Transcript Details

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Emerging Evidence in Second-Line and Potential Considerations in First-Line aGC and GEJ cancers

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Dr. Janjigian:
Hello, my name is Dr. Yelena Janjigian. I'm a Medical Oncologist and Chief of GI Oncology Service at Memorial Sloan Kettering Cancer Center. And it's a pleasure today to discuss advances in targeted therapy and the new treatment opportunities both in second-line and first-line therapies for patients with metastatic gastric, gastroesophageal junction cancer, particularly as it pertains to the space of HER2-positive disease.

This is CME on ReachMD. And it's a pleasure to have my colleague join me here, Dr. Sam Klempner. Sam, please introduce yourself.

Dr. Klempner:
I'm Sam Klempner. I'm a GI Med/Onc focused in stomach and esophagus at MGH up in Boston.

Dr. Janjigian:
Great, Sam, it's so exciting to be able to talk about treatment opportunities in the HER2 space beyond trastuzumab progression. Tell me how do you think this whole, you know, the validation of HER2 in second-line and third-line setting, what are your thoughts about the data? What are the opportunities in that space?

Dr. Klempner:
Yeah, so very, very active area of investigation. And that's a great thing for our patients. I think it's probably initially maybe worthwhile to back up a second and just talk about HER2. So as a reminder for everybody listening, this is one of the standard of care biomarkers, absolutely necessary to test for all advanced patients. Probably about 20% to 25% of patients, maybe a little more common in the GE junction than the stomach and little more common in intestinal type and diffuse type.

And the reason it's critical is that we have some of these great options. So we're going to talk about second line and beyond first, and then I'll come back to you, Yelena, to talk about some of the studies you've led in the frontline setting.

But historically, the benchmark was set by the ToGA trial where we learned and validated that HER2 was a target in the frontline setting. Then there was a series of efforts essentially to copy the breast cancer world in bringing some of the breast drugs into HER2-positive gastroesophageal, such as T-DM1 and pertuzumab. And, you know, unfortunately, they were a little bit a victim of the times, and we didn't understand as much about HER2, and these were largely essentially negative studies. Over the years, we've learned, thanks to some of the work from Yelena and her team, about the evolution of HER2 during therapy. So there's a substantial portion of patients who HER2 is lost or selected against after frontline trastuzumab. And so it does underscore the importance of understanding HER2 after

trastuzumab. So I know that both of us tend to repeat biopsy where possible and consider cell-free DNA to reassess the HER2 status.

But the data in the later line setting was really led by and revolutionized by trastuzumab deruxtecan. And so originally, this was a third-line and later setting DESTINY-Gastric01 trial from Asia, where we saw against investigator standard, so primarily irinotecan or Taxol, substantial activity with improvements in survival and substantial improvements in response rates around 40%. But because this was an all-Asian, trial, it left some questions open about the Western population. The FDA was optimistic about this data and actually approved the drug based on the Asian trial after trastuzumab in the US, so we had access to this a couple years ago.

And then more recently, we saw the DESTINY-Gastric02 data, which was a specifically second-line study in Western patients who had confirmed HER2 status, so they were HER2 positive after progression on prior trastuzumab. And largely the take-home point is that in this well-selected single-arm phase 2, we confirmed the activity of trastuzumab deruxtecan after trastuzumab in Western patients. Response rate, I believe, around 38% or 40%. And some durability to these responses as well.

So there is now an ongoing phase 3 trial to compare trastuzumab deruxtecan directly against paclitaxel and ramucirumab. It's primarily an X-US trial, as you know, and this is the DESTINY-Gastric04 study.

There are some other interesting combinations, and maybe we'll have time to come back to that at the end. But I think it's probably important that we talk a little bit about what's going on in the frontline setting. So I'm going to turn it back to you and let you discuss some of the frontline work with HER2 in 811 and DESTINY-Gastric03.

Dr. Janjigian:
For those who are just tuning in, you're listening to CME on ReachMD. I'm Dr. Yelena Janjigian, and joining me today is Dr. Sam Klempner. We're discussing the latest data on second-line and first-line therapies for HER2-directed agents in metastatic gastric and GE junction adenocarcinoma.

Yeah, thanks, Sam. It's so important to understand what is the context of HER2 amplification in esophageal and gastric cancer, and why, unlike breast cancer, where dual HER2 inhibition really worked well, in gastric cancer and esophageal cancer, because it is arising more in the setting of chromosomal instability and co-occurring alterations, we have not been as successful with use of dual HER2 inhibition in first- or even second-line setting. So the pertuzumab/trastuzumab studies have failed. Lapatinib/trastuzumab combination and so forth.

So only when we decided to go outside of the HER2 targeting alone and do combination of dual anti PD-1 with HER2 inhibition to really address the tumor microenvironment factor and co-occurring alterations in this disease did we see, finally, improvement over the trastuzumab chemotherapy with ToGA.

And so the KEYNOTE-811 data was really based on phase 2 data originally that showed benefit with pembrolizumab, trastuzumab, and chemotherapy over historical control. So it was nice to see the first interim analysis of KENYNOTE-811 demonstrating a change, a delta of 23% in overall response rate.

And so what will that mean for global, you know, approvals is to be determined based on survival updates and survival data. But suffice it to say in United States, we now have access to this pembro/trastuzumab combination irrespective of PD-L1, based on the dramatic overall response rate improvement.

This is nice to see. We know that antibody-drug conjugates [ADCs] certainly are exciting because they have this off-target effect, right? And again, addressing the tumor heterogeneity, which has really been a big barrier for us.

And as you mentioned, the ADC transformed and trastuzumab deruxtecan reignited our second-line space and third-line space for HER2 targeting. And so with DESTINY-Gastric03, we wanted to bring this strategy to first line, because the issue with HER2, as you so clearly stated, over time, tumors change, they lose HER2, or they become more chromosomally unstable, because that's a dynamic process, and then just become harder and harder to target. Right? So the earlier you go after it, and the question is should we even treat maybe early stage disease? But for now we're focused on first-line setting and using trastuzumab deruxtecan with combination strategies. Once again, we know fluoropyrimidines are critical in GI tumors, right? So we used capecitabine-based combination, which showed that it was feasible and safe. And in combination, now we're pursuing it with pembrolizumab, capecitabine, and trastuzumab/deruxtecan. So stay tuned for that data.

Where's the field moving forward? What will be the most sort of exciting combination in first line and second line is to really to be determined. It will come down to, I think, different characteristics of the tumor, and there's space for many of these agents to use for our patients. And these patients live longer and longer with their disease, which is very good to see.

It's been a fascinating conversation. And before we wrap up, Sam, can you share your take-home message for our audience?

Dr. Klempner:
Yes. I can try. First, I want to echo the enthusiasm about HER2 as a target. One thing I think is worth mentioning is that it's not only a target for pathway inhibition, but it's also a target that can serve as an anchor. So we've seen some interesting strategies of using the HER2 expression actually as an anchor to deliver agents that may modulate the microenvironment such as TLR8, CD47, STING. I mean, I think there's a lot of possibilities when we have antigens that are expressed on the tumor cells.

Speaking more practically, I think the take-home points are that HER2 needs to be assessed on every metastatic gastroesophageal adenocarcinoma patient. That's not optional; it needs to be known. And then as Dr. Janjigian mentioned, because we have more options, we really need to understand what's happening to HER2 during the pressure of HER2 therapy. So this underscores the need to repeat biopsy after each HER2 progression. Consider cell-free DNA as another tool for assessing HER2 amplifications and potential resistance mutations. Because really, the goal here is to optimally select patients and match them to drugs. And the more we understand about our patients, the better we can choose drugs and hopefully further optimize the outcomes.

And I'll let you wrap up any additional take-home points.

Dr. Janjigian:
Yeah, I think the most critical part for our listeners is to understand there's a lot of hope for HER2 positive patients. And we need to really understand that this is a rare disease. It's a rare subset of a rare diseases in the United States. So if there is a HER2-positive tumor patient that is eligible for a clinical trial, please refer this patient for a trial. We still have a lot of unanswered questions. And it's the only way we can do this, if we really work together and answer questions systematically. And you know, just this year alone, we had 3 FDA approvals over the last, you know, 18 months or so. So there's still a lot of work to be done.

That's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. Sam Klempner, for always being such a good colleague and conversationalist and for joining me and for sharing all of your valuable insights. It was always great speaking to you. Thanks so much.

Dr. Klempner:
Totally agree. It's always a pleasure to talk to you, and I look forward to the next time we cross paths.

Announcer:
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