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Chairperson's Perspective: HER2 in Solid Tumors – From Pathology to Personalized Treatment Plans

Opening:
Welcome to CE on ReachMD. This activity, titled "HER-2 in Solid Tumors: From Pathology to Personalized Treatment Plans" is provided by Axis Medical Education.

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Dr. Moore:
My name is Dr. Kathleen Moore. I am the Deputy Director at the Buffett Cancer Center in Omaha, Nebraska, and it's my great pleasure to present a short overview of HER2 testing and efficacy in solid tumors, from pathology to personalized treatment plans.

We're going to start off today by just talking about what we mean when we talk about HER2 expression and testing. But first, I want to take just a step back. I think all of us that take care of patients with cancer will agree, it's been an exciting time over the past—I'm a gynecologic oncologist, so I'd say the past 5 years, for the rest of medical oncology, radiation oncology, surgical oncology, I think there's been an exciting time maybe the past 10 years, with the rapid development and approval of targeted therapies, some of which have been truly targeted, what we call tissue-agnostic, really just if we have the mutation, if we have the expression, we have the fusion, whatever tumor type, we can access these novel and active medications.

So this slide just summarizes some of that exciting development really since 2017, with the approval of pembrolizumab in deficient mismatch repair or microsatellite unstable tumors, all the way to our most recent—what we're going to focus on today—in 2024, the approval of trastuzumab deruxtecan in HER2-positive solid tumors. So this is an exciting time for our patients.

Focusing just on HER2, this is you know a long story. This story and the remarkable evolution of the identification of HER2, first in breast and ovarian cancer. And you can see this trajectory with monoclonal antibodies, trastuzumab, pertuzumab, transitioning into tyrosine kinase inhibitors, lapatinib, neratinib, tucatinib, and then into the antibody-drug conjugate era, first with T-DM1 and now T-DXd, and even others in development. And so this has been a rapidly evolving story with benefit to many patients with solid tumors.

When we talk about HER2 alterations, in the past, we were really just talking about what we used for identification, mainly in breast and gastric cancers, around immunohistochemistry and amplification. And that has broadened quite a bit, especially with the recent tumor-agnostic approval for trastuzumab deruxtecan.

So what we're talking about when we're assessing a patient who has cancer, assessing their tumor for HER2 alterations, we're looking at all three of these categories now. We're looking for gene amplification. We're also looking for gene mutations, and these are incredibly important, for example, in lung cancer, breast cancer, a little less common but no less important in other solid tumors. This is detected

by next-generation sequencing. Most commonly now our eyes are scanning pathology reports, and you know if we send things out for panel testing, we're looking for that immunohistochemistry, which is an overabundance of HER2 receptors on the cell surface, and this is detected by immunohistochemistry.

So in large part—and I'll get back to this point—we're really testing the tumor for these alterations in our patients with solid tumors.

So I want to focus on the IHC component a little bit more, which we could talk for an hour about and would require an expert pathologist, but this is really an evolving landscape. In the past, we had a two-category system. It's either HER2-positive or negative, and well, I'm going to show you the CAP guidelines in the next slide, but that's really how a lot of us categorized the tumor in our notes. We would just say HER2-positive, indicating it was either 3+ or 2+ ISH+, or negative everything else. And now, because of the rapid evolution of trastuzumab deruxtecan, mainly in breast cancer, demonstrating efficacy at these other categories, HER2-low, HER2-ultralow, and I would say even 0, but that's a breast cancer story, now we're all having to go back and make sure if we said someone's tumor was HER2-negative, we know exactly what we're talking about there.

So it's kind of a catch-up phase right now to make sure that we're appropriately classifying our patients' tumors so we can assess whether or not T-DXd is an appropriate therapy for them.

The CAP guidelines for HER2 expression are always under evolution, but it's important to remember, even though we have this new approval based on gastric scoring, which you can see here right in the middle, breast and gastric and colorectal, to some extent, via the HERACLES trial, are really the only tumors that have CAP guidelines.

And the breast guidelines, as you can see here, are always under evolution. For UPSC, which is uterine papillary serous carcinoma, we don't have CAP guidelines; we have suggestions. But you can see how these differ, which is quite a challenge for our pathologists and for physicians in making sure that we're ordering you know the right assessment in the right patient setting, so that we know exactly what that tumor HER2 positivity or lack thereof correlates with in terms of the drugs we might use for that patient.

So this is really a complicated space and requires a lot of multidisciplinary interaction with our pathology colleagues to make sure that we get this right, depending on the tumor that we are assessing.

But again, what we're looking for here are HER2 expression which is from the tissue immunohistochemistry, and basically this was referring to an overabundance of HER2 protein on the surface of tumor cells. We're looking at amplification, which is an elevated number of HER2 or ERBB2 gene copies. Why? Because an increased number of transcripts leads to upregulation of signaling pathways. And then we're looking for HER2 mutations, which are activating mutations in the HER2 or again ERBB2 gene, which are less common but are targetable.

So we're looking for all of these for our patients. And when we look across tumor types, the size of the circle gives you the kind of highest prevalence of findings in that tumor. So for example, at the top here you can see salivary gland cancer. You'll find ERBB2 amplification in 40%, you'll find HER2 IHC 3+ in 15 to 37%, you'll find very few mutations, and that's kind of across the board what we see with mutations outside of like urinary tract cancer, for example. Uterine cancer, which is my world, we find HER2 2+—that's what this group is—pretty commonly, especially in TP53-altered tumors, 3+ less so, mutations almost never.

So this gives you a sense of how common some abnormality in HER2 testing is. The big question is, okay, if I find a 2+, if I find an amplification, if I find a mutation, what's the predictive value that has so I can tell my patient the expectation that that medication will benefit him or her is really what's under sort of rapid discovery.

So this just sort of reiterates the point that to this day, we only have CAP guidelines for breast and gastric cancer, and because of T-DXd's approval in pan-tumor, outside of established CAP guidelines, like for all of gynecologic cancers as an example, we're using gastric scoring in most settings, in addition to the next-gen sequencing, to really assess for whether or not our patients are candidates for some of these HER2-targeting agents.

So best practices right now at this point, we do want to identify all patients who may be eligible really for any of our HER2-targeting agents, but the most common one that our patients are eligible for right now is trastuzumab deruxtecan based on the recent FDA approval, and also NCCN listing in some tumors for 2+ and 3+.

We want to make sure we're doing IHC testing in all of our patients' tumors that are metastatic and potentially candidates for T-DXd, and have it ideally as a part of the initial biomarker workup, so we don't get into the position of having exhausted blocks or no access to tissue to do this testing. We can do biopsies, of course, but if we can avoid that for our patients unless necessary, that is ideal. And we want to make sure we're utilizing FDA-approved tests and following CAP guidance for reporting these tests out.

Let's just turn to how we got to the point of the approval in T-DXd in solid tumors, and it comes from 3 studies. There's a lot more studies that sort of fed in to, I think, the approval, but these are the 3 that led to the tumor-agnostic approval.

The first is DESTINY-PanTumor. This was a basket study of T-DXd 5.4 mg/kg in 7 tumor cohorts, each about 40 patients. They were eligible if they had local testing for HER2 and it was 2+ or 3+. Part 2, which has not been reported out yet, is looking at 1+ and 2+, and so we're very excited about this and hopefully we'll see results of the study maybe in 2026.

But let's focus on the original study, which was just in patients with 2+ and 3+ local testing. One interesting thing just to be aware of is many of these tumors had had prior exposure to a HER2-targeting therapy. For example, endometrial cancer, almost 1/4 of patients had received prior therapy, mostly trastuzumab, and those can be assumed to be those that were 3+ or 2+ ISH, because that was the recommendation in that setting. Other tumors, it was about 35%, biliary tract about 17%, so many of these patients had had prior exposure to a monoclonal antibody or an agent, but not an antibody-drug conjugate with a topoisomerase payload.

Here are the responses, and you can see that in the 3+, this is why the approval is in 3+, the response rate was 62%, with a duration of response that was almost 2 years, so pretty remarkable across the board responses except for pancreas cancer, that led to a lot of interest in getting this approved and available for our patients.

The second study that contributed to the approval was DESTINY CRC-02. This was a randomized phase 2 dose-optimization study of 6.4 mg/kg versus 5.4. Really, we can talk all day about the importance of dose optimization, but this is an example of where the lower dose was better. So it was randomized initially and then expanded in stage II to get almost over 80 patients at 5.4.

And this is that cohort, 5.4, you can see here the majority of patients were IHC 3+, almost 70%, and RAS wild-type, but there was a smattering of other cases. The majority of patients had metastatic tumors from the left colon, but you can see rectum and you can see right colon. So testing, irrespective of this, is important to identify the patients who may benefit.

And then when we look at efficacy here, you can see amongst this population, the response rate in patients who had received appropriate prior therapy was almost 40%, which is quite a nice signal. But what you can see here is that it's mainly in the 3+. The 2+'s, these are very small numbers, though, only 18 patients. So we have to take it with a grain of salt, but this really is a 3+, again pointing to why the FDA approval was limited to 3+.

And then the third study is DESTINY-Lung01, another randomized phase 2 clinical trial. I'm looking at cohort 1a, which is just the HER2 overexpressing 2+ or 3+. And here what you can see, again, just wanted to point out, these patients had received appropriate prior therapies, including platinum, immune checkpoint inhibitor, and docetaxel, and then came on this clinical trial and had a response rate of 34%, which was felt to be superior to what would be considered standard of care. Once again, though, the biggest driver of this were the 3+, where you have a response rate of 52% and only 20% for 2+, really justifying the FDA's decision to allow this really only in 3+.

And so these are the 3 studies that led to the tumor-agnostic approval, and there's a lot of confirmatory trials going on across different tumor types to really see where T-DXd best fits.

So conclusion one, the availability of HER2-targeting antibody-drug conjugates justifies the widespread testing, with currently gastric scoring for IHC unless otherwise indicated. Colorectal, we do need FISH. The question is, where do we prioritize this therapy in the lineup of available things for our patients? Given to that point we've got it in the recurrent setting, does it start to move up into earlier lines of therapy? Many trials—I'm just showing you an example in ovarian cancer—have moved T-DXd up into frontline maintenance in HER2-expressing tumors as an example.

And there's other examples in other solid tumors as well. Is this something that's relegated to the recurrent resistance setting, or do we move it up? And if so, in what population can we perhaps convert more patients to cure? So this is an exciting time.

We are excited, but we have to pay attention to the side effects, and these are well established. This is from DESTINY-PanTumor02. The side effects haven't differed from breast cancer and gastric cancer. We see common but low-grade GI side effects. We see hematologic side effects that are probably modest, 30% all grades, relatively low rates of high-grade bone marrow suppression. The highest would be about 30% of patients with neutropenia, 20% with grade 3 or higher. And then ILD, which is, of course, the rare or uncommon side effect that we worry most about, sits around 10 to 14%, predominantly grade 1 and 2, because of advanced mitigation and detection training and strategy.

And so this is just the event summary. We worry most about pneumonitis. We monitor for neutropenia, and left ventricular dysfunction with T-DXd is only about 4%, but we do have to monitor for it with periodic assessments of left ventricular ejection fraction and holds when indicated if we see drops.

The ILD strategies here are really developed from breast cancer and serve all solid tumors very well. Patients have to be made aware of what we're worried about. So if they have any new cough, any new respiratory symptom at all, they have to let us know instead of going to an urgent care facility. They need to be brought in. We need to do imaging, which includes a high-res CT and a pulmonology consultation.

And quite frankly, we want to be watching for changes on CT scan long before our patients ever report a symptom. And so this grade 1 identification of inflammatory changes on CT, grade 1 being before a patient has any symptoms, holding, consultation with pulmonology, low-dose steroids if indicated to get it to resolve quicker, is really our best opportunity to prevent high-grade complications from pneumonitis, allow resolution, and hopefully allow our patients to come back on this therapy, especially if it's providing clinical benefit with dose modifications.

Nausea with T-DXd, I would consider this a highly emetogenic regimen, and so at our site we premedicate with the regimen you see here right out of the gates. And if we still have nausea, we'll add on olanzapine PRN, and that can work quite nicely at helping patients feel very good while they're taking this medication. I would not recommend starting it and seeing how someone does because they're almost guaranteed to have terrible side effects.

I mentioned left ventricular dysfunction is pretty uncommon, only about 4%, but we still have to watch for it because you don't want to miss that. And so there's very clear guidance in the package insert, they're here for your records, on what to do if you see drops in either the left ventricular ejection fraction or decreases from baseline.

So clinical takeaways are really we want to test everyone. And if we find 3+ IHC, we want to consider T-DXd for our patients once they have received therapies with an expected survival benefit, but before things that clearly don't have a survival benefit. And then trials will hopefully elucidate where to best use this in the future.

And with that, I thank you for your attention.

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