had triple-negative breast cancer had a better event-free survival, which was substantial, 42% improvement in event-free survival, and they also had an improved overall survival, which was 48% better. So based on this study, many of us are using

capecitabine in the triple-negative breast cancer population who do not achieve a pCR.

All right, let's turn to advanced triple-negative cancer, so this, again, is a heterogenous group of cancers, but we're lumping them all under the rubric of triple-negative. It has a poor prognosis, it still has a median overall survival between 12 and 18 months in clinical trials, so this is an aggressive cancer. The workup of triple-negative breast cancer should include testing for germline *BRCA* mutations, it should also include testing for PD-L1 status based on the data I'm going to show you for both of those biomarkers, and this is the one group of patients where I think you should have a very low threshold to consider CNS screening because metastases to the brain are common, so if the patient has any CNS complaints whatsoever and it's worth taking a careful neurologic history for these patients, you should get an MRI of the brain to rule out brain metastases.

For treatments, we'll go through the treatments that are available for these patients. So one of the things that has become common is to use platinum agents, particularly when platinum hasn't been used in the neoadjuvant setting, which I would say is still the large majority of cases, and whether or not platinum actually does better than a taxane, which is the usual recommended first-line, single-agent therapy of choice. In general, patients with metastatic breast cancer get singlet therapies and sequential singlet therapies is what NCCN guidelines recommend. There's the occasional patient who has a visceral crisis or a very heavy tumor burden that will benefit from the doublet therapy at the first line of

therapy. I really don't think there's much value in doublet therapies after the first line because you're monitoring those patients very carefully, and so it's unlikely for them to get a big tumor burden once they're diagnosed. When they come in with diagnosis, of course they might have that depending on their previous history and when they've been seen. So carboplatin has become – or carboplatin doublets even – have become very common therapies; however, the TNT trial randomized patients for carboplatin versus docetaxel, and actually in this group, there was no real difference in response rate, which is what is shown there, about a 30% response rate. The patients who did have germline *BRCA* mutation were the ones who did better with carboplatin—not a terrible surprise. So that's the group of patients that benefit if you're going to use chemo with this group, and we have an alternative to that as I'll show you in a minute, and in converse, the patients who were wildtype actually did better from a response rate perspective and slightly better from progression-free survival as well, which is not shown on this slide for using docetaxel. So in the absence of a germline or a somatic in this study, *BRCA* mutation, probably taxane should remain the first-line treatment of choice for chemotherapy.

Well, chemotherapy in general for advanced triple-negative breast cancer, unfortunately, has modest activity, so if you look at those response rates for first-line therapy, they're really only about 30%, not terribly, you know, encouraging, and the progression-free survival is, unfortunately, even worse, only about 3 to 5 months on average, so these patients, these are somewhat older studies, but only about 12 months of overall survival, and as you would expect, in later lines

of therapy using different types of drugs, either eribulin or capecitabine or ixabepilone, you see somewhere between a 10 and 20% response rate and a median progression-free survival that essentially is at the next time you look at them at 2 months. So as in general, once you have metastatic disease, you do best with the first line of therapy and sequentially worse on average, so we have a lot of room for improvement here.

So the current standard of care, I'll just leave you with these takeaways, neoadjuvant chemotherapy I do believe is a standard of care that should be utilized for triple-negative breast cancers that are at least 2 cm or greater in most cases. We can get into the nuances during the questions if you have them. In general in my practice, we use dose-dense AC followed by paclitaxel, but there are other variants which, of course, can be used. For smaller tumors, the absence of anthracycline may not make a difference. You should consider adding carboplatin for the higher-stage patients and those that are either *BRCA* mutated or slow responders, but that's not certainly a solid or mandatory recommendation. Adjuvant capecitabine for residual disease is useful. I would recommend that in particular for using that RCB classification for those that are – it goes from RCB 0, which is a pCR, to RCB III, which means lots of cancer in nodes left behind, so for IIs or IIIs, you should definitely consider it. And as I mentioned, the neoadjuvant and adjuvant trials for PARP inhibitors, which we'll talk about in the metastatic setting, and the germline *BRCA*-mutated disease are in progress. In fact, they've completed enrollment in at least one of them, so in the next year or two, we'll see the value of using a PARP inhibitor earlier on, and

I just showed you the results of KEYNOTE-522 about the value of pembrolizumab in achieving a higher pCR rate, and we await to see the event-free survival as the study matures.

So we'll move on and talk about the recently approved or emerging therapies in triple-negative breast cancer. So this is the NCCN guidelines for invasive breast cancer metastatic disease that's *HER2* negative – well, actually it has both on it, *HER2* positive and negative, and I want to point out a couple things. So first of all, PARP inhibitors are options for patients with *HER2*-negative tumors and germline *BRCA1* and *2* mutations in the Category 1 recommendations for those, and then you've got your list of drugs, and we'll talk also about atezolizumab and albumin-bound paclitaxel, and also, I highlighted these biomarker points. So patients with *HER2*-negative disease, strongly consider for *BRCA1* and *2* germline testing, and patients with triple-negative breast cancer, assess PD-L1 biomarker status before you start therapy.

So we'll talk first about the PARP inhibitors. This is the OLYMPIAD trial, which was a trial of olaparib in patients with germline *BRCA* mutations and *HER2*-negative disease, so it included hormone receptor–positive and triple-negative breast cancer patients. They had to have received prior anthracycline and taxane and up to two prior lines of chemotherapy in the metastatic setting, and they had to receive endocrine therapy if they were HR positive. They were allowed to have prior platinum as long as they were not progressing right through it. Here's the outcome of OLYMPIAD: The progression-free survival showed an improvement of 3 months compared to chemotherapy with a hazard ratio of 0.58,

so a 42% improvement. The overall survival had a trend but was not statistically significant for improvement in this population of patients, which is not uncommon for metastatic breast cancer patients. It's hard to show overall survival improvement, although in the last session that Heather and I talked about HR-positive, we're seeing that now as CDK4/6 inhibitors, but that's more the exception than the rule.

The second trial and the second drug was talazoparib, another PARP inhibitor, versus chemotherapy. In both trials, chemotherapy of physician's choice, they had three or four choices of different agents to use, and like vinorelbine, eribulin, gemcitabine, capecitabine, four choices in the EMBRACA trial, and they were randomized to receive talazoparib or physician's choice of chemotherapy, a similar patient population, up to three lines of prior chemotherapy here. For both studies, progression-free survival was the endpoint. EMBRACA showed very similar results, 3-month improvement in progression-free survival compared to single chemotherapy of investigator's choice, and again a trend without statistical significance in improvement in survival as we saw with the OLYMPIAD trial as well. So you'll hear about the toxicities of these drugs when Heather comes back up, but I will say that in general, the toxicity of PARP inhibitors is much less than chemotherapy in these trials, and because – and I didn't show you, but the response rates were apparently better as well, so because of that, if you have a germline *BRCA*-mutated patient, would strongly consider treating with a PARP inhibitor before chemotherapy, and that's true for the triple-negative breast cancers.

So there's been a lot of excitement about PD-L1 inhibitors in cancer in general, and breast cancer has lagged a little bit behind some of the other metastatic diseases, and in part that's because as monotherapy, it hasn't been spectacular, and this slide shows you the monotherapy response rates, and these are small trials; they're heterogenous trials, some of these were patients who have been heavily pretreated, some of them were in the first line. In general, for late-line treated patients, the response rates are pretty low. First-line patients tend to be higher, somewhere around 20% to 25%, but still not as good as other standard therapies. What's interesting even in these early trials of phase 1 studies was the patients who respond tend to respond for a long time, so if you happen to be lucky and be that one out of 20 patients who responded, in that cohort of patients, some of them were ongoing for years, which obviously is not the typical pattern for triple-negative breast cancer, and that replicates what we see in other diseases that, you know, stimulating the immune system can have a prolonged affect.

So there was excitement about pursuing PD-L1 inhibitors, and I wanted to show you one other new trial, which was also just presented at ESMO a couple of weeks ago, the KEYNOTE-119 trial, and this study compared pembro to an investigator's choice of chemo, very similar to the other trials I just showed you. There were four options here. These patients could have had one or two prior systemic treatments for metastatic breast cancer, and they all had to have an anthracycline and a taxane; good performance status. They were allowed in whether they had PD-L1–positive or –negative tumors as well, and they were

allowed to come in with de novo metastatic disease as well. So here are the results: For the intent-to-treat population, there really wasn't a benefit of pembrolizumab here, and their primary endpoint also looked at what they called a CPS score, which means PD-L1 positive at a low level, and there really wasn't any benefit there, and there wasn't a clear benefit for CPS 10, but this was an exploratory endpoint looking at the patients who had even more PD-L1 of CPS 20 or greater, and there they saw some improvement better than chemotherapy, so it wasn't worse than chemotherapy, that's another way to look at it; it worked as well as chemotherapy, but it certainly wasn't better for all comers, but when you start looking at patients who express more, at least with pembrolizumab by this scoring system, and that's important to keep in mind, so I want you all to keep in mind that each drug has its own different biomarker for PD-L1 testing; they're not the same in lung cancer as they are in breast cancer, they can be different and you have to keep all that straight if you're treating multiple cancers. But at least the hypothesis generated that patients who had a high expressing composite score, which is PD-L1 positive in both tumor cells and immune cells, might get benefit from an immune checkpoint inhibitor as monotherapy.

So that brings us to the IMpassion130 trial, which was the first trial to definitely show a benefit from adding a PD-L1 inhibitor or an immune checkpoint inhibitor, in this case, atezolizumab, which is a PD-L1 inhibitor. In this case, in combination with chemotherapy, and the chemotherapy that was chosen was nab-paclitaxel. As you know, albumin-bound paclitaxel does not require steroid premedication, and that was one of the potential benefits here because steroids

can interfere with the activity of PD-L1 antibodies. So these were patients who had not had prior therapy for advanced triple-negative breast cancer, and I will point out that I think something like 40% of these patients have not had any prior chemotherapy, including no adjuvant or neoadjuvant therapy; 60% did, and these patients were tested for PD-L1, 41% of the patients on this trial were PD-L1 positive, and 60% were negative. In the intent-to-treat population, it did meet its statistical endpoint, but the clinical benefit was modest, less than a month and a half for the addition of atezolizumab. But when they look in the prespecified PD-L1–positive group, and this was tested using an antibody called SP142, which is the companion diagnostic for atezolizumab, and it just had to be positive, so any positive, not at any level, 1% or higher, but only in the immune cells. There was a good differentiation here. You see the curves separate, 2-1/2-month improvement in progression-free survival. What was most interesting was the overall survival, so even across the intent-to-treat population, there was about a 3-month improvement in the whole population in survival, but if you look at the PD-L1–positive group, and this is the updated data that was just presented also at ESMO and at San Antonio last year, so the last few months as the study matures, you see a 30% improvement in overall survival with the addition of atezolizumab to nab-paclitaxel, and if you look at the control arm, it's about as good as we would expect, 18 months, which is really on the high end of a control arm of chemotherapy, and yet we're getting out to 25 months for the whole group, and the study is still pretty immature; it doesn't have statistics associated based on the way the trial was designed in a complicated fashion. So it's not

definitive yet, but it was very encouraging. It was encouraging enough for the FDA to approve the drug, and I'll just show you here really all the benefit is confined to the group of patients, and overall survival, who had PD-L1 positive and got atezolizumab, the blue line on the top, and then the other three lines look about the same, whether or not they got atezolizumab or not. So the FDA approved the drug in March in combination with nab-paclitaxel for locally advanced triple-negative breast cancer with the companion diagnostic of SP142, and that should be used. In the interest of time, I won't get into the data about comparing them, the results that were presented at ESMO.

What about other drugs? So what else is in the hopper for triple-negative breast cancer? We have the two type class of drugs I just showed you—the PARP inhibitors for g*BRCA* mutated, and atezolizumab for PD-L1 positive—that still leaves a pretty large population of patients who don't have those biomarkers. I mentioned that there's a subgroup of androgen receptor–positive, triple-negative breast cancer. We have preclinical data that suggests that androgen inhibitors could work in breast cancer in a similar fashion to the way they work in prostate cancer, for example. About 25% of triple-negative breast cancer is AR positive, and this was a study we participated in looking at AR-positive, triple-negative breast cancer being treated with enzalutamide, which is an androgen receptor inhibitor, and the results were modest, but we did see clinical benefit in about 25% of patients, and some response rates in patients, so this work is ongoing, and we'll see more data on androgen receptor–positive, triple-negative breast cancer in the future.

A drug that many people are very excited about is called sacituzumab govitecan. This is an antibody-drug conjugate. The antibody is to a molecule called Trop-2. Trop-2 is not like *HER2,* it's found on almost all breast cancer cells, about 80 or 85%, and it's not a driver oncogene; it's just sort of a passenger as far as we know, but it's a good marker, so it's a target, and if you can target an antibody-drug conjugate to a cancer cell and then deliver the payload, which is chemotherapy, in this case a chemotherapy called SN-38, which is the active moiety of irinotecan. If you give that into the cancer cell, then maybe that would work. And in fact, sacituzumab govitecan had efficacy in heavily pretreated triple-negative breast cancer. You see the waterfall plot on the left, there were patients who achieved a complete response and patients who received a partial response, even the stable patients were significant, so the majority of patients had some benefit from sacituzumab. The response rate was 33%, the median number of prior therapies for this group I think was five, so this was a heavily pretreated population, there were even some CRs as I mentioned. The clinical benefit rate, which was stable disease or better at 6 months was 45%. These are very encouraging numbers. The swimmer plot on the right shows you that some of these patients had prolonged duration of response and were going beyond a year if they had a response, so it looks like a meaningful benefit. The drug is – this was a phase 2 trial. The phase 3 trial, confirmatory trial, in triple-negative breast cancer is completed enrollment and because these patients do relapse pretty early and progress, we should see the results within the next year of that trial, and that's heavily awaited. This is the toxicity of sacituzumab, it's mainly

diarrhea and neutropenia, two things we see a lot of. You do see some febrile neutropenia here, and some other GI toxicity, but it was very manageable, and most patients were able to stay on study and not discontinuing for adverse events.

There's a few small molecules in development for triple-negative breast cancer, and I'll talk about trilaciclib, which was just presented at ESMO, and a little bit about the Akt and HDAC inhibitors.

Trilaciclib is a novel CDK4/6 inhibitor. It was really tested for an endpoint not on its effect on cancer, but whether it would reduce neutropenia, which is what was found in the preclinical data. It turned out to be negative for that endpoint, and it was also interestingly negative for progression-free survival, but interestingly, it was positive for overall survival, something we typically don't see in a phase 2 trial, so this is kind of interesting. It has several of us scratching our heads, what's going on here? But this drug will be explored further in a phase 3 trial.

There's a lot of excitement about the Akt inhibitors. Akt is a downstream enzyme of PIK3CA. It's in the PIK3CA/Akt/P10 pathway. It's an important pathway for a metastatic phenotype and a cancer phenotype, so inhibiting, as you know, we have PIK3CA inhibitors now in HR-positive cancer. Akt inhibitors are being looked at both in triple-negative and in HR-positive, and we have two trials – two phase 2 trials with two different drugs, the LOTUS trial with ipatasertib, and the PAKT trial with capivasertib, which were both positive phase 2 trials, both for PFS and overall survival, so both of these drugs have moved

forward into phase 3 trials, and we'll see some results, and we may have a new class of agents in the next year or two for triple-negative breast cancer. So, and the HDAC inhibitors are also in phase 3 trials, and have some rationale in triple-negative breast cancer.

So key takeaways, you should test your patients for PD-L1 and germline *BRCA* mutation. If they're PD-L1 positive, I believe first-line therapy within atezolizumab and nab-paclitaxel is appropriate therapy based on that survival advantage we saw, and you're giving them taxane anyway, which is the standard first line therapy. If they're G-BRCA mutated, I would use a PARP inhibitor as first line therapy if they were PD-L1 negative, and after atezo plus nab-paclitaxel if they're PD-L1 positive, mainly because of that survival advantage you'll pick up on, and then still get the advantage from the PFS with the PARP inhibitor. If neither, I would recommend doing comprehensive genomic profiling on these patients to see if they're a candidate for a clinical trial, or you can find something else that's going on. Occasionally, these patients will be *HER2* mutated or *HER2* amplified even though you don't see it on your immunohistochemistry. If it's been 6 or 12 months since their last taxane, I would recommend a taxane. Don't forget anthracyclines. We're in a current year where they're not used; they're still – both taxanes and anthracyclines are the two most active drugs in breast cancer in general. Eribulin has been proven as a third-line or greater agent to be better than the others. Watch the CNS as I mentioned, and I think the breast cancer community is eagerly awaiting a number of these drugs, but particularly this

atezolizumab based on the very encouraging data. So I will turn it over back to Heather for the adverse event management.

HEATHER GREENE All right, we're going to close this out with – we're going to talk about PARP inhibitors and the immune checkpoint inhibitors along with some case studies, okay? Do we need some Aerosmith again in here or anything, or are we good? We're good? Okay. Some of you who were at our talk earlier are going to hear me repeat a couple of things, but if you didn't, then it's new and fresh for you. As Dr. Schwartzberg mentioned in the OLYMPIAD trial that brought olaparib to the breast cancer approval for triple-negative breast cancer, 97% of the patients on that trial experienced some type of adverse event. Most of those, 61%, were grade 1 or 2, and in fact in that trial, the olaparib arm had actually lower grade 3/4 toxicities than the control arm. The most common toxicities were mainly hematologic, anemia, neutropenia, and then GI toxicity, nausea, vomiting, diarrhea, and fatigue, and noting here that the only grade 3/4 toxicity greater than 10% was the anemia. So the starting dose for olaparib for 300 mg twice a day, 25% of patients on trial required some type of dose reduction due to adverse events, and that was most commonly for anemia, which makes sense based on the table that we just saw; 35% of patients required dose delays or dose interruptions, but only 5% of those patients required permanent discontinuation because of an adverse event, which to me suggests that despite the fact that patients develop these hematologic or GI toxicities, we should be able to manage them appropriately with dose reductions, delays, and interruptions, and keep them on therapy and get them through therapy. So there

are some dose adjustments, not just for AEs but also for some other certain situations that our patients may run into. If patients are on CYP3A4 inhibitors, they require an automatic dose reduction because of the potential for increasing olaparib toxicities if given concomitantly. So if for whatever reason patients have to stay on that drug, the dose reduction is listed here. For patients who have mild renal impairment, there's an automatic dose reduction. Patients with severe renal impairment or severe hepatic impairment, there is no safety data; those patients were not included in the trial. Toxicity dose reductions are also listed up here, and we're going to talk about that a little bit further in our case studies. I'm not going to go into that a whole lot here. There is a warning for the potential to develop myelodysplastic syndrome or acute leukemia; it occurred in less than 1.5% of patients on the trial, but it's certainly something that we need to keep in mind knowing that a lot of these patients can develop significant myelosuppression that improves when we hold the drug or dose reduce or delay. If you're seeing that patients are having prolonged cytopenias, it's definitely worth looking into and working up further with bone marrow biopsy to make sure that they haven't developed this not common, but certainly very devastating, complication. There's also less than 1% risk of pneumonitis, which would also require further workup if you're having patients come in with pulmonary side symptoms and would require permanent discontinuation, and both of these PARP inhibitors are potentially teratogenic, so if these patients have not already had their ovaries or removed or had some other type of intervention for that since

they’re germline *BRCA* mutated, they need to maintain contraception use during therapy for at least 6 months after completing therapy.

So patient education, it's important to make sure that patients understand how to take their medicine and that when you're going in the room to see these patients, that you're not just using your medical assistants, you know, clicking or checking of the box that they're taking their medicine. Make sure that these patients know that the dose is 300 mg twice a day, so that's two of the tablets twice a day, and it never fails when you talk to these people and, you know, you say, "Are you taking your medicine?" and they say, "Yes," and you say, "Are you taking two of them twice a day?" "Yes." "Are you doing that every day?" "No, not really." So we need to make sure that they're taking their dose every day as directed. You can't do anything to the pills, you have to swallow them, so they're going to want to come up with all sorts of ways to try and get around that, you can't get around it. Swallow it whole. And for our sweet little ladies who want to drink their grapefruit juice every morning, they can't do it while they're on olaparib. I don't know how you guys do it in your facility, but it's important to make sure that we give patients, you know, we know what we're looking for when these patients come into the office. We're looking at their CBCs, we know what signs or symptoms to ask them about that might indicate that they're developing some toxicities associated with these drugs, but when we have patients start any type of therapy at our clinic, on their consent form, we go through those toxicities and then there's certainly a list there of reasons to call the physician's office, which might indicate that they're developing a more significant toxicity than would

be comfortable with them dealing with at home, and we have that listed here, but we give a copy of that to the patient so that they can go home with it and refer back to it while they're at home.

All right, so the second PARP inhibitors from the EMBRACA trial, again, very similar to olaparib. A lot of patients, 65% of patients required dose interruptions for any type of adverse event while on the trial, and then another 53% of those patients required dose reductions; however, again, only 5% of those patients required permanent discontinuation, suggesting we can get them through if we manage them appropriately. The most common reasons for the discontinuation were the hematologic toxicities, and then we have a better table representation of that here. So similar to olaparib, we see the hematologic toxicities all right here. We do have more grade 3/4 toxicities with talazoparib than with olaparib, and then the GI toxicities listed down here. So the starting dose for talazoparib is a 1 mg capsule daily, and the dose reductions are listed here. Again, you're going to want to consider interruption with or without dose reduction depending on your patients. So when they come into the clinic and they're developing either these hematologic or GI toxicities, you have some wiggle room there to decide if you just need to dose interrupt and see what their counts do with a week off. If they don't improve a whole lot, and it takes a longer time, then you may want to restart with a dose reduction, and we're going to go into that in the case study like I mentioned. There is a dose reduction for patients who have moderate renal impairment and for those patients with talazoparib that had P-gp inhibitors that they're taking along with their talazoparib, especially if for

whatever reason they can't come off of that medicine or exchange it for something else that doesn't interfere. And the dose modification is listed here, so usually for grade 1 or 2 hematologic or nonhematologic toxicities, there's no dose interruptions or dose reductions, but for the patients who have grade 3 or 4 hematologic toxicities, you would want to hold the medication until it improves to at least a grade 2 or back to baseline and then resume with a dose reduction. Again, similarly, with olaparib, there are warnings for MDS and AML with talazoparib, and what I found interesting with this warning was that there was a patient on the drug for 2 years before they developed the MDS or AML, so even when these patients are on medication for a long time and you just kinda feel like you're in cruise control, if they're developing prolonged pancytopenias that aren't improving when you hold medicine, when you dose delay, you dose reduce, you need to work it up further and make sure they haven't developed this complication. Starting dose for talazoparib is like I said 1 mg capsule a day. You can't do anything to it, you have to swallow it whole, and then again, make sure your patients understand and know when to call the office with some of these symptoms listed here, which might indicate that they're developing these toxicities that you need to look into further.

Okay, so let's talk about this first case study. This is a lady in our clinic, she's 89 years old now. Despite her age, she has a pretty good performance that is ECOG 1, maybe 2. She has a medical history significant for hypertension, hyperlipidemia, type 2 diabetes, and coronary artery disease or, you know, otherwise known, she's lived in the south for most of her life. So she was actually

first diagnosed with breast cancer in 1993 when she was 63 years old. She was treated for this initial breast cancer at another facility, not with us. So we don't have a whole lot of information on it other than she had a left mastectomy, she had radiation therapy, she had adjuvant CMF chemotherapy, and I know we have a lot of experienced nurse practitioners in here, so you all know what I'm talking about, and tamoxifen, so we assume that it was hormone receptor positive. In April of 2016, she was referred to our clinic after being diagnosed with a new breast cancer. This one was triple-negative, 1.8 cm, grade 3 infiltrating ductal carcinoma, Ki-67 score of 37%, and she had a right mastectomy for a pathologic T1c node-negative breast cancer. So in between the time she was first diagnosed with her breast cancer in 2016, she also had a sister and a niece who were diagnosed with breast cancer at fairly young ages. They were tested for the *BRCA* mutation, and both found to be positive for a germline *BRCA2* mutation. This then prompted our patient to get tested, and low and behold she was also found to have a germline *BRCA2* mutation. When we first saw her in 2016 at that time mainly due to her age, she declined adjuvant chemotherapy, and also I think in the back of her mind, she was thinking, "I did well with my first breast cancer. I'm not going to live long enough for this one to give me problems." So that was basically her thinking unfortunately, despite the fact that we discussed with her the differences between hormone receptor–positive and triple-negative breast cancer – let me just make that point. So this year, in April of 2019, she developed a cough that wouldn't go away. She saw her primary care physician who did a CT scan of her chest, unfortunately, showing a right lower

lobe mass, 2.8 cm, and right hilar and mediastinal adenopathy, concerning for either a new primary or metastatic disease from her history of breast cancer. So her right lower lobe lung nodule was biopsied and was consistent with metastatic poorly differentiated carcinoma, consistent with breast cancer and was also triple-negative on her anatomic histologic pathology report. And the standard of care in our practice for patients who develop metastatic disease, their first occurrence, to also send their pathology for next-gen sequencing or a comprehensive molecular profiling, and for our patient here, the pertinent – and this is just a snapshot of what the pertinent markers look like when we get this, you know, 14-, 15-, 16-page report back – they give us a pretty good snapshot here of what's important or what's important to pay attention to for this patient. So we knew she was going to have a *BRCA2* mutation because we already knew she was germline *BRCA2* mutated, but just in referencing back to what Dr. Schwartzberg talked about and then potentially other treatment options in the future, she was PD-L1 positive, suggesting that she might benefit from immunotherapy, and then again confirming that she was triple-negative here. She's AR-negative, and I believe that was all that we saw on her comprehensive molecular profile that was at least pertinent for today's discussion. So her baseline PET CT scan – I like pictures, so I thought this would be fun. I'm not a radiologist, so I had them pick the best ones for me to be able to show you here. You can see where her adenopathy lights up in this right lower lobe lung nodule, and I'm showing you this now so we can see what it looks like in a couple of months. She did not obviously want chemotherapy, which was fortunate for us. If

we didn't have what we know now with the PARP inhibitors, that it is better than chemotherapy, she probably would not have done anything at all. She did decide to try olaparib, and she started on the standard dose of 300 mg twice a day. I've put up here kind of a baseline or a snapshot of what her counts looked like prior to starting chemotherapy – I mean, excuse me – olaparib. Here's her baseline here. She didn't start exactly on that day; she wanted to wait until after the Memorial Day holiday. So we brought her back about 4 weeks later, and her hemoglobin and hematocrit had dropped to about 10. She was a little tired; she's 89, but she really wasn't having a whole lot of problems at that degree of anemia, so we continued her on the therapy, no dose interruption or delay. We brought her back 4 weeks later, however, and there had been a significant change. Her hemoglobin had dropped to 7.7, she was very short of breath, very tired, and didn't want to take the medicine anymore. Because of her cardiac history, we did give her a unit of blood, we got her blood counts back up pretty quickly, we also held the olaparib, and she decided that if she wanted to go back on therapy, we needed to try and make it better for her. Her quality of life was obviously very important. So we made a pretty small dose reduction just knowing that we might need to do it again in the future. We went to 250 mg twice a day, and she was able to stay on that dose with mild anemia that she was not significantly symptomatic with, and she remains on that dose today. Three months into her therapy, we repeated her CT scan, and she's had a nice response in that right lower lobe lung nodule, and she's doing and feeling well.

So key takeaways for the PARP inhibitors, we want to just make sure that we're monitoring the CBC, both at baseline and then at least monthly throughout therapy; make sure you're keeping a high index of suspicion for those rare complications like pneumonitis or MDS and AML; make sure they're taking their medicine the way that they're supposed to, every day, all the time; evaluate their concomitant medications routinely; and as the APPs in your practice, become the experts in terms of being able to manage these patients' symptoms, know when to dose reduce, interrupt, delay. We want to try and keep them on therapy, and it's up to us to try and be the experts in our practice to get patients through these therapies.

And now we're going to totally switch gears and talk about immune checkpoint inhibitors, and I remember, I think it was just like 2 years ago, Dr. Schwartzberg and I were here at JADPRO talking about breast cancer, and literally every other talk in the whole conference was about immune checkpoint inhibitor therapy. We had nothing – nothing for breast cancer. It was like the only talk that didn't have immune checkpoint inhibitor therapy. So now we're here, yay, we made it, immune checkpoint inhibitor therapy for triple-negative breast cancer, and some of you may be familiar with immune checkpoint inhibitor therapy if you're using it for other diseases that you see in your clinic. I treat GI and GU malignancies as well, so we've been using it for quite a while there. We could probably spend an entire hour talking just about immune checkpoint inhibitor adverse reactions and how they occur, and the mechanism of action, but we're not going to be able to get into the mechanism of action so to speak tonight

due to time, but just know that these immune-related adverse events are completely different than how chemotherapy causes adverse events in our patients. Most of them are mild and easily manageable, steroid responsive, and you can get patients through it, but some of these can be severe, life threatening, and obviously irreversible. The spectrum of toxicity associated with immune checkpoint inhibitor therapy is universal. It literally can affect any and all organ systems in the body, so we're used to maybe associating immune checkpoint inhibitor adverse events with the more common ones like rash, arthralgias, fatigue, little less commonly, hepatitis, pneumonitis, colitis, but keep in the back of your mind when you have patients on these immune checkpoint inhibitors that when they come in the clinic and they're telling you some really strange or weird symptom, like, "I'm having trouble seeing," or, you know, "I just don't feel right," you need to work that up very thoroughly when patients are on immune checkpoint inhibitor therapy because really nothing is off limits as far as how these medicines can cause adverse events.

Okay, so I'm taking this directly from NCCN in terms of what they recommend for pretreatment evaluation prior to starting immune checkpoint inhibitor therapy, and needless to say, it's very thorough, but if we're going to be the ones managing patients when they come back in with immune-related adverse events, it would behoove you to make sure that you get a really good pretreatment evaluation so that you can better know, you know, this is how it was prior to starting immune checkpoint inhibitor therapy, so I know it's not related to that, and we can press on. NCCN recommends a complete physical exam, head-

to-toe CT imaging, MRI if indicated, and in this setting, like Dr. Schwartzberg mentioned earlier for triple-negative breast cancer, it might not be a bad idea to get a brain MRI. Blood work includes a CBC, comprehensive metabolic panel, serum cortisol, thyroid panel. In some of our care plans, we have pancreatic enzymes built in, like we'll talk about with our case study here in a minute. Certain patients may need individualized cardiovascular or pulmonary workup more extensive than just a CT of the chest or O2 sat or PFTs, a thorough dermatologic and musculoskeletal evaluation as well.

So again, similar to when our patients come in on the PARP inhibitors, we know what we're looking for, and we know what questions to ask, but it's important to make sure that when you start patients on these therapies that you're giving them the information, that they know what to look for at home in order to be able to call the clinic and tell your phone nurse triage or the primary care doctor or whatnot the problems that they're having. So there's tons of information out there that's unbranded about immune checkpoint inhibitor therapy and the adverse reactions associated with that. It's probably hard to get into one document all of the possible adverse events that can occur with immune checkpoint inhibitor therapy, but you can get the main points, and again, you can put this on their consent form. It doesn't have to be specific to whatever immune checkpoint therapy you're starting them on, but give them some sort of reference to look back to and be able to know that I need to call my doctor if I'm having, you know, an increase of four to six bowel movements a day and know that that's not

supposed to be something that's going to go away on its own. Okay? Actually, we're going to move on here.

So it would be impossible to walk through an immune-related adverse event today and be able to walk through the algorithms that are associated with all of those so, ASCO and NCCN have given basic standard recommendations for immune-related adverse events based on their grading, and for the most part, for grade 1 adverse events, you can continue checkpoint inhibitor therapy. So I think there's a little bit of a knee-jerk reaction; we've been so trained to hold immune checkpoint inhibitor therapy and start steroids right away, and that's certainly something that we need to keep in the forefront of our mind, but it's not always the indication, and make sure you're referring back to NCCN and ASCO, and we'll go through that here in a little bit to make sure you're doing the right thing. For most grade 2 toxicities, you're going to want to hold therapy and then resume once they return to baseline. In some situations, you may need to start a corticosteroid therapy that can be individualized based on your patient. Certainly for grade 3 and obviously grade 4 immune-related adverse events, you're going to hold therapy, and you're going to start steroids immediately. The recommended dose is prednisone 1 to 2 mg/kg per day, and if these patients have severe enough side effects that they're in the hospital, you're giving IV steroids at the same dose. Grade 4 immune adverse reactions warrant permanent discontinuation for the most part. I think there have been some case studies looking at retreating those patients, but that would be certainly on a rare and case-by-case, individualized exception to the rule.

So once you start steroids on these patients, we need to make sure that we're taking care of them in terms of the side effects that being on steroids for 4 to 6 or sometimes even 8 weeks can leave them with. Most of the time, patients are going to need to be on steroids for at least 4 weeks, sometimes longer depending on the toxicity. For patients that develop neurologic or cardiac or some of the hematologic side effects, they may need to be on steroids even longer. So remember that you need to GI prophylax these patients so that they don't end up with a bleed, consider thrush prevention, and if they're on prednisone at a dose of 20 mg a day for longer than 4 weeks, they should get PCP prophylaxis, fungal prophylaxis, and even consider zoster prophylaxis, so almost like a post-transplant patient.

There are a couple exceptions to the rule as far as the immune-related adverse events go for endocrine immune-related adverse events. You don't have to stop therapy, and you don't have to give steroids, so if someone comes in with a TSH of 10, all you have to do is replace that hormone so to speak, okay? So that's the exception to the rule there.

For patients who are steroid refractory, and initially they were thinking, you know, if they did not improve within 48 to 72 hours on steroids, you need to consider additional immunosuppression, but really the trend is moving more towards if they're not improving within 24 to 48 hours, you need additional immunosuppression with agents like infliximab or mycophenolate for patients who develop immune-related hepatitis events.

So if you are not familiar with the NCCN guidelines for the management of immunotherapy-related toxicities, I would encourage you to become very familiar with this. It's an excellent tool and resource and literally will walk you through every step of whether or not this patient really does have an immune-related adverse event and what you need to do for it. I came across this tool in making these slides, but it's not one that I use frequently. I use much more frequently the ASCO app; it's a free app. I don't know if you guys have that on your smartphone, but it's easy to download, and it's easy to get to even while you're in the room with the patient. But there's a section for immune-related adverse events, you can click on whatever toxicity you think your patient is having, they'll walk you through the grading, and then based on the grading, walk you through the management, so it's a very useful and valuable resource to use.

Patient resources as well – if you live in an area where your patients are going to be going to the local emergency room or their primary care providers and not able to drive say hours into the cancer center, make sure you're giving them these cards so they can give to the providers that they're seeing. The last thing you want is for one of your patients to be sitting in a community hospital somewhere with raging colitis for 2 weeks because those providers just think they're having a bad chemo reaction, okay? So these cards give those providers a specific way to get in touch with the oncology care team to make sure that these patients are getting taken care of appropriately.

Okay, bear with me, last case study: This lady is a 62-year-old female, ECOG performance status 1, she has a past medical history of bipolar,

depression, hypertension, and osteoarthritis. She was first diagnosed with a triple-negative breast cancer in 2013. She had a partial mastectomy, accelerated partial breast irradiation, and then adjuvant chemotherapy. She was lost to follow-up for several years and showed back up to the clinic in June of this year when she had presented to an outside clinic with pleuritic type chest pain. Her imaging at that facility showed numerous bilateral pulmonary nodules and a large sternal metastasis that you could see and feel on physical exam as well with cortical breakthrough measuring 3.1 x 3.4 cm, or at least the soft tissue component did, and like I said before, I'm not a radiologist, but if I can see that, you know it's a problem, okay? She had extensive axillary adenopathy and thoracic adenopathy in addition to this sternal mass. We biopsied that mass, and it was consistent with metastatic triple-negative breast cancer, and again, like I said before, we sent her tumor for molecular profiling, and the pertinent findings are listed here, noting that she is PD-L1 positive, remained triple-negative, and nothing up here that will change what we're talking about today. So she was started on atezolizumab and nab-paclitaxel. Built into our care plan are pancreatic enzymes, and I chose this study because it would be probably easier to do one where you get grade 3 colitis, and we start steroids and we do all of that, but I chose this because I had a new nurse practitioner shadowing with me, and she was actually seeing this patient when she came back in for Cycle 4 for her reevaluation, and she was nervous because the pancreatic enzymes had gone up some, and again, her knee-jerk, immediate reaction was to hold therapy and start steroids. However – I'm going to skip forward just a little bit here – and

go to the NCCN guidelines. There's a difference between acute pancreatitis and elevated pancreatic enzymes, and so if we walk through this algorithm, actually she did not meet the criteria for acute pancreatitis because she was asymptomatic. She didn't have any radiographic findings of pancreatitis on her imaging, and her pancreatic enzymes were not greater than three times the upper limit of normal, so the reason that we knew she didn't have any radiographic evidence of pancreatitis was because it was also a day she was getting her reevaluation CT scan, so that was just a great incidental finding to have along with it. But, I want to show you this: So the sternal mass that was here that you could see before, now you can't see. So that was really cool.

No time to spare, so the key takeaways for immune checkpoint inhibitor therapy: We play a very unique role in educating patients and their caregivers about the immunotherapy toxicities and management, so remember, keep in mind that side effects may develop, and I don't think I said this before, most of the time they develop right away, but they can occur at any point in time on immune checkpoint inhibitor therapy even up to a year after completing therapy, so these patients may have already moved on to another line of therapy, and when they call the clinic with abdominal pain and bloody diarrhea, remember that they were on an immune checkpoint inhibitor just a couple of months ago, so keep that in your differential. Maintain a high level of suspicion for an immune-related adverse event when patients call with new symptoms, and be a key player in helping to provide education about how immune-related adverse events differ from chemotherapy adverse events, not just within your clinic, but your

patients' caregivers, consultants, primary care providers, and emergency room physicians. Lastly, for Dr. Schwartzberg.

DR. LEE SCHWARTZBERG This is the only time I got the last word with Heather, I think ever. No, I'm teasing. So the current standards of care for triple-negative breast cancer can be optimized to provide improved outcomes for patients, and I really think as I said when I started that patients come in, and it is a disease to be feared and respected but not to be paralyzed by. There are things we can do and we have to encourage our patients that we have therapies, and as you've seen, we have new therapies that are now in the clinic and are helping many patients, as that wonderful case you just saw and others will be coming. So we have the immune checkpoint inhibitors for PD-L1 positive, we have the PARP inhibitors for germline *BRCA* disease, and hopefully very soon, we'll have sacituzumab govitecan for heavily pretreated triple-negative breast cancer. I think you're all very familiar on how to identify and manage these adverse events, but particularly the immune checkpoint inhibitors are a challenge because they can occur at any time, and I would just echo what Heather said that it can affect really any organ, so you have to have a very low index of suspicion if a patient comes in with an unusual complaint.

Okay, so thank you very much for your attention, we really appreciate it, and we're happy to take any questions.

FEMALE So with capecitabine being indicated now with less than complete response postoperatively, do you see the trend towards neoadjuvant for earlier stage disease, say in that 1- to 2-cm lesion?

DR. LEE SCHWARTZBERG That's a good question. So, yeah, I mean, it's an extrapolation from the therapy, but you could certainly consider that if you want. I think then you get into the issue, and this is a philosophical issue, about whether you're overtreating patients if you do neoadjuvant, particularly because you don't know their nodal status completely, so what I do in those cases with all my surgeons, this is a little bit digression, but it's an important point, so we do a lot of neoadjuvant therapy, and we typically don't do our sentinel lymph node biopsy until afterwards in clinically node-negative patients, but that particular situation is the one case where I ask them to do an FNA even on a clinically node-negative patient or a sentinel node because I want to know if I'm going to use – deescalate the chemotherapy there, so that's a little different than the question you were asking, but that's a more common scenario. I still think there are some issues with the CREATE-X trial, it was done in Asia. Asian patients have a different response to capecitabine, that's well known. The metabolism is actually slightly different. There are some other 5-FU oral drugs like S-1 that are approved in Asia that are not approved here, so there's a little bit of lingering issue around capecitabine in that setting, and the other piece of evidence that makes it a little bit lingering is there were many trials that looked to go from three drugs to four drugs in the adjuvant setting by adding capecitabine or gemcitabine, the other antimetabolite, and all of those failed. So the only study we have is this one. That said, you know, we're not going to lose an opportunity to help a patient that has a high risk of relapse, so because that patient had a

lower risk of relapse, it would really depend on how much disease. If they had no response, I would do it, or a minimal response in that setting.

FEMALE So you're sticking to that 2-cm direction?

DR. LEE SCHWARTZBERG No, I mean, again, I see patients who have a 1.8 cm, a woman with a small breast and wouldn't have a good cosmetic result if they had a lumpectomy, I'll do it in that case, but I want to know the node status there.

FEMALE Okay.

FEMALE How are you choosing which PARP inhibitor to use?

HEATHER GREENE Good question.

DR. LEE SCHWARTZBERG I think, in general, I think the efficacy data looks very similar for both of them. The studies had slight differences. I would recommend using either of them and getting familiar with the toxicity with either one.

FEMALE Any idea why they're using irinotecan as the conjugate versus an anthracycline, like doxorubicin which has known efficacy?

DR. LEE SCHWARTZBERG Yeah, that's a good question. So that has to do with the chemistry of antibody-drug conjugates, and they're complicated to make, so it took a long time to even get the technology to the point where you could attach, and most of the agents in use in antibody-drug conjugates tend to be anti-tubulin therapies. SN-38, though, you can't give it IV, it's too toxic to give IV, so irinotecan is actually a pro-drug, it gets converted to SN-38 in any setting. It actually does have activity in breast cancer; it's never

been developed in breast cancer, but I occasionally use it in the patient who is on eighth line of therapy, and I've seen responses to it, but, you know, the toxicity is high. It turned out to be chemically easier to link in a covalent way, so it wouldn't fall off in the serum, you know, before it got to the cell.

FEMALE Thank you.

DR. LEE SCHWARTZBERG Thank you.

JENNIFER WEBSTER Thank you both so much; it was excellent, absolutely excellent, and thank you audience for hanging in there.

[END]