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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Sequencing Strategies for Second-Line and Beyond Treatment of HER2+ MBC

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Dr. Sammons:
This is CME on ReachMD. I'm Dr. Sarah Sammons. Joining me today is my friend and colleague Dr. Carey Anders, and our discussion today will focus on sequencing strategies in HER2-positive metastatic breast cancer in the second-line and beyond.

So, Carey, I'm going to start out with a case. We have a patient: she is a high school teacher, and she developed de novo metastatic hormone receptor-negative HER2-positive breast cancer and has been on her trastuzumab pertuzumab after taxane induction for about 2 years now. And now, in case 1, we are seeing that she has progression in the liver, no evidence of progression, new brain metastasis, or anything like that. What choice of therapy are you going to think about for that patient in the next line?

Dr. Anders:
Oh, thank you, Sarah. And I think this is all too common in our clinic. So, I think in a patient, as you described, who's done well on dual antibody therapy for better part of 2 years and has developed an extracranial disease progression, I certainly would be thinking about changing therapy in that setting.

The best data that we have right now is largely trastuzumab deruxtecan based on the DBO 1 or DESTINY-Breast01 or DESTINY-Breast03 study. The latter being randomized against our prior second-line standard of care T-DM1, where we did, in fact, see a substantial improvement favoring T-DXd.

So, in the setting of a solitary liver progression with no other comorbidities, T-DXd would be my second-line therapeutic choice.

Dr. Sammons:
Okay. Yes, I think that's guideline-driven. I think second-line for the vast majority of patients is certainly with progression from the neck down is going to be to move to T-DXd. Now, I'm going to go in a more challenging case, but a case that we're seeing more and more.

So, same patient. She's been on HP for 2 years now. We get scans of her body, and she has actually no evidence of disease from the neck down, but she developed headaches, and we did a brain MRI, and we see two new small brain metastases. She undergoes radiation: what are you going to do next?

Dr. Anders:
Again, a very common scenario. So, we're now 2 years into dual antibody therapy and have solitary CNS progression. You described the lesions as small, so they're probably very amenable to radiosurgery. And I think on that setting, based on the ASCO guidelines, one option in the setting of stable extracranial disease is to maintain dual antibody therapy.

I think this is also a space that you and I are really interested in in terms of what we would deem a secondary progression. How can we

prevent a second intracranial event? And this is where clinical trials are looking at and evaluating bringing in some of our tyrosine kinase inhibitors, namely tucatinib, and after radiosurgery with dual antibody therapy.

Now, I wouldn't do that off of a clinical trial, but, in fact, there is a clinical trial nationally enrolling called the BRIDGET trial, which is evaluating bringing in tyrosine kinase inhibitors earlier in this setting.

Dr. Sammons:
I agree. I think very reasonable to continue her monoclonal antibodies and just watch her brain very closely. I think if she had another intracranial progression after that, I personally would probably change her therapy to something more intracranial, probably penetrant.

So, let's talk about a case: is there ever a time when you would not give trastuzumab deruxtecan in the second-line setting? Is there ever a time that you would choose a different sequencing approach? Like, let's say the HER2CLIMB regimen with tucatinib, cape, and trastuzumab?

Dr. Anders:
No, it's a great question, and in actually drafting the HER2-postive breast cancer brain metastasis guidelines, we did give some options here. So, I think in the HER2CLIMB study, similar to what we've seen across some of the, in particularly, the pooled analysis of DESTINY-Breast1, 2, and 3, we have randomized data for stable, progressive, or new brain metastasis.

I know we're not supposed to do cross-trial comparisons. But the intracranial response rate in the HER2CLIMB regimen was around 47% and, as you mentioned earlier, in the DESTINY series, a bit higher, maybe 60-70% in some series.

So, I think either of those regimens are very reasonable in the setting of progressive brain metastasis. I think it also depends on the patient. And as we've discussed, the T-DXd does have a risk, albeit relatively low, 10 to 12% of pneumonitis and interstitial lung disease, which I think, as a community, we're doing much better managing and preventing.

And then, with regards to the HER2CLIMB regimen, it does have an oral component. So, that can be challenging for some patients. It also portends more GI toxicity with diarrhea. So, I think also kind of understanding what your patient's predilection for side effects might be and helping choose based on those factors as well.

Dr. Sammons:
Yeah, I totally agree. So, to briefly recap, second-line for the vast majority of patients is going to be T-DXd. In the setting of highly active brain metastasis, T-DXd has efficacy and active and stable brain meds, which is kind of new data over the last year, which has been exciting.

So, still reasonable to use T-DXd in the second-line. Also, reasonable to use HER2CLIMB, and this is where patient preference comes in. I guess the only other thing I would say is alopecia with T-DXd is more —

Dr. Anders:
Great point.

Dr. Sammons:
— common than with HER2CLIMB, and some patients just really are not ready to lose their hair. So, discussing those risks and benefits is absolutely key.

Thank you so much for joining us today, and thank you, Dr. Anders, for joining me. And we hope this discussion will be useful in your practice.

Dr. Anders:
Thank you.

Announcer:
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