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Molecular Profiling for HER2+ Advanced Solid Tumors

Announcer:
Welcome to CME on ReachMD. This activity, titled “HER2+ Advanced Solid Tumors: A Fireside Chat on Harnessing Molecular Profiling to Improve Patient Outcomes” is provided by Prova Education.

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Dr. Tan:
So we talked about it earlier, HER2 positivity. But what does that mean? Is it HER2 3+ with amplification, or is it HER2 2+ without amplification, or is it HER2 1+? And in that context, how confident are you in pushing forward a tumor-agnostic indication for that patient who's in front of you?

The challenge now is that you have multiple tumor-agnostic indications and a variation in terms of the prevalence of these agnostic indications depending on the tumor you treat. And understanding whether or not you're likely to find that mutation or not can be challenging when you see the patient in clinic who's had multiple lines of treatment. And even if I give you this map now, that patient who's had 5 prior lines of treatment may have a very different profile in terms of how that tumor has evolved over the 5 lines of treatment you've given them. And so you might need to biopsy them again. And then you’ve got to think about whether you want to just test for one biomarker, or maybe we need to do more than just one, by testing for one by one.

And thankfully, genomic sequencing is now possible and it's cheaper and it's becoming more accessible. We are able to look at multiple genes at one go, if you can get the tissue and you can get the good quality DNA, and that's where the tissue becomes the issue.

But having that allows us now to look into more ways of developing treatments for these patients, and we do more and more biomarker-driven early-phase trials. In the past, when you would do a phase 1 study, you might be focusing more on trying to get safety and tolerability data, but today, because we're interested to find out what a drug is actually doing to the tumor, you biopsy them. You can look at target modulation. You look at molecular changes and cellular features. And these circulating DNA and RNA can be useful as well. We can quantify. We can see whether it goes down, it goes up. And that could be correlated with disease progression and radiographic changes. So we get better readouts of drug activity.

But most importantly, we still need to select the right patients, because clearly the tumor-agnostic indications suggest that if we can find the right patient, the right biomarker, we can get better outcomes and better efficacy data for our patients and approvals.

So I just want to talk about some of the precision oncology initiatives that are ongoing in my country. So in my institution, we have an Integrative Molecular Analysis of Cancer program that's been ongoing now for years, well, I would say about 8 years. And essentially, we profile and stratify patients for clinical trials. And we also do gene expression profiling for certain tumors where we've had gene expression define possibilities for stratifying these patients into treatments as well.

And then there's a National Cancer Center in Singapore. We have 2 cancer centers that also has an IMPACT program that does the same thing. But fundamental there is really having what we call a multidisciplinary tumor board, and evolved from our early-phase trials, the tumor board. And this was basically a group of us who decided when we want to put patients into these early-phase trials, we had to

talk about whether someone was fit, whether someone had the right biomarkers, and whether these biomarkers were kosher or not. I mean, you have to understand some of these mutational profiles. And even looking at p53, it's not just about whether it's mutated; it's what sequence of p53 is that mutation. Because there could be a relevant drug depending on the sequence of that mutation. The genotype could be very important as well.

And so you can see here that we really need our pathologists to help guide whether or not, and when you get a new referral, what that report says is really true about this cancer. When someone says it's p53 negative, what does that actually mean? Because someone could mean that it's negative for a p53 mutation, or is it because the expression of p53 is negative. And we had some very equivocal reports when they come from other countries. And going back to basics and asking your pathologists, can you do this again and tell me actually whether you think there is a p53 abnormality in this tumor, could be very relevant.

In terms of trial design and everything, obviously, a biostatistician could be relevant. But what we've also tried to incorporate are some scientists, because they might give you more insights into some of the mutations and some of the pathways that emerge when you look at some patients' molecular profile. I'm happy to say that in our institution, luckily, most of the patients in this phase 1 team are clinician scientists, and so often they have their own insights they can contribute, and so we often we don't actually need an independent scientist to be part of that as well. But we do also have a clinical geneticist who's part of this group, because if we see a mutation that we think and a clinical history that could be relevant, we would also highlight that that patient should be referred for cascade testing in the context of certain syndromes like PTEN mutations or p53 mutations when we think about Li-Fraumeni, if there's a pattern of mutations and tumors that we see in the particular patient.

So I think molecular tumor boards for us have evolved from there into now what we call a molecular tumor board for precision oncology. So we have now expanded our sequencing program to all our oncologists, regardless of whether they're part of the phase 1 team or not. And what that means is that if a patient comes in and they feel that this patient should have their tumor sequenced, then they'll have that profile sent to whichever company they feel is relevant. And then the most important thing is that, on a weekly basis when those results come back, they've got to take that result, bring it to the tumor board, present that patient, tell us about that patient, tell us about that patient's performance status, tell us about that patient's treatment history. And then we can talk about whether or not we feel this patient is suitable for a clinical trial that we have that could be biomarker selected. Or if we don't have a trial, is there a drug out there they could repurpose for this patient that's available that they might not be aware of?

So I think when we talked earlier about how often your tumor board needs to be, I think it does need to be quite frequent. Because, ultimately, you're making clinical decisions for patients based on their profile. It's all very well sequencing a patient, but if you don't know what you're doing with that profile, and you don't discuss that profile, then you shouldn't have done it in the first place. You're wasting your time. You're wasting the time for the patient and money for the patient as well, particularly here in Singapore, when the sequencing is not reimbursed by the government, so patients are paying out of pocket for that, or we have grant funding that helps to cover the cost of that.

So what we feel is important in our precision oncology program is to have that comprehensive genomic profiling program, the weekly multi-tumor specialty tumor boards, stratified therapies based on these results. And so this is where we have the advantage of being in a center which has a very active phase 1 team that translates to early-phase trials as well.

And importantly, when we collect this data, we also tell patients that once you sign up for sequencing, and we do give some grant support for covering their sequencing, we ask them to commit their data to a database. That database enables us, in the future, when a company comes along and says, "Look, I'm looking for a specific EGFR mutation," and I can look through that database immediately and say, in the last 5 years, we've seen 10 of those patients, and maybe it's feasible for us to recruit those patients in the study. So that's really important.

But on the other hand, it also gives us more information about what the prognosis is like for some of those individual mutations that could be very relevant for future studies, because that could also tell you whether or not you need to think about matching them to these trials earlier in your treatment journey, rather than giving them treatments that are not going to be very effective as well. And you only learn that when you accumulate and collect that data from your own genomic data sets.

So just to give you an example of one of the original studies that we did, and this was just a 50-gene profile, we just wanted to look at the feasibility of matching patients who are profiled using a 50-gene multiplex platform to clinical trials, and it was a matching rate of about 8%. But we did see some dramatic changes. I mean, this patient had really bad breast cancer that was eroding into the chest wall, and her tumor did resolve to some extent with the treatment using an AKT inhibitor in the context of a PIK3CA-mutant breast cancer.

But we sort of evolved from there, from a 50-gene panel, to now our workhorse, which is the FoundationOne panel. And we have a collaboration with Roche in order to get sequencing done for our patients. So this is a research collaboration we've had. And so as of May, we've had more than 2,000 patients that we've sequenced using this. And using that data does help us define feasibility and also the relevance of some mutations of interest when you're thinking about doing more clinical studies and trials and trial design and also benchmarking for outcomes for some patients.

Just to show that we published some of our data from our Breast Cohort in 2024 showing that, in fact, we get PFS and overall survival benefit. And all of these patients had their tumor sequence reviewed by the tumor board and then basically matched to a relevant treatment based on the molecular profile. And those who had a matched treatment seemed to have a better progression-free survival and better overall survival as well. It's retrospective data, but still, it's some data to suggest that what we're doing is relevant and could improve outcomes for our patients.

We've had other data from Centers of Excellence that have shown similar outcomes for their patients with PFS and overall survival benefit as well. But here, there was a match rate of 54% and it just gets to show that your match rate ultimately depends on how comprehensive your tumor profiling platform is and how many of those trials and match therapies you have. So really, it's all a question of how many studies you have and how many patients you can bring in and sequence often enough and discuss often enough that you don't lose the chance to put a patient into a relevant study.

The other study that we've talked about in the National Cancer Center has also shown similar data, showing that their top 3 sequencing targets are sort of mutations they identified when p53 EGFR carriers and PIK3CA, and their match rate was about 5%, so very similar, then, with our original match rate with the 50-gene profile as well.

Finally, just to say that some of these mutations can be very rare. Just looking at this, the most common prevalence of this TRK fusions is in thyroid cancer, which is about 6%. But I'm still sequencing all my cervical cancer patients in the hope that one day I will find that 1 out of 100 cervical cancer patient that will have that TRK fusion. Because if you find that TRK fusion, you might get a really stunning response in this patient. And it will be young patients. If you find that mutation, it could be transformative in terms of their outcome. Because we've had some TRK fusion patients who've been on entrectinib now who have been on treatment for 4 years and they still haven't progressed.

I've talked about how the genotype may matter. Because studies like this whereby you now have drugs that can switch what was previously a mutant confirmation of the protein into wild-type confirmation just by binding to a certain site. So we're looking now for patients with p53-Y220C mutations in order to put them on this particular trial with a drug that can basically stabilize that protein in the nucleus so that it can function in its role of apoptosis in cancers. And we've seen evidence of shrinkage in tumors, 6 out of 7 ovarian cancers with tumor shrinkage.

Dr. Tan:
There are sort of global and European guidelines in terms of how we classify mutations for application in the clinic. So I won't go into details. But certainly, if you have a molecular profile and you don't have a molecular tumor board, for example, or you're trying to start a molecular tumor board, something like this could be very useful as a reference point in terms of how you interpret your mutations when you start looking at the literature relevant to the mutation you find in a patient sample.

But of course, Asia presents its own complexities because of the variability of reimbursement, the variability of regulation, such that, even if there's a tumor-agnostic treatment available, it's not universally approved across this part of the world. And even if it's approved by the health authority, affordability is a big issue as well. And not just the affordability of the drug, but affordability of just getting the tumor sequenced, affordability of even get a HER2 test, even a mismatch repair, IHC, can be a problem.

So these are some of the real challenges that we face on the ground, and I think harmonization of some of these tests and maybe evolving to a point whereby we can even use AI to look at HNE samples, potentially to enrich for patients that may have some of these tumor-agnostic markers, could be very relevant to parts of the world where access to pathology and good pathology and good labs that can do the pathology are deficient.

But there is always, regardless of what you do, this problem with the Minions, which is that they all look yellow, but some have two eyes and some have one, and some like to cook and some like to kill. And the question then is, how do you manage that heterogeneity? If you look at this tumor, for example, if I did the biopsy in that top bit and then I biopsied the bottom bit, I'm looking at two very different tumors, even though this is the same tumor. And we see evidence of that in this case report where tumor slices were done in a single breast tumor, and you see KRAS amplification changing in terms of its frequency from the top of the tumor to the bottom of the tumor. And we see that also with homogenous and heterogeneous staining for HER2. And if you're thinking about giving someone treatment with HER2-directed therapies, this can be a real challenge if you don't really know how to interpret this. So it's great when your pathologist says homogenous, high levels of staining. You say, great, I know what to do with this patient.

But what if you get B or C, where you get patients with mixed clones of cells? And in the one on the right, even though the tumor is actually all amplified, you find that the expression is different. What does that mean? And how is it going to impact on someone's treatment? And these are some of the things that we don't really have all the answers to at this point.

Just to say that we did a study once asking a question, if you were to do one biopsy in the patient and you saw all the mutations, how likely are you to be able to predict that one mutation is likely to be the truncal mutation, as in the mutation that's present across all the

tumors? And how many biopsies do you need eventually to get to the point where you're confident that this mutation is prevalent across all the cores that you do the biopsy on if you've got to make a decision in terms of what's driving or what's the most actionable lesion in this heterogeneous tumor? And what we did find, interestingly, that if you did two cores and you found that mutation in two cores, there was a likelihood of 87.6% that if the mutations are present in two cores, that was present in all the other two cores, if you did four cores, as well.

So again, it means in the future, if you find something that you're not sure about, you might need to really biopsy again and maybe profile again to be confident that what you're going to offer this patient is relevant to the tumor.

Then you might have the situation whereby a patient has more than one actionable mutation. So here we have a patient who couldn't get a tumor biopsy but could get a liquid biopsy. On a liquid biopsy, we found that she had a BRCA mutation, and she also had PIK3CA mutations. And what do you do at that point? Well, if you're lucky and you've got trials that are combining 3 different agents together, maybe that's something you can consider. In fact, this patient was patient number 1 who had a really sustained response to this triplet combination that we've been running at my institution. So again, when we think about combinatory approaches in the future, having that molecular profile can also help to define whether these combinations can be relevant to the patient as well. And this is, again, where your tumor board can be very important.

So I'll just put it out. And this is something that was published in 2018 showing the range of putative actionability across the TCGA studies were individual tumors. And you can see that some are FDA-approved, some are clinical trials, some are case reports. But actually, I want to draw your attention to this big white space above the multicolored bars, and that's the space where we have unmet need. That's the space where we still don't have anything actionable for all these patients, right? And so how can we find the colors in that space? Well, maybe we go even further, beyond just the genome, but to the RNA, the transcriptome. And here, there was a study that looked at RNA and DNA sequencing, and interestingly, they were able to find that some of the variants of unknown significance could actually then be defined as pathogenic or lightly pathogenic, just with the addition of RNA information.

But of course, we are in the era of ADCs, and this is where the proteins now become extremely important. So moving from RNA, now we have proteomics. And the problem with proteomics, of course, is the fact that if you have a patient, an ovarian cancer patient, and you've got 6 different ADCs to give this patient, how do you decide which ADC to give? And I think, as much as a lot of the ADCs are being developed in a biomarker-agnostic space, I think more and more we do need to understand a bit more about how the various expression of these targets impact on outcome and toxicity for the patients to better give doctors an idea of how to select the best ADCs for our patients.

I'm not going to go into much detail, except to say that clearly ADCs, if you get the right patients, they work. But also that there's variability in response depending on the extent of expression of that biomarker. And this goes back to the point that I don't think you can say a biomarker agnostic approach is appropriate in all cases. And we hope in the future that we'll have something like this, where patients can walk in, get their tumor sequenced, get their tumor profile, and then appropriately stratified to the appropriate treatment of choice.

And so in conclusion, I think we can see that if you get the right patient to the right drug, you can improve outcomes. And multi-gene testing is now available, has been approved in many countries. And the issue nonetheless is still whether we have the right availability of the tissue and availability of the treatment options for the patients that we have in front of us. Molecular tumor boards are really important in this context. And I think if you're planning to start doing sequencing and profiling in your patients on a large scale, you need to think of some way of putting together a molecular tumor board. You need to think about intratumor heterogeneity as well, and then hopefully drug combinations in the future will become more relevant and more applicable to the multitude of mutations that you see in individual patients' profiles. And we hope the newer technologies on the horizon, like spatial imaging and RNA sequencing as well, may eventually be combined and integrated into genomic sequencing to better improve therapeutic stratification.

Thank you very much.

Dr. Moore:
Let's just get started. When we talk about HER2, it's amazing to me. I've been an oncologist now for 21 years, some of you less, some of you more, but we've been talking about HER2 since I was in – well, before medical school. A long time, a quarter century. And this is really how we started. We started with the identification of gene amplification and protein overexpression, first in breast cancer. In 1998, a long time ago – it doesn't sound like it, but it is – Herceptin [trastuzumab] was fast-tracked through the FDA for approval in breast cancer. And really a lot of work has gone into HER2 testing in breast cancer since then. But really, the pivotal study here, done by Cliff Hudis, who's now the CEO of ASCO, was looking at, in a large group of patients with breast cancer, HER2 staining intensity with immunohistochemistry versus FISH. And really kind of bringing us to the point of understanding that – and this led to the first CAP/CLIA test that when you really do a carefully validated test, one isn't superior to the other, which is what really led to the current standard of CAP/CLIA testing in breast cancer for 3+ IHC and then 2+ with ISH, qualifying for trastuzumab. And you can see that here.

But all of this work, which I just summarized decades of work in one poor minute, but all of this work was based on identifying a

predictive biomarker for response to a monoclonal antibody, trastuzumab or pertuzumab. And so now that we're in the era of antibody-drug conjugates and tyrosine kinase inhibitors, does this still apply as strictly as it does for monoclonal antibodies? And that's really the question we have not yet answered across the board. I'm just showing you this table to remind you – I'm going to say this several times, there's only two CAP-certified testing for HER2. One for breast, and you can see it here. It's gone through several iterations. The 2007 was the one I just referenced. It's been 2013 and then updated in '18. And then gastric. And that's it. Everything else, we're still trying to figure out what's the best way to test. And again, a lot of this work is related to trastuzumab and not to ADCs and tyrosine kinase inhibitors.

Here's the example for endometrial cancer. There's a lot of interest in HER2 right now, but we don't have a CAP test. So what has been suggested is kind of like the original 2007 breast; it's closest to that. 3+ is strong staining in over 30% of tumors; 2+ is pretty strong staining. But with FISH HER2/CEP17 ratio greater than 2, which is a little bit different than breast. So you can already see it's kind of making a new landscape here for endometrial cancer. But this is what was previously called HER2-positive, a nomenclature we're going to be getting rid of in the future, because it's going to be 0, 1+, 2+, etc. This is the new era.

Dr. Moore:
What does a 2+ non-amplified mean, if anything? What does a 1+ mean? We have to figure that out. And really, a lot of this centered in breast for a long time, until the approval of tucatinib and trastuzumab in colorectal cancer. And this was based on the MOUNTAINEER study. And then, of course, most recently, in the US, with the accelerated approval of trastuzumab deruxtecan, based on the results of DESTINY-PanTumor, which you're going to see many times in the next hour, so I'm not going to belabor it. But these are the results of trastuzumab deruxtecan in gastric scoring across all of these non-gastric tumors, 2+ and 3+ without reference to ISH. And so this is where we are right now.

And then, even further, we have evidence now for efficacy of trastuzumab deruxtecan in HER2 mutations of a variety of types. And Dr. Tan alluded to this; in many parts of the world, there's differential access to these comprehensive molecular tests. And so the access to these will vary, but they are becoming more common. You saw – I love the slide where he said that the costs are coming down. So these are going to be more accessible.

In many parts of the world, this is what we're doing. We're doing these panel tests that give us next-generation sequencing and immunohistochemistry, and so we're identifying HER2 overexpression by IHC, HER2 amplification or ERBB2 amplification, and increasingly HER2 mutations, which are rare, but since we're doing all of these panel tests, we're finding them. And the question is really, more and more, what's the predictive value of finding each of these in different solid tumor types? And we really don't know yet, but what we know, because we're testing so much, is that there's a lot of it.

And this was a beautiful review paper that came out this year, and I encourage you to take a look at it. But what you can see here is that in every solid tumor, if you look, you'll probably find some HER2 alteration, whether it's HER2 1+ or 2+ IHC, you can see that in light and dark blue, respectively, or in the coral dots, that is amplification. So in the upper left-hand side, you can see salivary tumors have a lot of HER2 amplification. So look and you'll find it, which is good. But what we really need to know is what's the predictive value when we do find it, and should you use this medication versus another medication? And so we just have a lot to do.

Again, this reference is down here for you. This is online. It's a beautiful tutorial in HER2 testing if you're interested. I went down this rabbit hole for many hours preparing for this talk, and it's a really good resource. So I can put this up here. And then highlighted here, you can see, once again, there's only 2 that are ASCO-CAP certified, and the rest of these are either using gastric scoring or these sort of, I wouldn't say made up, but customized scoring for endometrial and colorectal cancer, which we can talk about. And so this leads to some confusion.

I'm just going to show you a couple examples. This is, again, from that really nice review paper I mentioned. This is somatic mutations in ERBB2. And this is just too complicated to go through in the time that we have. But the majority of these mutations are in the intracellular tyrosine kinase domain or the furin-like extracellular domain 2. This is the dimerization domain of HER2. And the point here is that when we look across different tumor types, there's similarities between oncogenic ERBB2 mutations, particularly between, you can see gastroesophageal cancers and colorectal cancers right next to them, you'll see similarities, mainly with V8421 and S310F, those are the predominant ones.

But by comparison, if you look at non-small cell lung cancer over here, you'll have a higher prevalence of mutations in the tyrosine kinase domain like 65% of the time versus 45% of the time in colorectal cancer. And then, by contrast, you'll find extracellular domain 2 mutations predominate in biliary tract cancer and urothelial cancers. So what this underscores is there's a varying prevalence of HER2 mutations by tumor type. And this variation suggests a difference in the cancer biology imparted by these different mutations. And the question is whether or not this manifests into different predictive values of these different mutations when we try to use HER2-targeting agents across different tumor types.

And we can see some signal that the answer to that question is probably yes. This is from DESTINY-PanTumor01. And what you can see here is that when you have extracellular domain 2 mutations or tyrosine kinase domains, you have much higher response rates. So

this is higher, this is lower, with these two guys than in comparison with the R6782. These are small numbers. But it may be not just you have a mutation or not, but what type of mutation and what type of cancer do you get trastuzumab deruxtecan? We're going to get that individualized with therapies moving forward.

And when we come back to just the kind of IHC expression, what I'm showing you here is the gastric criteria, which takes into account what Dr. Tan was talking about, the heterogeneity. It's very different than breast cancer. It has different scoring for biopsy versus a resection. It's a completely different way to score. And when you look across multiple solid tumor types – there's a review of over 4,000 cases – up to 40% of the time, you'll find 1+ HER2 immunohistochemistry staining. And what we have to figure out is if that has the same importance in a biliary tract cancer as it does in a breast cancer in terms of how we're assigning therapies moving forward. And again, this is just a little review to remind you that that HER2 and gastric scoring and breast is entirely different as it is in colorectal and endometrial and all the other tumors, and we just haven't sorted this all out yet. This is going to get really complicated.

Dr. Moore:
And just as this is looking at gastric cancers, gastrointestinal cancers in particular, again, only gastric cancer has a CAP criteria, the gastric criteria. Everything else does not. So we send all the tests, immunohistochemistry, next-gen sequencing, sometimes ISH, these are the things that the pathologists should report out. And I'll just leave that up there. But we can look – just take a closer look at colorectal, because here's the colorectal criteria. You guys know breast; you're going to hear about it some more. We talked about gastric, it's 2+, 3+.

And then for colorectal, it's based on the HERACLES study. Here, it's 3+, but not just 3+, 3+ and greater than 50% of cells, you're good. If you're 3+ in 10% to 50% of cells, you have to be amplified. If you're amplified, you're good. If you're 3+ in 10% to 50% of cells not amplified, you do not qualify. If you're 2+ in 10% to 50% of cells and amplified, you qualify. So it's really based on amplification and number of cells. These are the HERACLES criteria. They were developed for colorectal cancer using trastuzumab and lapatinib. And you can see the results here. Most of the patients who came on the study, you can see in red, were HER2 3+, and they may have been amplified or just 3+ greater than 50% of cells; that's not differentiated here. Very few were 2+; those are blue.

But I think you can see here the suggestion that those that are 2+ and they were amplified as well didn't really benefit from trastuzumab and lapatinib. So you might say, well, that's because you didn't use trastuzumab deruxtecan, and that's the magic drug. Show me that. Okay, I'll show you that. Here it is. And this is using HERACLES scoring for eligibility. The smaller number over here, these are the 6.4, which we're not using that dose, so the study was expanded at 5.4 so that's why there's more of them. What I'm showing you here in the green circles here on this first portion of the figure, the red are 3+. The blue are the 2+. So you can see them clustering down here in the non-responders. So even though in the US in the NCCN for all solid tumors, if you're 2+ or 3+, we can use trastuzumab deruxtecan. And it's nice to have options, don't get me wrong, but if I have other antibody-drug conjugates or other therapies, is this the best therapy for this group of patients? I think we really need to look at this closely, and I'll be interested to hear Dr. Van Cutsem's thoughts on this as a colorectal expert.

This is really different than endometrial cancer, and I could show you tons of data here. I'm just showing you the STATICE study where 1+ and up, this medication works in uterine carcinosarcomas where nothing works. So tumor specificity is going to be important.

So in conclusion in the first part of my talk, really, I think my point here is, if I have one, is very excited about HER2-targeting therapies, especially antibody-drug conjugates, which I'm going to show you rapidly next. But I think we have a lot of work to do to really understand the predictive value of each of these biomarkers and, sometimes in combination, IHC and amplification in each disease type to really understand what value, what efficacy we expect for a patient receiving one of these medications so we can better sequence both the timing and before or after other therapies for patients individualized at our highest level. And these biomarkers are complicated, and so this is really going to require extensive collaboration with our pathology colleagues to get this right. There's just a lot of work to do, but it's an exciting future for us moving forward.

Dr. Moore:
So with that, I'm going to turn to just some of the clinical data, and I'm going to get through this a little bit quicker to get us back on time. And we're mainly talking – not entirely, but mainly about antibody-drug conjugates. There's 190 of these in development, which is exciting. I like this on the bottom because it kind of shows the global importance of drug development, especially in Asian countries where, this is the middle ring in China, majority are microtubule toxins. But really the kind of star of the show right now are these camptothecin payloads. Camptothecins aren't new. Again, some of these are older than me, and you remember this first described in 1966; that is before I was born, so not that old. But we don't like them, right? We don't like topotecan. I don't use it ever. I hate it. It doesn't work very well, and it's very toxic. But we solved this with antibody-drug conjugates, at least Daiichi did when they were able to really conjugate deruxtecans to allow us to use these camptothecins to its best effect. And by the very nature of ADCs, kind of taking up these medications into lysosomes, which are acidic, that makes camptothecins work better. So there really is a lot of rationale for the excitement behind these medications.

There's a lot of HER2-targeting antibody-drug conjugates in development. These are the 9 camptothecin. I left out the microtubule toxins, but I'll talk to you about them in a moment. And of course, we know the most, although others are catching up, about T-DXd. But

it is important to remember, if we have a HER2 target, what we don't know yet is if I can use a camptothecin ADC and then a microtubule ADC, or vice versa. In breast cancer, we've kind of superseded T-DM1, which I'll talk about in a moment, by T-DXd. But we don't know the same is true in other tumors. And so we don't want to throw the baby out with the bath water with these microtubule toxins. And I'll show you a little bit of detail in a moment.

Just to show you what we know, which is small numbers. This is trastuzumab deruxtecan in ovarian cancer. If you look over here, 40 patients, that's all the data we have. 2+, 3+ local testing for gastric scoring was allowed to come on. Response rate in the recurrent setting, 45%. That's pretty good. For centrally confirmed 3+ it's 34%. That's really good. Centrally confirmed 2+, 36%. So we like this and we want more data. But what I'm showing you over here, which is the progression-free survival curves, which don't have a control arm so they're hard to interpret. I know. But I just am making the point that in the 3+ right here, the median PFS is 11 months. Wow. In a recurrent setting, we don't see that very often. Versus 4 months in the 2+. Now this is small numbers that may be spurious. We need more information. But again, there may be significant importance to the predictive value of a 2+ versus a 1+ versus a 3+ in decision-making moving forward for our patients.

And it's not just HER2; it's the whole context of the tumor. This is a great study out of Korea where they looked at HER2 expression and BRCA and homologous recombination deficiency in a patient series with ovarian cancer. And what they found was not what I would have expected. I would have expected that HER2, because of the association with negative prognosis, would all be in the BRCA wild-type and the HRD test negative. And that's not at all what they found. So that's important, because if I move these up in lines of therapy, maybe to frontline, what do I pick? Certainly, for BRCA I'm going to pick a PARP, but otherwise, how does this fit in the treatment paradigm? It's not just HER2. It's all the other things. And what's the best predictive biomarker for that patient at that time? We have a lot to learn.

And there's new medications coming. Both of these were presented at ESMO just this year. Both of these studies – I put T-DXd on the left – IBI354 and JSKN003 both presented at ESMO, both done entirely in China. So these are very relevant to an Asian population with response rates over 50% in a very representative platinum-resistant population. And you can see the waterfall plots here, inclusive of 1+ tumors. Small numbers. We need more data, but this does kind of bode well for potentially moving one or both of these agents into the treatment armamentarium, at least in an Asian population. This needs to be validated more globally, but very exciting.

Endometrial cancer, I've already shown you this. Here's the traditional positive 2+ ISH or 3+. That's about 18% of endometrial cancer. But in antibody-drug conjugates, if I pull in the 2+ ISH negative, that comes to a total of 27%. All of those 27%. And then if 1+ benefits, that gets me another 17%. So all of a sudden, if all of these benefit from these medications, then that really is a pretty large proportion of mainly serous endometrial cancer who can benefit.

And is it a camptothecin or a microtubule toxin? Well, we do have data with T-DM1 in amplified endometrial cancer. And you can see here the response rate was 21%, which is okay. Not great, but okay. This study was amazing though because they did post-progression biopsies, which we don't do enough of, to understand the mechanism of resistance. And found that in this patient, who was 3+ coming in, went 18 months on this medication, which is amazing, still 3+ at the time of progression. So is that someone I'm going to use T-DXd on next? Yes, I am. But really understanding this is going to be important.

I think you all know the differences between T-DXd and T-DM1. So this is the T-DXd data in endometrial cancer. This is the all-comer group, 40 patients, again, 57% response rate. But look at this 3+; 85%, but it's only 13 patients. So we need a lot more data here. And even in those patients that were essentially – they came on saying someone thought they were gastric 2+/3+, but at the end when they were centrally reconfirmed, it was 0, but they had a 60% response rate in those 5 patients. We have – and this is my mantra – we have a lot to learn here to really understand who we should be treating.

And the level of biomarker may matter. Again, this is 3+ PFS and OS. And here's 2+ PFS and OS. There's definite differences here suggested with very small numbers of patients, and we're really going to have to sort out the predictive ability.

This is one of the other kind of up-and-coming antibody-drug conjugates in the space. This is DualityBio's 1303, or BNT323, looking very consistent with trastuzumab deruxtecan, but this is included from the beginning, 1+, and this data should be updating next year, so keep an eye on that. It does have breakthrough therapy designation by the FDA.

Cervical cancer, same story. HER2 positivity, 2+ or 3+ gastric is pretty uncommon, about 18% to 20%. But when you find it, patients appear to do very well. So that's pretty exciting, and this is hopefully going to move forward into a larger study as well. But again, we see the same thing, the 3+s, which are really uncommon, but they do amazing, 2+s less so. So there's a kind of common theme here we're going to have to sort through.

Dr. Moore:
And then I promised you I would not leave out the microtubule toxins. This is disitamab vedotin, which is a microtubule toxin targeting HER2, done again in China. So this is an Asian population with cervical cancer with a respectable complete overall response rate of 27%. Largely, you can see in blue, these are 1+ tumors. So a nice signal. It needs more work. It's like my mantra here, but I think gives

us a lot of hope for the future.

And then we can just sort of talk about the other tumors. This is bladder and biliary tract cancers. You can see in the middle, high levels of response in small numbers of patients. Here's bladder, and then here's bladder with less differentiation based on the HER2 positivity. But biliary tract, kind of you see that same spread. Is this the best medicine to use here? We'll talk about that in the discussion.

But we have a new player, HER2-targeting bispecific antibody. This isn't an antibody-drug conjugate. This is zanidatamab, which just had an accelerated approval based on HERIZON-BTC. This is in biliary tract tumors that have had at least one prior gemcitabine-containing regimen with a response rate of 50%. Just pretty amazing. I'm a GYN oncologist, and I think that's amazing. So I think we'll see what happens with this in confirmatory trials.

And I just want to end with kind of lung and colorectal. What about lung cancer? Here's DESTINY-PanTumor02 in mutated, not amplified, not overexpression, at a very high dose, 6.4. But the response rate is 55%, so pretty exciting in a recurrent lung cancer population. This is DESTINY-Lung02, which is a dose-optimization study, so important, and really established 5.4 mg/kg as the preferred dose. And I think we all know that. And these are just the PFS and OS results of DESTINY-Lung02. This is DESTINY-Lung01, that looks at overexpression – so that was mutated; this is over expression – with also a very strong signal of efficacy response rate of 34%. And you can see, without a control arm, just the median PFS and OS here. And this is the confirmatory trial, DESTINLY-Lung04, which is not yet resulted in mutated specific mutations, not all mutations, T-DXd versus standard of care with immunotherapy. So really going up against the best standard of care, and this will be an important study.

And then colorectal cancer, I talked a little bit about the HERACLES criteria. That was used for selection here in a RAS wild-type, BRAF wild-type, unresectable, metastatic colorectal. This is the dose optimization, again establishing 5.4 as the dose. Here is the response rate at 6.4 which is too high a dose. Here's the response rate at the right dose, 37%. Just under 40% in a recurrent setting is quite respectable. But I think the question is going to be, with all of this, and I'm going to turn it over to my colleagues, is it enough to ride the escalator on up to frontline? We did that in lung. Is it enough for all of these other tumors? Or do we need to hit the gas a little bit, figure out the biomarkers, and then move it up in the right population? I think that's the question to answer.

And with that, I'll turn it over. Thank you.

Dr. Yang:
I'll try to put that together and summarize to you what are the guidelines right now for different cancers and what are some of the evidence.

These are my disclosures.

In the beginning, I would like to start with breast cancer, because breast cancer is the paradigm that we use HER2 as a target initially. So for metastatic breast cancer, 2023 – and the guideline is still the same, as you can see, if patient had HER2 positive, meaning 3+ or 2+ plus amplification, the frontline choice is still taxane plus trastuzumab and pertuzumab. And then it was divided to if a patient had no or stable CNS metastasis, the second-line choice has become trastuzumab deruxtecan. And for those patients who had extracranial-dominant disease, meaning that they may have CNS disease with extracranial dominant, trastuzumab deruxtecan still is that second-line choice. And for those patients who had CNS dominant, now we do not have sufficient evidence for trastuzumab deruxtecan in CNS, thus tucatinib, which is a small molecule against HER2 has become standard, plus trastuzumab and capecitabine, or Xeloda, as a standard second-line choice. And for that, trastuzumab deruxtecan has moved to the third-line place.

So we know that with the newcomers, trastuzumab deruxtecan has completely taken over the second-line space for metastatic breast cancer. This is to replace T-DM1, as we know, the standard of care in the second line.

So what about HER2 expression? Can we go down from the breast cancer as a sample? Here, you see that these are epidemiology study for hormonal receptor-positive patient or triple-negative breast cancer patients. You can divide HER2 expression to IHC 0 or absolutely no expression, 1+, or 2+. As you can see, it's evenly distributed here for hormonal positive, but it was IHC 0 for most triple-negative breast cancer patients. And here are just what you can see from pathology.

There is a very interesting study for breast cancer just to push down the use of trastuzumab deruxtecan in terms of the expression level of HER2. Remember, these are traditional HER2 testing. The name of study is called DAISY. The number of patients are not many. So this is a HER2 overexpressing or traditional HER2 definition, 68 patients, and the response rate was 70.6%. Versus so-called low expressors, so HER2 1+, 2+, 72 patients. Lower response rate, now 37.5%, but still very significant. And for our so-called non-expressive 0, 37 patients, you still have close to 30% response rate. How does this happen? Remember, Dr. Tan told you that there are certain heterogeneity among these tumors that express HER2. So perhaps it was due to this fact that you are testing small tumor samples that some other areas do contain some HER2 expression. And these responses certainly are coherent with what PFS has shown, as you can see here in the Kaplan-Meier curves and also the duration of response.

So there are 2 very important studies to look at HER2 low expression in breast cancer patients. So first one is DESTINY-Breast04. So these are the patients who had previous treated with hormonal treatment. These are hormonal receptor-positive and had received chemotherapy before. So these are chemotherapy-treated patients, second line and further. So these patients who had been determined as HER2-low, meaning that 1+, 2+, if you use trastuzumab deruxtecan, they had a PFS of 10.1 months versus these are the best treatment of choice by the physicians, the PFS was only 5.4. Highly significant, as you can see from here.

So and then they move on to so-called 06 study. This study extended the expression of HER2 to even no level, null level. But what I want to show you here is the same definition of 1+, 2+. Here, in this study, they want to study whether a patient without prior chemotherapy – so all these patients had chemo-naïve history, hormone receptor-positive, but then received trastuzumab deruxtecan as the first frontline chemotherapy. Now the PFS has become 13.2 months. So if you compare 30.2 versus 10.1, obviously there was a benefit. We don't want to cross-trial comparison, but it tells us that this is chemotherapy. Chemotherapy is best when you use frontline.

But this is not going to translate into overall survival. Because overall survival, obviously it's better for 04 as you can see, a good hazard ratio. But for 06, this is chemo-naïve patients. You have a lot of subsequent treatment to go over afterwards. And many of these patients actually cross over to T-DXd, thus the hazard ratio was not as good as 04.

So this figure actually tells you how breast people view HER2 expression in HER2-low here. Even in HER2-low, there are some degree of differences. For example, in this IHC 2+, you see that the definition is weak to moderate complete membrane staining. As you can see, it's complete, more than 10% of tumor cells. And for 1+, the membrane staining was incomplete. As you can see, it staggers right here. And for so-called HER2-ultralow, meaning that it's incomplete, in addition to that, less than 10% of tumor cells were detected. And there is so-called HER2-null. But remember, these patients also responded to T-DXd.

So essentially, it's a spectrum of HER2 expression, but yet, the spectrum of activity also correlated to their expression level. So we do need to have better ways to view this, because over all these studies, we know that in breast cancer, trastuzumab deruxtecan is helpful for these patients, but with different degree.

So how do we do that in the clinical practice? Now I want to use NCCN Guidelines. I know that you use that often in this regard. So for trastuzumab deruxtecan in metastatic breast cancer, HER2 positive, so these are the traditional definition, it was the standard second-line treatment here as a category 1 evidence, preferred regimen. And for care for recurrent, unresectable hormone receptor-positive, HER2-negative patients, so these are patients who had HER2 1+, 2+, here it is a standard second line as well and category 1 evidence, so according to DESTINY-Breast04 and 06. And also for HER2-negative, triple-negative breast cancer, it was also used as a second line. But be aware that these patients, sometimes there are other options, so, for example, olaparib and PD-1 inhibition. Thus, the treatment paradigm was pretty complicated, as you can see from here. And the standard, though, is 5.4 mg/kg.

For non-small cell lung cancer, Dr. Moore has talked about this a little bit. We can say that it's separated into 2 categories at least. One is HER2 mutation that occurs in 2% to 4% of our population. And these are very strictly on exon 20 insertion mutation; all the others, we don't know anything about whether they are activating mutation or not. But it is a standard test for non-small cell lung cancer, so we get these tests.

But as you can see here, some squamous cell carcinoma were also recommended to consider for molecular testing up front, because some of these patients had never smoked, were female, and they may be squamous adeno histology; therefore, sometimes we still do these tests. And what are the recommendations? They are recommended as a second-line choice after systemic therapy has failed. So these are the standard therapies for HER2 mutation non-small lung cancer as a second line.

But for patients who had HER2 expression, this was shown in DESTINY-Lung03 that was recently presented by me in the World Lung Cancer Conference. Here, the HER2 expression definition is a little bit tricky, because over the trials, we use a different antibody. These antibodies are much more sensitive than the original antibody that we used to test breasts. So be aware that all these tests had different meanings, even if you qualify them as HER2 3+, 2+, or 1+, they have different meanings using different antibodies. So it is a very, very complicated area that we are going to discuss. Here, even in NCCN Guideline, as you can see, HER2 protein overexpression, this session is under development, meaning that we still don't know what to do with that. But it is recommended as a second-line treatment.

So colon cancer, you already heard that there are some patients who had HER2 amplification, HER2 overexpression. They all qualify to use HER2-directed therapies. Here, trastuzumab plus pertuzumab, perhaps, but of course, trastuzumab deruxtecan was recommended as one of the options, as was shown by the evidence Dr. Moore has shown to you. But the frontline still is a very complicated FOLFOX or FOLFIRI regimen that you're already familiar with.

For gastric cancer, it's a little different in that HER2 was already known as a target in roughly 20% to 30% of patients. So HER2 expression was already defined in gastric cancer. For these, HER2 overexpression patients, obviously the first frontline choice is still trastuzumab plus chemotherapy. But then when they failed, trastuzumab deruxtecan is a choice for them, as you can see from here. But then this is the only exception, that for gastric cancer, the recommended dose is 6.4, not 5.4.

For biliary cancer, it is a very, very fascinating area because there are a lot of new mutations being found after NGS. And there are a lot of patients who had HER2 alterations, including amplification, overexpression, and also mutations. And for all these patients, trastuzumab deruxtecan has shown some activities, but only in a very small number of patients. Be aware that this is recommended for HER2-positive patients, but I think we still need to get a lot of information. Here, for the sake of FDA approval, it's all IHC 3+.

In bladder cancer, the same. It was recommended for HER2-positive IHC 3+ patients. For pancreas, it's the same. But if you look at the data, there are only few patients with pancreatic cancer, and their responses are not that great. So I think, although it's called tumor agnostic, we still have to face that we are dealing with very, very small number of denominators.

So in summary, these are the recommendations for various cancers right now. It was approved by FDA that HER2 overexpression, you can use deruxtecan. But then you must use frontline therapies until.

Dr. Yang:
I want to spend about 5 minutes to talk about important side effects because we don't have enough time. What about the most important side effect? We know it's interstitial lung fibrosis. There are various mechanisms that are probably related to that. But most importantly, the disease antibody needs to enter one of these cells, either bronchoalveolar, epithelia, or alveolar macrophage or tumor cells. It has to be disintegrated into deruxtecan because deruxtecan plus probably the linkers are the toxic component that will hurt the normal cells.

The timing to develop ILD is very, very different from the timing of ILD for tyrosine kinase inhibitors. We know that for all of you who use EGFR tyrosine kinase inhibitors, ILD occurs very fast, a few days, a few weeks. Almost all of the patients develop that within 1 month or 2 months. But for T-DXd, it's a completely different story. Because, as you can see, the median time to develop ILD is 5.4 months, very late. And it accumulated until roughly 15%. If you don't have ILD after 1 year, you can expect these patients will not develop ILDs. And these are out of the more than 1,000 patients database.

Who are the patients who are prone to develop ILDs? Younger patients, Japanese, lung comorbidities, or baseline renal dysfunction and also higher dose. So these are patients who are prone to develop ILD. You need to pay attention to that.

So I want to, because of time, I want to skip some of that. And as you can see, these are the ILD that develop after 3 months. So beginning from 2 to 3 months, you need to be aware that these patients are going to develop ILDs. For this patient, for example, it has very good response. So you really need to judge risk and benefit, whether you want to continue or not. That's why we developed this consensus from Asia-Pacific area. You need to go through multidisciplinary team to figure out whether you want to continue or you want to stop.

So eligibility for patients who receive T-DXd. First of all, you need to review the history whether they are prone to develop ILD. If they do already have some ILD evidence, you shouldn't give T-DXd to them. And then you can monitor these patients with their symptoms, with scans. And there is still no consensus how long you should follow them. But as I can show you, that 5.4 months is a time when the median to develop ILDs; you know that you need to monitor them very carefully.

Why do we need to monitor them very carefully? Because we know that once you detect ILDs, you need to do various tests to rule out infectious disease, rule out many things. We know that this diagnosis is by exclusion. After this, you have to figure out whether you want to give steroid right away, even for grade 1. For grade 1, if you don't give them right away, sometimes they progress to grade 2 or grade 3 very rapidly. And for most of the time, because it is a fibrotic procedure, it is not really reversible at the end of day. So if you have suspected ILD, so this summarizes everything, withhold T-DXd. If you suspect, you have to withhold and do all these tests, radiology test, high-resolution CAT scan is recommended, and consider bronchoscopy. Bronchoalveolar lavage to gather information and consult pulmonologists, consult infectious disease specialists to test everything that you can, to rule out everything. And if you reach the conclusion that these patients do have ILD, consider to stop that at the right moment and give them steroids, see if that is reversible. If that is not reversible within 2 weeks to 4 weeks, probably you should stop that altogether.

So for grade 2, obviously permanently discontinue that, and you have to treat them very, very carefully. For grade 3 and 4, obviously completely stop the drug, give them high-dose steroids. Wish that it is reversible. Most of time it is not reversible.

And cardiac toxicity is another area that you should look at, because this is HER2. Remember that HER2 has cardiac toxicity, so you have to follow what trastuzumab has suggested and be aware that you still carry a toxin that is probaby even more toxic than trastuzumab itself. So there are various recommendations that you should follow. And for dose reduction, that's for 5.4 to 4.4 to 3.2. But to be honest, I'm not sure whether with low dose, it's really helpful.

And most important, education, education, and education. Educate yourself, your colleagues, your patients, your case manager that these can happen with trastuzumab deruxtecan. So there are various educational cards, booklets to be given out.

And in conclusion, this is a brand-new field that we are facing, brand-new drug. We do face new side effects, but we do have very good

activities that has never been demonstrated before. So we are moving forward with antibody-drug conjugate, but we also have to learn a lot of side effects that we have not experienced before. Thank you very much.

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