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https://reachmd.com/programs/cme/translating-research-into-practice-in-breast-cancer-emerging-data-and-the-expanding-role-of-adcs/57226/

Released: 07/27/2026
Valid until: 07/27/2027
Time needed to complete: 30 minutes

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Translating Research Into Practice in Breast Cancer: Emerging Data and the Expanding Role of ADCs

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Chapter 1

Dr. Traina:
This is CE on GLC. I'm Dr. Tiffany Traina, and joining me today is Dr. Sara Hurvitz. We're discussing updates to the role of antibody-drug conjugates, or ADCs, in the treatment of breast cancer. And in this chapter, we'll focus on the neoadjuvant setting and begin with a patient case.

So we'll jump right into the case. This is a 43-year-old premenopausal woman who has a strong family history and a pathogenic MUYTH mutation, who self-palpated a mass in the right breast. She underwent diagnostic imaging with mammography and ultrasound and ultimately was found to have a unifocal suspicious mass that was just over 2 cm, and also some enlarged axillary lymph nodes. The breast mass underwent a core biopsy, and it showed poorly differentiated invasive ductal cancer, ER less than 1%, PR less than 1%, and HER2-positive at 3+. Biopsy of the axillary node also confirmed carcinoma. And so she's referred by her gynecologist for medical oncology care, as so often happens.

And so with that, Sara, I'll turn it over to you and just see if you could share some of your thoughts on this case.

Dr. Hurvitz:
Yeah, thank you, Tiffany. This is not totally a typical situation when we see a patient who has a higher-grade invasive cancer. I usually think first it's either going to be triple-negative breast cancer or HER2-positive breast cancer.

We know that HER2-positive breast cancer, untreated, is associated with a worse prognosis than HER2-negative breast cancer. And in the last 15 years or so, we've begun to understand that there is value in treating tumors that are HER2-positive, especially if they're over 2 cm or node-positive, in the neoadjuvant setting with systemic therapy. This gives us information about the behavior of the tumor and whether the therapy we've selected to use in the neoadjuvant setting is working well. And the pathologic response at the time of surgery tells us not only the prognosis, but can we impact the prognosis by giving a different therapy in the adjuvant setting.

I think this is an important case because it does tell us this patient does have a high-grade tumor, it is over 2 cm, and the node does

have cancer in it. So I think the neoadjuvant treatment of this patient would be most appropriate if she is eligible for systemic therapy.

Dr. Traina:
Yeah, so beautifully said, and I like how you mentioned sort of being able to prognosticate a little bit better by using neoadjuvant therapy for a patient like this. And so often we're asked at the very beginning what the risk of recurrence is. I find it hard to say now that neoadjuvant therapy is such a paradigm, because I'm really waiting to see what the results are in response to our neoadjuvant regimen.

Do you see any particular clinical challenges for this patient before we kind of embark on talking about treatment options?

Dr. Hurvitz:
Well, I think we have to explore the patient's medical history. It's not just about the breast cancer. We don't make selections or recommendations in isolation, so we have to understand if there are comorbidities that we need to understand. We also need to know whether or not this patient has socioeconomic factors, family issues that are going to make it difficult for her to receive treatment. And then understanding the whole patient, we can come together to make a treatment recommendation with the patient's input.

Dr. Traina:
So beautifully said. So taking that into context, what are some of the treatment options that you would be discussing with her if she was in clinic with you?

Dr. Hurvitz:
I think, let's see, before, let's say, 6-8 months ago, a standard recommendation would be to give this patient taxane-based chemotherapy with trastuzumab and pertuzumab. Usually, we are able to omit anthracyclines. We have fairly robust data indicating that a taxane-platinum-trastuzumab-pertuzumab regimen, known as TCHP, is associated with high pathologic complete response rates but allows us to omit the anthracycline that you would have in an AC-THP-type regimen, which makes the regimen safer. That said, anthracycline-based regimens in some cases are appropriate for a patient.

And in the DESTINY-Breast11 neoadjuvant clinical trial, which is a 3-arm, randomized, multicenter, phase 3 clinical trial, patients that were similar to our patient here were randomly assigned to receive T-DXd alone for 8 cycles, T-DXd followed by THP, 4 cycles of each, or dose-dense AC-THP, 4 cycles of each. The T-DXd-alone arm was dropped because it didn't appear to be as effective in terms of pathologic complete responses. And the T-DXd followed by THP arm was superior by 11% improvement in pathologic complete response compared to the dose-dense AC-THP.

So this study did demonstrate improvement in outcomes by utilizing an antibody-drug conjugate, and this led to the FDA approval of this agent in patients with higher risk. Keeping in mind that in DESTINY-Breast11, patients were allowed if they had node-positive disease or if they had node-negative disease, T3 lesions, or inflammatory breast cancer. So this wouldn't be appropriate for a 2-cm node-negative breast cancer, but a higher-risk patient like ours, it would have been appropriate.

The safety in this study was also notable, and it’s interesting that the left ventricular dysfunction was lower for T-DXd-based regimens than of the AC-THP, as expected. ILD and pneumonitis was unusual. It was low in this clinical trial. In the T-DXd-alone arm, it was about 4.9%, T-DXd THP of 4.4%, and the dose-dense actually had numerically a higher rate of ILD at 5.1%.

So I think this is an option for our patient, but I think it requires a nuanced discussion. And I would just call out the fact that the control arm was not TCHP, which is most commonly used in the United States, has drawn a little bit of criticism. But it's an interesting time, and it's great we have this available now.

Dr. Traina:
I love how you describe both the superior efficacy and the win on the safety profile. I'm wondering, can you remind us, how did they monitor for ILD in that neoadjuvant setting? And if folks are adopting this in their clinical practice, do they need to be doing CT scans during those 4 cycles?

Dr. Hurvitz:
Yes, CTs were done of the chest every 6 weeks in the neoadjuvant study, and that's a fairly intensive monitoring regimen. They did see such low rates of ILD that I'm not sure our guidelines are ultimately going to recommend we be that proactive, but certainly have to warn

our patients about any symptoms that would suggest ILD and get imaging at the outset for patients going on this treatment.

Dr. Traina:
Yeah, such an exciting time to see T-DXd moving up into the early-stage setting with such impressive efficacy.

So thank you so much for your insights. You covered a lot of ground in just a few minutes. In Chapter 2, we're going to discuss the role of T-DXd in the post-neoadjuvant setting, so stay tuned.

Chapter 2

Dr. Traina
Welcome back, everyone. In the first chapter, we covered the role of trastuzumab deruxtecan in the neoadjuvant setting. In this chapter, we're going to discuss its role in the post-adjuvant setting, and as usual, we'll start with a case.

A slightly different case this time. So this is a 46-year-old woman who palpates a mass in her breast, and imaging and ultrasound reveal a 4.3-cm mass with multiple axillary nodes measuring almost 3 cm and 1.2 cm. Ultimately, the breast mass is biopsied and shows a high-grade invasive ductal cancer. ER is 90%, PR 90%, HER2 is 2+, but FISH amplified. And the axillary lymph node is biopsied, and it does confirm involvement with breast cancer.

So she goes on to receive neoadjuvant therapy with AC-THP. She moves on to lumpectomy and ultimately needs an axillary dissection and has a large amount of residual disease with ypT1cN1 disease, and that residual disease is strongly ER positive, and also tests HER2 3+.

And so with this, a slight modification of our first case, I'm wondering what your thoughts are on how we approach this woman, who, despite polychemotherapy, dual HER2-directed therapy, has a large burden of residual disease, unfortunately.

Dr. Hurvitz:
Yes, this is a very high-risk situation. This patient has an exceedingly high risk of invasive disease recurrence and distant metastases.

We know from the KATHERINE trial that utilizing T-DM1 in the adjuvant setting for a patient like this who has residual disease at the time of surgery not only improves the risk of an invasive disease recurrence, but improves overall survival compared to using single-agent maintenance trastuzumab, so we have that in our back pocket. But more recently we have data suggesting that T-DXd may be effective here.

We know that patients who receive anthracycline-based therapy do have a higher risk of cardiomyopathy from subsequent therapies, so we want to keep that in mind with this particular patient who did receive an anthracycline, likely due to the very high-risk nature of her disease.

I'd also like to call out the fact that this patient's disease expresses the hormone receptors, and so we do note that patients with hormone receptor co-expression, they will have a lower chance of pathologic complete response to neoadjuvant therapy, and we have the opportunity to utilize hormonally-directed therapies in the adjuvant setting for her.

So I do think we have an opportunity here to discuss a number of treatment options with her that will help reverse that very high risk of disease recurrence that's somewhere along the order of 30% to 40% or higher in the next, I would say, 5 years. I'm just sort of shooting from the hip here. Tiffany, correct me if you disagree.

Dr. Traina:
Yeah, I think that's probably about right. I think in the case she had almost 2 cm of residual disease, she had multiple positive nodes, and then I always round up significantly with the HER2-positive biology.

Dr. Hurvitz:
Absolutely.

Dr. Traina:
So you started to allude to DESTINY-Breast05 and how T-DXd may be moving into this space. Can you tell us a little bit about what that regimen looks like and what the data showed us?

Dr. Hurvitz:
Yes, DESTINY-Breast05 challenged the results of KATHERINE. KATHERINE came out and made T-DM1, or trastuzumab emtansine, the standard of care first option to use in the adjuvant setting for patients with residual disease at the time of surgery. So the DESTINY-Breast05 study took patients who had residual disease at the time of surgery, and either had inoperable disease at the time of their diagnosis or had lymph node-positive disease at the time of surgery after neoadjuvant therapy, and randomly assigned them to receive 14 cycles of T-DM1, the standard of care, or 14 cycles of T-DXd.

It was a 2-arm study. It was open-label, and there were over 1,600 patients in this large phase 3 clinical trial. And the results that were presented in 2025 indicated that the 3-year invasive disease-free survival rate was significantly higher with T-DXd, 93.4% IDFS for the T-DXd arm versus 83.7% for standard of care, so almost a 10% improvement in outcomes. The DFS rate was also significantly higher.

We don't have mature overall survival yet, and the safety findings did show low rates of ILD, but similar to other clinical trials of T-DXd, indicating that we need to be aware of this potential side effect and clinically monitor patients as such. About 9.6% of patients developed ILD in this study.

So this regimen was approved in the adjuvant setting and allows us to partly reverse that poor prognosis associated with such high-risk disease, giving us an opportunity to salvage a situation that would otherwise be associated with a very poor outcome.

Dr. Traina:
I mean, these are just incredible data, and yet it raises the question now that we have both indications for the neoadjuvant setting as well as the adjuvant setting, and we see that event-free survival and disease-free survival benefit there in the adjuvant setting, but we see disparity between risk of ILD. It's so nice to think about getting away with only 4 cycles in the neoadjuvant setting.

Like, how do you choose? How do you choose for these highest-risk patients that had node-positive disease right in the beginning? Are you leading with the T-DXd THP regimen? Or are you reserving it for those that are at highest risk and need an escalation of care later?

Dr. Hurvitz:
It's the question du jour, for sure. We're all sort of chewing on these data and discussing them and discussing them with our patients as well.

I am actually more biased toward its use in the adjuvant setting because it's more cycles. It's 14 doses of a highly potent, highly effective therapy. I find this very compelling in a patient population who, by definition from the clinical trial criteria, were extremely high risk for having a recurrence of their disease. So I want to use the neoadjuvant setting, in most cases, to test the sensitivity of the tumor to standard taxane HER2-targeted therapy, TCHP, and if a patient has high-risk residual disease, utilize T-DXd afterwards.

However, I do think that there may be a role for de-escalation using T-DXd, perhaps in lower-risk disease in the neoadjuvant setting, and I just am not yet convinced that T-DXd followed by THP for my highest-risk patients is enough. And we need to call out that the FDA has actually not approved use of it in both the neoadjuvant and adjuvant settings, so we do, as clinicians, need to choose between those 2.

With all of that said, and my bias included, I think that this warrants a careful patient discussion, and I think that there are equally valid arguments to use it in the neoadjuvant setting.

Dr. Traina:
Yeah, I think you framed that debate really beautifully, and this will end up being, really, a discussion incorporating so many members of the care team, with the patient being central to that, because there are logistical differences. There are, as you said, many patients who do beautifully with the taxane-trastuzumab-pertuzumab neoadjuvant regimen, and being able to reserve this escalation of care for those prognostically who need that benefit the most is really an interesting approach. So I think hopefully a lot of data to emerge to help guide us in this decision-making. I'm just thrilled that we have options for our patients.

Thank you so much for talking that through with me. In Chapter 3, we'll be discussing the role of ADCs, but we'll shift gears a little bit and talk about the treatment of advanced metastatic triple-negative breast cancer. So stay tuned.

Chapter 3

Dr. Hurvitz
Welcome back. In Chapter 2, we discussed the role of ADCs in neoadjuvant and post-neoadjuvant settings. In this chapter, we'll look at the role of these therapies in the unresectable or metastatic triple-negative breast cancer setting.

Let's first consider a case. A 39-year-old palpated a left breast mass while nursing. Imaging revealed a 2.5-cm mass with one suspicious lymph node. Core biopsy revealed a grade 3 IDC, ER/PR negative at 0, HER2 0, and FISH negative. A lymph node was positive for metastatic breast cancer.

She received the KEYNOTE-522 regimen of TC/pembro, followed by AC/pembro, and then had germline genetic testing done that was negative. At the time of lumpectomy and sentinel lymph node biopsy, there was 5 mm of residual cancer in the left breast, and 0 out of 3 lymph nodes were involved, plus 0 out of 2 axillary nodes. She received postoperative radiation, capecitabine, and pembrolizumab.

And 3 months after completing the full year of pembrolizumab, the patient developed dyspnea on exertion and a cough that progressively worsened. She had imaging done that revealed multiple pulmonary nodules bilaterally and a large left pleural effusion with a 2-cm liver mass. A biopsy is done, and it confirms ER, PR, HER2 all 0 by IHC, triple-negative breast cancer.

So, Tiffany, what are your thoughts on this case?

Dr. Traina:
Oh, my goodness, my thoughts? Just terrible. And this is something that happens all too often, right? So we know triple-negative breast cancer tends to occur in younger women. You're describing here a 39-year-old woman who's postpartum and still nursing. And so frustrating that while we do see a higher association between BRCA1 and triple-negative breast cancer, so frequently we do germline genetic testing and we never really have an explanation as to why this happened.

Given her tumor was quite large with an involved node, it was standard of care and quite appropriate to treat her with neoadjuvant therapy, and the KEYNOTE-522 regimen of taxane, platinum, AC, and pembro is by far the standard of care based on really high pathologic complete response rates and better breast cancer-associated survival.

And here, when she went to surgery and had residual disease, both in the breast, that is triple-negative breast cancer, this is very similar to the HER2-positive discussion that we had in cases 1 and 2. Having that amount of residual disease after seeing some of our best cytotoxic agents and checkpoint inhibitor really is associated with a poor prognosis, and so it's an opportunity to escalate care in the adjuvant setting.

There are many trials going on in this space, but what we have today includes capecitabine for our patients who have wild-type germline genetics for about 6 months and completing that year of pembrolizumab, and she received appropriate radiation therapy as well.

So to see only 3 months later a recurrence of disease with a large burden of disease causing symptoms and visceral crisis, if you will, is really disheartening, because this is reflecting some of the toughest breast cancer we have to treat today that is highly refractory to our standard of care array of chemotherapy agents and that full year of checkpoint inhibitor.

Unfortunately, these are patients that are often excluded from clinical trials as well because of that short, short, short disease-free interval of only 3 months. And it's been very difficult up until just recently to know what the right thing to do is for these patients. Often we would be reaching for eribulin as one of the remaining traditional cytotoxic agents that this patient's tumor may not have seen, and we would hope for response, but unfortunately, I think it's been quite unlikely to see great benefit from traditional chemotherapy here.

Dr. Hurvitz:
Yeah, very well stated. It is a devastating situation, and it makes it more complex to figure out how one should treat her now that she has established stage IV breast cancer.

So can you take us through the treatment options available for this patient whose disease has progressed or recurred so quickly after receipt of pembrolizumab, including would you even be looking at PD-L1 status and consider immune checkpoint inhibitor therapy? Are there ADCs that would be appropriate, or combination chemo?

Dr. Traina:
Yeah, so million-dollar question there on that disease-free interval question in IO, and we'll come back to that.

So we have 3 trials in this space now in the first-line setting of metastatic triple-negative breast cancer that all support the idea that antibody-drug conjugates targeting TROP2 are superior to our traditional chemotherapy.

So I do think the first step is understanding what is the PD-L1 status of the tumor, and let's talk that through for a moment outside of this case in particular.

For those tumors that test PD-L1 negative, we have 2 trials that have now shown superiority of antibody-drug conjugates. We have ASCENT-03, which tested sacituzumab govitecan up against chemotherapy, and we have datopotamab deruxtecan from the TROPION-Breast02 trial. So these studies, while they share some similarities, do have some design differences in the populations that were eligible for each of the trials.

So in ASCENT-03, this was a large, randomized, phase 3 trial. Patients were treated in the first-line setting for metastatic triple-negative breast cancer, and they were deemed to not be candidates for checkpoint inhibitor, and 99% of the time that meant that their tumor tested PD-L1 negative. There was a disease-free interval requirement of having at least a 6-month time period elapse from your early-stage treatment, and those patients that recurred within 6 to 12 months were capped at about 20% on the study. So patients were randomized to sacituzumab as a single agent versus standard of care chemotherapy, which included either single-agent taxane or the gemcitabine-carboplatin combination as a doublet. And the primary endpoint of the study was progression-free survival.

Crossover was built into the study as well, which was incredibly generous for patients participating in the study. This was a global trial, and access to post-progression ADC might have been compromised in certain regions of the world, so if patients were randomized to the control chemotherapy and progressed, they were offered and provided sacituzumab upon progression. And that's important as we think about endpoints like overall survival, where the trial is not powered to see OS, and crossover may have really made it challenging to see if there was an OS difference.

But the study did meet its primary endpoint. So median progression-free survival was significantly better with single-agent sacituzumab as compared to chemotherapy, with a median of about 9.7 months compared to about 7 months with chemotherapy. Objective response rates were actually pretty comparable, about 48%, 46%, in overall response, and even complete response was pretty comparable, but I think what was encouraging is that the durability of that response was prolonged with the antibody-drug conjugate. So duration of response was closer to a year with sacituzumab and only about 7 months with chemotherapy.

And there were no surprises in terms of adverse events. Most commonly, we're seeing neutropenia and diarrhea. And prophylaxis was not really mandated in the study, but we know in our clinical practice we will often incorporate growth factor and even prophylaxis for diarrhea.

So that has really led to sacituzumab being incorporated in NCCN Guidelines as a category 1 preferred option for patients with metastatic TNBC who are not candidates for a checkpoint inhibitor.

We also have the data from TROPION-Breast02. So now this is looking at the TROP2 ADC datopotamab deruxtecan in a patient population that was quite similar: first-line metastatic TNBC patients who were not deemed candidates for checkpoint inhibitor. In this case, about 10% of patients actually had PD-L1–positive tumors, and that could be because they had a contraindication to an immune checkpoint inhibitor, or they could have lived somewhere in the world—another global study here—where perhaps access to a checkpoint inhibitor was limited.

And so patients were randomized to datopotamab deruxtecan as a single agent given every 3 weeks or single-agent chemotherapy, and in this case it was either taxanes, carboplatin, capecitabine, or eribulin. But about 80% of patients in the control arm actually were

getting a taxane, so when we think about the comparator, it's largely a taxane comparison.

Other key differences in the study, there is no crossover in TROPION-Breast02. Datopotamab deruxtecan was not FDA-approved or a standard of care for metastatic TNBC, and so no crossover was built in.

And also a key takeaway is that the study is powered statistically for both progression-free survival and overall survival in that dual primary endpoint.

So what was seen was a significant improvement in median progression-free survival favoring dato over chemotherapy. Here, the median PFS with datopotamab was almost 11 months, and with chemotherapy it was about 5.5 months.

I should call out that a key eligibility distinction for this trial compared to ASCENT was the disease-free interval difference. So there was no minimum disease-free interval, and you had 15% of patients coming on trial who had recurred either on their adjuvant therapy or within 6 months, so it has enriched for some of our toughest rapid progressors, chemo-refractory type of tumors. The study also met that primary endpoint for overall survival, with median overall survival of almost 2 years, approaching 24 months with datopotamab, and about a year and a half with traditional chemotherapy. Response rates also were higher numerically with datopotamab at about 64% compared to 30% with chemotherapy.

And the safety profile was a bit different. With this antibody-drug conjugate, adverse events of special interest include dry eye and stomatitis, and there are prophylaxis recommendations that were built into the trial that are recommended, including lubricating eye drops and oral dexamethasone rinse to minimize stomatitis. Fortunately, ILD was incredibly rare, because this payload is the same as the trastuzumab deruxtecan payload. But ILD rates were down around 1%, so fortunately we're not seeing that as a concern here.

So NCCN has also named datopotamab deruxtecan as a category 1 preferred option in the first-line setting for our patients who have metastatic TNBC and are not candidates for a checkpoint inhibitor.

Dr. Hurvitz:
Wow, Tiffany, thank you so much for that really beautifully stated and thorough analysis of these 2 studies, which at first glance look very similar but have incredibly important differences that may have impacted the way the data read out.

One quick question for our particular patient. Given her disease-free interval of 3 months, am I to assume that you would recommend Dato-DXd as the more evidence-based approach here?

Dr. Traina:
Yeah. Thank you for bringing us back there. So I think what we saw in KEYNOTE-355—remember the first-line pembrolizumab with chemotherapy study that really established that as a standard of care—if you looked at the subset of patients who had a disease-free interval of less than a year, there did not appear to be much of an incremental advantage to adding the checkpoint inhibitor, and that was at a time and place when we were not routinely using a checkpoint inhibitor in the neoadjuvant or adjuvant setting.

So when I keep that in the back of my mind, and I look at the TROPION-Breast02 eligibility, where patients could be recurring within 6 months of their adjuvant therapy, I'm more inclined to lead with datopotamab in that population.

Dr. Hurvitz:
Thank you. Yeah, certainly a nuanced decision-making process, and perhaps if the patient had a history of ILD or something that would preclude using Dato-DXd, I think probably grabbing for sacituzumab govitecan would be the art of medicine, and us having to interpret the data in the context of the patient sitting before us.

Thank you so much, Tiffany, for this excellent discussion. And that's all the time we have today, so I want to thank our audience for listening in, and thank you, Tiffany, for joining me and for sharing all your valuable insights. It was great speaking with you today.

Dr. Traina:
Thank you. Likewise, Sara.

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