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/a-look-at-her2-targeted-tkis-how-does-target-specificity-impact-outcomes/15226/

Released: 03/20/2023
Valid until: 03/20/2024
Time needed to complete: 1h 02m

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

A Look at HER2-Targeted TKIs: How Does Target Specificity Impact Outcomes?

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME 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. Cercek:
I am Andrea Cercek. I'm a Medical Oncologist at Memorial Sloan Kettering Cancer Center and the Section Head of the Colorectal Section, and it's my pleasure today to talk about advancing the standard of care in HER2 targeted metastatic colorectal cancer, and specifically looking at HER2 targeted TKIs and how does the target specificity impact outcomes.

So we learned very early in metastatic colorectal cancer, even in preclinical trials in mouse models, that we need dual HER2 blockade, not just single agent as is the case in some cancer, some solid tumors. So here we see that the PDXs, the mouse models, were sensitive to dual HER2 blockade with lapatinib and trastuzumab, but not with either drug alone. And this has continued this pattern that we really need dual inhibition to get a benefit in colorectal cancer.

So looking at tucatinib and trastuzumab in terms of sensitivity in PDXs, in mouse models as well, we clearly see that the combination is needed; that we need dual inhibition with both tucatinib and trastuzumab to get the benefit. We just don't see it with either drug alone.

And then now actually with MOUNTAINEER data, which was tucatinib and trastuzumab in refractory HER2 amplified RAS wild-type metastatic colorectal cancer, the study was designed as a combination of tucatinib and trastuzumab. But in order to - when the results were positive to obtain FDA approval, there was a single agent just tucatinib monotherapy cohort. And so now we see clearly here that what we saw in preclinical models in the PDXs actually translates to patients. Because single agent therapy just did not work. The overall response rate was just 3% with tucatinib catnip alone, and it was incredibly robust in the combination, it was upwards of 40%. And so a huge difference really just supporting that we really should not treat metastatic colorectal cancer with one drug and that we really need dual combination monoclonal antibody and TKI.

And here again, just looking at what we know about this disease, we know that HER2 amplification is associated with anti-EGFR resistance. And that's in patients that are HER2 amplified RAS wild-type left-sided where we might treat with anti-EGFR therapy. What we see here, this is a study retrospective analysis of patients that received anti-EGFR therapy. And you can clearly see that the progression-free survival was significantly worse in those that were HER2 amplified. And so really suggesting that even if they're RAS wild-type, we shouldn't treat them with anti-EGFR therapy, we should focus on HER2 amplification as the target instead in this patient population.

So just looking a little bit more, sort of a deeper dive into biomarkers of resistance or sensitivity in HER2 amplified tumors, MyPathway was one of the earlier studies using combination therapy in HER2 amplified tumors. And here, patients with – all-comers were treated, including RAS wild-type, RAS mutated, PI3 kinase wild-type, PI3 kinase mutated. And what we learned here really is that the tumors need to be HER2 amplified, RAS wild-type, and preferably also P13 kinase wild-type, because we see that when they're mutated, when we have a co-occurrence of a RAS mutation, the response rate is just significantly worse. So in this case, the overall response rate in the

wild-type population was 17%, compared to just 1%, actually was just 8% rather, it was just one patient, and the response was very, very brief. So when utilizing this treatment, we really need RAS, wild-type tumors.

And the Heracles study also showed, you know, very similar data here that absence of RAS, BRAF, and PI3 kinase mutations in circulating tumor cells. So just a different way of looking at it, patients had circulating tumor cells, evaluated, and in patients who did not have emergence of these mutations or did not have the presence of these mutations, there was a significantly longer time to progression. Again, just stating the same thing that really the benefit here is derived in HER2 amplified RAS, BRAF, PI3 kinase wild-type tumors much more so than in mutated.

And again, in terms of what else do we know, we've seen this in Heracles, we've seen this in other studies as well that the benefit really favors higher gene copy number by FISH, higher amplification, 3+ by immunohistochemistry is really the key in terms of obtaining the best of a benefit that's sort of the deepest responses and the most durable benefit.

And then in terms of drugs, and does the drug matter? Does it make a difference? We know from data that tucatinib is a highly selective HER2 tyrosine kinase inhibitor, and that selectivity actually improves efficacy but also improves tolerability, seeing less of the sort of toxicity that we see with this class of drugs including skin rash, diarrhea, compared to less selective TKIs. And then also of course, that leads to better inhibition, better response, and then better compliance and better tolerability for patients as well. So really, the selectivity of the drug does make a difference in terms of outcomes and in terms of patient tolerance.

And you know, these are just the results to show you kind of the three main studies that have been done with dual HER2 targeted therapy. So the Heracles study utilized lapatinib and trastuzumab, MyPathways, I discussed was pertuzumab and trastuzumab, and then MOUNTAINEER, tucatinib and trastuzumab. And that's the number of patients listed, this was earlier data, but the response rates, you know, are higher in MOUNTAINEER, again with all the caveats of cross-trial comparisons, all three studies showing significant response rate, and this was all in the refractory setting, but just deeper responses, better response rate, and, better PFS, in MOUNTAINEER with the combination of tucatinib and trastuzumab.

And thank you very much for your attention.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.

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