Transcript Details

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Mastering HER2 in GI Malignancies: Incorporating a Multidisciplinary Approach Into Current and Emerging Management

Announcer:
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Chapter 1

Dr. Ciombor:
We know that HER2 [human epidermal growth factor receptor 2] alterations are commonly found across tumor types, but there are different alterations and, particularly in GI cancers, what type of alterations matter? So for instance, in some of the other tumor types, such as breast cancer, lung cancer, mutations may be important, but really for the GI cancers, it’s overexpression/amplification. And you can see in this figure here kind of the overall prevalence of these alterations based on tumor type.

We know that the HER2 oncogenic codes, the receptor tyrosine kinase ErbB2, and HER2 overexpression leads to constitutive activation with dysregulated cellular proliferation. And so in the clinic we typically traditionally have detected HER2 overexpression by immunohistochemistry [IHC] and FISH [fluorescence in situ hybridization) or, more recently, by next-generation sequencing. And so I’ve included some of these ways to detect, and it really is very critical in GI cancers, and we’ll talk more about this in the other lectures as well, about how important these features are, how to test, when to test. We’ll try to cover a lot of those different factors. Try to make it very practical.

Additionally, GI cancer – so even though HER2 is important across a range of tumor types, there are definitely some differences. So HER2 positivity in GI cancers clearly not like it is in breast cancer, where you can treat patients who have HER2 low disease. So GI cancer is really, at the current time, the response to anti-HER2 regimens are typically concordant with copy number and a degree of overexpression.

So we know now that tissue-based NGS, next-generation sequencing, identifies these HER2 amplifications with high concordance compared to IHC and FISH, and I’ll show you an example of that in a second, but there are some caveats to tissue-based testing, as we all know. Sometimes the biopsies can have low tumor content; we don’t know if there is HER2 heterogeneity. We’ll hear more about that later in the evening as well. And then the opposite question a lot of people ask, can we just do liquid-based, you know, blood-based next-generation sequencing? Is that good for HER2? And of course, there are many pros: minimally invasive, you can do it serially without much discomfort to the patient. But you have to remember that it’s also dependent on the amount of circulating tumor DNA [ctDNA] shedding and other factors.

So I mentioned that NGS is quite concordant with IHC and FISH testing. This is one example. We presented some data last year at ASCO from the MOUNTAINEER trial specifically looking – so these were patients treated with tucatinib and trastuzumab, but looking at

how their HER2 overexpression was diagnosed. And what we found was that the concordance between tissue NGS and IHC/FISH was very high, a 93%. A little bit lower when you were using blood NGS versus IHC and FISH or blood versus tissue NGS. But the concordance rate even in those was about 80%. So not perfect, but you do really need to consider your source when you're testing, which makes this a little bit tricky.

And then we'll hear more about this in the upcoming talks, but heterogeneity in HER2 determination, so not just in colon, obviously in esophageal and gastric. And a lot of questions about whether we need to re-biopsy. So can we find resistance mechanisms? Can we tell if that's really still a good target to hit? And there can be some discordance between surgical specimens and biopsy specimens. Again, the intratumoral heterogeneity, as well as intertumoral heterogeneity, which can make this a little bit tricky.

So we'll talk a little bit about re-biopsying and when that may be helpful and how to do that. Certainly re-biopsying as you go along the treatment path can help you detect acquired resistance mechanisms, and we know some of those now, such as loss of HER2 expression, acquired activation of the PI3-kinase pathway, and others. And then of course, there can be discordance between the primary and metastasis. So there've been several people who have demonstrated that. I just showed one example of one study in colorectal cancer [CRC] where the discordance between primary metastasis and HER2 overexpression was up to 15%.

But fortunately, we have a lot of targets now and a lot of ways to target HER2-overexpressed GI cancer. So we'll cover many of these tonight and talk not only about the data, but how to interpret the data, how to use the data, how to minimize toxicity for patients, too. We do want to make this very practical.

Chapter 2

Dr. Pientrantonio:
We all know that gastric cancer is a major health problem, and also for more than 10 years trastuzumab plus platinum fluoropyrimidine in chemotherapy has been the standard of care for patients with HER2-positive disease based on the ToGA trial results. However, over the last decade, several other randomized clinical trials had negative results with different anti-HER2 strategies or agents, including second-line T-DM1, trastuzumab beyond progression, lapatinib, and also the up-front use of dual HER2 inhibition with pertuzumab added to trastuzumab and chemotherapy.

And Dr. Ciombor showed us HER2 heterogeneity may have determined these negative results, but we can still improve the quality of HER2 testing in our daily clinical practice by promoting adequate tissue sampling; by finding surrogate strategies for biomarker testing, including liquid biopsy and, of course, HER2-targeted PET scan; by promoting interactions between pathologists and clinicians; and finally, by engaging pathologists in clinical trial design, education, quality assurance, et cetera. However, despite what I first heard, biology remains biology, and these studies show the changes of HER2 status over time moving from tumor biopsies to surgical specimens and moving from surgical specimens of the primary tumor to metachronous recurrences.

And other studies showed the loss of HER2 expression after trastuzumab-based first-line therapy, especially in initially IHC 2+ disease. So if the question, as we say it, is whether we should re-biopsy distant metastasis, recurrences, sites of disease progression, as we usually do in patients with breast cancer, the answer is probably yes.

Also, other studies show the coexistence of HER2 coamplification with other genomic drivers of primary resistance to trastuzumab, and these alterations include, RTK's amplifications, sub PI3K-PTEN pathway alterations, and also KRS amplification and mutations. And in parallel, secondary resistance to trastuzumab is associated with the emergence of multiple genomic drivers under the selective pressure of HER2 inhibition. And so this is the reason why long-term benefit from trastuzumab-based therapy is relatively uncommon.

So, however, in 2024, nowadays, there must be a better way to tackle tumor biology. So one strategy is the use of combinations, as the ToGA regimen itself is. And this slide summarizes the results of the HER-RAM phase 1b/2 study. As you can see, patients received the trastuzumab beyond progression plus full doses of paclitaxel and ramucirumab, and the activity results were quite promising, suggesting potential synergy. And also, in the subgroup of patients with available tumor re-biopsies after trastuzumab, the PFS [progression-free survival] and OS [overall survival] were quite similar in patients with HER2 positivity maintained or lost after trastuzumab. But of course, the most important therapeutic strategy to address tumor heterogeneity is the use of novel agents, so ADCs [antibody-drug conjugates]. The combination of different ADCs with different payloads, for example, and bispecific monoclonal antibodies.

So of course, trastuzumab deruxtecan plays a pivotal role because of the peculiar pharmacological properties and also because of the potential ability to bypass the primary resistance drivers in gastric cancer models and also in patients and the potential activity in HER2 heterogenous disease because of the bystander effect on HER2 negative tumor clones.

So moving to the clinic, we are aware of the design of the DESTINY-Gastric01 trial. This trial enrolled Asian patients with HER2-expressing gastric or GE junction adenocarcinoma after failure of at least 2 prior treatment lines, including trastuzumab. So patients with

HER2-positive disease, so IHC 3+/ISH+, were randomized 2:1 to T-DXd 6.4 mg/kg versus the investigator's choice chemotherapy with irinotecan or paclitaxel. And 2 additional non-randomized cohorts included patients with HER2-low disease, so IHC 2+/ISH- or 1+, respectively. And the primary study endpoint was overall response rate.

So regarding the results in HER2-positive disease, the trial met its primary endpoint since T-DXd significantly improved overall response rate with an ORR of more than 50%. But with internal consistency, this agent also improved the DoR [duration of response], the CR [complete response], PFS, and OS, reaching a median overall survival of more than 12 months in a heavily pretreated patient population.

So regarding the results in HER2-low disease, the activity of T-DXd progressively decreased with the decreasing HER2 expression, and the overall response rate was 26% in the 2+/ISH- cohort, and almost 10% in the 1+ cohort. Of course, these results are limited by the small sample size, by the non-randomized nature, and also by the lack of a clear distinction between HER2 low and HER2 heterogenous disease, which in my opinion, could be overcome in the future by the use of liquid biopsy.

And also, finally, to replicate the results of 01 trial in Western patients living in North America and Europe, the DESTINY-Gastric02 trial was designed. And as you can see, this trial enrolled patients who were eligible for second-line therapy with centrally confirmed HER2 positivity in a tumor re-biopsy obtained after trastuzumab-based first-line therapy. Patients were treated with T-DXd 6.4 mg/kg, and the primary endpoint was, again, overall response rate. We see the results here. So overall response rate was 38% in the initial analysis. It increased up to 42% in the updated analysis, suggesting that the quality and depth of response improve over time. Also, the median PFS and OS were 5.6 months and more than 12 months, thus being superimposable to the results of the 01 trial.

However, trastuzumab deruxtecan is approved based on a non-randomized trial in the second-line setting and a randomized phase 2 in the late-line setting. So we really need phase 3 data to establish the placement of this agent in the therapeutic algorithm. And this is the reason why the DESTINY-Gastric04 trial, which is an ongoing trial, has been designed. This trial enrolls patients, again, eligible for the second-line therapy with centrally confirmed HER2 positivity after trastuzumab, and it has recently been amended to allow local testing. So again, patients are randomized to either T-DXd versus standard paclitaxel plus ramucirumab, and this time the primary study endpoint is overall survival.

So in summary, we have more positive trials for patients with pretreated disease, especially with trastuzumab deruxtecan. And in the second presentation, I will show what's going on in the first-line setting. So we have interesting data and trials also in the up-front setting.

Thank you very much for your attention.

Chapter 3

Dr. Ciombor:
Filippo, you mentioned in the beginning of the talk about engaging pathology. How do you do that in a practical way, and what does that look like in your practice?

Dr. Pientrantonio:
Yeah, basically we do multidisciplinary meetings every week, so it is possible in our institution to review the pathology slides and to discuss the cases to decide whether a patient should go to a tumor re-biopsy, and we can decide treatment many times based on these discussions. So I think it's very interesting to discuss with other doctors and colleagues and especially with pathologists and molecular biologists to really improve the patient journey because, of course, when we do things alone, the outcomes of the patients are much worse than when we work all together.

Dr. Ciombor:
Yes. Thank you. Yeah, I think that's an important point, and certainly in GI cancers in particular, I think all tumor types are moving that way, but very multidisciplinary disease.What about – and anyone can answer this, too, and not necessarily in GE j

unction or gastric cancer, but when do you all re-biopsy, particularly when you're thinking about HER2 after you've treated someone with anti-HER2 agents?

Dr. Pientrantonio:
Well, especially my opinion when the IHC result is 2+, the probability to see HER2 loss after trastuzumab is higher, also the reverse situation when you have HER2-negative tumors, but located in the proximal side of the stomach. So the GE junction, intestinal-type with liver mass, all these are factors suggesting that biopsying the metastatic lesions may be associated with a different result with a HER2 3+ result or HER2 positivity in general, so.

Dr. Ciombor:

Raghav, how about you? What does MD Anderson do in terms of do you do reflexive testing for HER2? Or do you primarily do NGS? How do you look for HER2?

Dr. Raghav:
So in colorectal cancer we actually do NGS sequencing as well as IHC and ISH as reflex. I think the purpose of doing all of those is that we are still in the infancy of trying to understand the biomarkers that are associated with these responses, and there is different information that each of these things can give apart from just HER2 being positive or negative. We also sometimes do liquid biopsies, but liquid biopsies are more suited for when we, A, don't have tissue in first-line setting. And like you asked, before I will switch anyone from one HER2 therapy to another, I would like the confirmation of some sort of HER2 positivity, and liquid biopsy is a good medium to establish that positivity without re-biopsying the patient. But, however, if a patient was HER2 positive, got HER2 therapy, and now I'm seeing a reasonably good quality of ctDNA sample, but I'm not seeing HER2 amplification, I would like to biopsy that patient before exposing them to another anti-HER2 therapy.

Dr. Ciombor:
Yeah. Great point. Jim?

Dr. Harding:
I agree with what's been said. And for biliary cancer, I do think it is really, truly an emerging field for HER2-targeted therapy. You know, comparing GI to breast, I do think there's a greater heterogeneity. The HER2 loss, it's clearly a resistance mechanism, and that's been published in biliary tract cancer.

So I do think it is reasonable, if someone has responded to that therapy, before entering into another HER2 targeted approach would be to re-biopsy. But in biliary cancers there's this still kind of coming into mainstream usage, so. But I agree with what all has been said. Yeah.

Dr. Ciombor:
Does anybody ever biopsy just in general primary and metastatic site if one is HER2 positve?

Dr. Raghav:
Not in colon. I think our data in colon is pretty uniform that that there is really no major difference between metastatic and primary site. So we don't really biopsy 2 different sites and prove HER2 as positive in both as long as it's in 1.

Dr. Ciombor:
Yeah. Good. Okay. Great

Chapter 4

Dr. Pientrantonio:
First, just to say that HER2 testing and PD-L1 testing are recommended by all major guidelines to drive first-line treatment choices in patients with advanced gastric cancer. And regarding HER2-positive disease, let's start with reviewing the current standard of first-line therapy, which is represented by dual PD-1 and HER2 inhibition based on the results of the KEYNOTE-811 trial. This trial enrolled patients with centrally confirmed HER2-positive gastric or GE junction adenocarcinoma and no prior therapy for metastatic disease. And patients were stratified by PD-L1 CPS [combined positive score] using the cutoff of 1, and then randomized to either chemotherapy with FP or CAPOX plus trastuzumab with either pembrolizumab or placebo.

Despite the coprimary endpoints being OS and PFS, the initial analysis on tumor responses in a larger fraction of trial patients showed a significant increase of overall response rate and complete response rate, with the addition of pembrolizumab to trastuzumab chemotherapy. And these results led to the approval of this combination by the FDA [US Food and Drug Administration], but not by the EMA [European Medicines Agency]. So however, the results of the second interim analysis, and most importantly, the third interim analysis with more than 3 years of follow-up were presented at ESMO last year. And as you can see, the addition of pembrolizumab significantly improved the progression-free survival in the overall trial population, and also in the subgroup of patients with PD-L1 CPS 1 or more.

However, in the subgroup of patients with CPS less than 1, the hazard ratio was 1.03, even though the Kaplan-Meier curves were not reported. Regarding overall survival, this endpoint will be formally tested in the final analysis. However, in the third interim analysis, the median overall survival gain exceeded 3 months in the overall trial population, and it exceeded 4 months in the subgroup of patients with PD-L1 CPS 1 or more. So the magnitude of benefit with the addition of pembrolizumab increased using PD-L1 expression as a selection biomarker. But, however, the results were not formally reported in the subgroup of patients with CPS less than 1.

This is why in collaboration with Dr. Sundar in Singapore we did the Kaplan-Meier subtraction method to derive individual patient data

from the Kaplan-Meier curves and also to generate PFS and OS curves in the subgroup of patients with negative PD-L1 expression. And as you can see, pembrolizumab did not improve PFS and had a detrimental effect on OS in this subgroup of patients. And this is the reason why the FDA limited the approval of pembrolizumab to patients with CPS 1 or more and the EMA recently approved the combination in these biomarker-selected population.

So, however, the landscape of HER2 targeting in this disease is rapidly evolving thanks to new agents, antibody-drug conjugates, bispecific monoclonal antibodies, and cancer vaccines, among others, and so to bring to the first-line setting T-DXd-based combination, the DESTINY-Gastric03 trial has been designed. As you can see, part 1 of the study enrolled patients after failure of at least one prior treatment line, including trastuzumab, to establish the safety and the recommended doses of several T-DXd-based combinations including with fluoropyrimidines, the anti-PD-L1 agent durvalumab, and CAPOX doublet chemo. And part 2 of the trial is enrolling treatment-naïve patients using the same combinations established in part 1 of the study. So the focus is on the combination of T-DXd plus a fluoropyrimidine and pembrolizumab and whether this may be superior in the future to the standard KEYNOTE-811 regimen.

Also, the landscape of immune checkpoint inhibitors is rapidly evolving. And the MEDI5752 is bispecific monoclonal antibody targeting PD-1 and CTLA-4 and providing preferential CTLA-4 blockade in the activated PD-1-positive T cells in the tumor microenvironment and reducing the activation of naïve T cells. So this agent may be more effective and, above all, less toxic than standard anti-PD-1 and CTLA-4 combinations, and so there is a strong rationale to combine it with novel anti-HER2 agents. And this is the reason why the DESTINY-Gastric03 trial was amended, and now part 3 of the trial is evaluating T-DXd plus a fluoropyrimidine plus MEDI5752. Both in HER2-positive and HER2-low disease.

And also, finally, to bring T-DXd in the early stage of disease, we designed in Italy the TRINITY phase 2 randomized clinical trial. As you can see and as you know, patients with minimal residual disease after preoperative chemo and surgery have a very high risk of recurrence and probably limited benefit from the continuation of the same postoperative regimen. And we potentially benefit from switching a non-cross-resistant regimen. So this trial enrolls patients with HER2-positive resectable gastroesophageal adenocarcinoma treated with preoperative FLOT and surgery, and then those with minimal risk positive ctDNA after surgery are randomized to either T-DXd plus a fluoropyrimidine versus FLOT continuation. And the primary study endpoint is ctDNA clearance by the 1-year time point.

And now, let's shift for a bit the focus on other agents. For example, zanidatamab, which is a bispecific anti-HER2 monoclonal antibody with a biparatopic binding to 2 distinct HER2 epitopes. So providing potential superior activity compared to a more standard pertuzumab and trastuzumab combination. So our phase 2 non-randomized clinical trial evaluated the zanidatamab plus first-line chemotherapy. As you can see in combination with CAPOX, FOLFOX, versus platin 5-FU. And the primary study endpoint was overall response rate. So the results were presented at ASCO GI last year, and as you can see, overall response rate, PFS, and OS were quite promising. In the medium, PFS exceeded 12 months, which favorably compares with the results of the ToGA and JACOB trial. Of course, these results need confirmation with a randomized clinical trials and also, in a more contemporary setting, including the up-front use of immune checkpoint inhibitors.

But this is also the reason why the ongoing HERIZON-GEA-01 study has been designed. And as you can see, again, this trial is enrolling patients with centrally confirmed HER2 positivity, and these patients are randomized to either a control arm with trastuzumab chemotherapy or 2 experimental arms with chemo plus zanidatamab or chemo plus zanidatamab plus the PD-1 inhibitor tislelizumab. Here the coprimary endpoints are PFS and OS.

And finally, dual HER2 inhibition with tucatinib plus trastuzumab warrants investigation in combination with chemotherapy and/or pembrolizumab. So in this SGNTUC-024 trial, we have a first part evaluating the safety and, again, the recommended doses of tucatinib, trastuzumab with CAPOX or FOLFOX chemotherapy with or without pembrolizumab. And part 2 of the trial is evaluating the preliminary efficacy of the addition of tucatinib to a standard regimen with pembrolizumab, trastuzumab, and also a platin-based chemo.

So there is a lot of things ongoing in the first-line setting, and trastuzumab deruxtecan, zanidatamab, and tucatinib are emerging as promising first-line options for these patients, especially in combination with chemo and immune checkpoint inhibitors. But of course, the ongoing clinical trials are necessary to evaluate the efficacy and also the safety in a more rigorous setting.

And thank you very much.

Chapter 5

Dr. Ciombor:
One of the things I think about, and I think this is a theme of tonight and drug development in general, is once we find that something works, we want to move it earlier and earlier in treatment settings. And that can be a little tricky. You know, and 2 ways I'm thinking about. One is getting NGS or molecular profiling early enough, and I know that's a problem or a difficulty, an obstacle for all of us. And

then also, toxicity. Any concerns about toxicity, you know, increasing toxicity, especially T-DXd? We'll talk a little bit more about the unique toxicities there, but what are your thoughts, Filippo?

Dr. Pientrantonio:
Yeah. Of course T-DXd has some chemotherapy-related toxicities, so the safety profile when we think on combinations may be a limitation for combining it with aggressive chemotherapy regimen. So this is the reason why, probably, as we did in the TRINITY trial, which is an academic trial, we decided to combine this agent with a fluoropyrimidine monotherapy. Also, regarding the combination with immune checkpoint inhibitors, we should be aware that some toxicity may overlap, especially when we think on interstitial lung disease and toxicity. So, of course, trials such as the DESTINY-03 are quite important to establish the safety in a larger number of patients, and this is crucial because we really want to move earlier these agents in combination with other active agents, and even to early-stage disease when the goal of treatment is cure. So establishing the safety of these combinations is crucial, but we really want to do that.

Dr. Ciombor:
Absolutely. And I'm curious, with your TRINITY study with the ctDNA positivity, how long after surgery are you testing, and what are some of the details about that?

Dr. Pientrantonio:
Yeah, so we're testing 2 to 6 weeks after surgery. HER2 status is centrally confirmed in the surgical samples because it is not sufficient to test HER2 in the initial tumor biopsy for all of the reasons that we said before. And of course, patients with negative results are out of the study because they may have added benefit from preoperative FLOT, so they will continue to receive FLOT out of the trial. But those with positive minimal residual disease may benefit a little from the continuation of the same chemo. These are typically the patients we see with a high number of lymph nodes after preoperative chemotherapy, and we are not so comfortable in continuing the same chemotherapy regimen. And so this trial focused on switching to a non-cross-resistant regimen, whether it is T-DXd or other combinations, in my opinion, are important because early stage of disease means cure.

Dr. Ciombor:
Absolutely. I think that's a great study design, too. You know, because we've seen for so long that chemo – I mean, it's different with perioperative FLOT, but adjuvant chemo in general has not moved the mark very much, and maybe by understanding who's more likely to relapse and treating them when they have microscopic disease is the way to go.

So coming back to the toxicity question, Raghav, and I think you'll touch on this later in colorectal, but you know, we've seen that there's some differential dosing regimens, right, with T-DXd and some of these other agents. What are your thoughts in terms of the importance of figuring out the right dose and how that's going to be important for our patients?

Dr. Raghav:
Yeah. I mean, I think dose optimization is critical to these drugs, especially antibody-drug conjugates in general because we do notice differential sensitivity in various tumor types, and you can see that, you know, approvals are different in different tumor types. I think overall, the impression of HER2-targeted therapy as far as colorectal cancer goes, is that when you look at the efficacy and toxicity profile, there is significant benefit to these drugs. I mean, they're better tolerated than the conventional standards that we have, and that's why I think it's very critical to identify these patients early. But, you know, as Filippo pointed out, we need these patients, they're rare, so they should still be treated on clinical trials. It's very heartening to see the number of clinical trials in gastric cancer. I would really wish that we have more trials in colorectal cancer, and we actually do have some of these, but we should take all of this data as an indication that we've hit a home run and still try to identify these patients, try to improve them.

Dr. Ciombor:
Yeah. Completely agree. And I'm very heartened, too, to see all those ongoing trials.

Chapter 6

Dr. Raghav:
HER2 amplification has been a very targetable biomarker in breast cancer for a long period of time, and in fact, even in gastric cancer it has been the case. But HER2 amplification has been a very novel and new biomarker as far as colorectal cancer is concerned. Partly because of the low prevalence of this biomarker in this disease.

But we've increasingly started identifying this as a very distinct subset of colorectal cancer. So I'm going to talk about progression following front-line therapy, and the reason why the talk is titled this way is because there is no approval for first-line for HER2 drugs in colorectal cancer. And the first randomized trial exploring that question, which is MOUNTAINEER-03 is currently ongoing, which combines dual anti-HER2 therapy with chemotherapy versus standard of care chemo. So just keep that trial in mind as we go through

these slides.

So our agenda is, you know, what are the barriers and strategies for biomarker testing when it pertains to colorectal cancer what's the antitumor activity that we've seen so far, and what are options when it comes to the classic subsets of colorectal cancer, like RAS and BRAF mutant or wildtype tumors.

So colorectal is a very molecularly diverse entity. This is not just true for colorectal cancer, it's, you know, this slide could be used for pretty much any other tumor type, but you can see that we have these broad categories of RAS, wild type and mutant, and then we have the MSI high. We have few fusions. But what you notice in this slide is HER2 overexpression is seen in about 2 to 4% of all unselected colorectal cancer, but it is more towards the RAS BRAF wildtype patients, right? So the large bucket of these tumors are RAS BRAF wildtype colorectal cancer. So that's what we are going to talk about is this subset that involves this 2 to 4% of all CRC.

So multiple studies, what this slide essentially shows is you can do IHC/ISH, NGS. Almost all of them show that in an unselected cohorts 2 to 3, 2 to 4% prevalence. But in the studies that explore the differences between RAS mutant and RAS wildtype, you can see a significant difference because you can see that in the wildtype it's about 4 – 5 to 6%, whereas in the mutant it's about 1 percent or so. And that's where we fall on as far as colorectal cancer is concerned when it comes to HER2 amplification across different tumor types. So it's a low prevalence biomarker, but what I will try to emphasize during this talk is that it's such a critical biomarker to find in this disease. Just remember that MSI high colorectal cancer is also about 3 to 4% of all colorectal cancers, so it's a low prevalence biomarker in metastatic setting.

So what is special about this subset? So this subset is found more on left-sided tumors than right-sided tumors. It has more propensity for lung metastases and brain metastases This is actually even true for gastric cancer and breast cancer. And HER2 amplifications are more enriched in RAS and BRAF wildtype tumors. So you see them in 6 to 12% of RAS BRAF wildtype tumors compared to only 1 to 2% in RAS mutant tumors. The prognostic role, though, is uncertain, so we don't know whether this is like BRAF, like patients with HER2 don't really do as poorly as BRAF mutant patients do.

But one thing that we've learned about this is that HER2 in CRC is a negative predictor for anti-EGFR therapy. If you remember, this pathway your EGFR is upstream and then it activates the RAS RAF MAP kinase pathway. So if you have a RAS mutation, which is downstream, EGFR drugs don't work. Similarly, HER2 is a receptor on top of this pathway, and if your pathway is getting activated by RAS mutations HER2 therapy doesn't work. But more importantly, because HER2 is activating this pathway, EGFR therapy doesn't work on these patients, and you can see that the progression-free survival of these patients is 3 months compared to 9 months in a HER2 non-amplified population. So these patients should be identified early and before you start treating them with anti-EGFR, they should be moved towards clinical trials or anti-HER2 therapy.

So NCCN [National Comprehensive Cancer Network] Guidelines endorse HER2 testing in RAS and BRAF wildtype patients, so this is a standard of care now. And when you look at the antitumor activity across the spectrum, what we find is, even though it is seen in about 2 to 3% of cases, the response rates with most therapies, which I will show you, land somewhere between 30 and 50%. And there are two types of therapies that are currently using, as was mentioned earlier. There is dual HER2 inhibition, so you use trastuzumab as a backbone and then add to it either lapatinib, pertuzumab, or tucatinib. This is different from what was presented for gastric cancer. In gastric cancer, single-agent anti-HER2 has activity, whereas in colorectal cancer it has no role. And then the second type of agents is the HER2 antibody drug conjugates, specifically trastuzumab deruxtecan.

So I'm going to go through a slew of studies which were all done in refractory setting and what this study tells you is do not use single-agent anti-HER2 in colorectal cancer. It doesn't work. So HERACLES-A was the first study, Europe, trastuzumab lapatinib, treatment refractory population response rate of 30%. And even doing this first study, we started learning that it's 3-plus tumors that respond more and you can see that the progression-free survival is more. So if you do IHC, 3+ are likely to benefit more. MyPathway was a study that was done in the US that used trastuzumab and pertuzumab. This study demonstrated that when you have RAS mutant patients, they do not respond to anti-HER2 therapy, as is the case of anti-EGFR. So remember that dual anti-HER2 inhibition should be only used in RAS BRAF wildtype population. The TRIUMPH trial was a Japanese trial of trastuzumab and pertuzumab. The used ctDNA as well as tissue and showed that your median PFS and OS was similar whether you detected HER2 with tissue or with ctDNA. So these are all studies that are building up on our knowledge of how we should treat this disease.

The MOUNTAINEER trial was the first randomized, though non-competitive trial, of looking at trastuzumab tucatinib versus tucatinib by itself. So dual-agent anti-HER2 versus a single agent. And this led to the FDA approval of trastuzumab and tucatinib in HER2-amplified colorectal cancer. I want your attention on the response rate of tucatinib monotherapy. It's about 3% compared to 39% for the combination.

So single-agent anti-HER2 therapy should not be used in metastatic colorectal cancer. The MOUNTAINEER trial also showed us that

when you have a 3+ or a high HER2-amplified tumors your response rates are as high as 47% compared to only 20% when you have lower-level amplifications, or HER2 IHC of 2+. And you can see similar to the experience of anti-EGFR therapy, anti-HER2 therapies tend to work better in left-sided primaries than right-sided primaries.

SWOG S1613 tried to evaluate the relative efficacy of dual anti-HER2 inhibition compared to anti-EGFR therapy, which we know is a negative predictor biomarker. And one of the key points from this slide is when you distinguish the HER2 step ratio as less than 5 or greater than 5, greater than 5 meaning that more amplification, you can see that on TP [trastuzumab + pertuzumab] the response rate was 42% versus no one below that ratio actually responded. Whereas in CETIRI [cetuximab + irinotecan], the outcomes were exactly the opposite. So this tells us that this HER2 amplification colorectal cancer tends to appear on a spectrum where there are low amplifications, which may benefit from anti-EGFR therapy because they're not addicted to HER2, versus high-amplification where there's significant addiction to HER2 pathway, and these are the patients that respond to anti-HER2 therapy and unlikely to respond to anti-EGFR therapy.

Zanidatamab has also shown response rates of about 38%. Again, zanidatamab is a kind of dual anti-HER2 therapy because it is a bispecific antibody. But this drug is not yet approved in colorectal cancer. So once you've treated patients with dual anti-HER2 inhibition, the next step is to go on to antibody drug conjugates. And this is TDM1. For many reasons TDM1 does not have activity in colorectal cancer partly because of the payload, partly because of the low drug–antibody ratio. But this drug does not have activity in colorectal cancer.

Trastuzumab deruxtecan was the first antibody drug conjugate to show activity in HER2, and you can see the spider plots as well as the waterfall plot in a highly refractory population, which clearly showed the benefit of using this in HER2-amplified patients. Pay attention to that subgroup analysis because there were patients who had received prior anti-HER2 therapy, and they still responded to antibody drug conjugates. So you could change your mechanism and still get responses, and it also worked in both right-sided and left-sided primaries. This also shows us that 3+ always tends to respond better, even when it comes to the ADC story. Now, the question is, if HER2 is more seen in RAS wildtype, there are some patients that are RAS mutant, and we know that dual anti-HER2 therapy doesn't work in RAS mutant HER2-amplified colorectal cancer. So is there an option for this? And, when we looked at the biomarker analysis of CRC01 study, we found that there were responses in RAS mutant patients as well as RAS wildtype patients, and partly because this drug is not dependent on your pathway inhibition, it does more for targeted chemo.

So if you have the target, then you will get the response. And this was proven prospectively in DESTINY-CRC02 study which was a dose-optimization study, but also allowed RAS mutant patients. And you can see there was responses in RAS mutant patients and RAS wildtype patients, and patients with prior anti-HER2 therapy. The study also showed 5.4 mg/kg dose was equally efficacious as 6.4 mg/kg dose but had better toxicity profile.

I'll leave you with this picture. This is one of our patients who was diagnosed in 2013. Actually, the first HER2 patient that I diagnosed when I started. And this patient for the past 7 years has been on one anti-HER2 trial or the other and has done exceptionally well with very good responses. So I'll leave you with the slide and request your help in identifying these patients and moving them towards clinical trials because there's a long way to go. Thank you, everyone.

Chapter 7

Dr. Ciombor:
You mentioned that brain metastases are more common in HER2 positive colon cancer. The – do we know anything about usefulness of anti-HER2 regimens? Do either – do any of the MOUNTAINEER, trastuzumab deruxtecan work better in those setting? Have more penetration in the brain?

Dr. Raghav:
So I don't think, you know we have data from colorectal, because, yes, you know, it is more common, but we have to understand that these are, you know, smaller studies and, you know, our experience is still limited I think from breast cancer literature and perhaps from gastric cancer literature, also, there is more data about CNS penetration from tucatinib and trastuzumab, or tucatinib per se than there is from T-DXd. But as you improve your system of disease you are also going to have some degree of CNS control and I think that's what we are seeing in early stages in T-DXd in breast cancer so I think both have a certain role, but I would say there's more data for tucatinib for CNS penetration right now.

Dr. Ciombor:
Okay. Thanks. And then, a question for the panel: do you check copy number? So I know that a lot of the NGS reports don't necessarily report on that, but it seems like it's – especially in colorectal cancer, very important. What do you think?

Dr. Pietrantonio:
Yeah, it may be, but I still believe that the gold standard for HER2 testing in all the tumor types we're discussing about is IHC with or without ISH. There are limitations with IGS testing because of course because of the stromal contamination. You may miss some HER2 positive numbers if you just go for NGS testing, because of course, if you rely on copy number – HER2 copy number when you do NGS – bulk NGS you're getting a mixture of tumor cell and stromal cells. So in cases with relatively low HER2 copy number, such as, I don't know, 8 to 10 copy numbers you may miss some HER2 positive cases and if you look at them in the microscope, the samples, you really see maybe 3 plus tumor and you may miss it. So I think this is more complementary than the only way to go for a true testing. You can get information, so, for example, on the level of HER2 addiction and the level of HER2 amplification, which may be a prognostic or maybe even a predictive biomarker. But anyway, IHC is the gold standard for what is.

Dr. Raghav:
Yeah. I mean, I would also say that there are certain differences between tumor types So within the GI space and you know, I'm sure James has some opinion on this. But when you look at hepatobiliary disease or you look at upper GI disease, it's HER2 signature is a little bit different from colon cancer. For some reason the colon cancer staining is more in line with what breast cancer looks like than what actually the upper GI tumors look like HER2 in colorectal is not as heterogeneous as upper GI tumors is and there is a very tight correlation between IHC and gene copy number, so you always have high gene copy numbers when it comes to IHC 3+. It's the 2+ that creates the issue, but as you can see, the data is quite clear that the maximum benefit is still in that 3+ population. Right? So if you know, that is perhaps the reason why I said in the beginning that we still test all three mechanisms it's a great way of – NGS is a great way of screening, but if it is negative, I would not not test for HER2 still with IHC.

Dr. Ciombor:
Great.

Dr. Harding:
I agree with that. I'm dubious of negative NGS and I do like having the complementary IHC in biliary tract cancers. And as it's now embedded in the NCCN Guidelines to do that, I think more and more will see it but to your point I think across the subsets, HER2 stainings – it's not validated specifically in biliary; we use gastric. We – that's how we do it at Memorial. There isn't a set validated HER2 testing there which needs to be completed, and I think will be as these are developed in the field.

Chapter 8

Dr. Ciombor:
This is really the emerging role of targeting HER2 in biliary tract cancers and I think some of the themes that we're seeing in upper GI, colon, are recapitulated in biliary tract cancer. We have less data, but I think it's compelling that it's a critical target and I said my second slide in advance would be these are very different diseases, right? And they're uncommon, but they're different. So intrahepatic cholangiocarcinoma presents with kind of a space-forming mass in the liver. When you genotype this, probably 1 to 2% have HER2 missense mutations Probably about 5% have amplifications or even less. It's easy to get tissue for intrahepatic cholangiocarcinoma that's surgically resected. You can biopsy this.

Then moving to extrahepatic by perihilar distal cholangiocarcinoma the rate of missense mutations amplifications probably higher probably as high as 20% for amplification. But I just argue that here it's very hard to get ample tissue for this disease. A tumor the size of a penny could be deadly because it can't be removed, it's just dependent on its location. And sometimes in these tumor types even though it's quote-unquote endoluminal it's not the same as upper GI or colon where you can, you know, biopsy it easily. This is recurrent, like, a repeat ERCP.

For gallbladder cancer, this is by far and away actually the highest expression of HER2 both missense probably about 5%, amplification up to about 15 to 20% when you actually look at the Memorial cBioPortal – look back to one of your slides – it's actually one of the highest HER2-expressing tumors. And when you compare it to breast it is actually, probably higher proportionally for gallbladder cancer. So the critical point is that you need to look for this in this cancer type a lot of times people will ask, well, what does the risk factor imply about the genomics? That's remaining unclear. It's really based on the anatomic subsite that we enrich for a different for these alterations I think just historically we have to recognize this is a difficult disease, but there has really been a lot of change in the last 5 to 10 years This would probably be the current paradigm of how we treat biliary tract cancers. So in the first-line setting based on TOPAZ-1 and KEYNOTE-966 treatment is generally with gemcitabine, cisplatin and an anti PD-1 or L1 antibody based on superior survival compared to doublet chemotherapy That has been consistent Emerging data from Genomics in that subset does – it's not really clear that underlying driver has an important prognostic role in the disease with the exception of MSI high, which is very small subset.

In the second-line it's heavily dependent on the underlying genomics so here are listed some of either the FDA conditionally approved

agents or NCCN endorsed agents. I would say that most of this is based on single-arm Phase 2 data There's only one study that actually was comparative in the second-line, which is with IDH1 mutations So, we're really going to focus here on this emerging role treating biliary tract cancers that are HER2 driven. We've already kind of gone over this. There are many agents, as my prior colleagues have spoken about, and many of them have been tested in biliary tract cancers. This is a summation of, sort of, high-level evidence for anti-tumor activity I distinguish between overexpression amplification, which is the majority of the ongoing studies or planned studies are focusing on this subset. There's really only been one trial, which was the – the SUMMIT study that looked at can we block and treat tumors that are drive by specific point mutations in HER2. I'll show you some of that data, but in general, the responses in that subset is low, but probably represents still a targetable population to some degree. But the majority of the work is certainly in the amplified and overexpressed subsets.

So at present, as I said, there isn't an FDA approval for this This is the only agent or combination that is endorsed by the NCCN which is from a basket study, which is MyPathway as the combination of trastuzumab and pertuzumab this really looked at fairly heavily pretreated metastatic biliary tract cancers that had alterations in the HER2 pathway that were nominated by local testing. And this was kind of a mishmash of different HER2-expressing tumors, mostly HER2 amplified, a subset overexpressed, or both 40 – almost 40 patients in total you've seen the specific subsets, the primary endpoint was objective response rate, and this was some of the first data that indicated that there is a modest objective response rate in this population that it appeared, at least in this study, you see responses in a few of the – in all of the anatomic subsite. But the majority of patients progress relatively quickly. There are some that are fairly durable. And I think this is just kind of entering the pathway of here, we can target this disease.

In ADC-based technology, kind of the next, sort of, I think, interesting set. It was an IAT called the HERB study. This was a small group in Asia looking at a multicenter single-arm Phase 2, again, in a treatment refractory metastatic biliary tract cancer population that enrolled both HER2-high as defined here as well as low-expressing tumors And the primary objective was objective response by a blinded independent review It was a small study. Twenty-two HER2-high based on the investigator assessed criteria. There, we saw 36% response rate And then in the small number of low, there was also some evidence of activity but not as compelling, certainly, as the HER2 3+ IHC 2 ISH positive Trastuzumab deruxtecan has also been looked at in the DESTINY-PanTUmor02 study. This was a global basket study, advanced solid tumors, 2 plus lines of prior therapy, HER2 expression. Again, mostly assessed locally. IHC 3 or 2+ with local amplification. Allowed prior HER2 targeted therapy. All patients got T-DXd and there was a specific biliary tract cohort.

And this is just the summary data there indicating that, yes, there's response, but it's mostly in the IHC 3+ 56% response rate. Median duration of response was about 8.6 months, so clearly this subset is actionable and targetable. Less so in this IHC 2+. So this is an area where we really need to define in biliary tract cancer through combinatorial therapy.

I was asked just to mention a bit about trastuzumab deruxtecan and toxicity There is a bystander effect related to release of the chemotherapeutic warhead, as well as some toxicity that may be related to the linker technology, and there is a low risk of inflammatory lung disease. But this is very well tolerated in an active agent. Zanidatamab has already been discussed. This has been heavily tested in biliary tract cancers and as noted, a Phase 1 showed a promising signal in 20 patients with objective response rate 40% and this led to a global Phase 2B study which I think is notable in that this is one of the first studies that really had a central testing that required enrollment so that we could really look more carefully at HER2 expression overall in this cohort – in this patient population. Again, had to progress on prior gemcitabine. There were two cohorts All had to have amplification by ISH, so a little different than how gastric worked. You were either then placed in cohort 1, which was termed HER2 positive based on IHC 2 or 3+, or cohort 2 where there was IHC 0 or 1+ The primary endpoint was confirmed objective response rate by blinded independent review, but for cohort 1, everyone received zanidatamab.

And this is a typical patient population – I'm running out of time – but I'll simply say that here we again see meaningful anti-tumor activity, 40% response rate, again across the anatomic subsites based on color. You can see with asterisk where on the waterfall plot that's the HER2 IHC 2+, and you see in the subset analysis there really is, sort of, a distinguishing feature there that the 2+ just do not appear to do as well. But it was interesting in that here the median duration of response was about 13 months, which is notable for this disease, and I think that will be an area where we're going to see continued development, along with ADCs. I won't mention any more about neratinib, we already talked about that. But clearly, we're also seeing, you know, tucatinib as a TKI with trastuzumab this was from a basket study. Again, meaningful response rate enriched in the HER2 3+. And I think illustrating that this is an important disease that we can target. We're also now adding it to chemotherapy with GEM/cis/trastuzumab and a wonderful study that was conducted in India indicating that this can be done in the first-line setting and can have an objective response rate of about 55%, compared to GEM/cis of 20 to 25%. That's, I think, meaningful and worthy of further exploration. Similar thing with FOLFOX in the second-line. So it's really going to be now moving these newer agents in these combinations. We need to look at prognostic factors, how do we understand what's the best predictive marker, resistance, sequencing of these therapies I think there should be a strong push to move them into the front line and follow in the footsteps of the giants in upper GI and colorectal so that we can advance this field.

Chapter 9

Dr. Ciombor:
I have a case for you. This just happened in my clinic very recently. So gallbladder cancer, metastatic, got GEM/cis durva. Actually, had an amazing radiographic and biochemical response. Stopped the GEM/cis after 6 months, continued on durva. She's on durva about a year And then has recently progressed. Very strongly HER2 positive, so copy number like 20 if you could give any regimen, what would you give, and then what can you practically give?

Dr. Harding:
Well, I think that practically right now I think we are, you know, driven in part by insurers and guidelines and pertuzumab/trastuzumab is truly the only one that has that present endorsement I always favor clinical trial participation and there's a wealth of that moving into the clinic I mean, you could note that trastuzumab deruxtecan, tucatinib trastuzumab, these are FDA approved in other indications and some seek off-label utilization of those agents. Zanidatamab, as was stated, is not – is still investigational. So it is challenging. I have I agree with the comments related to ADCs and the ability to potentially overcome resistance, and I like the comments related to dual HER2 targeting, and then with failure and ADC of HER2 positive in colon We're just not, as a field in biliary cancer, at that stage. So it's a harder question to answer because how do you pick when we don't have an approval per se. But I do think that's going to change soon I think the DESTINY02 study has shown some compelling data I think they'll – there's movement in the field. So I hope I answered your question.

Dr. Ciombor:
Yeah. And I'll tell you what I did in a second, but Filippo, how is it in Europe? Same issue?

Dr. Pietrantonio:
Well, in Europe there is no approval for HER2 targeting in general in this disease so we encourage enrollment in clinical trials or off-label prescriptions So it's a different way to get access to these promising agents for patients. But I must say that the results I saw in biliary tract cancer really amazing. So hopefully we will have also Phase 3 trials because of course you need to also to –

Dr. Harding:
I think that we're in that space and that they are emerging in that way and so I think we will see change there. But I'm aggressive at addressing HER2. We reflex test everyone, IHC, ISH, and I send NGS, and you should do that for all, I think, gallbladder and biliary with a number of targets. And I didn't even mention RAS, which is emerging in all of them so what did you do?

Dr. Ciombor:
Yeah, so. I tried to give trastuzumab tucatinib. I couldn't get it, so I gave her trastuzumab pertuzumab. She got her first dose last week, so we'll see. But hopefully – I mean, it's so – those data are so compelling with these response rates and some of the new regimens.

Dr. Harding:
The response rates, I think, for zanidatamab trastuzumab tucatinib, and T-DXd are all very compelling and I think that's the next wave. And I think from older data with chemotherapy, you can build on that. I think there's an additive effect there and I anticipate we'll see that moving into the frontline and also, I think you can sequence these things, similar has been seen and done, and I think this will be the same paradigm. It's just going to take a little more time, but we'll get there.

Dr. Ciombor:
Yeah. It's an exciting time for sure.

Chapter 10

Dr. Ciombor:
We've talked a lot about the data and the efficacy but we never want to forget about toxicities and be real practical, too, about how we manage this, so hopefully we can kind of brainstorm and crowd source some of our tips and tricks in how to manage these toxicities, particularly as you think about targeted therapies and how they have really unique toxicities compared to cytotoxic chemotherapy.

So just a couple of slides here. We've talked about different classes of anti-HER2 agents, and this has a lot of implications for the types of toxicities that we can look forward to and it's important as these different drug classes are used more and more that we're aware – not only we are aware, but our teams are aware, our patients are aware of the potential toxicities to look for So we've talked a little bit about this, but of course, they're differing toxicities based on the mechanism of action of drug and dosing. So, we've talked a little bit about dosing schedules. So trastuzumab deruxtecan, as well as on and off target agent – effects of agents. And as I mentioned, anti-HER2 toxicity is not always similar to chemo. Of course, great example trastuzumab cardiotoxicity but now we're having to think about interstitial lung disease, GI toxicities, rash, and in some cases, especially with these combinatorial therapies, you really have to look for

synergy in these side effects and additive effects as well.

So just a couple of examples, and we looked at this a little bit already with MOUNTAINEER in colorectal cancer. This was the toxicity profile which is actually quite manageable. Very few grade 3 toxicities, so this is really nice to see. Of the toxicities that we did see, diarrhea, fatigue, so mostly GI toxicities were the most common there. But relatively easily managed. But then, if you look for trastuzumab deruxtecan of course, the interstitial lung disease very different. So it's important for our teams to know that our nurses who are often triaging patient calls and other things. And we have to have a high index of suspicion because it is important these can be fatal toxicities if not caught early and treated. And then Raghav showed us in DESTINY-CRC02 one of the big takeaways was that the lower dose of T-DXd was equally efficacious and actually less toxic, too, particularly in terms of ILD.

So what we wanted to spend the next few minutes just discussing a little bit is how we use our how we do multidisciplinary management. So we started off talking about multidisciplinary management, you know, treating the cancer, but how do we do that in a similar way with treatment-related toxicities. And wanted to talk about some best practices. So I'll open it up to the panel here. Anybody want to chime in with something that they do in their own practice to kind of manage and recognize these toxicities?

Dr. Raghav:
Yeah. I can start. I think, you know, whenever we start these drugs, because they're efficacious, it is also possible that the patients are going to stay on them for a longer period of time Specifically with, you know, diarrhea management, because sometimes that can land patients into trouble especially with dehydration and acute kidney injury, and ILD both those from the ones that you pointed out. One of the things that we've done in our clinic is whenever patients are being started on any therapy, we usually educate – we take that opportunity to educate our clinic staff because they're the ones who are going to be triaging those calls. That, you know, here are the three toxicities that are of concern for this patient, so if he ever calls or sends a message regarding those toxicities, you know, they shouldn't be handled, you know, normally. Like, you know, a person on FULFOX who complains of cough or shortness of breath could be different if he's having a runny nose, it could be different, but a person on trastuzumab deruxtecan, if they complain of sudden onset shortness of breath or cough, they need to be evaluated immediately. With regards to diarrhea we have good patient education and nurse education about aggressive management of diarrhea with up front prophylaxis in the hands of patients for you know, Lomotil, Imodium, everything to start with because, you know, by the time they call you, it's already too late.

Dr. Ciombor:
Especially with some of our stoic patients, right? Filippo?

Dr. Pietrantonio:
I think that also patient selection is a key because, of course, there are absolute contraindications to the use of trastuzumab deruxtecan for the risk of interstitial lung disease. So if we think on the exclusion criteria of the clinical trials, these are quite a few, but we should be aware of it. For example, the previous pneumectomy is a contraindication to the use of this agent. And also, active lung disease may be a contraindication. But then, there are more gray zones, like, so relative contraindications. For example, previous radiotherapy on the lungs or on mediastinal nodes. This is not an absolute contraindication, but we should monitor these patients more closely. And in general, close monitoring of interstitial lung disease with this agent is necessary. Even though at the beginning we may see just a grade 1 interstitial lung disease, in a symptomatic patient we should be aware that monitoring is the key because, we really don't know the onset of this toxicity – maybe a few weeks to over one year. So basically, monitoring is the key even if the initial presentation is mild. But anyway, it can worsen over time, so education is the key,TP engaging the patient. They should be aware of what to do and they should receive regular phone calls to be sure that the symptoms are not worsening. So there is a lot we can do. We learned a lot with the clinical trials, and I already think that in the clinical practice we can have the opportunity to learn even more.

Dr. Ciombor:
Absolutely, that's great. How about you, Jim? Any practical tips?

Dr. Harding:
No, I agree with that. I think it's critical – education. I tell patients just call me. Like, I want to know if you're having – not me personally, but they can if they want, I'll talk with anyone – but really to let us know. For T-DXd, the lung toxicity is just concerning to me, so I want to know about any of that and educate them if they're on those agents. But I agree with everything stated.

Dr. Ciombor:
Yeah.

Dr. Raghav:
Yeah, I do want to point out that this is not – you do need a high index of suspicion, but we should also do our due diligence to work these things up without ascribing them to the treatment, because these treatments are efficacious, so you don't want to, like, give up on

these treatments soon. I have an example of a patient who was getting trastuzumab pertuzumab, had some diarrhea, you know, pertuzumab was dropped. Trastuzumab by alone it was continued. We've seen single-agent is not as efficacious, right? They came to us for second opinion, continuing to have diarrhea despite pertuzumab removal, and actually the patient had C-diff all this time, right? So whether you have diarrhea or you have interstitial – sorry, pneumonitis kind of a picture, it is still important to work this up.

And this has happened multiple times. We had a patient on T-DXd who came in with some CT scan changes, but the patient also had upper respiratory type of illness and the patient actually was positive for RSV. Right? So I think working those patients up is the key.

Dr. Ciombor:
Yeah. Yeah. And I just want to point out, we have some algorithms in here and these are great starting points. But I had a very similar case. Instead of diarrhea, I had a patient on trastuzumab pertuzumab who's EF dropped. Asymptomatic, but we really, you know, it had been a pretty significant EF drop, and so we weren't sure what to do. But she was having an incredible response to therapy, and so after talking with her cardiologist and everything else, you know, we decided to keep her on treatment and fortunately, we have better cardioprotective agents now, too, which is also helpful. But I think all the points brought up by the panel are great.

Chapter 11

Dr. Ciombor:
Just in the last minute or two, just wanted to have each person just give a key takeaway if there's something they really want to impart to the audience or something they learned tonight. Filippo, I'll start with you.

Dr. Pietrantonio:
Okay, so my point is please refer all patients to clinical trials whenever possible, because we have seen the results of clinical trials may change the life of our patients. So it's important to continue clinical research in the academic setting, in the pharma driven setting. So I think that this is the take-home message from me.

Dr. Ciombor:
Great. Thank you. Raghav.

Dr. Raghav:
You know, in my clinic I always use this acronym, these are the 3 Ts of treating HER2, but it could apply to others. First, test, then trials, then treatment, right? So unless we test them, we're never going to know it is. When you test them, I totally agree with Filippo, no matter where you are, the first question you ask is, is there an access to a clinical trial that I have. If the answer is no, then yes, fortunately we do have good drugs now.

Dr. Ciombor:
And, Jim?

Dr. Harding:
Yeah. For biliary tract cancers, you've got to look for the biomarkers. Although we don't have comparative data for many of them, it's clear there's a subset that respond incredibly well and we have to identify those patients and treat them on trials. And I think that's my – definitely do that. Yeah.

Dr. Ciombor:
Yeah. Great. And mine, I think, is just as we just talked about the differential – have to have high index of suspicion for the toxicities, educate your patients, but also realize that there can be a wide differential of of etiologies of the patient's symptoms, so this is why we – this is why we do oncology, right? This is our game.

Dr. Raghav:
I like it. I'm going to steal that 4 Ts. Yes. The Test, Trial, Treat, and Toxicities.

Dr. Ciombor:
Toxicity, I love it. Perfect.

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