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First-Line Management of HR+/HER2-Low Breast Cancer With Brain Metastases

Announcer:
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Dr. O'Brien:
This is CE on ReachMD, and I'm Dr. Barbara O'Brien, a neuro-oncologist at MD Anderson Cancer Center in Houston, Texas, in the US.

Dr. Harbeck:
Hi, and I'm Dr. Nadia Harbeck. I'm the Director of the Breast Center at LMU University Hospital in Munich, Germany.

Let's start our discussion with a case. We have a 42-year-old woman. Her initial diagnosis was in October 2021 with hormone receptor-positive, HER2-low, 1+, G3 lobular early breast cancer. She received breast-conserving surgery, tumor turned out to be a T2N1 with 2 out of 3 sentinel nodes and a high-risk recurrence score. So we gave her 6 cycles of TC chemotherapy, radiotherapy to the right breast and regional lymph nodes, GnRH plus AI adjuvant abemaciclib until June 2024.

About 1.5 years later, she came back. She presented with intermittent headaches. Staging revealed multiple liver mets, elevated transaminases and bilirubin levels, disseminated bone mets, and 2 small intracranial lesions of 3 and 4 mm. Liver biopsy revealed hormone receptor-positive, HER2 2+, FISH non-amplified metastatic breast cancer.

So we felt that this was a visceral crisis, and there was no time to go down the endocrine-based targeted route, so we decided based on the DB06 data that we should start her on T-DXd as the first-line therapy, give her bisphosphonates. The initial restaging after 3 months revealed good systemic remission. The liver, the transaminases dropped, and the CNS lesions were not visible anymore, and she did not complain about more headaches.

So, Dr. O'Brien, how would you have approached this case? Do you think we did the right thing?

Dr. O'Brien:
So, yes, I would completely agree with that approach. I think this highlights a few important points in taking care of patients who have hormone receptor-positive, what we would call, HER2-low disease. She had what sounds like a short interval until she had progressive disease, and there's a large burden of liver disease and then of course the CNS mets.

And we don't really have strong, high-level of direct evidence for this particular approach in brain mets, but extrapolating from what we know from DESTINY-12 and the benefit of T-DXd in brain mets, and what we know from DESTINY-6 for patients with HER2-low

disease, I think this makes complete sense. And we can actually see that with this close interval follow-up, the patient had what sounds like resolution of those 2 small, asymptomatic mets, which gives us increased confidence that we're on the right track here.

Dr. Harbeck, can you review some more of the recent clinical data demonstrating intracranial activity of ADCs in hormone receptor-positive, HER2-low metastatic breast cancer?

Dr. Harbeck:
Well, certainly, unlike in the HER2-positive setting, though, the evidence in the hormone receptor-positive, HER2-low metastatic breast cancer area is limited with regard to activity of these ADCs, not because I don't think they work, but because the studies weren't designed that way.

We have 3 ADCs registered and approved in the luminal-like breast cancer space. That would be trastuzumab deruxtecan, based on the DB06 data, as we treated our patients in the first-line setting, but also DB04 showed substantial activity in the second-line setting. Then we have datopotamab deruxtecan, which is registered in the second-line and beyond setting based on the TROPION-Breast01 study. And we have sacituzumab govitecan based on the TROPiCS-02 study, also in the second-line setting.

We have the subgroup analysis from the trials, but I think for T-DXd, the best evidence we have is from the HER2-positive setting, DB12. And I think that there is no reason to believe it would not work the same in the HER2-low space. So we can discuss this maybe later.

The datopotamab deruxtecan, there's some interesting data from the TUXEDO-2 trial in the triple-negative active brain mets with about a 37% response rate, but it's only a few patients, so not very substantial evidence, but showing some activity, but obviously also these data not as good as the ones for T-DXd in general.

And then the sacituzumab, there is subgroup analysis from the TROPiCS-02 study, but the main body of evidence would be also from the triple-negative setting from the ASCENT trial, where we have about 12 patients with brain mets, and they have a longer PFS, although it's very short overall, but the overall survival then is similar. So there seems to be, if you want to summarize, that limited intracranial efficacy of sacituzumab govitecan relative to its systemic activity.

But I think for T-DXd, one can draw on the vast body of evidence from the HER2-positive space, and that's also the reason why we chose this treatment for our patient.

Dr. O'Brien, would you agree with that? Or do you have different thoughts about these ADCs in hormone receptor-positive HER2-low disease?

Dr. O'Brien:
So, yeah, I would completely agree. I think we've got the most compelling data for T-DXd. Sacituzumab, unfortunately, despite having a window-of-opportunity study that shows that it can get into brain metastasis, the real-world experience has been inconsistent. And of course, as you mentioned with the ASCENT trial, we didn't really see anything very compelling there.

But I think this does open the door to further exploration of ADCs in brain mets. And there was a time where we really didn't expect that antibody-drug conjugates, because of their size, would have much benefit in the CNS, but it turns out that we are seeing that. And I think another example of this is patritumab deruxtecan, which recently is showing some early but interesting activity in CNS mets, including LMD.

Dr. Harbeck:
Yeah, I think you're completely right. I think we now gain confidence that these larger molecules could be active in brain mets, and I think it's a step forward that we include patients at least with the stable brain mets in these trials today, which, I think, helps us to gain some evidence.

But let's play around with the case a little bit, Dr. O'Brien, and if the patient had had HER2 ultra-low disease, would you have changed this treatment approach? Maybe go more for a local therapy? Or do you trust that T-DXd also works in ultra-low disease in the brain?

Dr. O'Brien:

It's a great question. So these patients who have HER2 ultra-low disease, we just have this membrane staining, I think that based on some of the data that we have, again, it's not direct high-level evidence, but we do have some data where you could extrapolate that there may actually be some benefit from these patients.

Dr. Harbeck, I'm curious, what would your approach be in HER2 ultra-low?

Dr. Harbeck:
No, I completely agree. Be it CNS or systemic disease, I wouldn't do anything different, and I also strongly believe for the systemic disease we should treat ultra-low as we treat HER2-low.

Dr. O'Brien, if that patient had had prior stereotactic radiosurgery, is there anything we should do differently?

Dr. O'Brien:
I think it depends whether it was the same lesions that were treated with SRS or whether they're now in a different location. I think if the patient has already had SRS, this tells us that they're having the development of further brain mets, and so I might be thinking of the rate of the development of these brain mets, and it may actually, to me, make a more compelling case to use a systemic agent.

Dr. Harbeck:
Yeah, I completely agree. I think that T-DXd is a very good option for those patients as well. You can go back and do a stereotactic radiosurgery one after the other. There is really no limit, is there, if the lesions are small and if you can target them well, you can also go back in.

Dr. O'Brien:
When I'm thinking about this conversation that we're having, just a few years ago we wouldn't be able to have this discussion about sequencing systemic therapies with local therapies, and I think that's a beautiful thing. It's really nice to be able to sit in a room with a patient and also have that talk.

Well, that's all the time we have today, and we hope the discussion will be useful in your practice. Thanks so much for listening.

Announcer:
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