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Advancing TROP-2-Targeted ADCs in HR+ Breast Cancer: Navigating Today and Shaping Tomorrow

Chapter 1

Dr. Cortes:
Dear friends and colleagues, welcome to this educational program on TROP2-targeted antibody-drug conjugate therapy in hormone receptor-positive metastatic breast cancer.

This is CME on ReachMD, and I am Dr. Javier Cortes.

Dr. Rugo:
And I'm Dr. Hope Rugo.

Dr. Cortes:
Great to be with you today, Hope. Let's start our discussion with a case,

So this is a 46-year-old woman who was diagnosed with a T3, N1, grade 2 invasive ductal carcinoma, ER positive, PR positive, HER2 negative, 0+, Ki 40%. This patient received neoadjuvant chemotherapy with anthracycline and taxane-based therapy followed by surgery. She had a pT2, N1, 3 out of 15 nodes were positive, so she received adjuvant treatment with radiation therapy, goserelin, plus letrozole.

One year later, the patient experienced progressive disease in the liver, about more or less 10 months after adjuvant endocrine treatment. A biopsy of the liver was taken with the same pathology report as before, ER positive, PR positive, HER2 negative, 0+. The patient received at that time goserelin, fulvestrant, plus ribociclib. Unfortunately, 7 months later, the patient experienced progressive disease, so she received capecitabine and bevacizumab. Five months later, liver progression again was observed.

So the question to you, Hope, is what would you like to give to this patient? Any comments about this case? How would you choose the therapy for this patient?

Dr. Rugo:
Now, this is a really tough situation, and it's so disappointing for us when we see patients like this, a young woman who's gotten really good adjuvant treatment. And that if you're relapsing at 10 months on adjuvant endocrine therapy, that giving a CDK4/6 inhibitor is not going to prevent that, which is what we would do now for this patient.

I do wonder, based on the data we have from the studies looking at grade 3 ER positive disease and adding pembrolizumab, if maybe we have a chance for changing outcome for these patients by giving pembrolizumab as part of neoadjuvant therapy. But of course, we're waiting for additional data on event-free survival and eventually overall survival in the patients who are enrolled in the KEYNOTE

and [CheckMate] 7FL studies looking at pembro with chemotherapy. But they're similar to this patient, a lot of cancer in grade 3. So we end up with this terrible situation, really primary endocrine resistance, recurrence within 2 years of starting adjuvant endocrine therapy, rapid progression on a CDK4/6 inhibitor and fulvestrant. We would do next-generation sequencing and of course look for anything targetable, like a somatic mutation in BRCA or HER2. But most of these patients don't have those by far, at least 85% or 90% don't have any targetable mutations for us. And I don't think targeting ESR1 is going to work either.

And I think that we've been relatively disappointed with capecitabine now also in this setting, that we used to think about capecitabine being a great rescue in our ER-positive patients, and we still see some great responses. But in this kind of patient, not great. Five months is long, actually. And giving bevacizumab, something we can't do in the US, I like giving bevacizumab, so I wish we could. But that's a good first-line treatment for a patient with primary endocrine-resistant disease.

So now you're kind of stuck with a situation where you have to move on to IV chemo. And we don't have targeted agents to give with our IV chemo, so in this situation, I think we would turn to an antibody-drug conjugate to try and optimize her both progression-free survival and overall survival. And we have two antibody-drug conjugates that have shown improved PFS and OS, and also improved response rates in these patients who have chemotherapy-pretreated disease.

And the ASCENT trial, I think, looked in triple-negative disease and already led to approval of sacituzumab, which was then studied in the TROPiCS-02 trial in patients with hormone receptor-positive disease who'd received a median of three lines of prior chemo.

So let's look at this patient. She's had one line of chemo, but she relapsed quickly in the adjuvant setting, so she would have been eligible for the TROPiCS trial. And we've actually looked at the population of patients who had received just one line of prior chemo, and saw that the results were very similar to the overall trial, the TROPiCS-02 trial, that showed improved PFS and OS, comparing the sacituzumab govitecan to standard chemotherapy with the regular chemotherapy options we consider now, microtubule inhibitors primarily, and other chemotherapy agents.

We also have data with trastuzumab deruxtecan from DESTINY-Breast04 in this population, but they all had HER2-low disease, and this patient's done two subsequent, three, really, considering her core at diagnosis, pathology evaluations, has HER2-0 disease. So in this patient, I think that we would consider a sacituzumab govitecan as the most appropriate next treatment, keeping in mind that our goal is to prolong PFS and OS in this patient population.

And then there's been real-world data looking at sequencing. So if, for example, a subsequent biopsy showed some cells that were HER2-low, could you give T-DXd? And the data suggests that, in general, the first ADC works better than the second, but there's a subpopulation of patients where the second ADC works just as well, sometimes a little better. And we really haven't been able to find a pattern about this as yet. But I think that what we've taken from those studies is that it's worthwhile giving the ADCs we have available in sequence. Sometimes I break it up with a naked chemo drug or combination in between, but I do, if patients are well enough and up for it, generally sequence the ADC is with trying to put your best drug first, based on the available data and the patient themselves in terms of understanding their tolerance and underlying comorbidities to really make the best approach. So I think, based on our international guidelines, sacituzumab govitecan would be our next treatment here. We are sequencing, and then there are a number of prospective trials, I think overall around 5 of them, looking at sequencing the T-DXd and sacituzumab govitecan, which will, I think, provide us with very important data.

Dr. Cortes:
You made extraordinary comments, Hope. One of the issues I would like to highlight that you pointed out is the short treatment-free interval between the end of chemotherapy in the early breast cancer setting and metastasis, which was in the range of a year or even lower, so 10 months with endocrine treatment, and about 1.5 more months for chemotherapy. So I think this is a patient who was really resistant also to some of the best drugs we have, anthracyclines and taxanes, so I completely agree with you. I think this patient qualified for TROPiCS-02, and I think sacituzumab govitecan could be an extraordinary drug here.

So I have one more comment before moving forward. So Hope, how would you define endocrine treatment resistance? Or, in other words, when would you think that it is reasonable to move forward into a second- or third-line endocrine treatment? Or we should think about the chemotherapy world, maybe with antibody-drug conjugates today?

Dr. Rugo:

Yeah, this is such an important question. And I think that it's an area that's in evolution. We have defined primary endocrine resistance as progression on or within 2 years of starting adjuvant endocrine therapy or – and this is where it gets messy – in the metastatic setting within 6 months of starting endocrine therapy with or without a targeted agent in the metastatic setting. But obviously the use of a targeted agent is going to affect this, whether you've given a CDK4/6 inhibitor, now based on our most recent data from San Antonio, CDK after CDK, whether you've given a targeted agent to alterations in the PIK3 kinase/AKT pathway. These are all things which are going to change a little bit our definitions of resistance. That's primary endocrine resistance.

Secondary endocrine resistance are patients where I think we have a little bit more question about how we sequence therapies. These are patients whose cancers have grown within a year or while on adjuvant endocrine therapy, but after 2 years. So it's kind of a complicated group, but they clearly have been able to stay on endocrine therapy for some period of time, but their recurrence occurs within the year of ending their endocrine therapy or while on later duration endocrine therapy.

In terms of the metastatic setting, secondary endocrine resistance is really poorly defined. These are patients who progress on their endocrine therapy. They could progress at 12 months, or they could progress at 8 years, and they still have secondary endocrine resistance. So clearly, that doesn't really fit into our current world, and we're really working on trying to, I think, better to find that for our treatment choices.

Patients who have primary endocrine resistance, I think we generally think that they're unlikely to respond to subsequent endocrine therapy. And there's a little bit of a wiggle room with CDK4/6 inhibitors, and is it 2.5 years or 3 years? I have a patient who stayed on palbo and letrozole after having her ovaries out on PALOMA-2, who had relapsed at 3 years on tamoxifen in the early-stage setting.

So the endocrine therapy you're using, the patient, she had bone-only disease, all of these things are going to impact your treatment choice. And I think that if we can, we do want to give a patient a chance at endocrine therapy and CDK4/6 inhibitors. We've actually seen data now from a number of randomized trials showing that even in patients who have a lot of visceral disease, as long as it's not immediate organ failure, will benefit more from endocrine therapy and a CDK4/6 inhibitor than either combination or single-agent chemotherapy.

In this patient case, she was given that opportunity to see if, maybe by adding a CDK4/6 inhibitor and changing to an endocrine therapy agent that might work even if you had an unknown ESR1 mutation, that she still had a very poor response to that treatment, and then again to capecitabine. She has visceral metastases, so you're worried about what happens as the cancer continues to progress in the visceral organ.

So I think that that all really helps you want to put your best foot forward and give an antibody-drug conjugate in this setting in the second-line treatment, so that you can improve outcome and improve survival for this patient.

I will ask you one thing, Javier, in terms of your decisions in this patient's treatment, when do you get next-generation sequencing? I understand that there are geographic issues, though, if you weren't thinking about the fact that in Spain, they don't cover NGS as a panel, – when would you get NGS? And would you look for one mutation or many? And how would that influence things for this patient?

Dr. Cortes:
I think that's a good question. I think that unfortunately, in Europe, we do not have inavolisib approved yet in the first-line setting, which means that even if we will have a mutation in PIK3CA, the first-line setting would continue to be a CDK4 and 6 inhibitor plus endocrine therapy. But I think that if we have clinical trials and/or we have targeted agents available, elacestrant or PIK3CA inhibitors, I think that after first-line progression, so before second line, I think it's a very good time to go for NGS analysis.

I get a liquid biopsy always, but it has pros and cons, of course. But in Europe, at least before the second line is a very good time to do it.

Hope, I have a question to you before moving forward. Do you think, very quickly, that it is time to change the definition of secondary resistance with the era of CDK4 and 6 inhibitors, maybe moving from the 6 months to a 12 months, because I think that we have plenty of data now with with elacestrant, with INAVO studies showing that the 12-month cutoff seems to be much more interesting than the 6 months with CDK4 and 6 inhibitors. Any further comments about that?

Dr. Rugo:
Yeah, I mean, as I mentioned earlier, I think it's really important that we think about how we make these definitions now because they influence treatment, and some physicians, appropriately, still follow the guidelines, but they follow them very strictly. So we know that there are a lot of individual patient factors that play a role here. So I think that the definitions in the adjuvant setting are pretty good, and that we can continue with those.

In the metastatic setting, I would agree. I think that the 12-month endpoint for where we differentiate primary and secondary endocrine resistance, where we might have one path of thinking about targeted agents only in those patients who are more than 6 months but not quite at 12 months, whereas you really would go to chemo in the less than 6 months if you had a target, because it's possible that the – we'll see what happens with the next studies with inavolisib. But I think the triplet from INAVO120, where inavolisib, palbo, and fulvestrant, was better than palbo and fulvestrant in patients who had this early relapse. So these are patients with primary and secondary relapse on adjuvant endocrine therapy, or just after. And the triplet combination was much better, leading to approval in the US of that triplet and, I assume in this not too distant future, approval in other countries, that it sort of does beg the question about how we make these definitions. And if you had a patient on first-line CDK-ET who had a PIK3CA mutation, maybe you should still be giving them that option in that 6- to 12-month period. But otherwise, I think the 12 month for single-agent endocrine therapy seems to be really important. So I agree with you. I don't think we can just say this is primary, this is secondary. I think we're going to have to differentiate it further.

Dr. Cortes:
Right, right, right. Totally agree.

So let's go back to our patient, Hope. So she received capecitabine plus bev. She had, unfortunately, a very, again, quick, progressive disease. So now, you said that maybe sacituzumab govitecan could be a good option here. I have 3 questions for you. The first one is, why not trastuzumab deruxtecan? The second, why do you think that, or would you consider rebiopsy again to see if there is any change in HER2? Remember that we get a biopsy of the liver, and it was HER2-0. And the final question, can you make some high-level comments on the data that would support your decision?

Dr. Rugo:
So I think that the T-DXd is an important question. She was HER2-0 twice, and in the early-stage setting and I presume in her biopsy, so twice in the early-stage setting. But then I think the issue is she had early relapse in liver. You did a biopsy, she didn't respond to goserelin, fulvestrant, and ribo, it was only 7 months and then 5 months with PD again. So this is for somebody who has progression at 1 year after 2 sequential therapies.

And I think the question is, do you rebiopsy at 1 year? And there's some data from Dana-Farber that suggests that rebiopsy up to 5 times improves the chances of getting HER2-low. But in my clinical experience, I haven't found that to be true, particularly in the liver.

So I'm not sure that I would biopsy her first now versus treating her and then considering a biopsy after treatment. That might be my preference in this particular situation. But I think you could decide to rebiopsy too. It just takes a little while, and it's hard for the patient in some degree. But I think that you could go either pathway. At some point, I would rebiopsy again to look for HER2-low, so that a patient could access T-DXd, if she still was in good shape, and you want to treat her in the next-line setting.

Dr. Cortes:
I completely agree. I think that you might choose sacituzumab govitecan here.

So my third question is, can you just very brief summarize from the high-level perspective, some of the TROPiCS-02 data?

Dr. Rugo:
Yes, absolutely. And TROPiCS-02 randomized patients who'd received at least 2 but not more than 4 lines of chemotherapy for HR-positive, HER2-negative, metastatic breast cancer. All patients, in a contrast to DESTINY-Breast04 and to the TROPION-Breast01 trial that looked at the T-DXd and Dato-DXd, respectively, all patients had to have received a CDK4/6 inhibitor, as we felt it was the standard of care. The patients who were enrolled had received a median of 3 lines of prior chemo and mentioned you were eligible after one line in these rapid relapsers, like this patient we're discussing. And that's an important point for our patients, to offer the ADC if they've received one line with rapid relapse.

And then, interestingly, almost all of the patients had visceral mets. Over 90% had visceral metastases. So in our HR-positive population, once they've had all their endocrine therapy, a CDK4/6 inhibitor, and have received prior chemo, they almost always have visceral metastases. And that's important, because we know that that has predicted poorer response and response duration and well as poor overall survival with our traditional sequencing of chemo.

So patients were randomized to receive sacituzumab govitecan day 1 and day 8, every 21 days versus chemotherapy of physician choice. And a little over 50% chose eribulin, which I think is our standard in this more later-line setting. And a lot of people had received prior taxanes. And what we showed was a statistically significant improvement in both progression-free survival as well as an overall survival.

And what was interesting was there was an initial follow-up at the first scans that we see with all studies done in the later-line setting, because we can't predict the patients who have just resistant disease to everything. But after that initial scan, the curve separated and stayed separated over time, and there were patients who stayed on treatment for a long period of time. And when we looked at the 1-year analysis, 3 times as many patients were progression free at 1 year who received SG compared to those patients who received treatment of physician choice.

We looked at the subgroup analysis by both TROP2 expression and HER2 IHC, we wouldn't have expected any difference based on HER2 IHC. Didn't matter if you were 0 or HER2-low. Very encouraging. And we also looked at TROP2 expression. Interestingly, about 95% of the tumors had some expression of TROP2.

And the number of patients whose tumors had low, very low expression, like ultralow, it was so tiny, we couldn't really assess that, but it didn't really make any difference in terms of the sort of high and moderate in terms of response to SG. So that was encouraging as well.

Because of when TROPiCS-02 was done by a small company and the difficulties in getting studies approved at that time in Asia, and particularly in China, there was a very small Asian population. So another trial was done called EVER-132-002, very similar design to TROPiCS-02. This trial, which was recently published in *Nature Medicine*, also showed an improvement in PFS and OS in Asian patients. So really important additional evidence supporting the use of SG in patients with HR-positive HER2-negative disease.

Subsequently, there's always interest in how drugs work in the real-world setting. And so there have been some real-world data analyses. None of them the sort of formal flatiron analysis, but looking at either combined institutional datasets or others. And all of them relatively small, but all of them showing sort of in the range of PFS and OS that you would have expected from TROPiCS-02, and very similar safety data. So that's actually really encouraging.

And we've seen recent real-world data as well, as recently as looking at San Antonio this year, as well as at ASCO this year. In ESMO 2024, there was some small real-world datasets as well.

We've also seen some interesting updates on safety. When we've looked at these trials, overall, the safety of sacituzumab govitecan has been the same whether you're giving the drug in the triple-negative, heavily pretreated setting or in the HR-positive pretreated setting. I think that we're also seeing the emergence of data that there's a little less toxicity as we move the drug earlier in the course of therapy. And of course, the most common toxicities are neutropenia and then diarrhea less frequently, but also a more common toxicity.

Dr. Cortes:
So, Hope, it's difficult to add anything to all you have said. It's extraordinary listening to you. Always, I learn more and more, that there are some also quality of life data in TROPiCS-02 showing that it is really very good.

I would like to ask you something. Unfortunately, low drugs and also SG does have, in this case, also adverse events and neutropenia and diarrhea. Maybe these are 2 of the most well-known adverse events. Maybe again, in 2 minutes, some thoughts, some advice about how to manage these adverse events in the clinical practice.

Dr. Rugo:
Yeah. I mean, this is really important, because I think as we are proactive in managing known toxicity, we improve the quality of life of

our patients, but we improve efficacy of treatment because you can continue on the treatment for longer for that and you don't dose reduce as quickly and you don't have too many delays.

So what are the toxicities we really care about? Infusion reaction is very rare from sacituzumab. The real and interestingly, although you see nausea, it's less than T-DXd. If we give a triple-drug regimen before the infusion, and we rarely need rescue, maybe a couple of days of rescue medications. Works really well, so easy in my experience, to control the risk of significant or persistent nausea.

So what are the toxicities we really need to pay attention to? It's myelosuppression, and it's only neutropenia, you don't see so much thrombocytopenia, and then diarrhea. So neutropenia is very common, the most common toxicity, and it includes grade 3 and grade 4 neutropenia. And what we often see is the drug is given day 1 and day 8. So we see it at day 8, so that delays treatment or eliminates day 8. And we often see that as an issue starting the next cycle, because the trials use an ANC of 1.5 as a cutoff. In clinic, we use an ANC of 1000.

So the way we manage that is we give growth factors in patients who've needed growth factors for their last prior treatment. We monitor closely. We have a low sort of bar for adding growth factors around day 3 after each infusion. And some people that's enough. But for patients who need a little bit more, we tend to get pegfilgrastim after day 8, and that works beautifully. And then you don't need to give any other growth factor.

For diarrhea, the rate of grade 3 diarrhea is in the 9% range or so, at most 10% in some of the studies, and we feel that it's related to a poorer metabolism of SG with UGT1A1 polymorphisms, but we aren't routinely around the world checking for these. So what we do is we warn patients. I don't let people get treatment with drugs that cause diarrhea, this drug and many others that cause more diarrhea, unless they have loperamide in their pocket when they get the infusion, because they're not going to get up and get it at 3 in the morning. So that's a really important consideration. And from the support staff in your clinics and then for the diarrhea, giving loperamide works really well. But if somebody has a lot of diarrhea, dose reducing from 10 to 7.5 mg/kg makes a big difference and can allow patients to continue through. If it's immediate diarrhea, which is an interesting effect I haven't really seen, you can give atropine, but haven't really seen it much, but it does work. It's just rarely needed. But for patients who get this sort of persistent diarrhea after the infusion, as I said, dose reduction and an anti-diarrheal medications work well. But we've actually given octreotide to one patient who is a heterozygote, poor metabolizer, and that worked beautifully, completely controlled it and she was able to stay on drug for 8 months with terrible disease. So I think that that's important.

There's been one study called the PRIMED trial that updated data actually at San Antonio 2024 where they enrolled a group of about 60 patients. And they gave them standard sacituzumab, but they gave them GCSF on day 3 and 4 and day 10 and 11 for the first 2 cycles. And they gave them loperamide twice daily 2 mg, or once daily 4 mg, 3 days after each infusion. And what they saw was a marked reduction in the rate of diarrhea and neutropenia, grade 3 diarrhea and grade 3 neutropenia. I mean, really, huge reduction compared to what had been seen in the previous trials, and comparing it to giving it in triple-negative disease and HR-positive disease in the prior studies. So very encouraging.

Now I wouldn't do that because my patients would be very upset with that much loperamide. They hate constipation. But I think that's why it's so important to tell patients to start right away and to call in and then to have a low threshold for dose reduction for diarrhea and growth factors for neutropenia.

Dr. Cortes:
Thanks very much, Hope. It's always so great to learn from you. Thank you very much. We have learned about endocrine resistance. We have learned about how to treat patients with HER2-0 and basically with a very quick progression of the disease. We have been discussing about sacituzumab govitecan, the data we have, quality of life, adverse events.

So, Hope, thanks a million for your excellent discussion. It was absolutely amazing.

Dear folks, dear colleagues, in Chapter 2, we will look at some ongoing trials on the use of antibody-drug conjugates in metastatic hormone receptor-positive breast cancer. Please stay tuned. Thank you.

Dr. Rugo:
Thank you.

Chapter 2

Dr. Cortes:
For those just tuning in, you are listening to CME on ReachMD. I'm Dr. Javier Cortes, and here with me today is Dr. Hope Rugo. We are discussing the role of TROP2-targeted antibody-drug conjugates in hormone receptor-positive HER2-negative metastatic breast cancer.

Dr. Rugo:
Welcome back. Let's get right into the data. Here, in Chapter 2, we're going to talk about the ongoing trials that are further evaluating antibody-drug conjugates in HR-positive HER2-negative metastatic breast cancer. There is a lot going on in this area, and we're just going to talk about the top-level ongoing trials, because there's so many ADCs now in phase 1 studies as well.

Javier, can you summarize for us these top-line phase 3 trials, talking also about some of the most recent data that's been presented?

Dr. Cortes:
Thanks, Hope. We have great data in second and third line, so it's normal to understand that these drugs are moving into the first line of therapy. And we have data now coming from trastuzumab deruxtecan, which have been basically observed great data in the first-line chemotherapy world, hormone receptor-positive, HER2-negative disease, HER2- ultralow or HER2-low. These are data coming from the so-called DESTINY-Breast06. We all know the data, which were presented and published by Giuseppe Curigliano at ASCO 2024 showing a good improvement in progression-free survival, the primary endpoint of the trial, in the HER2-low breast cancer tumors, also will have an improvement in the HER2-ultralow. It was a very interesting signal also in terms of survival.

It is true that there are other ongoing clinical trials in the first-line setting with different anti-TROP2 antibody-drug conjugates. Sacituzumab govitecan is being explored in the ASCENT-07. It's important to highlight 2 or 3 key comments here. The first one is that all patients with chemo naïve for metastatic breast cancer. The second important aspect, patients were randomized to sacituzumab govitecan or chemotherapy according to physician's preference. And third, this trial has been completed for recruitment and we are waiting to see the results for the primary endpoint.

Other antibody-drug conjugates which are also in clinical development, for example, datopotamab deruxtecan. We have data coming from TROPION-Breast01. This is a trial in the second or third line of treatment. As you all know, it was presented at ESMO 2023 by Aditya Bardia, and the primary endpoint, progression-free survival, was also improved. we have data in terms of overall survival, and datopotamab deruxtecan was not superior in terms of overall survival compared with chemotherapy in this setting.

Last but not least, we should not forget another antibody-drug conjugate against TROP2, which is called sacituzumab tirumotecan, or Saci-TMT. Also, this drug is involved in phase 3 clinical trials in the ER-positive setting.

Finally, I would like to make maybe 2 or 3 quick comments about how to optimize the monitoring of our patients. We all remember the data from the PADA-1 study, which was a randomized phase 2 study in the estrogen receptor-positive patient population. Patients were taking endocrine therapy plus palbociclib. And when we observed an increase in the ctDNA, patients were randomized to continue with the same drug or change into fulvestrant. This trial was positive and has been the basis for other randomized phase 3 studies, for example, SERENA-6.

I think in the future, maybe we should incorporate ctDNA or liquid biopsy or other assessments to try to understand patients who experience progressive disease earlier, than waiting and see what happens according to the CT scan or MRI scan, and maybe we will be able to optimize the treatment sequence and also to decrease the price or drug which is not working. I think that this could be some of the most interesting future aspects that we should consider when we design clinical trials.

Dr. Rugo:
I think this is great. I mean, first of all, that was an excellent summary of all the things that are going on. And there are even more TROP2 ADCs that are in other trials as well. So it's really an exploding field. And I think you did a nice job of exploring some of the controversies, as well as the HER2-ultralow and then the sequencing issues, do you give it first, second, third, and in which setting do people benefit with survival improvements based on the sequencing of the ADC?

And I think that sort of relates to your question about ctDNA monitoring. I don't think we know yet that changing early, before you have clinical evidence of progression, improves outcome. And the primary endpoint for SERENA-6 looking at ctDNA for changing the endocrine therapy, is PFS. And we don't know if you switched after you had clinical progression, that you would change the survival or the PFS too. So I think SERENA-6 will be fascinating. I mean, it completed accrual and there should be data maybe as early as next year, I think, which will be really fascinating, and maybe that will change our approach.

At the moment, I don't think there's a role for changing therapy based on ctDNA monitoring. And I think the question that's going to come up is, is it the emergence of a mutation that you see on 2 subsequent tests, or is it rising ctDNA that we use? And we spent decades convincing people not to use rising tumor markers without clinical progression as a reason to change therapy. We saw that CTCs, rising circulating tumor cells, changing therapy with the agents we had available didn't change outcome.

I think the real key here is, do we have better agents? And can we target specific mutations, not just rising ctDNA? So it's an ongoing question, I just think, still very much in the research arena, and will take some time to really be shown to be important in the metastatic setting. We're having trouble even figuring out how to manage it in the early-stage setting, so it's still working along.

So the data we have, I think, does impact clinical practice. We should see results from the first-line triple-negative trials next year with ADCs. We've already seen first line, meaning after resistance to endocrine therapy. So first-line chemo with T-DXd in DB06, we'll see ASCENT-07 which has completed accrual in the not too distant future. And I think that, along with all of the data that we have at present and understanding sequencing as we talked about in the first chapter where there are a number of prospective sequencing studies, this is all going to really impact the way we treat our patients in the metastatic setting, hopefully for the best.

But I think the understanding of sequencing is going to be critical as we make these decisions, because we know that some treatments are easier for patients to tolerate than others and we want to have a good reason for using one versus another up front. And also, there's the cost consideration around the world.

Dr. Cortes:
Right. And I couldn't agree more. How interested could it be to explore also ctDNA maybe in optimizing the sequencing in the next future? Maybe, well, I don't know, but we have so many things to learn about and so many clinical trials to be designed.

Hope, this has been a great, fascinating discussion with you. Thanks so much for joining me today. And thanks to our audience for tuning in today.

Dr. Rugo:
Thanks so much, Javier.

Dr. Cortes:
Thank you.