Practical Guidance for the Community Oncologist
Incorporating Advances in Therapy for Metastatic TNBC:
A Focus on TROP2

Host: Thank you everyone from the University of Florida for taking time out of your day to join Dr. Hurvitz. She will be speaking to Practical Guidance for the Community Oncologist – Incorporating Advances in Therapy for Metastatic TNBC: A Focus on TROP2. So, I'd like to welcome Dr. Hurvitz and we appreciate her time today. Dr. Hurvitz is a Professor of Medicine at the University of California Los Angeles UCLA. She's also the co-director for the Santa Monica UCLA Outpatient Oncology Practice and also the Medical Director Clinical Research Unit at the Jonsson Comprehensive Cancer Center at UCLA.

She's also lead director of Breast Oncology at the Simms/Mann UCLA Center for Integrative Oncology in Los Angeles, California. So welcome Dr. Hurvitz and I will turn it over to you.

Sara Hurvitz, MD, FACP: Thank you so much. It's my pleasure to be here presenting this triple negative breast cancer talk that was chaired by Hope Rugo, and you can see the other faculty, including myself that are a part of this.

So the learning objectives are to discuss new and emerging targeted treatment approaches in the setting of triple negative breast cancer, discuss the role of ADCs and TROP2 for triple negative disease and implement strategies to facilitate the use of novel and emerging therapies for triple negative breast cancer in the community based settings. And this activity is supported by an educational grant from Gilead Sciences.

Here is the accreditation and credit designation, this Rush Medical University Medical Center is jointly accredited by ACCME and ACPE and ANCC. And

so you will be able to get one AMA Category 1 Credit and one nursing contact hour.

And then here are the financial disclosures for all of us, mainly relating to the research that we conduct with research support paid to our institution. And then just a statement regarding off-label. Here is the agenda. We're going to go through some challenges of triple negative breast cancer, the ABCs of ADCs, TROP2 as a target, additional ADCs being evaluated in triple negative breast cancer and strategies to incorporate anti-TROP2 ADCs into treatment paradigms, and there will be a couple of cases and then Q&A at the end.

So let's first jump into challenges of triple negative breast cancer. Triple negative breast cancer comprises somewhere around 10 to 15% of all breast cancers. Defined by immunohistochemistry by what the cancer is not rather than what it is. Of course, this is not a very sophisticated way to sub-classify a cancer. Just defining it based on its lack of expression of ER, PR, and HER2. However, as a group they tend to be more aggressive, higher grade, more responsive to chemotherapy, perhaps related to its higher proliferation.

Tends to have different sites of relapse. More often in the liver and central nervous system, which differs from that of ER-positive breast cancer. Affected patients often are younger and women of color, including black women. P53 mutations are common and triple negative breast cancers seen more commonly in *BRCA*1 mutation carriers in those with *BRCA* pathway dysfunction.

We know that the outcomes long-term associated with triple negative breast cancer are poorer compared to other subtypes, in spite of optimal chemotherapy treatment. You can see stage for stage, stage II, III and IV here,

with triple negative being in the blue line. The outcomes associated with this disease in terms of survival, breast cancer specific survival are much poorer.

And so the NCCN guidelines have published optimal therapy in the preoperative and adjuvant, or postoperative setting for HER2 negative breast cancer. Included in there is triple negative breast cancer, with these chemotherapy options as listed in the top three, preferred regimens. Olaparib is now available to patients in the adjuvant setting with high-risk germ line *BRCA*1 or 2 mutation-associated HER2 negative breast cancer, both triple negative and HR+, HER2-negative.

And then we now have the availability of immunotherapy, pembrolizumab in the preoperative setting and adjuvant setting in patients who received it in the preoperative setting, in combination with platinum taxane and anthracycline-based therapy. We also have the use of capecitabine in the adjuvant setting where the data is most supportive of treatment in triple negative breast cancer for those with residual disease after standard neoadjuvant therapy.

Now we do have some biomarkers that are associated with FDA-approved therapy. As I mentioned, any patient with a *BRCA*1 or 2 mutation can have olaparib or talazoparib in the metastatic setting, and we now have the availability of olaparib in the adjuvant setting for high risk BRCA mutation carriers based on the OlympiAD study. In triple negative breast cancer, we can use pembrolizumab and chemo in the metastatic setting. And in the neoadjuvant and adjuvant setting can use pembrolizumab regardless of PD-L1 expression.

And then we have rarer alterations, including *NTRK* fusions, which can lead to the use of larotrectinib or entrectinib. These are very rare in breast cancer. But when we do next gen sequencing in the metastatic setting, we have the

availability of these agents for those rare patients who have those. If a patient has micro satellite instability high or dMMR, we can use pembrolizumab in the metastatic setting. And if the tumor mutational burden is high, defined as at least ten mutations per mb, pembrolizumab is available.

So these are relatively uncommon findings with the exception of PD-L1 expression that lead to our ability to use the targeted therapy. More commonly we are stuck with single agent or combination chemotherapy. Until recently, we have the first ADC approved for triple negative breast cancer, sacituzumab govitecan.

So PD-L1 testing is done by immunohistochemistry. The current NCCN guidelines recommend testing PD-L1 using the 22C3 antibody, with a CPS score of at least ten being defined as the indicator for use of pembrolizumab in the metastatic setting. Now of course recently we had the withdrawal of FDA approval for atezolizumab, which is why we're no longer testing PD-L1 by SP142 because the drug is no longer approved.

All right, let's talk about ADCs. What is an antibody drug conjugate? It has high – a highly selective monoclonal antibody, shown in the blue on the left for a tumor associated antigen. So a protein or antigen that is expressed uniquely or over expressed on tumor cells compared to normal cells. Linked to a potent cytotoxic agent, which is generally a small molecule drug, like a cytotoxic chemotherapy with high systemic toxicity that is designed to induce tumor cell death after being internalized into the tumor cell and released.

And then a linker that is stable in circulation but releases the cytotoxic agent in target cells. So ADCs have all three of these components. The antibody links onto the tumor associated antigen, causing internalization. Once inside the ADC linker releases the drug and the bomb goes off. So mechanistically

ADCs exert their activity by selectively binding to that tumor internalization, degradation of the linker and release of the payload, leading to cytotoxic cell death.

TROP2, trophoblast cell surface antigen 2 is a glycoprotein that spans the epithelial membrane surface. It plays a role in cell self-renewal, proliferation and transformation. And it does have an essential role in embryonic development, including placental tissue formation, embryo implantation, stem cell proliferation and organ development. But in the adult human it is expressed in all types of breast cancer cells and has been shown to be linked to poor prognosis in patients with breast cancer.

So sacituzumab govitecan is a first-in-class ADC that targets TROP2. It has an antibody that's highly specific for TROP2. The drug to antibody ration is 7-8-1. Meaning there is 7 to 8 molecules of the cytotoxic payload per antibody. The internalization and enzymatic cleavage by the tumor cell is not required for liberation of the payload from the antibody. So you can see off target toxicity with this drug because the drug is not just internalized in the tumor cell. The payload can be released in the area of the tumor. Hydrolysis of the linker also releases SN-38 extra cellularly in the tumor microenvironment, leading to bystander effect, which kills nearby neighboring cells.

Now SN-38 is a topoisomerase 1inhibitor, similar to irinotecan, but it's more potent than the parent compound irinotecan. And this drug was approved in April of 2021 for metastatic triple negative breast cancer. And it works regardless of TROP2 expression level, and I'll show you some data relating to that.

So although the accelerated approval of sacituzumab govitecan was based on a phase one two study, single arm study showing marked benefits with this

drug in heavily pre-treated triple negative breast cancer, the full regulatory approval of this drug was based on the phase three ASCENT trial shown here. In this study patients with heavily pre-treated, at least two prior chemos for metastatic triple negative breast cancer were randomly assigned to sacituzumab govitecan, which is given at a dose of 10 mgs per kg IV days 1 and 8 every 21 days. So two weeks on, one week off, versus treatment of physician's choice. And clinicians and patients had a choice of chemotherapy that could be given, single agent chemotherapy.

There was no upper limit on the number of treatments patients were allowed to have had before they came on. One of the regimens could have occurred in the adjuvant or neoadjuvant setting, as long as their disease recurred within 12 months of that. It was a 529 patient study with a primary endpoint of PFS in the patients who did not have brain metastases or a history of brain mets. As well as overall survival as a secondary endpoint.

And this is the progression-free survival shown here. You can see that the PFS was significantly improved with sacituzumab govitecan, with a hazard ratio of 0.41, highly statistically significant. This represented a close to four month absolute improvement in progression-free survival compared to treatment of physician's choice. And the overall survival was also significantly improved with a hazard ratio of 0.48 over a 50% relative improvement in overall survival. Highly statistically significant as well.

In terms of TROP2 expression we did an analysis to evaluate whether higher levels of TROP2 actually led to a better outcome for patients treated with this antibody. And whether or not patients who had medium TROP2 expression or low TROP2 expression didn't benefit from sacituzumab. And actually, if you look at the curves here, in blue are the sacituzumab treated patients, and in pink are the treatment of physician's choice. In the dark blue are those patients

with high TROP2 expression and compared to the dark pink you can see there is a significant benefit with sacituzumab in those with high expression. Then the medium blue colored ones are medium TROP2 expression level. They do better as well than patients treated with medium TROP2 expression who were treated with treatment of physician's choice and so on.

And then in the table at the bottom you can see, the TROP2 expression level is based on the H score, an IHC index, you can see that sacituzumab govitecan was associated with a medium PFS of 6.9 in the TROP2 high level, versus 2.5 for treatment of physician's choice. For those with medium H scores, the sacituzumab govitecan was associated with a medium PFS of 5.6 versus 2.2. And then even with low TROP 2 expression levels, now the numbers are getting very small, but the medium PFS was better with sacituzumab than with treatment of physician's choice. So you don't need to use TROP2 expression level to determine whether your patient is a good candidate for sacituzumab. The benefit does appear to be better for patients regardless of level. It is interesting that lower TROP2 expression levels do appear to be associated with worse outcome overall, which is kind of an interesting finding.

Now in terms of treatment-related adverse events, the grade 3/4 AE rate was noted in 64% of patients. It is important to note that this drug, sacituzumab govitecan, is associated with chemotherapy-like side effects with neutropenia, grade 3/4 neutropenia being seen in 51% of patients. So, in some of our patients, especially those who are more heavily pre-treated and are coming onto therapy with relative pansitopenia, it's important to think about growth factors and watching their neutrophil levels. The neutropenia rates were higher with sacituzumab than they were with treatment of physician's choice.

Moreover, diarrhea is also seen at a rate of grade 3 in 10% of patients, which is worse than seen with treatment of physician's choice. So, I make sure all my patients have antidiarrheals at home. I'm checking in with my patients for several days after their first infusion to make sure that they're not having diarrhea that's out of control at home and giving them guidance.

And then finally patients should be warned that they will experience alopecia. All of the patients I have treated have had full alopecia with this agent. Just underscoring that this is an ADC, but it does have off-target effects, leading to chemo-like toxicity.

So shown here again, neutropenia, diarrhea, leukopenia, anemia and febrile neutropenia were all numerically higher with sacituzumab compared to single agent chemo. G-CSF was used in more patients. Close to have of the patients on sacituzumab arm received G-CSF compared to 23% in the single agent chemo. However, dose reductions due to AEs were similar for the two treatment arms.

Now datopotamab deruxtecan, another mouthful, is a newer TROP2 ADC that's in development. This has the same payload as we see in trastuzumab deruxtecan, or TDxd. But it is attached to an antibody that targets TROP2. The circulating free payload is negligible due to the high stability of the linker. So it limits systemic exposure and non-targeted delivery of the payload. So potentially this could be less toxic than sacituzumab, but we'll have to wait for a comparative trial to know.

The payload itself, DXd, is membrane permeable, just like in TDxd. It requires TROP2 mediated internalization for release. But then once the payload is released, it can permeate that cell membrane and kill nearby tumor cells. The drug antibody ratio for this ADC is 4, in contrast to 7 point

something with sacituzumab. And it has a longer half life than sacituzumab, 5 days with datopotamab compared to 11 to 14 hours with sacituzumab. And the DLT is neutropenia with sacituzumab, but for this particular ADC the dose-limiting toxicity is maculopapular rash and stomatitis. So very different drug, even though the payload is very similar, targeting topoisomerase 1.

TROPION-PanTumor01 is a study that enrolled multiple different solid tumor types, and there was a triple negative breast cancer cohort that enrolled patients with advanced triple negative disease that had progressed on standard treatment. Again, similar to the ASCENT study, patients were not selected based on TROP2 expression. All comers were allowed. They had to have measurable disease. And in contrast to sacituzumab, which is given day 1 and 8 every 21 days, Dato-DXd is given 6 mgs per kg every 3 weeks.

The current analysis that was presented previously included 24 patients treated at the 6 mgs per kg dose and 8 mgs per kg dose. Treatment's ongoing in the majority of patients. Six patients have discontinued treatment due to disease progression. And the primary endpoints of this study were safety intolerability while efficacy was a secondary endpoint. The objective response rate was a healthy 43% in this heavily pre-treated patient cohort. A disease control rate of 95%. You can see the 8 mgs per kg is in the pink bars, and you're seeing very nice responses with the 6 mgs per kg dosing level. And the spider plot on the far right side shows the length of therapy and the change in target lesions over time. Some patients being on quite a long time. So I think these are quite impressive data, early data, but impressive data in heavily pre-treated triple negative breast cancer. So I'm excited to see this drug going forward in phase three testing.

Let's talk about other ADCs in triple negative breast cancer. Now we know that TDxd or trastuzumab deruxtecan, which targets HER2 has also shown

some efficacy in HER2 low breast cancer. Now how often does HER2 low occur? HER2 low meaning one plus or two plus expression, but not over expression or amplification. And actually if you look at the pie charts on the right you can see for hormone receptor positive breast cancer, roughly two thirds of these breast cancer subtypes have low expression of HER2. And for triple negative breast cancer actually 34% of them have low expression of HER2.

So if TDxd is effective in HER2 low expressing breast cancers, this could actually provide patients—a good proportion of patients—a new therapy to be used that is not just for HER2 amplified or over expressing cancer. So, phase 1b clinical trial looking a trastuzumab deruxtecan was published by Shanu Modi. These are the data on the far left, the waterfall plot for the 48 patients with HER2 low breast cancer. The objective response rate was 37%, media PFS 11 months. And you can see in the dark blue are those patients who had an IHC of 2 plus, shown in the middle panel and those with a 1 plus IHC on the far right in the light blue. And you can see actually you're seeing objective responses in both the 1 plus and 2 plus patients. There doesn't appear to be much of a difference in the efficacy. So, 1 plus and 2 plus both appear to be having benefit.

And this has led to a larger study called DESTINY-Breast04, which is comparing trastuzumab deruxtecan to chemotherapy directly in patients with HER2 low breast cancer that have progressed on endocrine therapy for hormone receptive positive and 1-2 prior lines of chemo. The primary endpoints progression-free survival, this study has completed enrollment and my hope is that we'll see some data from this study in the next year.

And then the BEGONIA study is a trial looking at TDxd plus immune therapy for HER2 low breast cancer. Part one was looking at durvalumab with

paclitaxel. Part two is that combination plus capivasertib, an AKT inhibitor. Another group five is looking at oleclumab, a CD73 inhibitor. And then you can see the other combinations there. This is metastatic triple negative breast cancer in the frontline setting. Patients may have relapsed from early-stage disease but have to be at least a year from taxane treatment and have to have 1 plus or 2 plus expression. If the objective response rate is at least 57%, then the arms would go into part two expansion of a durva combination.

And so here are the early data from this clinical trial. You can see there were 18 patients who had completed at least 1 on-treatment assessment, 12 of whom had response evaluable disease. And the confirmed objective response rate was 66.7%, 8 out of 12 patients. The responses were observed in PD-L1 positive and PD-L1 negative groups, although the numbers are quite small. And on the waterfall plot here you can see the PD-L1 expression is negative in blue and positive in pink, and you're seeing a lot of very nice responses regardless of PD-L1 expression. Now keep in mind the TDxd is quite an effective therapy. We've seen some very nice responses in HER2 low already from the study I just showed you. The relative contribution of durvalumab to these responses is not known as this wasn't a randomized study. But it is really interesting data, and I'm excited to see it go forward in a larger randomized trial.

So here's some ongoing additional clinical trials. Sacituzumab govitecan in localized triple negative breast cancer, the NeoStar study. We have sacituzumab govitecan with or without pembrolizumab. Sacituzumab govitecan in HER2 negative breast cancer and brain metastases. And then there are some planned studies looking at sacituzumab in earlier line settings. Not in as heavily pre-treated breast cancer. And I think a lot of talk about looking at this drug in early stage disease or the neoadjuvant setting.

So what about strategies to incorporate these ADCs into the treatment regimens? Here is one way of thinking about how to sequence therapy. So in the first line setting, if a patient has PD-L1 positive disease, as I mentioned, a CPS of 10 or greater by looking at the 22C3 antibody, patients should receive chemotherapy plus pembrolizumab as the frontline setting treatment. Pembro can be paired with paclitaxel, nab paclitaxel or gem-carbo based on the KEYNOTE trial. And then at the time of progression can be offered sacituzumab govitecan. If patients in the frontline setting are PD-L1 negative, which is roughly 60% of patients, single agent taxane or platinum or other single agent chemo could be offered in the frontline setting. In the second line setting they can be offered sacituzumab govitecan or another single agent chemotherapy and then sacituzumab govitecan in the third line setting or beyond. The FDA has approved sacituzumab govitecan in the second line setting and greater.

For those patients who carry a *BRCA* mutation or even a germline *PALB*2 mutation, the use of single agent PARP inhibitor with olaparib or talazoparib, is FDA approved. My choice would be to give that after pembrolizumab-based therapy if the patient's PD-L1 positive or after standard chemo if they are chemo naïve and PD-L1 negative. But I would probably give that before sacituzumab govitecan given the PARP inhibitors tend to be better tolerated and are oral therapies. So we're keeping patients out of the infusion room. Those rare patients with high tumor mutational burden can of course receive pembrolizumab. I am checking next-generation sequencing in my patients with stage four triple negative breast cancer to see if they have a rare end track mutation or another mutation that might make them eligible for a clinical trial.

In the future there are potential strategies looking, as I mentioned, at targeting HER2 low disease with an antibody drug conjugate or use of Dato-DXd in patients with triple negative breast cancer. I'll be interested in seeing how

Dato-DXd compares to sacituzumab govitecan in terms of efficacy as well as safety.

Now common AEs that occur at least in a quarter of patients with anti-TROP directed chemotherapy. Neutropenia as I've mentioned, GI toxicity, alopecia I've mentioned, anemia, constipation, anorexia, rash and abdominal pain. These are all things that are seen with both Dato-DXd as well as sacituzumab govitecan. There are black box warnings relating to neutropenia and diarrhea for sacituzumab govitecan. There can be severe or life threatening neutropenia that may occur. So SG should be held for an absolute neutrophil count below 1500 or neutropenic fever. Blood counts should be monitored very closely. So on day one and eight at least.

I am using a lot of G-CSF in my patients. I would say probably two thirds of my patients if not more are now getting G-CSF to help support their neutrophils. And this may be due to the fact that patients tend to be more heavily pre-treated who are receiving this therapy and come in with pansitopenia already. And use anti-infective treatment with febrile neutropenia without delay. This is, like chemotherapy, this is a chemotherapy agent. It's not like CDK46 inhibitors where you can ignore the neutropenia. It needs to be treated seriously.

Severe diarrhea may also occur. So IV fluid hydration, electrolytes as needed, definitely anti-diarrheals. If there is late onset diarrhea, rule out infectious causes. And then of course withhold SG if severe or complicated diarrhea occurs.

Here are additional dose modifications for adverse reactions with ADCs. The first occurrence you can dose reduce. The first occurrence of grade 4 neutropenia or grade 3 febrile neutropenia, you should dose reduce by 25%

and administer G-CSF. The second time it occurs, 50% dose reduction. I have a couple of patients that I've had to do 50% dose reduction. Or if at the time of scheduled treatment you note grade 3 or 4 neutropenia, delaying the dose by 2 or 3 weeks for recovery to at least grade 1, follow these guidelines as well.

If a third occurrence has occurred, discontinue treatment. So again, very careful attention to neutropenia is called for with sacituzumab govitecan with very close management. I think this tables provides a very nice framework within which to work. The first time – at the time of scheduled treatment if a grade 3, 4 neutropenia occurs which delays dosing beyond 3 weeks for recovery to grade 1 or better, discontinue treatment. So these may seem overly aggressive, but the neutropenia can be very severe. And so it is important to follow.

For non-neutropenic toxicity here are some guidelines for the management of sacituzumab govitecan. If you are seeing any of these, grade 4 non-hematoxicity of any duration, grade 3 to 4, nausea, vomiting, diarrhea that's not controlled or grade 3 to 4 non-hematoxicity persisting over 48 hours despite optimal medical treatment. Or grade 3, 4 non-neutropenic hematologic or non-hematologic toxicity that delays dose by 2 to 3 weeks, follow this. First time any of these occur, 25% dose reduction. Second time, 50%. Third time, discontinue treatment. And then if it takes 3 weeks or longer for any grade 3, 4 reaction to recover, discontinue treatment at the first time that that occurs.

All right, so in the closing we will talk about – do some case-based discussion. The first case is Wendy. She's a 64-year-old woman with a PD-L1 negative, triple negative breast cancer, a germline *BRCA* mutation who received adjuvant ACT chemo. And she had locally advanced tumor progression in the supraclavicular region. It was not deemed to be respectable. So locally

advanced, unresectable. She was given a PARP inhibitor. And then after experiencing some level of response or benefit, developed further local progression.

So aside from radiation therapy, what potential treatment options do we have to treat Wendy? I think there are a number of options one could consider. She's had ACT and has had a progression event within a year and then a second line PARP inhibitor. So in this particular patient you could consider single agent chemotherapy or sacituzumab govitecan, what potential adverse events should you monitor for and counsel on.

So here are the therapies available based on NCCN guidelines for HER2 negative disease. And as you can see, we have all these preferred chemotherapy regimens. But given this patient's relatively fast, locally advanced, unresectable progression, as well as progression after a PARP inhibitor given. She has a *BRCA* mutation. I would probably turn to sacituzumab govitecan. I think it's important also to look at next generation sequencing to make sure that there isn't tumor mutational burden that's high or an *NTRK* mutation or something else that would lead to a clinical trial opportunity for the patient or one of those rarer mutations that could lead to a standard of care therapy.

It's important to note that our treatment algorithm for patients in the non-curative or palliative setting is to continue therapy until progression or unacceptable toxicity and then of course to switch therapy if that occurs. We can sometimes treat patients with three, four, five different lines of therapy. But in each time I think it's very important for us as clinicians to have goals of care discussion, consider the patient's quality of life, the patient's own desire to receive more therapy.

I have a patient right now on third line therapy with sacituzumab govitecan who is absolutely exhausted from therapy and really feels that she would rather die than continue on therapy her quality of life is so poor. And so she's opted to take a one month break over the holidays and then reconsider if she wants to resume therapy in early 2021. I think the use of palliative care clinicians to help guide discussions about goals of care in the palliative setting, especially with triple negative breast cancer that has such poor outcomes is very appropriate. And of course aggressive supportive care is indicated for our patients.

So it's always important for us to sort of do an internal check as we are considering next treatment options and be open with our patients about the likelihood of benefit with each subsequent line of therapy.

So we have our second case, Brenda. She's a 59-year-old woman who has metastatic triple negative breast cancer. She develops systemic progression and brain metastases that are not amenable to stereotactic radiosurgery. So we can of course refer Brenda to have whole brain radiation therapy or a clinical trial if there's one available for patients experiencing CNS progression. And then talk to her about systemic therapy options. And again, in this situation, patients going on second line therapy and you have the availability of sacituzumab govitecan. She's not a *BRCA* carrier, and is PD-L1 negative. So use of single agent chemotherapy would also be an option as would looking for potential clinical trials and considering next generation sequencing to look for those rare mutations that might lead to an agent that would be potentially effective.

So I won't beat a dead horse here and go through this again. But what I'd like to do now is, with the help of our host, open it up for Q&A.

Host: Thank you so much Dr. Hurvitz. We do have quite a bit of time for Q&A. So feel free to un-mute your microphones or use the chat function at the bottom of your screen to submit questions. We'd love to hear from you, and we have our expert Dr. Hurvitz here to answer those questions. So I will open it up to the University of Florida for questions. Here's a question for you Dr. Hurvitz. Have you experienced issues with coverage for sacituzumab govitecan? If you have experienced challenges with access, what have you done to help ensure eligible patients receive this medication?

Sara Hurvitz, MD, FACP: When it was first approved by the accelerated approval mechanism, I did experience some difficulty with obtaining approval from the insurance company. But since the phase three publication and full regulatory approval of sacituzumab in this past April, I have not experienced issues with insurance coverage, as long as I'm using it in the FDA approved indication, which is second line or greater.

What I've had some difficulty with is getting up front use of growth factors, G-CSF for patients. And so for those patients who I'm really concerned about being at high risk for febrile neutropenia, I am following them very carefully and very closely and having them come in between day one and eight to check their counts. Because I have had some patients have precipitous drops in those first few cycles in their neutrophils when they've started with lower counts.

So that's been sort of a challenge. But I haven't personally had any issues with getting sacituzumab covered. It did show a significant improvement in overall survival and progression-free survival compared to standard of care chemo. And that's something the insurance companies really can't fight.

Host: Great, thank you for that Dr. Hurvitz. I just had someone submit a question. Great talk Dr. Hurvitz. Do we know if Dato-DXd has longer lasting AEs compared to sacituzumab govitecan due to longer half-life?

Sara Hurvitz, MD, FACP: Yeah, the longer half-life would make one wonder whether or not it would have longer lasting adverse events. We don't have comparative evidence. And we don't have a huge amount of data. I mean, we're talking double digit data with Dato-DXd in breast cancer. We do have that TROPION pan-tumor study with multiple other tumor types, but it is kind of hard to tell.

The one thing that may be in favor of Dato-DXd from an AE profile is its linker technology. Sacituzumab is releasing the payload before the ADC is even being internalized. Internalization is not necessary. And I think that relates to a much higher payload release and off target toxicity, causing all these chemo side effects. Also Dato-DXd has a lower DAR, drug antibody ratio, which may optimize the therapeutic index. So my gut is saying that Dato-DXd in spite of the longer half life may actually have a better toxicity profile. But we're going to need to see a bigger dataset to know for sure.

Host: Great, thank you for that submitted question. I want to go back to the selection of one chemotherapy regimen over another. So how does one select one chemotherapy regimen over another for TNBC? Maybe you can describe that for us Dr. Hurvitz.

Sara Hurvitz, MD, FACP: Well, in taxane naïve patients, taxanes really are the preferred regimen given ample evidence that taxanes are the most effective therapy for breast cancer. We don't have any evidence that platinum-based therapy is better than taxanes. In fact in the TNT clinical trial they were equivalent for BRCA – for patients who are not BRCA carriers. And so I think that the use of a taxane in somebody who's never been exposed to one, for example,

somebody with de novo metastatic triple negative breast cancer would make the most sense.

In terms of how to sequence beyond first line taxane or in a patient who's received taxane within 12 months in the adjuvant or neoadjuvant setting, we really don't have much data. We do have data supporting the use of eribulin compared to treatment of physician's choice or capecitabine in the later line setting. So perhaps eribulin should come before capecitabine in patients with metastatic triple negative breast cancer. But we don't have a ton of data to tell us how to position other drugs. Anthracyclines are also effective against cancer and could be utilized there in the metastatic setting for patients who are anthracycline naïve and haven't had a high exposure to it in the adjuvant or neoadjuvant setting.

But it's hard for us to tell. And then you have to insert what the patients want, what their goals of care are. None of these regimens in the metastatic setting are curative. And some of my patients, for example, are just adamantly opposed to going through full hair loss without clear evidence that it will significantly extend survival to use an agent that will induce hair loss. So I've had patients choose to use capecitabine or GemCarbo in the first or second line setting just as an effort to stay out of the infusion room or to omit the alopecia associated with infusional chemotherapy. So I think it's important for us to take into consideration our patient's goals of care when we're making treatment recommendations.

Host: So another question that was submitted Dr. Hurvitz, in the neoadjuvant setting, if you don't mind going back to that, when using pembrolizumab, the trial used paclitaxel and carboplatinum. Is that something you are doing regularly? Or in which patients might you use paclitaxel alone? And if using paclitaxel alone, do you still use the adjuvant pembrolizumab?

Sara Hurvitz, MD, FACP: Yeah, so the increase in pathologic complete response seen with the addition of pembrolizumab regimen paired with the improved invasive disease-free survival after – or in the adjuvant setting, makes me want to follow the clinical trial design, my patients with high risk triple negative breast cancer in the neoadjuvant setting. So yes, short answer is, I am using platinum taxane, paclitaxel carboplatin followed by AC when I combine it with pembrolizumab. I want to give the patients the advantage that was seen in the clinical trial. So I'm not deviating from that design.

There are a couple of reasons for that. First of all, we have mounting evidence that platinums may be particularly important in triple negative breast cancer when added to taxane. And so I think that gives patients a higher chance of path CR and there's some evidence it improves long-term outcomes. I know it increases toxicity as well. But I think that we have pretty good evidence that it's improving outcomes.

So when I have a node positive triple negative breast cancer, I would like to incorporate the platinum into the neoadjuvant setting. Second of all, another immune therapy trial utilized taxane platinum without anthracycline, the NEOTRIP trial and failed to show an improvement in path CR rate. That was with atezolizumab. And so I think using the anthracycline backbone as well is important. So yes, I'm following that design to a T in my patients who I feel are at high risk with triple negative breast cancer. And I do think that the important in the long-term outcomes with this regimen do provide support for us to follow the way that the trial was done.

Host: Excellent. Thank you for these great questions everyone. These are fantastic. I've had another submitted question Dr. Hurvitz. Can you comment on if you are switching patients off of atezolizumab after its withdrawal?

Sara Hurvitz, MD, FACP: I actually have only one patient who was achieving benefit with atezo at the time of the withdrawal. And she actually switched her care to me on nab paclitaxel atezolizumab. And nab-paclitaxel, I don't know if you're aware, there's this national shortage of it. We're having to rationalize the use of nab paclitaxel. And so I wasn't able to get it for her at UCLA and couldn't switch her to paclitaxel atezolizumab based on the negative data from IMpassion 131.

So in that patient I switched her to pembrolizumab plus paclitaxel, given the benefits were shown in the Keynote study with that combination. So as a general approach, I think if you have a patient who is doing really well on nab paclitaxel atezolizumab, you're able to access nab-paclitaxel and aren't experiencing a shortage, then I think it's fine to continue that therapy until the time of progression. Most patients will progress within a year. Some a little bit longer. And so I don't see a reason to switch over. Because if you look at the progression-free survival benefits in PD-L1 positive patients from IMpassion 130, they look fairly similar. That hazard ratio looks fairly similar to what we saw in the KEYNOTE trial.

So I don't see a reason to switch it over except if you are experiencing difficulty accessing nab-paclitaxel, as that's the only agent that we should be giving atezolizumab with.

Host: Great, thank you for that Dr. Hurvitz. Just to reiterate, would you combine capecitabine with pembrolizumab adjunctly in patients with capecitabine with less than path CR after completing neoadjuvant? That was a question just submitted.

Sara Hurvitz, MD, FACP: Yeah, so the question is whether or not to use adjuvant capecitabine with adjuvant pembrolizumab in patients who have residual disease at the time of surgery after their pembro TC/AC regimen. And this is uncharted territory. Pembro and capecitabine should be safe. It has been looked at in the metastatic setting. I think the combination is safe. However, in the Keynote trial that was not evaluated. That was not allowed. Patients didn't get capecitabine with pembro unless they came off study.

So it would be sort of operating outside the standard of care. I don't think it would be wrong if you had somebody who had a ton of residual disease and you were very worried about their recurrence. You could do that. I wouldn't hold the pembro for the eight cycles of capecitabine. So, the soft answer is, yes, I would consider it, knowing that that hasn't been fully explored in a larger trial.

Another question that's come up in a couple of patients that I have is, would you give pembrolizumab concurrently with olaparib if somebody is a *BRCA* mutation carrier with triple negative breast cancer and residual disease? And again, this is uncharted territory. We don't have data to support the safe combination in the curative setting with those two therapies. And I think these are individual patient-based decisions that need to be taken into consideration. I think a discussion is warranted. But again, we're outside the reservation when it comes to these types of situations and need more data before routinely doing it.

Host: Great, thank you. I think we have time for one or two more questions. Have you heard when datopotamab deruxtecan may be available for patients with TNBC as well?

Sara Hurvitz, MD, FACP: So we're waiting on the TROPION study, which should be open, if it's not already opened, looking at this drug in both hormone receptor positive HER2 negative breast cancer. There was a study I think called TROPICS2 doing that and then the TROPION trial looking – randomized Dato-DXd versus treatment of physician's choice. So we need those trial data before I think we're going to have it approved and available to our patients. So what I would say is, if you want to access it, look at where trials are available for these agents. There are a number of ongoing studies looking at this drug.

Host: Great, and we had one more last question come through. So looking on the same note of choosing therapy for TNBC, I'm curious about the diversity of treatment options for the treatment of physician's choice arm in the SG trial. Is this a common treatment arm in TNBC studies? Is there sub-analysis comparing what those physician's choices were? It might be a basic question, but would be helpful to answer.

Sara Hurvitz, MD, FACP: Yeah, so it's a good question actually. Treatment of physician's choice is commonly used now in tumors where you have limited options and multiple different chemo options may be available. So the EMBRACE clinical trial that led to the approval of eribulin looked at eribulin versus treatment of physician's choice. The THERESA trial looking at T-DM1 in HER2-positive breast cancer compared to treatment of physician's choice. So, it's a study design that is supported historically based on other studies and has been used to support FDA approvals.

In the majority of cases when a study is designed like that, you do specify which chemos are allowed. So, for example, in ASCENT the chemos were capecitabine, gemcitabine I think vinorelbine and one other. And then on

subset analysis and if you look actually at the KEYNOTE trial of pembrolizumab plus chemo, you had a choice of chemo as well in both arms.

When you look at the subset analysis there doesn't appear to be one chemo that's doing better than the other and sacituzumab is benefiting regardless of the chemo chosen. So it's a very good question, not a basic question and it's something that is looked at on subgroup analysis often when a study is designed like that. But it is – usually the different chemo options that are provided are fairly similar in their progression-free survival. So this is an acceptable study design.

Host: And last but not least, I'd like to thank Dr. Hurvitz for her time today. It was an excellent discussion with everyone, and we appreciate everyone being here today and especially Dr. Hurvitz and her expertise.

THE END