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In the Medical Spotlight: Antibody-Drug Conjugates in Advanced HER2-Positive Gastric/Gastroesophageal Junction Cancer

Announcer:
Welcome to CME on ReachMD. This activity, titled “the Medical Spotlight: Antibody-Drug Conjugates in Advanced HER2-Positive Gastric/Gastroesophageal Junction Cancer” is provided by Prova Education.

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Dr. Marshall:
This is CME on ReachMD and I’m Dr. John Marshall. Today, I’ll be highlighting the key messages and clinical data presented at a satellite symposium by Prova Education in conjunction with The World Congress on GI 2023 Annual Meeting and was entitled In the Medical Spotlight: Antibody-Drug Conjugates in Advanced HER2-Positive Gastric/Gastroesophageal Junction Cancer. I presented at this symposium along with my esteemed colleagues, Dr. Elizabeth Smyth and Dr. Mar Iglesias.

So our meeting was really focused on antibody-drug conjugates in advanced HER2-positive gastric and gastroesophageal [GE] junction cancer, and as I said, it was presented in Barcelona, Spain, on June 30, 2023. It was an exciting meeting, and we got together and really drilled down on the key components to this very fast-moving field.

So you know very well that gastric and gastroesophageal junction cancers are common, in fact, the third most common cause of cancer deaths globally. We know that lots of patients – the majority of patients present with metastatic or unresctible disease. We also know that our survivals are not good. Even with localized disease, we are only in about the 70% range, but with distant metastatic disease, very few patients make it past even a year or 2. And so our goals of care while we are trying to figure out how to cure this disease is, in fact, to prolong survival, have patients feel better with an improved quality of life, and reduce their symptoms. And we also know that the best way to deliver the best care today is to understand what biomarkers are making this particular cancer tick. And so you have to know for every one of these cancers HER2 expression, you have to know MSI [microsatellite instability] or MSS [microsatellite stable], and you have to know PD-L1 expression in order to pick the best biologics to partner with your traditional chemotherapy approaches. One of the things we really focused on is when to test and how to test, and the punch line answer there is early and with all of the right tests that are available for your patient today.

So if you look at HER2 therapy, we know that it’s embedded in our global guidelines. You know that our ESMO partners clearly incorporate HER2 targeting if you are HER2 positive by the addition of trastuzumab. We know the Japanese, likewise, in a very similar fashion, if HER2 positive, incorporate trastuzumab into combination chemotherapy approaches. And likewise, NCCN [National Comprehensive Cancer Network] has the same approach, but also, in addition, adds immunotherapy for those patients that you think may be appropriate. So for front line, not only HER2 targeting, but also immunotherapy in the form of pembrolizumab is added in front line according to the current guidelines. So everywhere in the world you need to know HER2 testing.

And the story really begins with the ToGA clinical trial. And this was an innovative study done back when we were just understanding more about HER2 positivity in breast cancer. And this, as you can see, was many years ago, more than a decade ago. This trial was

done in HER2-positive gastric cancer, and our hope was that in this subgroup of patients, we'd be seeing the same dramatic positive benefit that our breast cancer colleagues see in HER2-positive breast cancer. We have to be more humble in GI cancer because our results were not as dramatic. They were positive and established a new set of guidelines that I just reviewed for you for all patients who are HER2 positive, measured by immunohistochemistry or by FISH [fluorescence in situ hybridization] positivity. And if you were positive, the addition of trastuzumab generated an overall survival advantage and a response rate advantage.

And then, just as in the breast cancer world, we began to pile on by trying to add other molecules that were working in breast cancer that we hoped would work also in gastric. But here's the first one of those, if you will, failures – or at least not as exciting a positive. And this is where pertuzumab was added to trastuzumab, again, in the frontline setting, chemo plus or minus this, and while you can see those curves are slightly separated, they did not meet a statistical or clinically meaningful benefit, and so never reached approval. You can see a slight bump in the response rate, but never to that level where we said, okay, we need to add pertuzumab to all of our patients.

And then comes conjugated antibodies. TDM1 was the first one of these that came through. And this came through in second line after patients had already seen first-line trastuzumab. So it's kind of salvage therapy. But unfortunately, while this drug, again, has worked in other diseases, it did not deliver in the gastric cancer space, and so, again, not on response rate, not on survival - any measure did this work in the second-line setting.

And so we had these collections of studies where we had the ToGA study that was positive, but we had a collection of other clinical trials that really fundamentally didn't benefit patients in HER2 positivity. Of course, you think, well, why would this be? What's so different about the biology? One of the things I got to sort of dive into during the meeting was that our drivers in GI cancer, gastric cancer in particular, are not nearly so powerful. Our cancers are not nearly so dependent on these 1-driver pathways, and so when you block it, sure, it helps a little, but our cancers figure out how to go around these pathways. And so particularly in through-lines of therapy, we don't see the same level of benefit when you come at HER2 from a variety of different approaches.

And that really is until the DESTINY-Gastric01 study, and this was one of the main areas we focused on. These were patients who were HER2 positive, they had locally advanced or metastatic gastric or GE junction, had 2 prior therapies. And if you look in the table there on the right, you can see that all of them had prior trastuzumab but lots had had prior other treatments as well. These patients had to have been HER2 positive by immunohistochemistry or by FISH. And so you can see the patient characteristics, and it was randomized against either irinotecan or paclitaxel, and that's that chemo arm, if you will, that you can see there. And you can see most of these were men, they were good performance status, and you can see they were from around Asia, with Japan and Korea being where this study was done. And the results clearly showed benefit. You saw a dramatic improvement in overall survival, you saw a dramatic improvement in progression-free survival, and to me maybe most importantly at all, you see an improvement in response rate. This is a higher response than is often seen in frontline therapy with combination treatment. And so this refractory therapy that's worked so well in other diseases was also working very well in the space of patients with gastric GE junction who were HER2 positive.

We then did the Gastric02, the DESTINY-02 study, and you can see the dose that was used was 6.4 mg/kg. This is a high dose, but it did deliver very good response rates. This is kind of a rest-of-world, EU kind of trial. Seventy-nine patients accrued, and you can see that we again see a nice high response rate. When we used the lower dose, believe it or not, it turns out you get an even better response rate, at least based on the published data. So we probably don't need to go to this high of a dose in our gastric cancer patients. But DESTINY-02 actually just confirmed that this therapy, T-DXd – trastuzumab deruxtecan – was, in fact, active in this space.

Now, the side effects are significant. And one needs to remember that this is a monoclonal antibody, trastuzumab, with chemotherapy attached to it, so you get chemotherapy side effects. And so you're comfortable with dealing with these, but you understand they are somewhat more significant than single-agent chemotherapy. And this table does a good job of depicting the side effects. One thing that does not make this slide but is very important for us all to be aware, there are the rare but highly significant lung toxicities that can be seen in this patient population using this drug, so you have to watch out for that.

Well, we're not holding still here because a lot of what we're doing is moving forward, taking some of the novel targeted agents and combining them with immunotherapy. This is a partial listing of all the activity that's going on in the gastric and GE junction space using HER2 immunotherapy in various combinations. So we are hopeful that these will, in fact, generate even further positive benefit as we go forward through different lines of therapy.

So our key takeaways from our meeting is you have to test. You have to recognize that all of these patients need HER2 testing in addition to MSI and PD-L1. It needs to be done at baseline, needs to be either by immunohistochemistry, FISH, or nowadays can be done with next-generation sequencing. HER2-targeted therapy in positive patients is appropriate in first line. Depending on where you are, different combinations of therapy are open to you.

In subsequent lines of therapy, we now have a new monoclonal-targeted antibody that, in fact, is delivering 50% response rates, or quite high response rates, duration of response, progression-free survival, overall survival in randomized studies, and so you want to know HER2 not only for first line, but now through lines of therapy.

In closing, it was a great meeting. Everyone was excited to have been there. Barcelona is always a special place to be. But we hope this short review gives you what you need to know from our symposium.

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