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Optimal Sequencing of ADCs in Endocrine Refractory HR+/HER2- Metastatic Breast Cancer

Announcer:
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CHAPTER 1

Dr. Jhaveri:
Welcome to this case-based educational series on sequencing antibody-drug conjugates, or ADC therapies, in endocrine refractory hormone receptor-positive, HER2-negative metastatic breast cancer. In this first chapter we'll explore the challenges of endocrine resistance.

This is CME on ReachMD and I'm Dr. Komal Jhaveri. And joining me is Dr. Javier Cortes.

Dr. Cortes:
Hi, Komal.

Dr. Jhaveri:
Let's start with a case. We have a 54-year-old woman with a history of de novo metastatic breast cancer. ER 90%, PR 0%, HER2 1 plus by immunohistochemistry, which is involving bones, lungs, and liver. Her disease has progressed on letrozole with ribociclib, exemestane with everolimus, capecitabine, and most recently on paclitaxel. She has a good functional status and normal organ function.

Dr. Cortes, I was wondering if you could talk about the challenges in determining the next steps when patients have failed endocrine-based combinations and are now on their chemotherapy journey. And then, when we star the chemotherapies, what more can we do?

Dr. Cortes:
So, thanks, Komal. I think that's a very important question for the clinical practice. I think that we have to try to understand what the mechanism of endocrine resistance might be. And although it is true that in many places, unfortunately, we are unable to get a liquid biopsy or a solid biopsy to try to understand different mechanisms, for example, limitations in the estrogen receptor gene 1, or PIK3CA or whatever. I think that sometimes we might understand which the mechanism of resistance might be depending on the time the patients receive CDK4/6 inhibitor-based therapy. For example, we note today that depending on the duration of CDK4/6 inhibitors in the first-line setting, we might understand which mechanism of resistance were involved, just very briefly. About 20 to 35% of patients experience progressive disease during the first year of CDK 4/6 inhibitors.

And maybe the PIK3CA mutations, the RAF mutations, or alterations in different signaling pathways may be involved there. And the other way around, when this is higher or longer than a year, maybe the estrogen receptor G1 mutations might appear. So, depending on this, we might decide that we continue the endocrine-based therapy plus different targeted agents alone, or we should discuss the role

of chemotherapy to these patients.

Dr. Jhaveri:
Yeah. Does the disease burden really have an impact on your treatment decision?

Dr. Cortes:
Well, that's a very good question. I think that it might help us, but not independently. So, for example, if you have a patient for more than 3, 4 years under palbociclib, ribociclib, abemaciclib, whatever, and they have zero metastases, maybe we could consider continuing with endocrine therapy and the other way around. If the tumor progression is very quickly, maybe, even if the tumor burden is lower, maybe I would consider starting with the chemotherapy or with any other agents.

Dr. Jhaveri:
Thank you so much for that. And maybe, you know, just so that we can think about this even further, you very well summarized that if you have an ESL 1 mutation, you have another therapy, you have therapies you know, specifically targeting PIK3CA mutations. What about patients whose tumors don't harbor any mutations? How do you approach those and what kind of therapies do you offer in that instance?

Dr. Cortes:
Well, I think that we have beautiful data with everolimus plus exemestane, or maybe fulvestrant as well, and tamoxifen. We have three randomized trials. One of them I run my Phase 3 or 2. And these are the benefit of everolimus is in both PIK3CA mutant and non-PIK3CA mutant tumors. So, I think that I would consider, but again, depending on different clinical aspect, the duration of CDK, the amount of disease. But that's something that I would consider.

For me, in my opinion, single agent endocrine therapy is something that could be considered, but for a very minimal amount of patients.

Dr. Jhaveri:
I agree with you. I think the data from the EMERALD trial with elacestrant, you know, certainly was exciting for patients with ESR1 mutations, but I think the excitement is more, especially in those cohorts of patients that stayed on their first-line therapy for a longer period of time where single-agent endocrine therapy can really give you that prolonged duration of benefit. Otherwise, the four month's progression-free survival is not necessarily that exciting.

Along those lines, what are your thoughts about CDK 4/6 inhibitor use beyond CDK 4/6 inhibitor progression?

Dr. Cortes:
Well, we have today three randomized Phase 2 studies and one of them was positive, which is the MAINTAIN, I don't know if the name is the best one because, really for the 90-plus percent of patients they received palbociclib before and changed into ribociclib. There was a positive study. So, maybe for selective patients that's something that we could consider.

We have two other trials. PACE and PALMIRA. In the great majority of patients received palbociclib and continued with palbociclib. And in PALMIRA, for second-line palbociclib-after-palbociclib, we did not observe any benefit of continuing palbociclib. We are awaiting a randomized Phase 3 study with abemaciclib in patients who previously received palbociclib or ribociclib. So, depending on this data, I think that this is something that we will consider more and more in the future.

Dr. Jhaveri:
Thank you so much. I think, you know, we have many of these therapies. We're still figuring out the most optimal way of sequencing them. But needless to say, endocrine resistance, you know, we try and target with these therapies, but then, eventually deal with endocrine refractoriness where we then switch over to single-agent sequential chemotherapy. And then once we start doing that, we now have antibody-drug conjugates that are already approved. So, maybe a brief comment on what do you think about the role of antibody-drug conjugates in this setting for hormone receptor positive breast cancer?

Dr. Cortes:
Well, I think that is very good news to see that these drugs have shown an improvement, not only in progression-free survival, but also in overall survival in patients who were previously treated with chemotherapy. And we have here two important clinical trials, DESTINY-Breast04. Basically, it explored the role of trastuzumab deruxtecan, an antibody-drug conjugate against HER2, with Topo1 inhibitor, the payload. This drug was explored in second, third-line, and the trial was clearly positive for both, as I said before, PFS and survival.

Now, we have a second study, TROPiCS-02, which explored another antibody-drug conjugate, in this case, an anti-Trop-2, also Topo1 inhibitor as the payload. And sacituzumab govitecan, and this drug was explored in the third-line or beyond against chemotherapy, also showing a nice improvement overall survival. And what we can discuss is maybe one of the trials, which was conducted in second-line,

the other in third-line or beyond. Different patient populFor thoseations. Very difficult to make comparisons among these two trials. But both of them beautiful results in terms of overall survival.

Dr. Jhaveri:
Yeah. That is such exciting news for our patients because I think, prior to having these antibody-drug conjugates, I think there was just one clinical trial, actually led by you. the EMBRACE trial where we saw overall survival for eribulin, and that was 13 months with eribulin for third-line patients. But this was, you know, predating the CDK 4/6 inhibitors era. So, essentially, after we've had the introduction of CDK 4/6 inhibitors, we've never been able to show an overall survival benefit with systemic chemotherapy or antibody-drug conjugates. And now that we have two of these drugs that really cause an overall survival benefit as well, has been very, very exciting to have as an option for our patients with hormone receptor-positive disease.

Dr. Cortes:
That's totally correct, Komal. And indeed, in the TROPiCS-02 it was a requirement to have received CDK 4/6 inhibitors before. So, we can formally say that the CDK, trastuzumab deruxtecan improved survival with chemotherapy in a great majority of patients also received CDK in DESTINY-Breast04. So, I think that we can say something very similar here in the DESTINY-Breast04.

Dr. Jhaveri:
Yeah, absolutely. I think, you know, we will talk a lot more about exactly what patient population we think about when we think about DESTINY-Breast04 or TROPICS-02. How do we think about these drugs. But I think the point that you know, the overall survival that we have seen including with TROPICS-02 where patients were so pretreated and 98% had received prior CDK 4/6 inhibitors. It's rather impressive to at least have, and now talk to our patients about where we can say very comfortably that not only do we see at least a 5-year overall survival with first-line CDK 4/6 inhibitors, but even when they are pre-treated and are now getting antibody-drug conjugates, we're seeing overall survival benefits. So, certainly a good time to be. Certainly, more work needs to be done, but at least we're better off than what we were a few years ago when we didn't have this data.

So, thank you for that. This has been really great. Before we wrap up this first chapter, Dr. Cortes, any one key takeaway from this chapter that you'd like to highlight?

Dr. Cortes:
Well, I think that unfortunately, metastatic breast cancer continues to be an unmet need. We need more drugs, we need better and more combinations, we need to explore more the sequencing of these antibody conjugates. So, good time for clinical research, but again, we should not forget that we have patients out there that need us and need more and better drugs and combinations.

Dr. Jhaveri:
Absolutely. Thank you so much.

Dr. Cortes:
Thank you.

Dr. Jhaveri:
So, in chapter 2, we'll discuss the role of antibody-drug conjugates and the treatment of endocrine refractory hormone receptor-positive HER2-negative metastatic breast cancer. So, stay tuned for that. Specifically, we'll talk about personalizing treatment by differentiating the antibody-drug conjugate therapies.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Komal Jhaveri, and here with me today is Dr. Havier Cortes. We're discussing optimal sequencing of antibody drug conjugates in endocrine-refractory hormone receptor-positive HER2-negative metastatic breast cancer.

CHAPTER 2

Dr. Jhaveri:
So, welcome back to this chapter, and we'll explore a case of progressive endocrine refractory hormone receptor-positive HER2-negative metastatic breast cancer here. So, let me start with this case. We have a 61-year-old woman with history of T3, N1, M0, Grade 2 invasive ductal cancer of the right breast that is ER 90%, PR 20%, and HER2-negative, which is IHC 0. She was treated with the curative intent but developed recurrence involving the bone 4 years later while receiving adjuvant anastrozole therapy. Both biopsies that was performed confirmed metastatic carcinoma. Again, ER-positive, this time around now 50%, PR negative, and HER2 remains negative with IHC 0.

She was treated with endocrine-based therapy, which included fulvestrant and palbociclib, and then upon progression on that regimen, received tamoxifen with everolimus. A liquid biopsy that was done at that time did not show any mutation in ESR1 or PIK3CA. She

developed progressive disease in the liver and was started on capecitabine. Eight months after receiving capecitabine, restaging scans show progressive disease in the bone and in the liver.

Dr. Cortes, here, what do you think would be an appropriate next step here? Would you think about utilizing a treatment regimen and move forward with a treatment option, or would you consider a re-biopsy in this case to see if that might help further understand what would be the best appropriate next treatment option?

Dr. Cortes:
Well, first of all, I think that this is a patient who behaves relatively as might expect from hormone receptor positive, HER2 negative breast cancer. She received palbociclib-based therapy in the first-line setting followed by tamoxifen and everolimus. And the first-line chemotherapy was capecitabine, and she was 2 mil with capecitabine for about 8 months. So, I think this is something that we would have expected.

So, the first question is, this patient did have a liquid biopsy and we did not observe any PIK3CA nor histogenesis or gene 1 mutation at that time, so I think, at least in my opinion, that if we do not have available clinical trial at this time. I don't think if adding a second liquid biopsy will add a lot to the patient care. So, I think that it would not be completely necessary.

The patient received capecitabine in the first cycle, so I would proceed to antibody-drug conjugates, and I think that this is a second-line treatment in the chemo ward, so I would consider in this case because the HER2 was 0-plus. I think that sacituzumab govitecan, based on the TROPiCS-02, would be good According to some of the guidelines, the requirement is to have received two prior systemic lines of therapy. So, this would apply to this patient. But it's true that according to the clinical trial, it was required to have two prior lines of chemotherapy. So, I think is reasonable to discuss about sacituzumab govitecan.

Finally, if we get another biopsy and we find HER2 1-plus or 2-plus, the so-called HER2-low expression, I think that this patient would also apply to DESTINY-Breast04. So, maybe trastuzumab deruxtecan would be a very good option as well. So, for me, it's very clear. I would go for antibody-drug conjugates.

Dr. Jhaveri:
I completely agree with you. And yes, I have done both where sometimes when I'm really worried about the disease and want to get started and not want to delay initiation of therapy with another biopsy, maybe I would just get this started with sacituzumab given both biopsies are so far, biopsy – 0. And in certain other cases, I have gone and seen if somehow the dynamic nature of HER2 we will find 1-plus or 2-plus because of HER2-low, offer them T-DXd. So, I've done both. But I completely agree with you, switching to antibody-drug conjugates seems like the most appropriate treatment course here.

Dr. Cortes:
The point here is which is the best option. So, trastuzumab deruxtecan or sacituzumab govitecan. So, first of all, I think that both of them are good approaches to the patient, but it is true for trastuzumab deruxtecan today, we need to have a HER2-low. You know very well that we are exploring in DESTINY-Breast06 in the first-line setting, if those patients with ultra-low tumors also benefit from trastuzumab deruxtecan. But today, we don't have enough data to suggest that trastuzumab deruxtecan will work in HER2 0. So, maybe in this patient I would go for sacituzumab govitecan for this reason.

Dr. Jhaveri:
So, just expanding on what you were already mentioning, you know, the DESTINY-Breast04 trial did look at trastuzumab deruxtecan where we had patients who could've had a CDK 4/6 inhibitor. So, in that case, about 70% of these patients in DESTINY-04 had received prior CDK 4/6 inhibitors. What was really important to recognize is this is only for patients with HER2-low tumors, So, these were HER2-low tumors that a HER2-low could've been detected in the primary tumor, it could've been detected in the metastatic tumor, highlighting the point that as long as you have some tissue that did show HER2-low, that that patient could've been a candidate for trastuzumab deruxtecan-based therapy. And 480 patients, which were HR-positive HER2-low, which – which is really the natural prevalence that we know of HER2-low for HR-positive disease. And 58 patients had HR-negative and HER2-low were included. And both of these cohorts, the primary endpoint was specifically for the HR-positive, exploratory analysis looked at the HR-negative cohort. But in both cohorts, we did see a statistically significant improvement in both progression-free survival and in overall survival, leading to the approval of this agent for both of these patient populations. And so, we really think about utilizing this drug as long as the patients have had at least one line of chemotherapy. As in this case, this woman would've had one line of capecitabine. But could have offered this even in the third-line as long as they've had only two lines of chemotherapy.

So, TROPiCS-02 led to the approval of sacituzumab govitecan, which again, is a Trop-2 directed antibody-drug conjugate. In that trial, the majority of the patients, as you pointed out, had received prior CDK 4/6 inhibitor, so that was about 98% of the patients. They were required to have a minimum of two lines of chemotherapy, no more than four lines of chemotherapy. So, really pretreated patients.

While we saw an improvement in PFS and OS, the benefit of PFS was rather modest. But when we look at the numbers, it was a one-and-a-half-month delta of benefit over the stand-of-care arm. But when you look at the landmark analyses, we know that a larger proportion of patients were progression-free and were surviving in the sacituzumab arm compared to the physician choice chemotherapy arm. So, for such a pretreated patient population, including median 3 prior lines of chemotherapy, I thought that was clinically meaningful. And certainly, something that we do.

I know you pointed out a very important thing that some guidelines now allow to use sacituzumab even early on in the treatment course. And yes, that's true. I think we think about utilizing for HER2-low tumor T-DXd. For those tumors which are IHC 0, or for patients who are not candidates for T-DXd, such as those with baseline interstitial lung disease or pneumonitis, where you would worry about that side effect from T-DXd, sacituzumab could be used in the second-line the way we think about T-DXd as well. And so, I think for our patients that we were talking about for IHC 0, sacituzumab is a good option that we can offer our patients. But it's interesting to see how this has really shaped up our guidelines currently for second-line and beyond with antibody-drug conjugates.

Dr. Cortes:
Let me add just two quick comments. The first one is, don't forget that HER2 is a very dynamic biomarker, and you may have HER2 0 for two or three biopsies, and afterwards to have HER2 1-plus, 2-plus, so that's something that we should look at. And the second aspect, which is important in my opinion, is that these two drugs have been explored in the first-line chemo setting. TROPiCS-06 – DESTINY-Breast06, trastuzumab deruxtecan and ASCENT-07, sacituzumab govitecan. So, maybe in the next few chapters we'll be able to see these drugs just after endocrine therapy.

Dr. Jhaveri:
Absolutely. I wonder if you could briefly comment on the adverse event profile and the dosing scheduling for the two antibody-drug conjugates that we have?

Dr. Cortes:
These drugs are different in terms of administration. We should not forget that trastuzumab deruxtecan is being administered once every 3 weeks with specific adverse events. I would like just to highlight maybe neutropenia, nausea and vomiting, which could be very high in the rate of 70% of patients having any grade of nausea. And also, asthenia, fatigue, something that we might observe in the range of 50% of patients. And of course, the very well-known ILD pneumonitis in DESTINY-Breast04 was reported in about 12% of patients being Grade 5 in 3 of them, so 0.8% of patients unfortunately did have

Grade 5 event and passed away as a consequence of this important adverse event. Regarding TROPiCS-02, regarding sacituzumab govitecan, different toxicity profile. Very important to highlight the neutropenia in the range of 70 to 71%, being Grade 3 or higher in 52% of patients. Maybe I would like also to highlight diarrhea. Diarrhea was observed in about 62% of patients being Grade 3 in the range of 10%. So, different toxicity profile. Important to remember that sacituzumab govitecan should be administered on day 1 and 8 every 3 weeks. So, based on those, so all these aspects, maybe we might also have some aspects to discuss with the patient, do we prefer one or the other agent?

Dr. Jhaveri:
Yeah. No, I completely agree. I think sometimes it is such an important patient/physician decision-making process when, you know, you have justification to try and think about both of these, but maybe when you talk about the dosing schedule, when you talk about the toxicity profiles, that patients will have a preference.

This has been really great. I think Dr. Cortes. Before we wrap up, what's your one key takeaway from his chapter that you might want to share?

Dr. Cortes:
I think that antibody-drug conjugates are here to stay and if possible, we have to do all our best to give the opportunity to our patients to receive at least one of them when they need it.

Dr. Jhaveri:
Thank you very much. We'll move on to the next chapter.

CHAPTER 3

Dr. Jhaveri:
So, let's get into the case. We have a 56-year-old woman with history of T3 N1 M1, Grade 2 invasive lobular cancer of the left breast that is ER-positive more than 95%, PR-positive in 50%, HER2 negative at IHC 1-plus, and a FISH ratio of 1.1.

At diagnosis she had a biopsy proven metastatic disease involving mediastinal lymph nodes. ER was positive at 95%, PR-positive at 75%, HER2 negative at IHC 0, and FISH ratio was 1.2. Next generation sequencing revealed mutations in PIK3CA and CDH1, and no pathogenic germline variants were identified. She received endocrine-based therapy with letrozole and ribociclib followed by fulvestrant with alpelisib. She then developed progressive disease and received weekly paclitaxel.

Restaging scan showed progressive disease with peritoneal carcinomatosis and pleural thickening. Biopsy showed invasive lobular cancer that is ER 70%, PR 40%, HER2 negative and IHC 0, and a FISH ratio of 1.1. She was initiated on treatment with trastuzumab deruxtecan and after 8 months, had progression.

Dr. Cortes, you can talk about what factor led to the choice of trastuzumab deruxtecan, and then what do you think about treatment options for this patient after progression on trastuzumab deruxtecan that she's had.

Dr. Cortes:
It's interesting to see that the biopsy scored 0 for HER2, but we should not forget that this patient did have at the very beginning HER2 1-plus. And as we have discussed many, many times, if we have any prior biopsy being HER2 1-plus or 2-plus, this patient might qualify to the use of trastuzumab deruxtecan. And when we see the data that this patient did have progression-free survival in the range of 8 months, which means that the drug worked here. So, unfortunately, patients who've received and progressed after an antibody-drug conjugate it's a clear unmet need. So, my first comment is we have to try to find clinical trials to optimize the patient journey from the future. But if no, the obvious question is, what is better? To continue with a second antibody-drug conjugate or to jump into the classical chemotherapy. We do not have this question's answer. I think that it depends case-by-case based on my patient for it's not very clear if one of them is superior to the other one. My personal opinion is to continue with chemotherapy and maybe considering a second antibody-drug conjugate with the same payload after at least one line of chemotherapy between.

We do not have the answer for that, again. But the data we have basically for San Antonio 2023 observed that the second antibody-drug conjugate did not have the same benefit compared with the first one. It is not very clear if suci followed by T-DXd is better or worse than T-DXd followed by suci. I think that we do not enough data to suggest that one is superior to the second one, but clearly, the data with the second one is not as good as the data with the first one.

Dr. Jhaveri:
Clearly a lot more work that needs to be done here to best understand exactly how to optimize sequencing for these antibody-drug conjugates. Should an intervening sandwich chemotherapy really be a way to deal with this? Will that truly re-sensitize the tumor just because it's a different mechanism of action? Or will it necessarily not make a big difference? Something that we're trying to learn actually from research efforts including prospective trials such as TRADE-DXd. So, that's a trial that is actually looking at trastuzumab deruxtecan and another Trop-2 ADC for which we have data.

Similarly, we also have another research effort through the Translational Breast Cancer Research Consortium where we're doing a registry for patients who would have received trastuzumab deruxtecan and then get sacituzumab or vice versa. while we're waiting for all of this, this might be an approach we will still want to consider for our patients in clinic because our bar with systemic chemotherapy is so low that even though the ADC 2 PFS is lower than ADC 1, it might still be superior than a chemotherapy drug, because these ADCs have it better than chemotherapies, as what we've shown in so many trials.

Dr. Cortes:
I think that we have, unfortunately, many unanswered questions today. If the question is, if antibody-drug conjugates might work in a sequence way, the answer is clearly yes. I think that we have to understand, as you said before, from the clinical trials which is ongoing, which is better? To change the payload, to change the antigen, to change both? So, I think that, of course, there are patients out of there that will benefit for the sequencing, no doubt. Is it for everybody? Clearly, no. The point is how to define who will benefit or not. You make a very good point. If we understand the mechanisms of resistance, we will be able to optimize therapy. Unfortunately, this belongs to clinical research, not to clinical practice. So, we need to understand much better how these drugs works in sequence.

Dr. Jhaveri:
Yeah, I think, needless to say, we really need more. So, one is to optimize our current drugs and figure out what's the best sequence. Two, to try and bring them sooner in the treatment paradigm, so DESTINY-06 and ASCENT-07 are good examples. Would utilizing them in the first-line really have an impact on outcomes? And three, adding newer drugs and understanding the resistance mechanisms for these current drugs, such that we can now start using different novel antibody-drug conjugates for our patients and continue to further improve and have an impact on outcomes for our patients. So, I think so, so important to have that.

I know this drug is not approved yet, but we did see the results of the TROPION-Breast01 trial. I am just wondering, how are you thinking about those data?

Dr. Cortes:
So, as you know, the randomized Phase 3 study with datopotamab deruxtecan has been exploring second- and third-line. We observed an improvement in progression-free survival, but data in terms of overall survival is still immature, so we cannot formally say that it improves survival. So, the data in terms of the hazard ratio was quite similar to TROPiCS-02, but again, we are talking second third-line in TROPiCS-02, third, fourth, fifth-line. So, it's a different patient population. But the data are very consistent. So, these drugs work in this setting.

The point is even more complex because now sacituzumab is moving into the third-line setting. Trastuzumab deruxtecan also for the third-line setting. So, what would happen if we had data in terms of survival with datopotamab in the second third-line? So, I think that we have to wait and see what happens with survival with the third-line treatment options we will have.

Dr. Jhaveri:
Needless to say, exciting data, exciting days. We really have to do a lot more still in terms of waiting for newer drugs and understanding how to best utilize our current drug options.

But, I'd say, at this time today, I just want to thank the audience for listening in and thank you, Dr. Cortes, so much for joining me and for sharing all your valuable insights. It was really great speaking with you today.

Dr. Cortes:
Always a pleasure. Thank you, Komal.

CHAPTER 4

Dr. Cortes:
Hello. My name is Javier Cortes, and I would like to review today the updates in antibody drug conjugate therapy for hormone-receptor positive HER2-negative metastatic breast cancer that were presented at ASCO this year. This is CME on ReachMD, and as I said before, I'm Javier Cortes.

So I would like to start with the data, the most important data, that was presented about sacituzumab govitecan. And let me start maybe with a randomized phase 2 study presented by Ana Garrido-Castro from Dana-Farber Cancer Institute. So in brief, she presented a beautiful randomized phase 2 study of sacituzumab govitecan with or without pembrolizumab in this patient population. Although the study was negative for the primary endpoint, there was clearly a trend in favor of the combination of the antibody drug conjugate, SG, plus the immune checkpoint inhibitors for both progression-free survival and also overall survival. And there was even more evidence for the group of patients with a double-strand DNA breaks.

I would like to discuss briefly the PRIMED study. It was presented by Jose Perez for the International Breast Cancer Center in Barcelona, and we wanted to demonstrate here if we might prevent two of the most important adverse events with SG, neutropenia and diarrhea. The primary endpoint was to look at the incidence of grade 3 or higher neutropenia and grade 2 or higher diarrhea, giving GCSF in a prophylactic way, and loperamide. The results of this study was that grade 3 and 4 diarrhea was observed in about 16% of patients, 4% grade 4, and neutropenia grade 2 or higher in 16%, grade 2 12%, grade 3 4%, grade 4 0%. So as a summary, giving loperamide and GCSF will clearly decrease the expected neutropenia and diarrhea adverse events that we observe with this drug in many other trials.

Last but not least, I want to make some comments about a subgroup study that was conducted by Aditya Bardia and colleagues called TROPiCS-Breast02. Remember, it was a randomized phase 3 study with SG versus physician's choice in the hormone receptor-positive population. Basically, what we analyzed in this study was the data of the benefit of SG over physician's choice in the group of patients with DDR pathway alterations. Although the trial was not specified for this endpoint, we observed that the genes in this pathway might contribute to the efficacy observed with SG over TPC, something which makes sense when we are talking about Topo1 inhibitors.

Two more abstracts that were presented with T-DXd and SG related to the sequencing of these two drugs. Unfortunately, we do not have, at this time, prospective clinical trials evaluating the sequence. But according to the data we knew at ASCO, we also have two things. The first one is that the median time to progression according to the real-world evidence of these drugs in the subsequent line is always inferior than when we use these drugs earlier lines. So clearly T-DXd in the first line was better than SG in the second line, but also the other way around; SG in the first line was superior to T-DXd used in the second line. First and second line means first and second treatments; it's not just the line of therapy.

So again, I think that we need prospective data, and even in the hormone receptor-positive population, we cannot say that one is superior to the other, and we should wait to see definite results in the future.

Finally, I would like to make just two very quick comments about, 1: T-DXd in the HER2-low and ultra-low space. Giuseppe Curigliano presented the first data of the randomized phase 3 DESTINY-Breast06 in the first-line chemo or with T-DXd compared with chemotherapy. The trial was positive for the primary endpoint, progression-free survival, and this benefit was seen in both HER2-low and HER2-ultra-low. The signal in survival was also there, but this was immature at the time this was presented for overall survival.

Finally, I would like to make a very brief comment about datopotamab deruxtecan. Remember the data from the TROPION-Breast01, second and third line, hormone receptor-positive, metastatic breast cancer, datopotamab deruxtecan, another antibody-drug conjugate compared with chemotherapy. Sonia Pernas from Barcelona presented the data regarding the patient-reported outcomes. In brief, the most important data showed that when we analyzed the global healthspace and quality of life, clearly, the worsening, the treatment to deterioration on quality of life was delayed when datopotamab was used compared with chemotherapy.

So just to summarize very briefly, good data from antibody-drug conjugate than trying to decrease to optimize quality of life with these drugs, maybe giving prophylactically, a GCSF and loperamide. Regarding sequences, sequencing more data coming from the real-world evidence, we need prospective data clearly to define which is the best sequencing approach. And I would like maybe to highlight these data coming from Ana Garrido showing that adding immune checkpoint inhibitors to sacituzumab govitecan maybe we might improve outcomes. The signal is clearly there, but we have to define much better which is the group of patients that will benefit or not in the next future.

Well, dear friends, dear colleagues, this has been a brief but great discussion. Unfortunately, our time is up. Thanks for listening.

Announcer:
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