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Navigating the HER2 Treatment Paradigm for Gastric Cancer

Announcer:
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Dr. Ilson:
Hello and thank you for joining us on this webcast titled “Navigating the HER2 Treatment Paradigm for Gastric Cancer.” I’m Dr. David Ilson, Professor of Medicine at Weill Medical College at Cornell, and a medical oncologist at the Memorial Sloane Kettering Cancer Center in New York City. I’m joined today by my colleague, Dr. Jaffer Ajani of MD Anderson Cancer Center. Jaffer, please introduce yourself.

Dr. Ajani:
Hi, David. It’s a great pleasure to join you this evening. I’m a GI medical oncologist, and I work at MD Anderson, and like you, I focus on gastric and esophageal cancers.

Dr. Ilson:
Well, I look forward to an engaging discussion. We sort of have a lot of interesting and exciting data to review, and practice-changing studies. Before we get started today, let’s review our learning objectives. Upon conclusion of this webcast, participants should be able to recognize the appropriate histological subtype and cancer stage that should be tested for HER2 overexpression in patients with gastric or gastroesophageal junction cancers. We’ll describe the incidence of HER2 overexpression and gastric and GEJ adenocarcinomas, and we’ll talk about the selection of appropriate first and second-line treatment regimens for patients with advanced, metastatic, HER2-overexpressing gastric and GE junction adenocarcinomas. And we’ll identify appropriate monitoring and management strategies for adverse effects, related to HER2-targeted therapies. So I’m going to let Jaffer lead us off, and talk about some background issues.

Dr. Ajani:
Yeah, so David, you know, gastroesophageal cancers are actually pretty common. If you combine adenocarcinoma up the esophagus and GE junction, plus gastric cancer, we are talking about 41,000 new cases per year in the United States. But the burden is even larger, 1.6 million new cases, predominantly gastric adenocarcinoma, and we are focusing on HER2 as a target today. So, it’s a very legitimate target, and since there are two major phenotypes of gastric adenocarcinoma, we kind of always make a distinction between intestinal type and diffuse type, and it so happens that HER2 is more frequently overexpressed in intestinal type than in diffuse type, so in intestinal type, it can be up to 20%. Of course, the numbers vary considerably, depending on different studies. And the other issue is that – maybe you can also add to this – is the heterogeneity of expression. So, you know, my question to you would be, I mean, where do you biopsy? And if you – one biopsy is negative, do you take another sample?

Dr. Ilson:
Yeah, I think pathologists now are encouraging to assess even several samples. There can be discordance between primary and metastasis, and sometimes patients will test initially HER2-negative in the primary, and they may have positive tests later, but there

clearly is heterogeneity and we even see this sometimes in differential responses at different sites of disease. But it's hard to biopsy every site of disease.

Dr. Ajani:
Yeah. So, let me also ask you whether you think liquid biopsy can overcome that kind of heterogeneity?

Dr. Ilson:
Yeah, I think liquid biopsy certainly assesses the whole body, so if we're sampling a site that's HER2-negative, and we have a HER2-expressing site, we should be able to pick it up with HER2 amplification and liquid biopsies. To me, its greatest utility is in retesting patients. You know, once they've been exposed to HER2-targeted therapy and may potentially lose HER2 overexpression, it might be a way of screening patients to make sure at least some of the tumor burden is still retaining HER2 overexpression, and blood-based testing would be one consideration.

Dr. Ajani:
So, the initial testing – we will also expand on this – is either by immunohistochemistry, in some cases by FISH testing, looking at gene copy number. Unfortunately, the cancer cells are pretty smart, and they will express a lot of other pathways that confer resistance simultaneously, so that means that there's a lot of heterogeneity also in the HER2-positive patients. As you mentioned, maybe you can mention a little bit more, what do you get if you have a patient with HER2-positive tumor, the frontline treatment fails, but then you want to retest again. What kind of results do you get?

Dr. Ilson:
Yeah, well, we know series indicate anywhere between 15-30% or more on re-biopsy, may lose HER2 expression. Either they lose the IHC or they lose the gene amplification, and increasingly we are using circulating tumor DNA, to assess for HER2 gene amplification and one study in second-line showed us as much as a – up to a 60% loss. So this is a potential, one area of resistance, as well as, you mentioned, up front. Up to 55% of patients have co-expression of potential resistance pathways, and we know that patients that have been exposed to trastuzumab actually acquire, as well, some of these resistance pathways, including EGFR, MET, and other pathways. So, some of the recent trials have not mandated re-biopsy, and, you know, obviously, if we just biopsy one area, it could be a sampling error, and I think that one benefit, potentially, of circulating tumor DNA is it's a more whole body assessment of whether or not we retain HER2 gene amplification.

Dr. Ajani:
So, immunohistochemistry testing produces kind of a simple result. If you have three-plus, then you don't need to go any further. If you have zero or one-plus, also you don't need to go any further, because your tumor is considered negative. The issue is when it is two-plus, then you have to do subsequent testing, which is by FISH, and looking at amplification of RB2 copy number. And how often is that going to be positive, in your experience, if you had like ten patients with two-plus IHC?

Dr. Ilson:
Yeah, it's probably almost up to half of patients, so it's definitely worth testing. And also, there's also the degree of FISH positivity. You know, sometimes, you know, the cutoff is, you know, greater than two, and sometimes it's just marginally above that, so there's also the degree of FISH positivity. But the positivity rate is high enough that it's clearly warranted to test.

Dr. Ajani:
So, if it's okay with you, I was just going to mention the first-line trial. The ToGA trial that was reported almost ten years ago, which compared standard chemotherapy versus standard chemotherapy plus trastuzumab, and we were all very excited about the results. By today's standard, they are kind of modest, but in those days, you know, it was really something. And I think the new twist is the addition of pembrolizumab. This one pilot that originated at Memorial Sloane Kettering, and the other pilot from Korea – they are showing very similar and very exciting data. So if you add pembro, David, tell us what do you get.

Dr. Ilson:
Yeah, well, in our Phase 2 trial, we saw a response rate slightly in excess of 80%. And the progression-free survival was very encouraging. It was beyond a year, and overall survival extended out beyond two years, so it was a very strong signal from the Phase 2, and really did not add significant toxicity. I mean, you know, we know there are toxicities that we see with pembrolizumab, but it's in a relative minority of patients, so this very positive pilot study, which actually also did not show dependence on PD-L1 expression for benefit, led to KEYNOTE 811, the randomized Phase 3 trial, which you will comment on.

Dr. Ajani:
Yeah. So, you know, this very interesting. The KEYNOTE 811 is the largest, HER2-directed trial that has already accrued close to 700 patients, and very simple, elegant design. So, trastuzumab plus chemo versus trastuzumab plus chemo and pembrolizumab, and the

primary dual endpoints are overall survival and PFS. But we don't really know those primary endpoint results yet. I'm hoping that by next year, we should have them, but what we have is the response rate and response duration results in about 260 patients, at the initial release of the data. And that led to approval of pembrolizumab for front-line treatment, to be added to trastuzumab plus chemotherapy. So, as you mentioned, with the pilot trial, the response rate was very high, and if you would like to comment on these results on 260 patients.

Dr. Ilson:
Yeah, I think, you know, we always get excited about Phase 2 trials, and then we do the Phase 3 trial and we get disappointed, and what was remarkable from KEYNOTE 811 was, indeed, a 50% response rate for conventional treatment. It went up to 75%, with the addition of pembrolizumab, which actually approached almost the response rate we saw in the Phase 2 trial. So, obviously, a significant increase, and based on that, we got regulatory approval in this interim analysis – conditional approval – and response durations were pretty good, about nine to ten months. I think the caveat here is, despite the higher response rate, the duration of responses seem to be similar, so we'll have to see how the trial reads out with progression-free and overall survival. Also, the vast majority of patients were three-plus HER2, so the patients most likely to benefit, more than 80%. And also, the vast majority were PD-L1 positive, at 1% or higher, more than 80%. So, this certainly is a population that is reflective of likely to get the greatest benefit from these drugs.

Dr. Ajani:
So tell us what the new stuff is going on.

Dr. Ilson:
Well, I think originally, you know, there was a lot of nihilism about the fact that esophagogastric cancer, HER2-positive, did not behave like breast cancer. We just weren't seeing that all the agents that we used in breast cancer, we didn't get the same benefits, because we did mention in the first-line the negative results for lapatinib, the negative results for pertuzumab, and initially we had similar negative results for HER2 second-line therapy. Patients that had gotten first-line trastuzumab with progression, and we had negative results for trastuzumab with emtansine – T-DM1 – was no better than treatment with a taxane alone. In a trial that treated almost 350 patients, very similar overall survival. And then the TITAN trial looked second-line at paclitaxel plus lapatinib, and in a small trial, showed no significant improvements. There might have been some subsets with higher expression, but not a clear benefit. And then lastly, unlike breast cancer again, continuing trastuzumab into second-line chemotherapy did not improve outcome compared to chemotherapy alone. This was the T-ACT, randomized, Phase 2, Japanese trial, which showed no differences in progression-free and overall survival, when we continued trastuzumab into second-line treatment. And this is one of the studies that documented persistent HER2 amplification and circulating tumor DNA in only 60% of patients, so a significant percentage loss there of HER2 expression. And now, I think we'll move on to really what's exciting in the new drugs in this space. We're particularly excited about some of the newer antibody drug conjugates, and bispecific antibodies. We'll spend a little time talking about trastuzumab/deruxtecan. This is trastuzumab conjugated to a topoisomerase 1 inhibitor, exatecan. This drug conjugate is a little bit unique in that the chemotherapy payload is very potent, and the chemotherapy payload has the potential to diffuse out into neighboring cells, so there might be a bystander effect. And a pretty remarkable, 43%, response rate in the initial Phase 1 and 2 trial, in HER2-refractory, HER2-positive gastric cancer. This, then, led to the positive randomized Phase 2 trial, that led to regulatory approval for trastuzumab/deruxtecan, both in the United States and Japan – the DESTINY-Gastric01 trial. In Japan, the drug is approved third-line or later. In the United States, it's approved second or later line in HER2-positive patients.

Dr. Ajani:
So I think it makes sense to approve it in second line, because there is no – if the drug is so effective, you know, I mean, we have to be careful about toxicity, which you mentioned, with an active drug. I would not want to necessarily wait until third-line, so… Made a good decision, I think.

Dr. Ilson:
Yeah, I think we have the option now, and certainly the Gastric01 trial showed an improvement in response rate over chemotherapy, from 14 to 40%, as well as significant improvements in progression-free survival, as well as overall survival, which were secondary endpoints. And this, pretty convincingly, even despite it being a randomized, Phase 2 trial, and only done in Asia, led to approval.

Of course, one of the drug effects that we have to be very cognizant of is lung inflammation, or pneumonitis. We've seen this in the breast cancer studies, and the colon cancer studies, and the rate is between 5-10%. Most of it is Grade 1 or 2, but occasionally, we do see more severe pneumonitis, and there actually were some fatalities from this, in the breast and the colon cancer studies, fortunately not in the gastric cancer studies. So I just want to mention briefly, we're going to talk about management of the lung toxicity, but I just want to mention the Gastric02 study, because this was a companion trial to really test this drug in a western population, because, you know, the Gastric01 was really a trial conducted in Asia, and DESTINY-Gastric02 was a single arm, Phase 2 trial looking at patients in the second line, receiving trastuzumab/deruxtecan. The trial did mandate that persistence of HER2 positivity had to be shown in repeat

tumor biopsies. And this – data from this study were recently presented at the ESMO meeting, and really confirmed a response rate of about 40%, so this is very similar to what Gastric01 showed in the Asian randomized, Phase 2 trial, and progression-free survival wasn't as high, but it still was about six months. And so I think we saw a validation of activity for this drug in a western population, which I think reinforces the need for this drug to be available.

Dr. Ajani:
So it looks like we are gaining ground with targeting HER2 with drugs like this.

Dr. Ilson:
Yeah, I think the lung disease – most of it is Grade 1 to 2, and we usually – the treatment, as with any of these inflammatory toxicities, is steroids. And usually a lower dose of prednisone for Grade 1 to 2, and then the more – higher dose, 1 mg per kg, in the patients that have Grade 3 or 4, stop the – obviously, stop the trastuzumab/deruxtecan. Usually continue the steroids for at least two weeks, before there's a taper, and then monitor the patients carefully. And we have to watch for cough, shortness of breath, fevers. You know, we're getting scans on these patients every two months anyway, so we monitor them already fairly carefully. So I just wanted to move on and talk about some of the other drugs that are emerging in this space. Just to complete the discussion of trastuzumab/deruxtecan, there are two other ongoing trials of this drug. DESTINY-Gastric03 is now evaluating trastuzumab/deruxtecan in first-line combinations, with chemotherapy, with checkpoint inhibitors. And then, you know, we addressed the issue of should we use the drug second-line or third-line. You know, sort of standard second-line treatment, in all patients, has been paclitaxel/ramucirumab. And DESTINY Gastric04 is a randomized comparison of trastuzumab/deruxtecan compared to paclitaxel/ramucirumab in second line. I want to mention margetuximab – this is another novel antibody. It's engineered with an anti-HER2 component, with the FC domain engineered to activate CD16A on NK cells, so it may enhance immune recruitment. Very promising Phase 1 and 2 data, with pembrolizumab plus margetuximab, particularly in the IHC 3+, PD-L1 positive patients.

And we'll talk a little bit about the ongoing, randomized trial – the MAHOGANY trial. Zanidatamab is another promising drug. This targets two epitopes on HER2. It has both activity as a single agent, and with chemotherapy. And tucatinib, which has shown promise in breast cancer – it's a promising HER2 tyrosine kinase inhibitor – studied in combination with trastuzumab in second and later line, and there will be a randomized trial, MOUNTAINEER 2, which will look at a fairly large patient population of this drug in combination, in later line, HER2-positive patients.

Dr. Ajani:
This is a very impressive list, and of course, we are going to mention that HER2 can be a target for other vaccines, for example, CAR-T cells and NK cells. So it's getting very interesting.

Dr. Ilson:
Yeah, the – just to mention the ongoing trials – margetuximab has an arm, which is chemotherapy-free, which combines margetuximab with an anti-PD1 drug, in the IHC-3 plus PD-L1 positive. And then the randomized, cohort B, is comparing trastuzumab/chemotherapy versus margetuximab/chemotherapy, with or without a checkpoint inhibitor, and also they are looking at a novel, LAG-3, PD1 bispecific antibody combined with margetuximab and chemotherapy.

Dr. Ajani:
Interesting.

Dr. Ilson:
Zanidatamab, just to mention briefly – promising activity as a single agent in a Phase 2 – about 35-40%, and even a 60% response in combination with capecitabine or paclitaxel. And we recently saw, at the ESMO meeting a few weeks ago, first-line zanidatamab plus 5FU combination chemotherapy, with a rather impressive, 75%, response rate which is somewhat reminiscent of the KEYNOTE 811, pembrolizumab study, with a median duration of response of more than 15 months. So, I think we look forward to hearing more about zanidatamab combinations. Diarrhea is a concern with this drug. I know we've seen this with – particularly with trastuzumab/pertuzumab in breast cancer, but diarrhea with zanidatamab in first-line 5FU-based chemotherapy, grade three or four, was about 40%, so they did use antidiarrheal prophylaxis.

Dr. Ajani:
So, I have a little experience with zanidatamab, because we participated in the Phase 1 trial also, where the fourth and fifth-line patients – some of my patients – received this drug, and the response rate was, you know, something like 35%, which, as you well know, you will never get a high response rate like that with standard of care agents. So this is very promising.

Dr. Ilson:
Yeah, I think now we have a competitive space, with potentially margetuximab in the first line, zanidatamab. But we also have to

remember that these drugs should be investigated in later line as well. You know, how do we – if they all turn out to be positive, how do we sequence them, and we now have margetuximab as an approved second and third-line agent. So this is actually a good problem to have, that we have a wealth of active options, and you know, we'll see whether will the first-line standard of care – which is now trastuzumab/chemotherapy and pembrolizumab – whether it will evolve to include some of these other, newer agents.

Dr. Ajani:
Right. You're right. So, can you just give us a summary of some of the newer agents that are coming out, and then your, sort of, overall impression of where we are with – in this field?

Dr. Ilson:
Yeah, I just wanted to mention a few other names, so they're on your radar. There are other anti-HER2, anti-HER3 drugs that are promising. ZW49, which is another antibody drug conjugate, which is combined with an antimicrotubule drug. Then there is a drug, PRS-343, which is a bi-specific antibody construct, which targets HER2, as well as CD137, which may be an immune agonist and recruiting element. Then there's some other biologic agents, and you mentioned earlier cell-based therapies, potentially CAR-T cells, you know, targeting HER2. So, we really have an exciting group of new agents. We've finally moved beyond first-line, HER2-targeted therapy. We're now with an approved second-line agent, and many new drugs in the pipeline that are looking very promising. So I think to summarize our discussion, HER2 is an important target in esophagogastric adenocarcinoma. It's key that we screen all patients for HER2 positivity at initial diagnosis of advanced metastatic disease. And again, we talked about IHC testing, as the first line, and then in IHC-2+, we would do confirmatory testing with FISH. In the first line, we now have a new standard of care. We now use chemotherapy, trastuzumab and pembrolizumab in first line, given the response rate achieved on the KEYNOTE 811 study. And we talked about some other promising agents that are being screened in earlier line as well. And now, second or later line, we have an approved drug – trastuzumab/deruxtecan – approved third or later line in Japan. In the United States, we have the option of second or later line. And consideration for repeat HER2 testing – this was done in the Gastric02 western trial, to document persistent HER2 amplification. And an awareness of the unique toxicity – a pulmonary toxicity of pneumonitis – which is treatable, but we need to be cognizant of that, so that we keep it manageable and potentially avoidable toxicity. And then, as I said, we have new agents – new technologies to follow patients, with circulating tumor DNA.

We also have some – even some specific HER2 imaging testing that's being done. And one thing I'll just comment on briefly – we don't yet have data to support the use of HER2-targeted therapy in the adjuvant setting. Some initial negative studies, and whether HER2 combinations will move that field forward, that remains to be seen.

Dr. Ajani:
Fantastic summary, David. Thank you so much. I just, sort of, re-emphasize what I said earlier, that HER2 is one unique target that you can go back to. So, fortunately, you know, you can go back second time, and hopefully in gastric space, just like the breast space, you can go back third time, fourth time and fifth time.

Dr. Ilson:
Yeah, no, I think this is an encouraging time, and I think we've had a great discussion. We've reviewed the key issues, and a lot of enthusiasm and hope for a new drug development.

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