Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/the-evolving-treatment-landscape-for-mbc-emerging-therapies/29831/

Released: 12/30/2024
Valid until: 12/30/2025
Time needed to complete: 1h 32m

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

The Evolving Treatment Landscape for MBC: Emerging Therapies

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Gradishar:
Hello, this is Bill Gradishar from Northwestern University on CME for ReachMD. And in this brief lecture or discussion I'm going to talk about some of the emerging strategies for treatment of metastatic breast cancer.

And within this space, we know we've had much progress made in all of the different subtypes of breast cancer, whether it's triple-negative breast cancer, HER2-positive disease, or endocrine-sensitive breast cancer. And among the strategies that have been employed have included novel targeting therapies that are often combined with endocrine therapy; as an example, immunotherapies and indeed also newer antibody-drug conjugates that have proven to be very effective in both triple-negative breast cancer as well as in HER2-positive disease.

So with that said, one truism is that metastatic breast cancer is not cured, so there is an unmet need with respect to trying to improve outcomes. Even though we have very effective therapies that have prolonged survival, extended the time between treatments needing to be changed, newer therapies are clearly needed.

In that space, there are a variety of different drugs. I mentioned a few of those already, but among the antibody-drug conjugates that are turning out to be quite interesting, include datopotamab deruxtecan which has been evaluated in a number of trials that are referred to as the TROPION trials, and two of them, TROPION-Breast01 and TROPION-Breast02, are two trials that I'd like to comment on.

In 01, this was a population of patients with hormone receptor-positive disease who were not considered to be endocrine-sensitive any longer, could have had a couple of prior chemotherapy regimens, and they were randomized between datopotamab deruxtecan or chemotherapy of physician's choice. And in this experience, which has been reported, there was an improvement in PFS favoring Dato-DXd by about 2 months. So a clear signal that compared to sort of standard chemotherapy, this may offer some advantages.

Now, TROPION-02, also evaluating datopotamab deruxtecan, or Dato-DXd, is being conducted in the neoadjuvant setting in patients with triple-negative disease who are not viewed as candidates for immunotherapy. And as you all know, based on the KEYNOTE trial with pembrolizumab, this is often a standard in the neoadjuvant setting for triple-negative breast cancer. So in the TROPION-B02 trial, patients are either receiving Dato-DXd or chemotherapy. And this is a trial that will be conducted in approximately 600 patients. We don't have data yet from this trial. But again, we anticipate that will be emerging with time.

Now, there are a couple of other clear areas of interest with respect to antibody-drug conjugates, and one of the drugs that has emerged in the last 5 years that has made a huge impact is trastuzumab deruxtecan. It's been evaluated in a variety of settings, in the metastatic disease setting. This is a drug that is targeting HER2 and initially clearly shown to have significant benefit in that space, but subsequently, it was also determined that in patients with HER2-low and ultra-low, that it may also have activity.

So there are a variety of DESTINY trials, this family of trials that is evaluating trastuzumab deruxtecan that have either been reported or are ongoing, and I'll just mention a few of those. The most recent one that got a lot of attention was DB-06, or DESTINY-Breast06. And this was a trial that looked at patients with HER2-low or ultra-low compared to chemotherapy of physician's choice, clearly showing the advantage of trastuzumab deruxtecan over chemotherapy, including in the patients with ultra-low. And this is a population not yet clearly defined by ASCO-CAP guidelines, but it's more than 0, less than 1%. And again, it really highlights that a significant fraction of all breast cancer patients may ultimately fall within the space of either HER2 positive all the way down to HER2 at minimal levels of expression, where a strategy like this might be helpful.

The other trials, including DB-08, DESTINY-Breast08, is looking at combinations of trastuzumab deruxtecan with a variety of agents, including chemotherapy like capecitabine, anti-hormonal agents like aromatase inhibitors and fulvestrant, targeted agents like capivasertib, the AKT pathway agent that also targets PI3 kinase, and also in combination with immunotherapy like durvalumab and paclitaxel. Again, we don't have data from this trial, but that will be emerging, looking at how combinatorial strategies may be employed.

And then DESTINY-B09 is also looking at whether or not we can supplant, move out of the way, the CLEOPATRA regimen. And as you recall, the CLEOPATRA regimen, which is our first-line treatment of choice for patients with HER2 metastatic disease, includes a taxane, trastuzumab, and pertuzumab. And in this trial, the DB-09 is comparing the CLEOPATRA regimen to T-DXd with pertuzumab or on its own. And this will be a very important trial, because it may ultimately show – we don't know yet – that trastuzumab deruxtecan is superior to the taxane-pertuzumab- trastuzumab regimen. So we await the results of that trial.

Now, within the space of small molecules, still in the HER2 space, we of course have had another agent recently, in the last several years, approved, and that is tucatinib, which follows in the lineage of lapatinib, neratinib, and now tucatinib, targeting the HER2 population. We know the HER2CLIMB regimen with trastuzumab, capecitabine, and tucatinib was superior to capecitabine and trastuzumab, and that emerged as an option for patients with HER2-positive breast cancer with activity and CNS disease as well.

The HER2CLIMB-02 trial compared T-DM1 to tucatinib and T-DM1. And this also showed that you could incrementally improve the PFS with that combination. Now, of course, within that same space, we have other combinations that could be considered, including T-DXd. So where this might be used is not entirely clear, but there is evidence that combinations with the small molecule and T-DM1 is better than T-DM1 alone.

And then finally, the HER2CLIMB-05 trial is looking at, in essence, the CLEOPATRA regimen, where after 4 to 8 cycles of treatment, patients who are responding typically stop the chemotherapy and then continue on the antibodies alone. That would be what we view as standard. In the 05 trial, patients will either continue as the standard of care on H and P, or they'll switch to the combination of tucatinib with HP. And again, the idea is that if you add a small molecule to HP in the setting, might you further prolong the time until disease progression? So we don't have the results of that trial, but we anticipate that in the coming year or two.

And then finally, within the space of ER-positive disease, we have a number of different agents that have been approved, small molecules to combine with endocrine therapy, including, several years ago, alpelisib for PI3 kinase mutations. And then drugs that target the AKT pathway, which include capivasertib. And the CAPItello-291 trial, which led to the approval of capivasertib, clearly demonstrated that if you combine capivasertib with fulvestrant versus fulvestrant alone, particularly in patients who have abnormalities in this pathway, that you enhance the PFS significantly. So that drug is approved. Probably has fewer side effects, particularly with respect to hyperglycemia, than was seen with alpelisib. So this is another example of where small molecules that target a particular pathway can improve the outcome of patients with ER-positive breast cancer.

So what we have in some are a number of different strategies that are being explored. Some have led to drug approvals available to us now. Others are still in trial, and we'll see what that data shows us when the results emerge. But the ultimate goal is to improve the time patients are able to stay on a given therapy and prolong their overall survival. And these strategies are among those that are being explored to achieve that goal.

Well, I want to thank you for your attention. I hope you gained something from this insight overlooking some of the trials that we anticipate coming along in the next couple of years.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Prova Education and is part of our MinuteCE curriculum.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.