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Chairperson's Perspective: TROP2-Targeted ADCs in TNBC and HR+ mBC

Opening:

Welcome to CE on ReachMD. This activity, titled **"TROP2 Targeted Antibody Drug Conjugates in Triple Negative Breast Cancer and HER Positive Metastatic Breast Cancer: Advancing Care Through Clinical Evidence and Interdisciplinary Collaboration"** is provided by **Gilead Sciences, Incorporated.**

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Dr. Brufsky:
Well, hello, and thank you today for listening to this talk. I am Adam Brufsky. I'm a Professor of Medicine at the University of Pittsburgh at the UPMC Hillman Cancer Center, and today I'm going to give you my perspective on TROP-2–targeted antibody-drug conjugates in triple-negative breast cancer and hormone receptor-positive metastatic breast cancer.

So there clearly is an unmet treatment need in hormone receptor-positive HER2-negative metastatic breast cancer. With CDK4/6 inhibitors in the first line, we get a PFS of anywhere from 2 to 3 years. But after that, I think that generally in the second line and third line, we really have lower progression-free survivals and a poorer prognosis, especially with endocrine-targeted therapies in the second line, current therapies after CDK4/6 resistance are about 5 to 7 months, and third line and beyond with single-agent chemo is about 7 months, with trastuzumab deruxtecan is anywhere from 10 to 13 months. So we do have an unmet need here.

Antibody-drug conjugates are comprised of an antibody to a particular antigen. They're internalized into the endosome, degraded in the lysosome, and then the payload is released. We also have cleavable payloads which we can actually have release of the payload in the extracellular space as well, leading to what's called a bystander effect.

TROP-2 in particular is an antigen found on trophoblast cells. However, it turns out is expressed at fairly high levels on hormone receptor-positive metastatic breast cancer. About 60% to 70% have fairly substantial expression. And again, the early trials of TROP-2 ADCs confirm a response rate in this setting of about 31% to 32%.

And we now have three large randomized phase 3 trials of three different TROP-2–targeted ADCs in hormone receptor-positive metastatic breast cancer. The first one is sacituzumab govitecan. This has an antibody-drug ratio of 7.6 to 1. It has a linker which is hydrolyzable, it's a CL2 linker. And it's hydrolyzable and low pH and for SN-38, which is a metabolite of irinotecan, the antigen is TROP-2 antibody, and again, SN-38 is more potent than irinotecan.

The TROPiCS-02 trial took 532 women with metastatic or locally recurrent inoperable hormone receptor-positive HER2-negative metastatic breast cancer progressing after at least one endocrine therapy, taxane, and a CDK4/6 inhibitor in any setting, at least two but

not more than four lines of chemo for metastatic disease and with measurable disease by RECIST 1.1, randomized into sacituzumab govitecan or treatment of physician's choice, which was various chemos, capecitabine, vinorelbine, gemcitabine, or eribulin.

As the progression-free survival was improved, and what is really interesting, even though it's only 4 months to 5.5 months, the hazard ratio was statistically significant at 0.66. As you can see looking at these Kaplan-Meier curves, within the first 3 months, about 60% of the patients progressed on the physician's choice of chemotherapy, where only 20% progressed on the sacituzumab govitecan. This actually was maintained. So about 20% of the patients had a clinically meaningful benefit to this therapy in terms of PFS that did appear actually to be sustained, as you can see from these Kaplan-Meier curves.

Looking forward, this did result in overall survival. Relative risk reduction was about 21%. Hazard ratio of 0.79. *P* value was significant. Overall response rate was a little bit better, 61% versus 47%.

Now, there are other TROP-2 ADCs that have been developed, datopotamab deruxtecan, again as a humanized anti–TROP-2 antibody with a topoisomerase inhibitor payload. In this case, an exatecan derivative, DXd, and a tetrapeptide-based cleavable linker.

And I think that the trial of TROPION-Breast01 is very similar to TROPiCS-02, a little bit different. These are patients, again, with hormone receptor-positive HER2-negative metastatic breast cancer that had progressed with at least one or two lines of chemo, this is more of a second- and third-line regimen, and they were randomized to Dato-DXd or investigator's choice of chemotherapy, in this case eribulin, vinorelbine, gemcitabine, or capecitabine. This was about 360 patients per arm, and there were dual primary endpoints of PFS and OS in this study.

And as you can see here, PFS was improved. Again, very similar hazard ratio to TROPiCS-02, about a hazard ratio of 0.63. That was statistically significant. Absolute benefit was 6.9 months with Dato-DXd versus 4.9 months with investigator choice of chemo. And about 25% of the patients progressed on investigator choice of chemotherapy in the first 2 months, versus only about probably 15%. So about 15% of patients had a benefit here, again very similar to the TROPiCS-02 data but in a second- and third-line setting.

Given the fact that you know this was post CDK4/6, it's interesting to note that it didn't matter the duration of prior CDK4/6 inhibitor here, that generally what the benefit was, still that hazard ratio of 0.61 with a benefit of about 2 to 3 months over investigator's choice of chemotherapy, whether you had a rapid progression on CDK4/6 inhibitor or more than 12-month progression on CDK4/6 inhibitor.

Additionally, though, there was no difference in overall survival, which is about 18 months in both arms of the study, a little bit less than I think a lot of us have seen in trials of this type, but nonetheless, there was no difference. And if you actually censored the use of another antibody-drug conjugate in the control arm, in this case most people in the control arm, at least those treated in the United States, were likely given trastuzumab deruxtecan for HER2-low disease. But if you censor those patients, you can see here still not statistically significant, but a little bit of a trend from 17.5 months to 19 months. But still, nonetheless, it's not a surprise because there were so many other therapies the patients received after they progressed on Dato-DXd or the control, that I think it's difficult to see a survival advantage in this population.

The last of the three drugs is sac-TMT, or sacituzumab tirumotecan. This, again, is an antibody-drug conjugate with a novel pyrimidine thiol linker conjugated to a novel topoisomerase inhibitor with a drug-to-antibody ratio of 7.4. Again, I think that it has improved stability of the antibody-drug conjugate, but you can get extracellular hydrolysis of the linker, even though it is more stable, allowing a bystander effect.

And the OptiTROP-Breast02 study was presented last year at ESMO. Again, very similar to the other two studies we talked about, women who had hormone receptor-positive HER2-negative metastatic breast cancer had prior one to two lines of chemotherapy and had to have at least one endocrine therapy, CDK4/6 inhibitor, and a taxane in any setting. Received sac-TMT at 5 mg/kg every 2 weeks versus investigator's choice of chemotherapy, eribulin, capecitabine, gemcitabine, or vinorelbine. Primary endpoint was PFS. Again, I think that it was a stepwise statistical trial. In other words, if you met the PFS endpoint, then you could go to the OS endpoint of this particular study.

And you can see here, PFS was really quite dramatic with this particular drug. It's actually a doubling or more of progression-free survival. Sac-TMT is 8.3 months versus 4.1 months with chemotherapy, with a PFS rate of 61% versus chemotherapy alone of 25%. That seems to be a little bit lower than the other two trials. The control arm didn't perform as well, which is one kind of issue with this

particular study. It was done mostly, if not all, in a Chinese population, and so therefore it wasn't as diverse a population, so that is a potential limitation of this data. But nonetheless, the hazard ratio is 0.35, which is statistically significant.

And again, I think fairly dramatic data with an actual overall survival benefit. Again, very few events in a trial of 400 patients, it appears that well, 52 patients have died, but nonetheless, the hazard ratio for death was 0.33, again subject to a very short follow-up, only 7.4 months, so to be continued.

So at this point in time, the NCCN guidelines do recommend for hormone receptor-positive disease that has either visceral crisis or endocrine-refractory disease, they recommend trastuzumab deruxtecan, which we didn't talk about, for those patients that are HER2-low, or those patients who are HER2 IHC 0 or not a candidate for trastuzumab deruxtecan. Generally, you could give sacituzumab govitecan, which is category 1, or generally datopotamab deruxtecan also. So these both are in the NCCN guidelines for second-line chemotherapy and beyond in this setting. So we do have two interesting agents.

OptiTROP was not approved yet by the NCCN, given the limitations, as I described before, but nonetheless, I think it's something that we are actively pursuing in the US population and further phase 3 clinical trials.

So now we'll talk a little bit about triple-negative breast cancer. Again, the first one is sacituzumab, and we have the ASCENT study, which is published in the *New England Journal of Medicine* almost 5 years ago now. And this took women with metastatic breast cancer and patients with metastatic breast cancer, occasional man, with more than two chemotherapies for advanced disease, and at least one in the advanced setting; 529 patients were randomized to physician's choice of chemo or sacituzumab govitecan. The primary endpoint was PFS. Secondary endpoint was OS.

PFS was improved from 1.7 months to 4.8 months with a hazard ratio of 0.41. Overall survival was improved from 7 months to about 12 months with a hazard ratio of 0.51. And actually, the FDA granted a regular approval to sacituzumab for patients with unresectable, locally advanced or metastatic breast cancer who had received two or more prior systemic therapies, at least one of them for metastatic disease.

Now, I think the natural trial to do was a trial like ASCENT-03, which is to try sacituzumab govitecan as first-line therapy. And so ASCENT-03, which was initially presented at ESMO this year, published in *New England Journal of Medicine* late last year, took patients with previously untreated, locally advanced inoperable metastatic breast cancer who were not candidates for PD-1/L1 inhibitors, either they were CPS less than 10 or CPS greater than 10 and previously treated with a PD-1/L1 inhibitor in the curative setting.

They were randomized to sacituzumab or govitecan or chemotherapy with paclitaxel, and they had paclitaxel or gemcitabine/carboplatin. Now, 81% of the patients actually in the chemotherapy arm crossed over to second-line sacituzumab govitecan. That's an important aspect of this trial.

As you can see here, sacituzumab did improve over chemotherapy with a hazard ratio of 0.62, 7 months in the chemo arm versus a little under 10 months in the sacituzumab arm. And again, this is really maintained at 12 months and beyond. The 12-month PFS is 41% sacituzumab versus 24% with chemo. And so that's the first trial in the first line. So now this is potentially moving this drug to the first line.

For PD-1/L1-positive patients, these are patients now with a CPS greater than 10, in ASCENT-04, 443 of these patients are randomized to sacituzumab and pembrolizumab or chemotherapy and pembrolizumab with a primary endpoint of PFS and secondary endpoints of overall survival.

And as you can see here, giving chemo with sacituzumab resulted in a PFS of 11 months versus about 7.5 months, 7.8 months with chemo and pembro, for a hazard ratio again of about 0.56. A 6-month PFS rate of 72%, 12-month PFS rate of about 50%. So this is clearly an improvement over the standard and really does represent, potentially, as we're going to say at the end, a new standard of care to give the antibody-drug conjugates earlier in the treatment of triple-negative breast cancer.

Overall survival was not reached, but again, not a lot of events had occurred here, 53 overall survival events out of 221 with the sacituzumab arm versus 61 in the chemo arm. But again, 81% of the patients did cross over. So while there was a trend, it's unclear, given the fact there is a survival advantage of sacituzumab in the second line, whether this will actually result in improved overall

survival.

Dato-DXd was also tested as first-line therapy in the TROPION-Breast02 study. And these are patients, again, with triple-negative breast cancer, had no minimum disease-free interval after progression, were randomized to Dato-DXd or investigator's choice of chemotherapy with dual primary endpoint of overall survival and PFS. This, again, is first line.

And as you can see here, the PFS hazard ratio is 0.57, 5.6 months in the control arm and almost 11 months sacituzumab arm, again statistically significant. There was also a statistically significant survival advantage here. As you can see here, the hazard ratio is 0.79 with a 12-month overall survival rate of 75% versus 67% with the investigator's choice of chemotherapy. The median OS was about 2 years versus about a year and a half for the chemotherapy control arm. So again, this is for patients who are PD-1/L1 negative or unable to receive a checkpoint inhibitor as first-line therapy.

And as you can see in this population, like the ASCENT-03 and -04 study, or ASCENT-03 in particular, there was a statistically significant PFS benefit. And in this case, unlike ASCENT-03, there was an overall survival benefit.

The final study really to talk about is the OptiTROP-Breast01 study. This is sac-TMT in previously treated or locally recurrent or metastatic breast cancer. And again, these are patients who have relapsed or are refractory to two or more prior chemotherapy regimens. Again, at least one of them could be in the neoadjuvant setting. This is very similar, I think, to the ASCENT trial. This was sac-TMT versus physician's choice of chemotherapy and treatment until disease progression, with a primary endpoint being PFS by a blinded independent review, the secondary endpoint being overall survival.

As you can see here, this data was recently presented at ASCO 2024. And as you can see here, the PFS again was fairly dramatic. The PFS difference was 2.5 months in the chemotherapy arm and was 6.7 months in the sac-TMT arm, with a 9-month PFS rate of 34% versus 6% in the chemotherapy arm, a hazard ratio 0.32.

So again, the criticism of that last trial is that it was performed mostly in a Han Chinese population, and I think that whether we get those improved survival advantages in a more genomically heterogeneous population is unclear.

So I think the guidelines at this point in time have now been changed. The most recent guidelines from the NCCN from about a month or 2 ago and in early 2026, and you can see here for patients with a CPS greater than 10, regardless of BRCA status, the preferred regimen at this point in time is sacituzumab govitecan and pembro as category 1. With a CPS less than 10 and no germline BRCA mutations, I think that sacituzumab govitecan or datopotamab deruxtecan are both recommended by the NCCN. In the second line, if you've got a germline BRCA mutation, I think a PARP inhibitor is preferred, or if you haven't had sacituzumab at that point, that would be a reasonable place to put it per the NCCN guidelines.

So again, I think that TROP-2 ADCs really have revolutionized the care of patients with hormone receptor-positive metastatic breast cancer and triple-negative breast cancer. Again, as I said before, the real effort now is to move all of these TROP-2 ADCs into first-line treatment of metastatic disease.

Thank you very much for listening to me, and I hope you enjoyed this presentation.

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