Transforming Metastatic Breast Cancer Management: Harnessing the Power of Antibody-Drug Conjugate Therapies

CEC Podcast Transcript

Lee Schwartzberg, MD, FACP:

Good evening everyone, and welcome. Thanks for joining us for this presentation this evening, *Harnessing the Power of Antibody-Drug Conjugate Therapies*. Tonight's presentation is brought to you by Creative Educational Concepts and is supported by an independent educational grant from Gilead Sciences, Inc. Here we go. To claim credit, you have to complete the necessary requirements, the pre-test, the post-test, and then claim your credit. Dr. Rugo will be here shortly. She will be moderating the program after she comes. She's Professor of Medicine, Director of Breast Oncology and Clinical Trials Education, and Medical Director for Cancer Infusion Services at UCSF Helen Diller Family Comprehensive Cancer Center in San Francisco.

Very pleased to have Srigowri Kota with us, who's an advanced practitioner in Genitourinary Medical Oncology at Rutgers Cancer Institute of New Jersey in New Brunswick, New Jersey. I'm Lee Schwartzberg, Chief of Medical Oncology and Hematology at Renown Health–Pennington Cancer Institute and Professor of Clinical Medicine at University of Nevada Reno. Our learning objectives for the evening are number one, to implement strategies to mitigate breast cancer health disparities based on specific drivers of inequity. Two, to integrate the latest data on antibody-drug conjugates (ADCs) to individualize treatment for metastatic breast cancer (mBC) based on recent clinical evidence and updated guidelines. And three, to develop strategies for the management of adverse events (AEs) associated with ADCs used to treat patients with mBC. We're going to start with a section on health disparities in the management of mBC, and I'm introducing you to Deltra James, who is a patient and patient advocate, and she is going to be joining us on several videos.

She is a New England–based mother, poet, and patient advocate. She was diagnosed with mBC at age 33, and she has worked in a variety of venues to bring the word about mBC and triple-negative breast cancer from the patient perspective. She has had a notable career in advocacy and cancer communities. She works with Touch, The Black Breast Cancer Alliance, Project Life, Bright Spot Network, and the Cactus Cancer Society. She's really passionate about, as you'll hear about, mental wellness, therapeutic creative expression, and disparities. She, interestingly, ventured into death care work as a death doula to assist fellow patients in accomplishing necessary end-of-life planning while addressing fears. The recordings you'll hear are her thoughts and the thoughts of other women with breast cancer. We're going to start with Deltra talking about her impression of what is ideal care.

Deltra James:

Ideal care to me is my oncologist feeling like a teammate. It's important for them to provide me with their full attention when we are together. I'm very aware that they have many patients and they have a limited amount of time, but I think that how they spend the time with me is very important. I think it's important that they are very clear in explaining things to me so that I understand the plan in no uncertain terms. And I also think it's really important for them to make sure they are getting to know me as a person, not just me as a cancer patient or my body and what it's doing and assessing what it needs.

I think it's really important that they're aware of my needs outside of my physical needs and making sure that those are getting met. And I think a big part of that is making sure that I'm aware of and have access to the

entire team. So, not just my oncologist, who will care for me physically, but also nurse navigators and social workers within my cancer center, and also connecting me with community, whether it's within the cancer center like support groups or outside of it. I think that's ideal care.

Lee Schwartzberg, MD, FACP:

You'll hear more from Deltra in a few minutes. I think two things that resonate with me from what she said is that when we care for patients with cancer, it's easy for us as oncologists to focus on the cancer, but what patients are thinking about is the cancer only as one segment of their life and hopefully not the dominant segment, although it's important. But understanding their hopes, their needs, their goals during cancer treatment, particularly for mBC, is so critical, and the fact that there is a team that is taking care of the patient. It's not just one person. And the team approach is so important. Srigowri, do you want to say anything about them?

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

Yes, Dr. Schwartzberg. I totally agree. It is very challenging when patients come in and as providers we have a 1-hour slot for a new patient and a 30-minute slot for a repeat visit, and then someone's on chemotherapy and they have issues and side effects and they have questions. I think a multidisciplinary team definitely helps because the nurse will talk with the patient about a few things that maybe the doctor will not address, and then a social worker can talk about something different that the clinicians may not address, nutritionists, financial counselors. I think when someone has all these different aspects we cannot assume that cancer is the predominant factor in their lives.

Lee Schwartzberg, MD, FACP:

I think what Srigowri talked about goes for everyone and what Deltra talked about, and we want to focus part of this on some specific populations that don't do as well in mBC. When you look at this slide, you see the data broken down by race and ethnicity in terms of breast cancer incidence and mortality by age. We've known for a long time now that the breast cancer–specific survival rates for Black women are significantly lower than White women. That gap has been present now for many years. Even though the mortality rates are going down for both groups, they're not yet reaching unity. Moreover, for women, the median age of death for Black women is much younger than for White women, 63 years compared to 70 years for White women. You can see on the graphs that although the incidence of breast cancer is a little bit lower particularly as Black women get older, the mortality is higher and earlier.

We also know that triple-negative breast cancer is more prevalent in Black women than other races or ethnicities. In fact, worldwide, the highest rate is found in Black women in the United States and in West Africa. We know that triple-negative breast cancer has traditionally had a worse prognosis than other subgroups of breast cancer, and that does contribute to the excess breast cancer–related mortality for Black women, but it's not the sole explanation. If you correct for other factors, Black women still have a higher mortality rate. In fact, it's still two-fold higher. And moreover, triple-negative breast cancer disproportionately affects younger premenopausal women. You can see the prevalence of triple-negative breast cancer on the right and that non-Hispanic Blacks have the highest incidence.

What we're going to talk about tonight is some of the unmet needs in mBC and some of the ways that we're addressing them with ADCs. The largest subgroup of breast cancer patients is the hormone receptor (HR)-positive human epidermal growth factor receptor 2 (HER2)-negative subgroup. And that represents about two-thirds to three-quarters of metastatic disease.

HER2-positive patients represent about 15% or 20%; about half of them are HR positive and half are HR negative. And then triple-negative breast cancer, estrogen receptor (ER) negative, progesterone receptor (PR) negative, HER2 negative is about 15%. Over time, although HR-positive HER2-negative breast cancer patients get treated with effective endocrine therapy today, particularly in combination in the first line and in multiple lines, at some point endocrine therapy stops working for the patients and they go on to chemotherapy. So, the endocrine therapy–refractory HER2-negative group represents the large majority of breast cancer, about 85% at some point in their journey through mBC. As time goes on and then patients move into chemotherapy, their survival gets shorter and shorter for each line of therapy. So, giving the best therapy earlier in the course is really critical to get the best outcomes for our patients with mBC.

We've learned over the last few years that biology in cancer is important, but so are the social determinants of health. There are multiple risk factors that impact the outcome for patients with cancer, including socioeconomic disparities and poverty. They tend to have lower rates of screening. They present with a later stage and they don't get the same care. And many patients who are underinsured or non-insured do not get adequate care, something that's forgotten sometimes. I know from my own experience working many years in Memphis, Tennessee, a predominantly Black and poor population, that simple things that some people can accomplish many people who live in poverty cannot do. For example, if they're working, they can't take the time off or they have to use public transportation to get to the doctor's office or no one can watch the kids. There's no one there to help them.

And all of those things play a very strong role in getting the best or less-than-best care. Then of course there are the structural disadvantages, some of which we just talked about, and geographic barriers to care, including not only in urban areas but in rural areas. Lifestyle also plays a role as we know that people who live in poverty have higher rates of tobacco and alcohol use and higher obesity. Tobacco and obesity are the two most common lifestyle reasons for getting cancer, and so forth. And then many people, especially those who are in lower socioeconomic groups, live in food deserts and can't get access to healthy nutrition. Have you found that in your population?

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

Yes, absolutely. Although New Jersey is considered to be one of the more geographically advantageous and accessible areas in the country, that is a huge advantage for patients because they have multiple options in terms of picking a provider who's closer to them or someone who checks off a lot of the boxes. But that's having addressed that major factor. What we see in our practice are disparities still caused by social determinants like lower income, education, health literacy, insurance, transportation, personal finances, social support structure, housing, etc. A few things that are more obvious would be lack of communication when someone does not speak English. We see that it's very pronounced in the New Brunswick area where it's a predominantly Hispanic population. And as clinicians I feel guilty that I may not spend as much time as I do with an English-speaking patient, trying to educate them because we are trying to get by educating them about the basic facts. This is your chemotherapy. These are the most common side effects. This is what you need to tell us. There's no time

for extra information that we would otherwise give someone who is educated and has more questions. So, that is one thing that they miss out on because of not being able to communicate in the same language.

The age of diagnosis is also an important factor. People who are younger with younger children, jobs where they are not financially settled yet, as opposed to people who are older, they may not have kids or they may not have someone to lean on for support, they may be depending on their retirement income. That's another barrier that we see. And, again, where I work we have nutritionists, social workers, financial counselors, pharmacists, navigators. We have so many resources. Despite all that, we do see that it helps with some inequities but not all of them.

There is another factor of a personal bias. It's very difficult to convince someone who has no previous health literacy or education that evidence-based practice, evidence-based therapies are something that they should consider where there is so much misinformation lately. Everywhere you see social media, people talk about intravenous (IV) infusions of vitamin C and health retreats where people forego conventional therapy too. It's almost like shooting in the dark because they want to do that. They don't want to lose hair and they don't want to be nauseous, so they want to try something that appeals to them emotionally. That's one thing. And the biggest thing is the clinical trial enrollment challenge. It's very difficult to have minorities participate in clinical trials. Even now I think there is a stigma associated with the word *trials*. People think of themselves as guinea pigs. They think of most of these as experimental. The population we serve and treat is not the same as in the clinical trial. I think we are studying a group of people and not necessarily treating the same group.

Lee Schwartzberg, MD, FACP:

Let's hear from Deltra and her impression of what the major barriers are to effective care.

Deltra James:

What I see as major barriers to effective care is it's two-sided. I do see it as systemic and I see it as health care not always being easily acceptable as well as people having their personal biases, which I think it's important for those in positions to be providing medical care to be really aware of theirs and constantly educating themselves on the people that they're caring for. On the flip side of that, I think it's important for patients like myself to be challenging and educating ourselves on beliefs that we held when it comes to health care because it's very important that we are able to trust our team. And so just like any relationship, part of it is me as the patient fully believing that someone is there to help me and has my best interest in mind and challenging them when I'm feeling as if they do not.

I think it's being provided with materials that would challenge beliefs I have on things like clinical trials that may be beneficial to me, but that someone like myself may be wary of. And, again, I just think it's all about trust. And that starts with our oncologists, with our medical team, making us feel seen as a person, as an individual, so that whenever they're presenting something to us that has to do with our care, they're not just telling us “This is what you're going to do” or “This is what we always do.” It needs to feel individualized and I want to hear why you think it's the best option for me. I think that those things not happening are big barriers to effective care.

Lee Schwartzberg, MD, FACP:

I think another way of saying what Deltra was talking about is the importance of shared decision-making. And we've learned that we've moved from a paternalistic type of relationship between the providers and the patients to one where it's collaborative, and meeting the patient where they are is so important. She talked about having access to care, and one of the things you can see is quite plain here from geographical disparities, is that if you look at the population living in poverty, mostly across the south compared to the north, and then if you look at the cancer death rate, particularly in the Mississippi Delta area and Appalachia there in red, you can see that there's a close correlation between people who are living in poverty and their chance to survive their cancer. So, I'll just finish up this part and then turn it over. So here's Deltra on race and ethnicity and how other socioeconomic factors affect care.

Deltra James:

I do hear from other women how where they live or the color of their skin or their income level affects their care or their access to care. And that may seem really wild for someone to imagine. I hear people complain often about feeling like they don't have access to maybe the latest and greatest. If you don't have access to one of the larger cancer centers, maybe you're not aware of clinical trials that are happening that perhaps you'd be eligible for. And then even if you do hear about those clinical trials perhaps online, how are you going to access them? How are you going to get to them? And that's where financial barriers can come into place. And that's also a great place where oncologists, if they know the needs of their patient, can step in and provide some resources on occasion. Say someone wants to go get a second opinion but they don't have the resources to travel to do that. Well, there are some wonderful nonprofits that help people do things like that. But without that kind of support, not everyone gets to have the same kind of access. And some people don't want to burden their families, so they'd forgo treatment that is life-saving for them instead of trying to figure that out or putting that financial strain on their loved ones because their cancer treatment itself is already perhaps a financial strain.

And then of course we have people who, unless you have a team that happens to look like you, it can be really difficult because, again, the trust can be missing. You can be subjected to people's prejudice, whether they're aware of it or not. And it shows and people become aware of that if it's there. They see it in how their oncologist interacts with them. They see it when they talk with other patients receiving care from that person and they realize, "Oh, I'm not getting offered the same things," or, "I'm not even receiving possibly even the standard of care." That is a really common conversation that comes up. And I think it's something that, as I mentioned before, that's where the trust part comes in. Part of it is on the patient side and a huge part of it is on the side of our care team, our medical care team.

Hope S. Rugo, MD, FASCO:

I will say I don't know what your diversity is like where you work, Lee, and whether or not you find that the economic barriers that she was talking about play a big role. In your cancer center, do you have a lot of patients who are more challenged by cost or distance?

Lee Schwartzberg, MD, FACP:

Well, it's interesting. I mentioned earlier that I was in Memphis for many years with the largest, predominantly Black and poor city, and we had those challenges of being in urban, being in Reno for 3 years. I've been struck by

how many advanced cases I'm seeing, more than I saw at diagnoses of locally advanced or de novo metastatic cancer. Partly because there's an underserved population, a large Hispanic population, many of whom don't, as Srigowri was saying, do not speak English. We have that barrier.

Lee Schwartzberg, MD, FACP:

As Srigowri was saying, they do not speak English and we have that barrier. And also the rural population, I have a great respect for the problems that they have because we take care of all of Northern Nevada and people come from 200 miles away and they have additional barriers there. So, transportation is an issue, leaving work when they're self-employed to come, and the culture of sometimes not seeking care because of what I might call a frontier mentality or the western mentality is really is there as well. So, let's hear from Deltra again.

Deltra James:

I would like oncologists to approach their patients as if they were much more than their diagnosis, their cancer, their body. I'd like them to look at them as more than just a chart. I think it's important for them to get to know who's your family, who's the support system that you have around you. And, again, they have limited time with us, so I think maybe streamlining that with some sort of interview process, whether it's on paper or done online, I think it's important for patients to know that we have access to our oncologists. They're easily accessible between appointments. I know we have the technology to make that happen now, but for me, I think it's important for oncologists to make sure that they know their patient so that they're building trust.

Lee Schwartzberg, MD, FACP:

I think to summarize the addressing disparities is we talked about research, how critical it is. The clinical trials that are done to get most drugs approved are a failure in the sense that they don't adequately represent in the United States and people that are being treated in the community. And we've all realized that now the manufacturers, the U.S. Food and Drug Administration (FDA), the advocacy groups, all of our organizations, we're making steady progress now, although there's a long way to go in terms of getting representative clinical trials, having more of the disparate populations and trying to achieve equity, not just equality, but making sure that additional support is given to those populations so they can receive the clinical trials and we understand how they do with new drugs as well as standard of care. And then approaching the structural barriers, which are a more difficult issue.

But we have to do this as a community, as an oncology community, as a society. And we have to address the implicit and explicit biases that we have, further diversify the workforce, address in ways that we can do both internally at our own institutions as well as a society, the social determinants of health. And a lot of that is helped by patient navigation. Maybe, Hope, you could talk about how that works at UCSF and your patient navigation and how you help your patients.

Hope S. Rugo, MD, FASCO:

I was mostly the one who was going to ask. I'm not really prepared to talk about it. And I think that navigation programs really depend on the institution. We don't have patient navigators per se, but we have triage nurses and practice assistants who are helpful in managing. We have created videos to help people manage the process as well. And then it's an interesting question about navigators now because if you use an electronic health

record (EHR), people are messaging all the time. So there's a lot of communication back and forth with the clinic about what to do and when to do it, which I think is a huge improvement over what we had before for patient communication. It presents a relatively large burden on the health care practitioners. So, it's trying to balance that right now, which can be really challenging.

So, we do have our triage nurses who are phenomenal. They only do breast cancer, which is also really helpful for us so that they can, they're quite a bit more, I think, attuned to what the questions are on my way here, which took a really long time as I noticed. I said it's 2 hours earlier and a patient messaged in about when she's having her paracentesis and she doesn't want to get chemo on Monday, and I asked them to call her. So, we managed what her preferences are and what she wants to do in this way, which I think is a whole lot better than what people did before, which was leave messages on answering machines. Some programs have a navigator you can contact and they help you through the process of making appointments. I think our nurse practitioners and nurses together really fill that role for us and that's worked out better in our setting. But I think every setting is unique and so it really depends. I don't know if you have a navigator.

Lee Schwartzberg, MD, FACP:

We do.

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

We have nurse navigators. They are tumor-specific and they help patients from the point of diagnosis when they're brand new all the way to hospice.

Hope S. Rugo, MD, FASCO:

These are, I think, what we would call our triage nurses. They deal with all of the issues, they manage, and they talk to them all the time. They do the chemo teaching and they manage resources. Our social workers also help with that as well.

Lee Schwartzberg, MD, FACP:

Yes, it definitely takes a team. I do think, I agree with you, that the best part of the EHR is in fact the communication capabilities across the institution and the portal that patients can use. It's much better than it used to be. But these are complex issues and patients have a lot of things on their plate. So, having navigators helps as well. And that goes to the multidisciplinary oncology care team. Today it really does take a village to take care of cancer patients and patients should be, and typically are, assessed by a social worker and also their emotional status. We screen every patient for distress and we have an algorithm by which that we can escalate the type of care they get, including social work, including psychological support if they need it. We all have financial counselors now that help patients navigate the difficult finances of getting therapy.

We also have to pay attention to their cultural context, their ethnicity, their gender and social relationships, as Deltra said. We have a big issue with health literacy, as Srigowri talked about earlier. It's complicated even for people who are relatively sophisticated. It's brand new jargon, it's new terms, it's new concepts, and it's very, very difficult. Making sure that we have the appropriate staff to help and to bring up health literacy, particularly in those populations that may have less education or language barriers, is really important. And connecting

those patients to resources, including, as we just talked about, the navigation and support resources. So, get to know your patient. I think Deltra said that, and I think we all agree that that's our goal. I will turn this over to you, Dr. Rugo, to talk about the evolving landscape of mBC.

Hope S. Rugo, MD, FASCO:

I think that the previous session really gave you both the patient and different practice approaches to managing patients in the metastatic setting and of course translates into early-stage disease as you pointed out before. I think the idea of using the scales, which you talked about briefly – did you talk about that earlier?

Lee Schwartzberg, MD, FACP:

No.

Hope S. Rugo, MD, FASCO:

Do you use them in your clinic?

Lee Schwartzberg, MD, FACP:

We do a distress screen and a depression screen on every patient at intake and periodically.

Hope S. Rugo, MD, FASCO:

And does it automatically result in referrals?

Lee Schwartzberg, MD, FACP:

It does and depends on the level numerical score.

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

The score.

Hope S. Rugo, MD, FASCO:

And you have the same?

Lee Schwartzberg, MD, FACP:

Yes.

Hope S. Rugo, MD, FASCO:

I think that's actually an amazing thing that can be done through the EHR, these automated referrals, so that when you see the patient you have to actually click it and make it go through, and the scoring system of what patients ask when they are coming in to see you each time will help give you these scores that help with referrals. Then you don't even have to think about which referral you're making them to. The specific score

brings up a referral. That may or may not be appropriate for the patient. That's why you have to go through and decide about signing it, etc. I think that's a great new approach.

So, we're going to talk about ADCs now and change to something a little bit different. Another way of managing our patients and treating patients who have advanced disease is to try to improve outcome. We're going to hear a lot about ADCs at this meeting, both at the plenary session in the session for breast cancer on Sunday morning and then multiple other presentations, which I think will be quite interesting. I think everybody here are, I don't know if you had an idea of how many people are practicing or did you ask earlier? I know because we're starting late because of the traffic, but how many people are given ADCs? Are you treating patients? Anybody? So some people. And then other people who are involved in patient care? Yes. Okay, great. So, ADCs – we refer to them as a revolution in delivery of chemotherapy and it's a targeted delivery mechanism for chemotherapy. But there are a lot of other aspects to ADCs. The key things about these drugs are an antibody that delivers the payload to the cancer cell.

But it turns out that the antibody actually has been a relatively stagnant thing. We have a few antibodies that we've been able to capitalize on, HER2, Trop-2 largely, and then there are a lot of investigations going on with others, but the linker technology has changed tremendously. The linkers really have allowed this bystander effect where you may have the payload that can kill cells that don't express the target very much, and that can make a big difference, I think, in the efficacy. Also, we've improved the payload, not for all ADCs, but we're working on improving the payload. The issue about the payload is you want something that is highly potent in small amounts and doesn't have cumulative toxicity over time. Most of the payloads that are being given are not effective as naked drugs because you have to give enough in the circulation, you get toxicity that's not manageable.

But if you can give them in small amounts and they're delivered in a high concentration to the cancer cell, that's not the same issue. We seem to be able to give these ADCs and deliver a highly potent small amount of toxin to the cancer cell with a lot of efficacy. This idea of the bystander effect is quite intriguing because many of the ADCs have effects in the brain and we know antibodies are really big; they're not supposed to get into the brain, but in this situation there may be some degree of a bystander effect where a drug is carried into the cerebrospinal fluid even when it's not attached to the antibody because we've seen quite significant effects. As I mentioned, we have fairly stable antibodies right now that we've been using and there's a lot of interest in pushing this forward and looking at how we can capitalize on this novel mechanism of delivery of chemotherapy.

There are true Trop-2 ADCs that have been studied in breast cancer and are being studied in other cancers as well. Sacituzumab govitecan, approved for several cancers, has a drug-to-antibody ratio of eight to one, datopotamab (Dato) deruxtecan four to one. Of course the payload is different, although both of them are topoisomerase inhibitors. SN-38, the active metabolite of irinotecan, is the payload for sacituzumab, whereas for Dato it's deruxtecan, an exatecan derivative. That's the same drug that's on trastuzumab deruxtecan (T-DXd), but that ADC has a drug-to-antibody ratio of eight to one. So, these are all quite different. There are also some differences in the linker itself. They're all cleavable linkers but one is a hydrolyzable pH-sensitive linker for SN-38. The other is a tetrapeptide-based cleavable linker for DxD (exatecan derivative for ADC), and that actually determines the drug-to-antibody ratio to some degree, and also delivery of drug. So, drug-to-antibody ratio, certainly not the end-all we thought it was when these first came out. But it's not the end-all in efficacy by any means because the delivery of the toxins and their mechanisms are quite different.

Both of these Trop-2 ADCs have a bystander anti-tumor effect. As far as we can tell, Trop-2 is expressed on most tumors. In breast cancer we found more than a 95% expression. And as you know from HER2, we're not great at determining the even small amounts of expression with antibodies. I think that we do believe there's a bystander effect, but it's a little bit hard to characterize. The payload for sacituzumab has a long half-life and the payload deruxtecan has a relatively shorter systemic half-life. So, let's talk a little bit about triple-negative breast cancer. Lee, do you want to talk about it?

Lee Schwartzberg, MD, FACP:

Thank you. We're going to start with the data from sacituzumab govitecan again, and the ASCENT trial was a phase III study based on phase II studies that showed that there was efficacy in triple-negative breast cancer. As we mentioned earlier, triple-negative breast cancer remains a persistent problem in metastatic disease. In general, we have limited resources to take care of this standard chemotherapy and in the first-line setting using immunotherapy as well with pembrolizumab for patients who do express PD-L1 based on our current data.

But once you get to second line and beyond, our standard approaches have been to use single-agent chemotherapy, which has been less than spectacular at improving our patients' lives, their progression-free survival (PFS), and their overall survival (OS). This was a phase III trial comparing sacituzumab govitecan to treatment of physician's choice. That included several different chemotherapy agents as not any single one is not necessarily better than the other. Patients were eligible for this trial if they had had two or more chemotherapies. This was a heavily pre-treated group of patients, although there were some patients, and we'll see the subset analysis of those who had neoadjuvant or adjuvant therapy and one line of chemotherapy. And also, interestingly, patients with stable brain metastases were allowed in this trial.

Sacituzumab govitecan is given in a day 1 and 8 every-21-day schedule, so there are two doses every 21 days. The treatment of physician's choice was given depending on how that particular drug is given in a typical schedule. The primary endpoint was PFS. Here are the data in the brain metastasis–negative population, which was the majority of patients in ASCENT. And the ASCENT trials did demonstrate statistically and clinically significant improvement in both PFS and OS over single-agent chemotherapy in the primary study population. If you look at the left-hand curve, the Kaplan-Meier curve there, you see that the median PFS for treatment of physician’s choice standard chemotherapy was very short. Again, these patients had two, three, or four lines of prior therapy and essentially the median was less at the first time they were evaluated at 2 months after, so only 1.7 months for PFS.

However, sacituzumab govitecan improved the PFS to 5.6 months, a 61% improvement in PFS. And the study is now mature enough to look at OS in the right-hand curve. You can see that it's almost a doubling of OS from 6.7 months median in the treatment of physician’s choice to 12.1 months in the sacituzumab govitecan group, and that represents a 52% improvement. If we look at a landmark analysis at 24 months, over 22% of patients were still alive who got sacituzumab govitecan, compared to only 5% with chemotherapy. This looks at a subset of patients who were treated with two lines of therapy, one of which was in the adjuvant. So they only received one prior line of therapy. It's a smaller subgroup here, but these are patients who were also at higher risk. You can see in this subgroup population that the median progression pre-survival remained intact at about 5.7 months for sacituzumab govitecan only, 1.5 months for treatment of physician’s choice.

Here again, a 60% improvement in these more aggressive patients, but only one line of therapy and the OS continues to show a very strong doubling again of OS from 4.9 months to 10.9 months median and hazard ratio

0.51. There are ongoing trials based on this encouraging data. The drug sacituzumab govitecan was approved for triple-negative breast cancer based on the ascent. And now it's being studied in other populations, including in the first-line PD-L1–negative triple-negative breast cancer population. As I mentioned, the standard approach for most patients who are PD-L1 positive in the first-line metastatic triple-negative breast cancer is a combination of pembrolizumab and a chemotherapy regimen, much like as shown here in treatment of physician's choice. But these are for the PD-L1–negative population. So, here we're doing head-to-head, sacituzumab govitecan, ADC versus standard chemotherapy. And these patients had to be all be tested for PD-L1 and it had to be at least 6 months since they finished treatment in the curative setting.

Interestingly, anti–PD-L1 agents are allowed in the curative setting. That has become a standard for us now for triple-negative breast cancer patients in the neoadjuvant and adjuvant setting, based on data from KEYNOTE-522. This is a very important trial because for this 60% of patients or so who are PD-L1–negative, we still don't have in the first-line setting yet an approved therapy other than standard chemotherapy. And these patients will be treated for PFS.

And ASCENT-04 is essentially comparing to what we do with PD-L1 positive, sacituzumab govitecan and pembrolizumab versus chemotherapy and pembrolizumab, very similar to what I just discussed. These two trials together will give us some very valuable information, and I will pass it back to you, Hope.

Hope S. Rugo, MD, FASCO:

We'll talk a little bit more about HER2-low status when Lee talks to us about T-DXd in a little bit. But it's interesting if you look at. I think that we don't really know that we're detecting HER2-low well. This is the data that was published by Schettini et al that suggested that more patients who are HR positive or HER2-low disease defined as 1+ or 2+ without gene amplification compared to triple-negative breast cancer where about 66% were zero. And there is a group that has no expression, but we'll hear on Sunday about T-DXd in 150 patients with ultra-low disease who are not zero, but less than 1+ by American Society of Clinical Oncology (ASCO)–College of American Pathologists (CAP) criteria. I think that will be interesting. I mean, we have seen some other data we'll look at in just a moment that suggest you can have sort of continuous efficacy, but it goes down as you have less and less expression, but it doesn't go away.

So it's going to be very interesting, I think, to look at that. It brought up a lot of interest in ADCs and HR-positive disease. And, of course, the most common subset of breast cancer worldwide is patients who have HR-positive HER2-negative disease, and TROPiCS-02 evaluated sacituzumab versus treatment of physician's choice. And I have to say in all of these trials, with the exception of what we'll hear Sunday, because that was a different group, most of these patients had already received taxanes. That's why you don't see taxanes in the treatment of physician's choice. But if you're like post-taxane, we mostly give eribulin. So, about 50% in every single trial that is in the second line or greater setting, patients got eribulin. And then unlike ASCENT, which allowed any number of lines of treatment, the TROPiCS trial said you could have one but not more than four lines of chemotherapy for metastatic disease.

It is interesting because when we're thinking about ADCs, this group of patients had a median of three lines of prior chemotherapy for metastatic disease, so they're very heavily pretreated. And the primary endpoint was PFS. We saw a statistically significant improvement in PFS and OS, comparing sacituzumab in this heavily pretreated group of patients compared to treatment of physician's choice. And, notably, at 12 months, three times as many patients were free from progression, who got sacituzumab versus those who got standard

chemotherapy. You can see that at 12 months there was also a big difference in OS if you look at the number, it's more than 13% or close to 14%. I think for patients this is very meaningful. Also, there was an improvement in response, which we would expect, and there's always concern about balancing benefit versus toxicity. Here we saw an extended time to deterioration of global health status and fatigue versus treatment of physician's choice.

The only difference was with diarrhea, which is a side effect of sacituzumab, which we'll talk about later, where the quality of life was relatively similar but it wasn't better with sacituzumab when we look at individual scales. We looked at immunohistochemistry (IHC) status just because there was a lot of interest in whether or not this was before. I think we understood that HER2 IHC status when it's not HER2 positive has no impact on anything really much, and it didn't have an impact here either. There was no impact on efficacy. It was seen across whether it was IHC-0 or 1 to 2+-ish negative. This is the OS data, which also shows similar lack of impact of HER2 status.

Hope S. Rugo, MD, FASCO:

So now maybe I'll just mention DESTINY. You want to mention it?

Lee Schwartzberg, MD, FACP:

Yes, either way.

Hope S. Rugo, MD, FASCO:

We talked about HER2-low a little bit. And I think everybody's aware of DESTINY-Breast04 that was presented 2 years ago at this meeting right after the pandemic. Everybody's very excited to see a positive trial in the plenary session, T-DXd versus treatment of physician's choice, and these patients had centrally confirmed HER2-low disease. They had received a median of one line of prior chemotherapy for metastatic disease, and the endpoint was in the HR-positive HER2-low population. You can see 50% of patients received eribulin.

These are some updated data that were presented at European Society for Medical Oncology (ESMO) last year from the *New England Journal of Medicine* paper from 2022. PFS was markedly improved with T-DXd compared to treatment of physician's choice, and that was continued at the updated analysis. The PFS initially was done by blinded independent central review, so the hazard ratio was 0.51. Once they switched to the investigator review, which was the update, the hazard ratio went to 0.37, which is interesting because the investigators, generally, when they like a drug, we're waiting to call progression apparently longer than the…because this wasn't longer than the blinded independent central review.

And the HR-positive cohort is on the left for you. Then all patients, which included a small exploratory cohort of HR-negative HER2-low disease is on the right. That included just 58 patients. So, 40 got T-DXd and 18 received standard chemotherapy. And then the updated OS, very similar here. In the bottom table, the original primary analysis is broken out for the HR-negative patients. Again, overall response was also improved, as you would expect in a trial like this with, again, nice results.

I mentioned DAISY. This goes along with the HER2-low idea. You can see in the pink is IHC-0. There were 37 patients. The PFS was better if you were HER2 positive than if you were HER2-low. Then, if you were HER2-0, it was the lowest. There's definitely a continuum there, even by IHC. You can see that for the patients who had

HR-negative disease the PFS was just 2.1 months. For HR positive it was 4.5 months. I think that these numbers are so small, it's a little bit hard to know, and we'll see a lot more about this ultra-low population Sunday morning when Giuseppe Curigliano presents DESTINY-Breast06 with T-DXd and HR-positive disease in the first-line setting.

And then ASCENT-07 is an ongoing study in the first-line chemotherapy setting for HR positive, regardless of HER2 IHC, which is enrolling very nicely. It's planning for about 654 patients, again randomizing sacituzumab versus treatment of physician's choice but in the first-line setting you can use capecitabine or a taxane.

Lee Schwartzberg, MD, FACP:

I think it's really interesting that we've moved beyond this trying to ascertain 1+ versus 2+ and we'll see. And it looks like if you have better drugs that it really doesn't matter.

Hope S. Rugo, MD, FASCO:

Yes, it's really interesting. I think we'll see more. Our colleague, David Rim at Yale, has been working on trying to make a quantitative test for HER2 IHC. There's a lot of interest in looking at this, and they might have some data later this year, I think maybe at ESMO, about the impact of the quantitative assessment, looking at RNA and quantitative protein measures to see how that affects efficacy. I think this kind of data will help us a lot in the clinic moving forward. But we don't have it yet.

Lee Schwartzberg, MD, FACP:

Yes. And IHC was originally designed to separate HER2 positive, and those patients who would benefit from trastuzumab versus lower, not designed for a lower threshold. That's what Hope is talking about. Hopefully it will allow us to define that much better.

Hope S. Rugo, MD, FASCO:

And, of course, DESTINY-Breast06, I think people are aware of it being presented 7:30 in the morning on Sunday, T-DXd versus chemotherapy of physician's choice in patients. So, 850 patients, but they enrolled about 866. Of the 850 who were enrolled, 150 were designated to be ultra low, so not zero and less than 1+. It would be very interesting, there has already been a press release saying that PFS was better with T-DXd as we expected in the overall population, but also in the subset of patients with HER2 ultra-low disease. And that's the extent of the press release, as you can imagine. We'll see that later. I think this slide is really just to show you that expression of Trop-2 doesn't impact the efficacy of sacituzumab similar to expression of HER2 for T-DXd.

Do you want to speak a little bit to the guidelines?

Lee Schwartzberg, MD, FACP:

Yes. These are the updated guidelines from National Comprehensive Cancer Network (NCCN). I think they're really useful for us in the clinic because it really breaks down by this is first for triple-negative breast cancer. If you're positive for PDL1 and/or *BRCA*. All patients should be tested for *BRCA1* and *BRCA2* mutations because we have therapy for that, olaparib and talazoparib, and they're all Category 1 and preferred. We use the biomarkers, even in triple-negative, biomarkers are important, PDL1 and *BRCA1* and *BRCA2*. In the second-line

setting, sacituzumab govitecan is Category 1, preferred, based on the ASCENT data that we showed, as long as there is no germline mutation and patients had not received prior poly (ADP-ribose) polymerase. And then T-DXd is also Category 1, preferred for the second-line setting. And then beyond that it's based on other biomarkers or systemic therapy.

For HER2-negative HR-positive patients, again, these patients should be encouraged to undergo germline *BRCA1* and *BRCA2* testing because we have the same therapy. It's agnostic to whether or not they're HR positive or negative. Systemic chemotherapy has been the standard of care up until now. And in second line, based on the data you've seen, T-DXd is Category 1, preferred. If they're not a candidate for T-DXd then sacituzumab is preferred as well.

Hope S. Rugo, MD, FASCO:

We mentioned earlier that we have another kid on the block, Dato deruxtecan. We talked about the fact that you can actually give the drug every 3 weeks. Sacituzumab is given day 1 into 8, every 3 weeks. They have different dose-limiting toxicities. In dose escalations, sacituzumab was neutropenia; for Dato it was rash and stomatitis. So, of course, these drugs are now dosed in their final dosing schedule.

So Lee, tell us a little bit about TROPION-Breast01.

Lee Schwartzberg, MD, FACP:

TROPION-Breast01 is a phase III trial of Dato-DXd versus chemotherapy in the HR-positive population, very similar to what we saw in the previous trials in terms of design, one to two prior lines of chemotherapy, good performance status. The characteristics are shown there. Most of these patients had one line of prior therapy. Importantly, the vast majority of them had had a prior cyclin-dependent kinase (CDK)4/6, which is our standard, and virtually all of them had taxane or anthracycline.

And here's the PFS, again by investigator assessment here. You see there was a superiority for Dato-DXd versus treatment of physician's choice at each landmark analysis. The hazard ratio is 0.64. The time to subsequent therapy is much longer as well. This is important for patients with HR-positive disease in particular. They stayed on Dato longer than standard therapy. As you'd expect, again, the response rate was substantially higher for Dato-DXd compared to investigator's choice. We don't have the survival data yet. The study is still relatively immature. But already, there is a trend favoring Dato-DXd with a hazard ratio of 0.84. We'll await further updates which are protocol-specified.

Hope S. Rugo, MD, FASCO:

Yes, it's actually really interesting. We are now so used to seeing OS benefit with these ADCs in HER2 positive and HER2 low, triple negative, HR positive – all survival benefits from ADCs. Now the ADCs are available certainly in the United States. They're not available for everybody around the world. So, these trials are going to be impacted, we think, by the geography of where patients are enrolled and the availability for rescue with another ADC, if you have randomized to control and you have access to another ADC, or sequential ADCs, that may negate the survival benefit that we've seen. It's going to be very interesting to see what happens with subsequent therapies. We saw this with MONARCH 3, right?

Lee Schwartzberg, MD, FACP:

Right. It's a great problem to have. It's one we didn't have until recently. When we used 2 months the PFS was herald. And we've gone beyond that. Patients are doing better. As Hope mentioned, there are some specific treatment-related AEs that occur with Dato-DXd. There is, in particular, the toxicity of dry eye, which is mostly low grade, not a big problem. There is nausea and mainly stomatitis, which is a somewhat less common toxicity for some of the other drugs. And the stomatitis does occur, mostly low grade, in about half the patients in this trial. And then the typical fatigue. And we do see some alopecia with this drug as well. So, mucositis and stomatitis are things that we have to pay attention to. I will bring your attention to the fact though that there was no prophylaxis in this trial…

Hope S. Rugo, MD, FASCO:

There was.

Lee Schwartzberg, MD, FACP:

...designated for stomatitis, initially anyway.

Hope S. Rugo, MD, FASCO:

We told everybody to use steroid mouthwash.

Lee Schwartzberg, MD, FACP:

Right.

Hope S. Rugo, MD, FASCO:

TROPION-Breast01. But the problem is it's not available around the world, so they didn't provide the prophylaxis.

Lee Schwartzberg, MD, FACP:

Right.

Hope S. Rugo, MD, FASCO:

But a lot of people used it in the United States. I think it did contribute to a lower rate of stomatitis, but we can't even track who used it or who didn't. In many countries where it's not available, there isn't a compounding, where you could take IV dexamethasone and dilute it, but you have to have a compounding pharmacy. People would take the dexamethasone pills and crush them. And who knows how that works. So, it is still an ongoing question that's going to be answered by clinical trials.

Lee Schwartzberg, MD, FACP:

And one more thing about this drug, it's deruxtecan. So, there is a little bit of interstitial lung disease (ILD), but it was low grade and the percentages were lower than we saw with T-DXd, for example, at least in this trial.

Hope S. Rugo, MD, FASCO:

Yes, really important. And the dry eye doesn't seem to be a big issue either. We do see some grade 3 stomatitis, and we'll present on Monday data from Dato-DXd plus durvalumab from the I-SPY2 trial where we just gave four doses as an initial block of treatment. We did see stomatitis, but, again, mostly it was lower grade. But there are a few people who get high grade, grade three, and we don't really know why. They respond to dose reduction. So, it's an interesting question. I'm sure there are some pharmacogenomics, which we seem to have figured out with sacituzumab a little, as we'll talk about in a moment, but not here yet. And then of course TROPION-Breast02 and triple-negative disease in the first-line setting in patients who have PDL1-negative disease, or in countries where PDL1-targeted agents are not available.

Lee Schwartzberg, MD, FACP:

We have a new challenge now because we now have multiple ADCs in the clinic, and we don't have a lot of data yet on sequencing. We don't know if we can see responses, if the payload is similar, for these. They're not identical, but they're both topoisomerase I inhibitors. What are the mechanisms of resistance to ADCs? This is a very important area of research right now in terms of just understanding how starting with one and going to a second agent. We have T-DXd. We have SG. And we'll soon, presumably, have Dato-DXd, which is not yet approved. What is the best strategy? These are very important issues that remain to be elucidated.

Hope S. Rugo, MD, FASCO:

In our consortium, we have a trial called TRADE-DXd. We also have a registry trial. This one is looking at T-DXd and Dato-DXd in sequencing for both ER-positive and ER-negative disease. It will be interesting to see whether this is rethought based on the data from DB-06. We'll wait and see whether we'll include patients who aren't so classically HER2 low. But that trial is starting off this year, in the next few months I think. Then there's a registry study also looking at sacituzumab and T-DXd, run by my colleague Laura Harbert, also through our consortium.

We're going to talk now a little bit more about AEs. I think we all agree that this is a really exciting area of treatment. But obviously we want to manage AEs up front and be aware of them. I'll turn the podium over to you Srigowri.

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

Talking about the safety profile for sacituzumab govitecan, the two more prominent side effects, across all studies, have been neutropenia and diarrhea. They both have black box warnings for breast cancer and they also have dose-limiting toxicities, like we mentioned.

In the management of neutropenia with sacituzumab and breast cancer, primary prophylaxis with the granulocyte colony-stimulating factor was not used in clinical trials. The plan was to do a complete blood count on days 1 and 8. The guidelines dictated that if an absolute neutrophil count (ANC) was less than 1,500 on day 1 of any cycle, or less than 1,000 on day 8, with or without neutropenic fever, the plan is to hold it and resume when recovered. For severe neutropenia, dose reductions were encouraged.

Hope S. Rugo, MD, FASCO:

Before you move on from neutropenia, we're presenting in a poster tomorrow a pooled analysis of over 1,000 patients with toxicity with sacituzumab and in a variety of different diseases and studies. It's interesting, people who got prophylactic growth factors, remember these patients had a lot of prior treatments. The data that exists are not in patients treated in the first-line metastatic setting or in the post-neoadjuvant setting where we have trials now. But if they got growth factors prophylactically, less than 10% required any hold or dose reduction. So, clearly, growth factors play a really big role in managing the neutropenia proactively for these patients.

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

Have either of you done an every-2-week dosing?

Hope S. Rugo, MD, FASCO:

It's an interesting question because we don't have the data on it. But I have treated an 82-year-old with triple-negative disease with every-other-week dosing, full dose. She stayed on for 8 months. And she definitely could not have tolerated day 1 or day 8. I think it's an interesting idea, maybe for the gastrointestinal toxicities also.

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

Yes.

Lee Schwartzberg, MD, FACP:

And I would say in the community, in doing some focus groups over the last few months, it's growing in use, even without data because of that trouble with day 8. When you hold, what do you do? Do you start the next week?

Hope S. Rugo, MD, FASCO:

You have to reschedule everything.

Lee Schwartzberg, MD, FACP:

You have to reschedule everything. So it may be an interesting approach.

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

At our place, we have a patient who is at the 2-year mark with the every-2-week dosing. And a little bit of nursing intervention here. We try to educate patients that neutropenia is asymptomatic but it does increase the susceptibility to infections. The one thing I always make sure is that all patients have thermometers. You'd be surprised how many people don't have thermometers at home. And they have to promptly notify a fever of 100.4, cough, sore throat, little things that people don't really associate with neutropenia. So that will be my nursing interventions section.

The management of diarrhea. I've also seen, again, based on my nursing experience, that the classification, or grading, is very important. If someone has a baseline of bowel movements at three per day, if they're having five

bowel movements a day, it sounds like a lot, but really it's still grade 1. So, I think it's assessing is it acute diarrhea, is it delayed diarrhea, is it combined with abdominal cramping? Is there may be a chance that they have an infection like *Clostridioides difficile*? All of these are considerations. Usually we do go for the high-dose loperamide, which is 4 milligrams, two tablets of 2 milligrams, first dose. And then one tablet of 2 milligrams, every subsequent loose stool. We do it typically for a total of eight doses, and octreotide may be considered for more severe cases.

Hope S. Rugo, MD, FASCO:

We have a patient, too, and we'll talk about pharmacogenomics in a moment, but she's an intermediate metabolizer and had a lot of diarrhea but fabulous response with terrible resistant triple-negative disease, so we kept trying all these things. If you don't have the immediate diarrhea, which I have never seen, and it's this delayed diarrhea, giving atropine with your treatment isn't going to help at all, right? And I haven't given oral atropine, but we put her on octreotide. It was actually a recommendation by my advanced practice provider (APP). It's a very painful injection, but if you ice it beforehand that seems to work pretty well. It completely controlled her diarrhea, completely controlled it, and it's the only thing that works. She took all the oral drugs. It is something I feel more encouraged about.

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

And for severe diarrhea, we do consider hospital admission and a little bit more aggressive treatment. We try to hold treatment until symptoms resolve to grade one and then resume with a level one dose reduction. This is if we have a nutrition consult. That definitely helps. And also, encouraging the patients to report anything right away instead of sitting on it and trying to see if it gets better without any intervention. Oral hydration, and if not possible, we bring them in for IV hydration.

We'll talk a little bit about nausea and alopecia. At our facility, we do the triple combination before, which is a 5-HT3 antagonist, a dexamethasone, or plus or minus NK-1 antagonist. So, we have not really seen a lot of nausea and vomiting in these patients. And we do discharge with a home supply of either ondansetron or Compazine. I'm not sure if you see a lot of nausea in this patient population?

Hope S. Rugo, MD, FASCO:

No, I really haven't. We give our triplet premeds and we taper off in some of the patients because they just don't get that much nausea and they don't get any delayed nausea, so that's really good. It's not a major toxicity for sacituzumab for most patients.

Lee Schwartzberg, MD, FACP:

Yes, I would agree.

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

A little bit about alopecia. I know that for women who've been through this before, or maybe they have a little bit of regrowth, and then to be back on sacituzumab, which almost 50% will have prolonged alopecia, we do suggest a wig beforehand. For some patients whose loss of eyebrows is especially distressing, we recommend

microblading. When done safely, that's pretty effective. We really do not use scalp cooling. Other common sense kind of advice would be avoiding heavy eye makeup. You always use a sunscreen, maybe baby products, which usually don't have a lot of harsh chemicals, mild shampoo, and moisturizing.

Lee Schwartzberg, MD, FACP:

Have you used Latisse for eyelashes?

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

Not really. In worst cases, we have sent them for a dermatology consult, but Latisse never came up.

Hope S. Rugo, MD, FASCO:

We give Latisse all the time.

Lee Schwartzberg, MD, FACP:

I've used it fairly often in early-stage cancer.

Hope S. Rugo, MD, FASCO:

Yes, I think it's better for faster recovery than possibly preventing hair loss of eyelashes hasn't really been studied there. But for recovery, it's really good. And a fair number of our patients use scalp cooling. We don't have the data on it. Scalp cooling is a funny thing. You have to have a lot of experience in the capping et cetera. We don't really know how long to leave it on. But we've had some people who were successful in keeping their hair. It's much harder with sacituzumab govitecan than with, say T-DXd, where hair loss is variable. And if you use a cold cap, it completely eliminates the hair loss in our experience, in any case.

We have a few questions that we'll get to in just a moment. This slide talks about the polymorphisms that I was talking about earlier. UGT1A1 is a polymorphism that affects enzymatic function. People treated for colon cancer are given irinotecan. It's a classic measurement to see whether or not you're going to get too much toxicity. We looked at this because SN-38 is the drug that needs to be metabolized by UGT1A1. We looked at the most common phenotypes. There are many others, and you can see about 13% in ASCENT, and 9% in TROPiCS-02, or *28 homozygous. In that group now, it's about 10% in 1,000 patients, that will present tomorrow morning who were *28 homozygous. These patients have more diarrhea, in particular, and a little more neutropenia. We're pretty good at managing neutropenia, so you might not notice that as much. It's the diarrhea that's really an issue.

And then I have my one patient. If you look at the *1, *28 heterozygotes, the diarrhea rate does not look like it's increased much. But if you look at TROPiCS-02, it's double that of *1. It's just there aren't very many patients. So, my experience is that it was associated with more diarrhea in our patient and dose reduction in octreotide were effective. But 40% of patients are heterozygous. There's also, not a lot of data, but this is one paper that's looking at racial and ethnic heterogeneity. There are many other poor metabolizing phenotypes that are not that common in the largely Caucasian population that's been studied. So, here you can see that there are a fair number of poor metabolizers around the world and that they vary a lot based on ethnicity, albeit with small

numbers. There's a study being proposed to the alliance by my colleagues, trying to look at this in a larger population of patients and then dosing based on the polymorphism, which I think would be really fascinating.

Lee Schwartzberg, MD, FACP:

I think in general pharmacogenomics have been underutilized in oncology.

Hope S. Rugo, MD, FASCO:

Absolutely, because they're so complicated.

Lee Schwartzberg, MD, FACP:

They're very complicated. But even for irinotecan, it's in the label, and it's usually ignored.

Hope S. Rugo, MD, FASCO:

Yes. We have just a little bit of time to talk about the toxicity of T-DXd.

Lee Schwartzberg, MD, FACP:

Sure. T-DXd does have a black box warning for ILD, pneumonitis. The immunologic toxicity is common, neutropenia as we talked about, and the other, fatigue, alopecia about 40% of patients, and nausea and vomiting was a problem initially with T-DXd, but it is now recognized by NCCN as a highly hematogenic regimen, and using a triplet or quadruplet as per the NCCN guidelines gets rid of most of the nausea and vomiting associated with it. You have constipation, diarrhea, as we just talked about.

The ILD is something to spend a bit of time on. We know that ILD does occur. It's around 12% to 15% across all indications if you lump at the dosing that's used, the 5.4 mg/kg, most of them low grade but occasionally fatal. So, it has to be addressed. It has to be thought about in any patient who's getting T-DXd. In grade 1 asymptomatic ILD, hold the drug and observe or treat with steroids. Most people are treating with steroids grade 2 or higher. Treat with steroids and discontinue. But what to do with grade 1? Hope, do you want to address that?

Hope S. Rugo, MD, FASCO:

We looked at the incidence of patients who had grade 1 ILD recovered and then were re-treated with T-DXd. Was that safe and could you retreat, because that's the recommendation? It includes DB-04, but also gastric cancer and lung cancer patients, as well as the original umbrella trial. It was really interesting because we found that most people were able to re-treat at the same dose. The median time to re-treatment was about a month, which wasn't bad. A small number of patients had a second ILD. There was no mortality from ILD in any of these patients, which was really encouraging. And the patients, regardless of whether they had a second ILD or not, a third of the patients were re-treated for more than 6 months, and 18% were re-treated for more than 12 months. Clearly this is a huge benefit for patients to be able to re-treat them if they've recovered from grade 1 ILD.

And overall we could re-treat about 70% of patients without a dose reduction. I have reduced one patient who had recurrent, had an ILD-2 event, and she was able to stay on for another 8 months with a dose reduction

without recurrent ILD. I'm a big treater with steroids though for grade 1 ILD to speed up recovery, which I think may help. It's hard to know.

Neutropenia, interestingly about T-DXd and the same is true for Dato-DXd, there's just not a lot of bone marrow suppression, but we see other types of toxicities. And here are the ILD instructions that Lee went through with you in detail. In terms of nausea?

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

Yes, we give a triplet therapy and it's usually effective.

Hope S. Rugo, MD, FASCO:

It is really effective. The one thing about T-DXd that's interesting is this delayed nausea. We use a lot of olanzapine for that, which can help a lot because there are people who are nauseated out to 10 days, etc.

Lee Schwartzberg, MD, FACP:

Definitely seeing longer nausea and vomiting after multiple regimens, and olanzapine is a great drug for them.

Hope S. Rugo, MD, FASCO:

We started at only 2.5 milligrams though, and sometimes give half that.

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

Yes, 5 is extremely sedating.

Hope S. Rugo, MD, FASCO:

People get sleepy. I just wanted to bring up a few of the questions before we get into the case study. One question was "In my rural area, access to care is challenging, distance and financial. Is there anything we can do, you know resources, to improve access?" Because dealing with a population you come from far away, having done some rotation in federal health planning in Nevada in 1979, I think. It was a really far drive.

Lee Schwartzberg, MD, FACP:

Yes, I know. And we have people who don't have a hospital that's fully equipped within 100 miles and it's difficult. I think one strategy that can work is a hub-and-spoke type of model, where you have good communication with the primary care practitioners or have a trained APP in particular who is very good at managing toxicity, as most of them are, and can communicate with the oncologist. And also one of the good things about the pandemic is the ability to do virtual and telemedicine. We are doing that. We do that with Winnemucca and we can actually do cardiac evaluations and have the patients at the hospital. It's almost as good, not quite as good, as having them in person, but it definitely makes a difference.

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

We actually have a mobile screening unit led by an APP.

Lee Schwartzberg, MD, FACP:

Oh, that's wonderful.

Srigowri Kota, MSN, BA, APN, AGNP-C, AOCNP:

Yes. Going into the community.

Hope S. Rugo, MD, FASCO:

Screening is great. I think the care of the metastatic patients can be quite complicated though. I do think telemedicine has made a really big difference in that. And the other thing is our communication. We talk to physicians in rural communities, and I talk to people around the world all the time, about managing various strategies. Having a group collaboration makes a really big difference. And there's actually this international collaboration that one of our faculty, Sam Brunfield, developed and there's an educational manuscript on this. It's a community of practice, they call it. The whole idea is for international education and educational tools to help. I think that's another thing that can help people who are practitioners, who are practicing in quite rural communities. There's also a question about why ADCs will work when there's little to no antigen expression in the tumor. Why should they work? I mean, why should we all be checking for HER2-zero and Trop-2-zero?

Lee Schwartzberg, MD, FACP:

That's a great question. I don't think we know enough about it yet. I mean, HER2 is expressed, to my knowledge anyway, in every breast cancer cell. There are multiple, it's just that it's tenfold to a hundredfold higher in a HER2 positive. So, what we don't know is the lower limit of antigen expression and with the bystander effect you may not need a lot of cells in a cluster to get the effect, which is a clinical effect. But I think there's much to be learned there. Trop-2 we didn't mention before, it's not a direct immunologic effect and it's not blocking a signaling mechanism, at least directly. It's really there as an antigen and a target for the antibody. So, it may be that very low levels are all we need if we have effective drugs.

Hope S. Rugo, MD, FASCO:

I think the same is true for Trop-2. Looking at Trop-2 expression, we really couldn't see differences even in that heavily pretreated population in ASCENT in Trop-2, so we do not recommend testing. And we don't, as you know from the HER2 controversy, we don't even really have great antibodies for looking for very low levels of expression, which is probably enough for these drugs to work reasonably well. There's another question about T-DXd. We talked about ILD. Do you routinely do high-resolution computed tomography (CT) scans and how frequently?

Lee Schwartzberg, MD, FACP:

I think that you have to pay attention. Many people will scan every 8 weeks in the first few months. One of the problems with T-DXd though, it's unpredictable as to when the ILD will occur and it can be late. In fact, I think the median was about 6 months in most of the trials. You have to pay attention, high index of suspicion, try to find it when it is asymptomatic. High-resolution CTs at periodic intervals, even if you're not necessarily scanning for response that often, at least at the beginning I think makes a lot of sense. Is that what you do?

Hope S. Rugo, MD, FASCO:

We do. We make sure we have high-resolution CT and not a positron emission tomography (PET) with a fused CT. I don't think it's as good for picking up the early ground-glass opacities, which is what you're looking for. It can be very complicated, a patient with asthma or viral infection, etc. But we generally will take it as truth. Okay, ground-glass opacities, were going to hold a dose and whether you use steroids or not, if you really suspect it's due to a viral infection, one of my patients recently, then I'll hold off. But otherwise I give a 0.5 mg/kg of steroid. There was a study done published in ESMO open, looking at the risk factors for ILD, but that was when the higher doses were being given as well. Higher dose of course increases your risk. But, interestingly, renal insufficiency did and being more heavily pretreated.

If you have a patient with renal insufficiency, in that patient population or elderly heavily pretreated, I usually get my first high-resolution CT after two doses, so at about 6 weeks, the day before they come in for their third dose. For other patients I do it at 9 weeks, just shy, as you just mentioned, 8 weeks. And then we continue doing that for most of the first year. It depends on the patients doing; 87% to 88% of cases occurred in the first year, but there are sometimes late cases and one of those cases was fatal. So I think we have to be cautious. You do not want to pick this up when people are symptomatic for the first time, if you can avoid it. There's clearly some individual susceptibility because there are patients who develop symptoms right away, first cycle, and those patients of course have to go off. And there are a lot of people interested in testing re-treatment with symptomatic ILD, but we can't do that in clinical practice right now. There's also a question about why do you think switching might work? Do you need to know the mechanism of resistance before you switch?

Lee Schwartzberg, MD, FACP:

Well, I don't think we know the mechanism in a specific patient of resistance yet. So, I think the trials that Hope outlined about switching are going to be really important because that will tell us clinically if there's partial resistance or total resistance, if the payload is the same or if the antibody is the same. I think we have to answer those clinically while our translational work is based on trying to figure out the mechanisms in general.

Hope S. Rugo, MD, FASCO:

Yes, I think it's really interesting. There was a fascinating paper from a Leif Ellison's group at Massachusetts General, where they looked at a patient who received sacituzumab, and when she died they were able to do fresh autopsy and they found that there were both Trop-2 and Topo-1 mutations in different organs. So, there were different mutations, tumor in different organs, in one patient. And then one patient had Trop-2 mutation, one patient had Topo-1 mutation, and so you don't know. That's one of the reasons right now that it's really hard to test and this sequencing is going to be important to try and understand whether or not we can predict who's going to benefit from sequence therapy. But I can tell you I've had a patient who didn't respond well to sacituzumab. He responded to T-DXd and the exact reverse. No response to T-DXd and response to sacituzumab. So, we need to understand this moving forward. We just don't yet. It's a really a great question that somebody asked.

Lee Schwartzberg, MD, FACP:

My anecdotal experience is the same. I've seen responses in both directions.

Hope S. Rugo, MD, FASCO:

Yes, really, and we wouldn't have expected to.

Lee Schwartzberg, MD, FACP:

It's fascinating.

Hope S. Rugo, MD, FASCO:

Yes, it's really interesting. And if you had triple-negative breast cancer with HER2 low, what would be your first choice of ADC?

Lee Schwartzberg, MD, FACP:

My first choice would be sacituzumab govitecan, based on the data. We have a large phase III trial and good OS there, and I think we need some more data in triple negative with small populations, DB-04. So, sacituzumab govitecan is my first choice there.

Hope S. Rugo, MD, FASCO:

I usually go with sacituzumab govitecan first as well. I'm guessing there will be a lot of real-world data over time and we'll figure that out. If you had a specific reason not to give sacituzumab govitecan or you can switch because of toxicity either way, that's really helpful. But I generally will use sacituzumab govitecan in a triple-negative patient first. And then a complicated and difficult question. If Dato-DXd were approved, when Dato-DXd is approved, what would be the advantages or disadvantages compared to sacituzumab govitecan?

Lee Schwartzberg, MD, FACP:

We don't know the answer to that question yet. Again, the sequencing data will be important. The payload's different, remember, the DXd is a very potent payload. So, it really goes back to what you were talking about. Is it a payload resistance or is it an antibody target resistance? We don't know in an individual patient.

S. Rugo, MD, FASCO:

We don't, and I think the issue is that for individual patients there may be one or more that are better. I mean some of it has to do with frequency of dosing day 1 and day 8 versus day 1 every 3 weeks. Some of it will have to do with toxicity profiles as we understand more and look at these drugs over time. And the additional data that will come out from the drugs I think will also impact which drugs are being given in which situation.

Lee Schwartzberg, MD, FACP:

Yes, I would say initially it will be based on toxicity and based on prior experience for individual patients since we don't have the efficacy data. But I think we're pretty good at managing, figuring out which patients to treat based on their prior toxicity, and to favor one drug or another based on its AE profile.

Hope S. Rugo, MD, FASCO:

I agree. And it's interesting, I don't know what the hair loss will be, but in our hands in the I-SPY population, we saw a lot of alopecia with Dato, more than T-DXd. So, I don't know. Other people have had different experiences. Do you want to very quickly, we're over time, but I thought maybe we just very quickly go through the case just so they do those questions.

Lee Schwartzberg, MD, FACP:

Sure. I'll go through it very quickly. Stage 3 breast cancer, received neoadjuvant therapy, had residual disease and node positivity, and you got additional capecitabine.

Hope S. Rugo, MD, FASCO:

Which we heard today doesn't work in basal-like disease. Just in case you missed the mini-orals.

Lee Schwartzberg, MD, FACP:

Oh yes, I did. Thank you. She developed metastatic disease and she got pembrolizumab, gemcitabine, and carboplatin and then progressed. So, we're up to second line in a PD-L1–positive patient and she receives sacituzumab, does well with the first two cycles, and then develops acute cramping and diarrhea on cycle 3 during the infusion and then worsening diarrhea later. What's the most appropriate next step for managing the cramping and diarrhea that occurs during the sacituzumab govitecan administration? Continue and you can use your iPads, I believe, for this. Continue the infusion, it's expected, stop the infusion, it may be hypersensitivity, slow the infusion rate, or administer atropine? Okay, the answer is to administer atropine. This is a rare but acute cholinergic effect and can be abrogated by using the atropine. Okay, most people voted for that. Great.

And then she develops in cycle 5 a low ANC of 1,100. That's on day 1. What do you do with an ANC of 1,100 on day 1, based on the label? Continue and give pegfilgrastim, hold it until the ANC recovers to greater than 1,500, continue to reduce the dose level, or continue without reducing the dose level? As per the label, it's hold sacituzumab govitecan until the ANC recovers to 1,500.

Hope S. Rugo, MD, FASCO:

Do you do that?

Lee Schwartzberg, MD, FACP:

Not typically.

Hope S. Rugo, MD, FASCO:

Never.

Lee Schwartzberg, MD, FACP:

And particularly at cycle 5, right. And in day 8 it's not infrequent to see ANCs of 850, 900, and we tend to go on and give growth factor.

Hope S. Rugo, MD, FASCO:

We've actually been really happy with using pegfilgrastim after day 8. And then sometimes you don't need to give any growth factor after day 1. It works really well for patients and they feel better.

Lee Schwartzberg, MD, FACP:

That has become almost a standard for us.

Hope S. Rugo, MD, FASCO:

The pegfilgrastim.

Lee Schwartzberg, MD, FACP:

Yes, pegfilgrastim after day 8. Okay, quickly. The second patient is a 65-year-old, de novo metastatic breast cancer to bone, ER positive, HER2 negative, got palbociclib, anastrozole, everolimus, fulvestrant, and capecitabine, so two lines of endocrine and one chemotherapy, now has progression and she begins T-DXd for HER2-low progressive disease. She receives triplet premedication for nausea and in two cycles develops fatigue, dyspnea, and cough. A high-resolution CT scan shows patchy interstitial infiltrates in both upper lobes with a low oxygen saturation. What should you do? Continue without modification, discontinue T-DXd, start oxygen console pulmonary and prednisone 1-2 mg/kg, or hold it, start all those other measures, and if it resolves in greater than 28 days reduce one dose, hold it, do the other measures, and if it should be in less than 28 days, reduce one dose level? Symptomatic patient with infiltrates and discontinue is the correct answer here. This is a grade 2 ILD.

Most people said to resolve in less than or greater than 28 days. So, just a subtlety. If grade 2, the label says to discontinue the patient, which gets to Dr. Rugo's point about very carefully monitoring these patients. You want to detect grade 1 if possible because that can be treated and the drug can be restarted with grade 2, that is any symptomatic patient, start steroids, other measures. And at least, per the label, the drug should be discontinued.

Hope S. Rugo, MD, FASCO:

I think that it’s really important you start the steroids. This patient we would admit because they're hypoxic, and it’s so very hard to get oxygen delivered on the same day. And I think you want to give steroids and make sure that you intervene as much as possible. It's interesting there are some patients who don't recover quickly with the steroids, although I haven't had that experience and they've now been given more immunosuppressive therapy with pulmonologists who specialize in pneumonitis. But we don't have data on the efficacy yet, although I've heard of a patient who was treated, one of my colleagues' patients, who got better but stayed on the immunosuppressive agent for some time.

Lee Schwartzberg, MD, FACP:

I think getting a pulmonologist involved is important. Sometimes doing transbronchial biopsy will help. Sometimes it is confusing. It could be viral, could be cancer with lymphogenic spread. There are multiple

etiologies, so keep everything in mind. But it is a diagnosis of exclusion for the most part. It's the most common diagnosis if you have those infiltrates.

Hope S. Rugo, MD, FASCO:

So, we want to really thank you guys for being here and sticking it out with us because we started late because of the horrible traffic, which is really unequaled, including when Taylor Swift was here. I've never seen traffic like that. We hope that you've enjoyed this session, which had a unique combination of different areas, including trying to manage what the patient wants and the information we can provide to patients, improving access and information. We want to know the patient as a person as much as possible and understand unique needs. We have shared with you the most recent clinical trial data until Sunday, regarding ADCs and the care of your patients with HER2-negative metastatic disease. And then EHRs are really helpful for us. We've talked about managing AEs with a lot of experience from our group here, which also hopefully you felt was helpful and you certainly answered the questions really well. That was good. With that, thank you very much for your participation. We also answered the questions that were put on the iPads, which we really appreciate as well, and hope to see you during the rest of the meeting.

Lee Schwartzberg, MD, FACP:

Thank you very much.

