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Enhancing Treatment Strategies With Molecular Approaches in HER2+ Gastrointestinal Cancers

Announcer:
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Dr. Tabernero:
My name is Josep Tabernero, and the topic of this symposium, as you know, is how we can optimize the treatment with a molecular-based approach in HER2-positive gastrointestinal cancers.

So the first thing that I want to do of course, is to introduce the faculty that we have in this session. First Sara Lonardi, a well-known medical oncologist and the chief of the oncology unit at the Veneto Institute of Oncology, based in Padua, Italia. And Zev Wainberg, also well-known GI medical oncologist, co-director of the UCLA GI Oncology Program, professor of medicine, as well, from UCLA in Los Angeles, US.

So these are our disclosures that you can find everywhere.

So without any further delay, I'm going to cover the first part of the session that is more related to general aspects of how we optimize molecular approaches in HER2 gastrointestinal cancers. Of course, in the field of precision medicine, we all love to have targeted therapies, and this is the real way that medical oncology is moving forward. But for that actually, we need robust and well-validated biomarkers. And we know that in some instances, including gastric cancer, we have special complexities and challenges, especially regarding the tumor distribution, but also the heterogeneity. And in particular for gastric cancer, we have to deal also with the sample that we get to evaluate the tumor, whether each tumor is the primary site or a metastatic site. And as you know, for some of or most of the markers that we are using in gastric cancer, blood samples are not really up to date to get that diagnosis.

Also important, when we have overlapping of the different biomarkers, how we can deal with the best therapy for our patients. And this is really important in the first part of our discussions in the multidisciplinary approach.

The survey that was conducted a couple of years ago looking at the quality and also the access of precision medicine in Europe in different tumor types, this is not only gastric cancer, actually posted disparities and challenges within Europe. As you can see, the access as a global name seems to be quite good, but when we go into the details of whether single biomarker tests are accessible, or even more, when multi-biomarker tests are accessible, then we start seeing disparities on the amount of patients that can have access to these precision medicine based on biomarkers. But also importantly, on quality aspects, and this is something that we have to remark.

For HER2, actually this is a well-validated target with prognostic characteristics that are different between the tumor types, but especially predictive characteristics. We know that HER2 oncogene encodes the receptor tyrosine kinase receptor called ErbB2 or HER2. HER2 overexpression, usually by gene amplification but not always by gene amplification, leads to constitutive activation of this receptor and, therefore, activation of the signaling transduction pathway, mainly ERK-mediated, but not exclusively. And this produced, at the end,

dysregulated cell proliferation.

Detection has been based mainly by immunohistochemistry with different reagents and monoclonal antibodies. And also, by looking at the amplification of situ, it's more recently by in situ visualization, either FISH or ISH, right? And more recently as well, by NGS for amplification. The results are considered negative if immunohistochemistry 1+ are considered equivocal. If they are IHC 2+ at least in gastric cancer, and they have to be validated by FISH or ISH, and positive by immunohistochemistry if they have 3+. Obviously, when we look at the FISH or ISH technology, actually, we are looking at different proofs that basically look at the ratio between the HER2 and CEP17. And it's considered a positive ratio if 2 or more.

Interestingly, in different tumor types, but particularly in gastric cancer, we know that there is interpatient heterogeneity. But more importantly here, we are talking about intra-patient heterogeneity. On a temporal basis but also on a geographical or tumor composition basis, and it's important. One of the multiple studies that have evaluated this, this is a study by Dr. Catenacci, the PANGEA trial, that looked at the heterogeneity between primary tumor samples and metastatic sites. When you look at that actually in the same times, so without any change in the temporal distribution, there was 35% of heterogeneity for all tumor markers, right? But even when we look at the heterogeneity from a temporal perspective, so comparing, for example, baseline and the situation before second-line, or even more second-line between second-line and third-line, actually the percentage of heterogeneity was even higher, very close to 50% in some of the markers, right?

And when we look at HER2, actually, this is the case. So the data replicates quite well what we had. A little bit less expression usually in the metastatic sites, although you know that there is also heterogeneity depending on the area where you look for. But also, importantly, we'll discuss later on on that, the negativity of the conversion. And this is very clear in this study: up to 45% of the patients converted to be negative when they were positive at baseline after the pressure of the treatment.

Of course, we know that the HER2 expression is not equally the same in all gastric and gastroesophageal junction cancers depending on histology. The percentage of patients with intestinal histology have a higher expression, close to between, different sites, 16% to 34%, usually in the range on 20%, 22% compared to the diffuse histology, that it's much lower, around 6%, 7%. But also, we know that patients that have gastroesophageal junction cancers actually have a higher expression of HER2 compared to those that have gastric cancers located in the main body.

So as mentioned before, the definition of positivity in this case is either IHC 3+ or IHC 2+ ISH or FISH positive. But again, as mentioned briefly before, there is important heterogeneity that we have to address.

Obviously, as higher the expression it is, several studies, mainly retrospective studies, have shown that the activity of HER2-directed therapies is higher. Is higher it's expression, both at the gene level, but mainly at the expression level of the protein. So this is really very important. We know as well that there is up-front resistance to HER2-directed therapies by multiple mechanisms, and this is going to be addressed later on. But also, as mentioned before, we have to take into account that the concept of loss of heterogeneity under pressure by previous therapies is important.

Moving very rapidly to one of the compounds that is being developed right now. And these are antibody-drug conjugates, and you know that several companies have been pursuing ADCs for a long time. But actually, the technology has improved right now, designing better antibodies, number one, but also very important payloads and even more very precise linkers that bind the drug, the payload to the antibody. So, this is really well characterized. The mechanism of action, obviously the antibody binds to the receptor or to the protein in the membrane. It's internalized, and then the payload is free into the cytoplasm, and then, the agent produce its activity.

Couple of remarks on that. So we have mentioned that we have more important payloads, and this is really important. But also, we have been seeing that many ADCs actually play with the drug-to-antibody ratio. And you will see that there are some that have a DAR of 8, or there's 4, or there's 2. It's not the same for all tumor types; we can discuss later on that. We also know that the linkers are very stable, most of them, and this is really very important for the precise effect into the malignant cell. And also, we have seen that these compounds are really very active in heavily pretreated patients. So they have posed a new generation of activity in this setting.

Also, we know that there are multiple mechanisms of resistance to antibody-drug conjugates. This slide actually shows the more relevant ones, not the only ones. The first one is, as mentioned before, by antigen downregulation, either by degradation of the target antigen, but also by downregulation of the transcription process of the target. This is number one.

Also it has been described that resistance can occur through alteration of intracellular trafficking, or especially on the process of lysosomal drug breakdown. And finally, as these drugs have an effluent movement, the payload can get tolerance to the efflux transporter mechanisms of the cell.

Now go to the second part of the presentation and it's my pleasure to introduce Sara Lonardi. Thank you.

Dr. Lonardi:
And thank you, Josep, for this wonderful presentation. And I will now try to wrap up some of the results we have in the gastric and GI junction cancer.

So obviously, all of you know that inhibition over HER2 is a standard of care since more than 10 years with the TOGA trial, and now the outcome is improved with the combination of pembrolizumab for a patient where the tumor is PD-L1 positive. But unfortunately, multiple attempts have been done during a long time to combine other inhibitors or to prolong inhibition across multiple lines of treatment without achieving any success, unfortunately. And Josep already outlined that we have multiple reason to experience these more result and intensificating to inhibition. And the point is now how to overcome these pitfalls linked to tumor heterogeneity, acquired resistance, low expression. And one strategy to overcome these problems is for sure to change our way to use HER2 as a receptor. And antibody-drug conjugates are compounds, obviously, that are not only inhibiting the biological pathway, but they are mainly using it like a door to internalize and release a more classical chemotherapy drug. Theoretically, they were studied to overcome this theoretical reason of resistance to inhibition.

But the first time we saw the clinical application and we had a confirm of the biological background was with the DESTINY-Gastric01 trial. This was the first trial, a phase 2 randomized in patients heavily pretreated, and where we had in the main cohort of HER2 positive, 3+ or 2+ with FISH positive, randomizing 2:1 to receive trastuzumab deruxtecan or the investigator choice of standard of care.

As you obviously know that the trial met its primary endpoint of response rate with 51% of objective response rate. That is very high considering that we are in late line here. And also, with a nice deepness of response that I think it's important in gastric cancer patients because, you know, often they have high burden of disease, they are heavily symptomatic. And so to reduce the tumor and to have a good shrinkage, as the possibility also to improve symptoms and quality of life. And the trial was also positive in progression-free survival and overall survival. Obviously, there were secondary endpoints and for the first time, we saw a median overall survival exceeding 12 months in heavily pretreated patients. And so really, a result that we never saw before.

And recently, a paper has been published by Kohei Shitara showing us some translational analysis and biomarkers. And the message is – we have 3 main messages from this paper. The first one is that the higher the expression, amplification, gene copy number, whatever you measure in the tissue or in the plasma, the higher the level of HER2, the higher the response rate. But it doesn't mean that if you have a lower level, the drug is not working. It is simply a gradient of response.

The second message is that when we re-biopsy the patient after trastuzumab and we have HER2 positivity, we can see – and you can see the dark blue and dark green curves. We amplify the gain of trastuzumab deruxtecan. But also the reverse. And so if we use the HER2 status before trastuzumab, we still see a benefit from trastuzumab deruxtecan, and we can see here, in terms of response rate, this one with HER2 tested at the beginning, before trastuzumab. And those with more gain, obviously having a re-biopsy. And also here, the light blue and light green, you see that trastuzumab deruxtecan is again – obviously, it lost the statistical significance due to the fewer number, but the benefit is there.

And the third message is that the molecular alteration that usually we consider as a negative biomarker for trastuzumab efficacy did not impact on trastuzumab deruxtecan efficacy. And so compared to trastuzumab, we cannot say that if we have, you know, HER2 overexpression. A RAS-mutated is quite rare. But if it is the case, trastuzumab deruxtecan is working anyway due to its specific mechanism of action.

The trial that established and confirmed the same benefit in the Western countries was the Destiny-Gastric02, and you can see here it was a single-arm phase 2 trial. But you can see that the results are confirmed, and especially overall survival exceeding 12 months, even in this Western country population. And according to these 2 trials, trastuzumab deruxtecan have been approved both in US and in the EU for patient pretreated with trastuzumab.

But the story of DESTINY is now looking to new horizons, and we have the DESTINY-Gastric04. The enrollment is still open in some countries, not in all the countries. And enrolling patient in second line and comparing trastuzumab deruxtecan versus the standard of care of paclitaxel and ramucirumab, trying to setting up the placing therapy in second line for trastuzumab deruxtecan.

And also, the DESTINY-Gastric03. This is a platform trial with multiple cohorts investigating the combination between trastuzumab deruxtecan and chemotherapy and/or IO. And so that's the Gastric03. Still open in some cohorts. It is constantly changing, closing and opening new cohorts. But I think that we are going see nice results from those trials.

Obviously, there are a lot of other molecules that are under development. And within them, we have margetuximab. We see nice result with pembrolizumab in this phase 1b/2 trial. And now it is under investigation in the MAHOGANY trial in first line. And zanidatamab, bispecific antibody. These are the preliminary results, and according to this nice activity, a phase 3 has been launched in first line

comparing standard of care with zanidatamab and chemo plus or minus tislelizumab.

And so to conclude, we know that HER2-targeted therapy may lead to a reduction in HER2 expression and the emergence of alteration. Therefore, re-biopsy is important after disease progression on trastuzumab, but it's not mandatory. And so if we can perform without high risk, it's good to go for a re-biopsy, but it's not mandatory to prescribe trastuzumab deruxtecan in second line. And I think that for now, trastuzumab deruxtecan is the most promising HER2-targeted drug across multiple lines of treatment, but obviously we are going to see in the next year if other HER2 inhibitors will lead to other positive results.

And thank you for your attention.

Dr. Wainberg:
Thank you, Sara, and thank you for the invitation. Happy to switch gears a little to colorectal cancer, which has some distinguishing characteristics. The first thing to keep in mind is that it really is a different clinical behavior sometimes, this subset, and it usually almost exclusively comes from left-sided. It is very common to have lung metastatic disease compared to HER2 negative, high-incidence. I've seen a number of patients with brain metastatic disease which is something that should trigger reminders, and it's usually almost exclusively amplified in wild-type tumors. So truly the RAS mutant HER2, truly HER2-positive group is extraordinarily uncommon. There's a lot of questions about the prognostic role of HER2, but there does seem to be no significant association with survival. That being said, it's a very, very small subset, as we all know.

So what do we know about the guidelines? I mean, this is sort of one of the NCCN pictures of how we use guidelines in the United States, of course, that have often single-agent data sets for circumstances where the mutation or alteration is extraordinarily rare, like HER2 colon cancer. But here, you could see in our current guidelines, we have 2 options, which include trastuzumab in any number of combinations, along with trastuzumab deruxtecan. And we're going to go over, obviously, some of the data that led to those guideline recommendations.

So the other important variable, and this is really work done by MD Anderson, Raghav and his colleagues over there. The first demonstration that HER2 was interesting in colon cancer came from its back biology showing that these patients who received EGFR did very poorly. And one group that did particularly poorly is the group of patients who had HER2 amplification, and that, obviously now in retrospect, makes sense to some extent based on biology and feedback loops of HER2 and HER1, which is EGFR, recognizing that the amplification is something that's dominant despite blocking. So this is sort of a recognition now that if you know someone is HER2 positive, you really should avoid EGFR inhibitors in this particular subgroup. Many times, we don't know that, of course, until much later.

The first group of trials, which are really done out of Italy, looked at combinations of trastuzumab/lapatinib and subsequent combinations. But perhaps some of the later, more contemporary data included this study, which was a MyPathway combination of the double-antibody blockade that indicated that with double blockade, you could indeed have response rates emerging in the 20% to 30% range. Again, almost exclusively in wild-type. So this pertuzumab/trastuzumab was added subsequently to the NCCN Guidelines based on this study.

Now more recently, we've seen some newer data, and we know now that tucatinib, which is a HER2 TKI, a very specific HER2 TKI, much more specific than the earlier lapatinib drugs. It was combined with trastuzumab in this study, and what the study was obligated to do, in essence, was to see if the contribution of components of tucatinib and trastuzumab was absolutely necessary. So there was actually a small cohort of patients who received tucatinib alone in the study. Again, response rate being the primary endpoint. What was interesting is that there was certainly, here you could see, a 38% total confirmed response rate in the combination. Almost no responders in the tucatinib alone. So this really is very important for the FDA now in the United States to assign contribution of components earlier on rather than waiting towards randomized trials. So here, this contribution was very clear that the necessity was for double HER2 blockade in this context. And again, showing that the group of patients who had the most benefits were almost exclusively left-sided primaries.

Now safety did become a concern with this combination, particularly with kinase inhibitor toxicities. There is some GI toxicity which does emerge in the combination of tucatinib/trastuzumab, which is obviously much greater than with trastuzumab alone. Now this is the subject of a large randomized trial, which is very, very difficult to enroll, so if you, of course, have patients and have this open, it's worthwhile to try to complete the study which is adding FOLFOX trastuzumab and tucatinib in the experimental arm versus investigators' choice. There's a lot of controversy here about the eGFR inhibitor, whether that should be removed, and for now, at least to my knowledge, that is still an option, although few investigators are choosing that option.

Now the DESTINY-CRC01 study was the next study to come along with trastuzumab deruxtecan. You've already heard about that drug. Originally, this looked at both patients with IHC 3+ or ISH positive, and cohort B was IHC 2+. There's a very, very small Cohort 1, which we won't talk about too much. But here is the main efficacy results. You can see here, the overall response rate 45%, very nice waterfall plot. Almost exclusively in the IHC 3+ with maybe 1 responder in the IHC 2+, showing that, indeed, consistent with gastric cancer,

higher overexpression, higher amplification rates do seem to correspond with response.

Now what became a concern, and this was the first study in the GI field, really, to show a higher rate of ILD than we might have expected. In fact, in this original CRC01 study, there was 3 cases of patients who died from interstitial lung disease despite being aggressively treated with steroids. These cases actually led to changes in some of the guidelines, interestingly, as we'll talk about later. This led, though, interestingly, to a study we almost never do nowadays in oncology, which is randomizing patients to the same drug but 2 different dose levels. These are usually, obviously, determined in advance, and this is a rare thing that Dr. Raghav did and was presented last year at ASCO, in which they randomized the same group of patients to either 5.4 or 6.4, with the recognition that perhaps 6.4 was excessive and induced a higher rate of other toxicities beyond ILD. And Dr. Lonardi will talk about toxicities later. But certainly, this was encouraging, that with the 5.4 mg/kg every 3 weeks, the median PFS of 5.8 months was virtually identical to that with 6.4. So despite a dropping of the dose, you do not compromise efficacy. And of course – and this was true, obviously, with an early snapshot of overall survival, as well, that there is no compromise in efficacy.

Now, what made that interesting, and Dr. Lonardi will talk about that later, is how this group of patients performed was better with toxicity. So there really is, I think, one proper dose for this drug now moving forward which is the 5.4.

So, then, I will move to the next section in the interest of time. And so this is also assigned to me, biliary tract cancer. So this is a group of heterogeneous tumors, as we know. We're going to hear a little more about this in the next day where there's some original data being presented. But certainly, we know that with the current landscape of this disease, we have overall survival expectation of about a year with the addition now of checkpoint inhibitors in frontline therapy.

Second-line therapy's become complex, with chemotherapy being used in some patients, but an increasing number of patients here, of course, do have actionable alterations, allowing one of these novel inhibitors to be used. Now about 5 years ago, or a little more than 5 years ago, we started to see the emergence of all these actionable biomarkers. So in terms of which tumors are the most receptive to next-generation sequencing among GI, it's probably biliary tract cancers in which you have many opportunities to introduce agents. But over the last 2 to 3 years, it's become even more complex where within subtypes of tumors, such as FGFR2 or IDH1, you could even see differences in IDH1 and 2. And of course, MMR and MSI, which is exceedingly rare. But HER2 has become a more relevant topic with 10% to 15% which are a little more predominant in the extrahepatic and gallbladder cancers.

So here you could see what we know about HER2 inhibition and HER2-driven biliary tract cancers. Again, more common in gallbladder cancer; second, extrahepatic; and, third, intrahepatic, which is the opposite, of course, of the other actionable alterations. But here you can see there was a number of basket studies that were done. We're going to go over some of these in detail, including some of the drugs we've already heard about, like trastuzumab deruxtecan, and also some newer data with some bispecific drugs.

So the first study, and this is, you know, I realized very recently that in the United States, we have something called tumor agnostic approvals, which apparently are very uncommon in Europe. And I thought for many years this was common around the world. But we have a very interesting concept which allows us to do these basket trials and try to get tumor-agnostic approvals. So this is one example of that where patients were enrolled with a number of different cohorts, who had received, for the most part, prior HER2 therapy. But you could see here, biliary tract cancer with T-DXd at 5.4 mg/kg was studied.

And what was interesting here is that they ended up enrolling 41 patients with an overall response rate of about 20%. Again, this is a – let's call it an orphan indication, a rare situation in this disease. So these allow us to study these agents that allow us to get access to these patients, these drugs. And this duration of response was quite promising with 8.6 months among the patients who responded, which is why the overall survival was higher than we might have expected with chemotherapy alone.

Now, with respect to safety here, of course, also there was less concern, although there was 1 death in the group of patients, the all-comers patients that was adjudicated as ILD. But there were some other toxicities that related to typical chemotherapy that Dr. Lonardi will discuss in her talk. Now there was, subsequent to that or almost simultaneously with that, another study with tucatinib that looked, in particular again, at the combination of tucatinib and trastuzumab in this group of patients who had biliary tract cancers, again, with the overall response rate. And here too, we had 30 patients, a little smaller of the data set, but there was a higher response rate of 43%, 46% confirmed. So duration of response of 6 months, so here, a nice overall survival result here. So again, 2 options for these patients with biliary tract cancer.

Now zanidatamab, as you just heard about, is being developed extensively in gastric cancer, but it's also been developed to some extent in other cancers as well. And zanidatamab is unique in that it's a bispecific antibody that blocks 2 separate domains within HER2. So usually bispecific antibodies are designed to block 2 separate antigens, but here of course, the idea is that if you do double epitope binding, you can have tighter binding of HER2, and that could lead to better HER2 blockade, and that seemed to be the case because this drug has single-agent activity in GI cancers, which is not the case with trastuzumab.

So this led to a HORIZON-BTC-01 trial in which patients were enrolled after receiving gemcitabine-based therapy to either Cohort 1, which had IHC 2+ or 3+, or Cohort 2, which was very, very low. And the idea was single-agent zanidatamab, again an antibody – we don't usually see single-agent antibodies in use. But this is a bispecific antibody that has a history of having a single-agent activity. And the primary endpoint again, of course, here was overall response rate.

So you could see here, I thought this was remarkable how high they had a response rate with single-agent zanidatamab of 68%, and this has been confirmed at 41% with the duration of response of a year, and this was presented about a year ago and subsequently published.

So beyond those agents that have been now extensively studied to the extent that they can be – and this is something that, I think, we will have a very difficult time doing randomized trials in this rare cancer of a rare subset, so we have to rely on the data sets that exist. There is history here with trastuzumab/FOLFOX. And this is the data that was presented, a single-arm study which was a study that looked at overall response rate. You could see that it did achieve 30%, although – and this is higher than one might expect with FOLFOX alone, although this, of course, is the fit patients who are able to be receiving FOLFOX chemotherapy in second line.

Now finally, just like in the other HER2 cancers, I think there's recognition that some of these cancers that have HER2 lose HER2, or so-called loss of HER2, which may reflect heterogeneity and may reflect secondary alterations. But certainly, in this disease, there has been some suggestion that there's both loss of HER2, along with secondary mutations within HER2, which develop as a consequence of continued HER2 blockade. So this is something that is very challenging to study in this disease. But now with the ctDNA, there's a nice paper that came out last year, in the last few years, that have shown that, indeed, that is the case of patients who become resistant. So I think that will be the next subject of interest is how to develop post-resistant therapies.

Dr. Lonardi:
Let's go now, briefly, to the safety considerations. And I think that all of us as oncologists are biased in thinking that, generally, targeted therapies are better tolerated than chemo. And I think that this was a bias affecting our management of the tolerability of those drugs at the beginning when we started using them. But it's true that we have different compounds, and they are working in different ways. And obviously toxicities are linked to their different mechanism of action, and also different dosing, and also we are going to see that we can have a slightly different incidence and spectrum of toxicity in different tumors.

And so just as an example, you can see that tucatinib plus trastuzumab showed adverse events that are really similar to that of chemotherapy, like diarrhea, fatigue, and nausea. And also with ADC, we have to remind that the payload is a chemotherapy drug. And so, obviously, we need to keep in mind that we can see some toxicities that are more in the spectrum of chemotherapy than in the spectrum of target agents. And for sure, the most important from the point of view of seriousness of the risk for the patient is the interstitial lung disease. That is due to inflammation and fibrosis of the interstitium in the lung and can lead to some symptoms like cough, fever, and dyspnea.

And obviously, we need to be able to recognize it to manage, because the high grade, 3 to 5, are quite rare, you can see here, but the global incidence is not so low if we look to the grade 1 and grade 2. And also you can see here that there is variability if we look to different sites of disease, and sometimes it was related to the doses, but sometimes also to other conditions, like obviously if you have lung cancer you have also competitive reason of having pneumonitis. And in gastric cancer and in colorectal cancer we can see that high grade, 3 to 5, was quite rare. It was 1.6 in gastric cancer and 3.7 in colorectal cancer.

We need to be aware of this possibility and we need to monitor the patient and be able to recognize when we are at the beginning of the development of the ILD because, as I have mentioned, we need to manage properly since the beginning. And actually, if we have a grade 1, that is obviously the low-grade, we have to withhold trastuzumab deruxtecan until resolution and start corticosteroid.

And in the case of a grade 2, that in my mind is still a low grade, but it is sufficient to permanently discontinue trastuzumab deruxtecan and obviously continue the proper treatment with corticosteroid. And obviously, if we have, unfortunately, a grade 3 and 4 ILD, the patient needs to be hospitalized to receive oxygen and support. And also, we have to consider immunosuppressant like infliximab or other. And so it is important to recognize and stop before we reach grade 3 and 4.

And this is a clear point on that, because if you look to the incidence of a higher grade of pneumonitis, it is clear that after the introduction of the guidelines on the management of ILD in 2019, we saw an improvement and a reduction in grade 3/5 ILD. And so if we properly stop the event at the beginning, we are able to avoid higher grades.

But there are also more, I would say, classical toxicities like the more important. And I think that if ILD is the more important in terms of seriousness for the patient, nausea/vomiting is the more important in terms of quality of life for our patient, because it may be very impacting. And we see here, the 2 doses, 5.4 and 6.4, and as already told by Zev, I completely agree that 5.4 should be the dose now

for T-DXd. And you can see here that we have any grade 75% and 42% for nausea and vomiting, respectively. And we have 6% and 3% of grade 3/4. And so not too many grade 3/4, but 3 out of 4 patient experiencing nausea, and we need to treat them to avoid an early interruption of the treatment, because obviously, if we interrupt due to toxicity, the risk is that we are not seeing any gain in efficacy. And so trastuzumab deruxtecan were upgraded to the high emetic risk class, and we should start since the beginning with a combination prophylactic antiemeticogenic support with NK1 inhibitors, 5-HT3 inhibitors, dexamethasone, and also consider olanzapine just to avoid the, since the beginning, the development of nausea and vomiting. And also, it's important patient counseling to help them manage these symptoms in their daily living.

And so to conclude, yes, for sure, targeted therapies, if we can call them targeted therapies, are often better tolerated than chemo, but some toxicity might be severe, some other can impact on quality of life, and obviously, awareness is the key to promptly treating them. And also discussing with other colleagues because the multidisciplinary and multi-professional management can be useful in some cases. And this optimal management is required if we want to mitigate the risk of an early interruption of the treatment that obviously can impact on efficacy.

And thank you for your attention.

Question:
I have 2 clinical questions. One, you mentioned that there is a loss of the HER2 with time. Can we determine it by ctDNA?

Dr. Tabernero:
I can address that. Actually, by ctDNA you only can detect genomic alterations, right? So you can detect amplifications, deletions, fusion proteins, but not expression by immunohistochemistry for the time being, right? Things may change, but for the time being, we can only go to the genomic events.

Question:
And a second question. In these cases that there is loss of the HER2, can we treat with cetuximab, for example? Because there is no more resistance to cetuximab?

Dr. Tabernero:
Well, it depends on the indication, but what actually happens is that by the pressure of a previous treatment, you have the regulation of a protein. So what could happen or will happen is that if you stop the treatment, the HER2-directed treatment, after some weeks or some months, actually, the expression of HER2 upregulates again. Right? So something to consider. Right?

Dr. Lonardi:
Josep, can I ask you and would you consider in a patient having loss of HER2 overexpression after trastuzumab and then you treat with paclitaxel and ramucirumab, for instance, would you consider to repeat a biopsy before third line and to try to use again trastuzumab deruxtecan in third-line if the HER2 reappears?

Dr.Tabernero:
Yeah. Absolutely. I mean, from a scientific point of view, it's very valid. So all these loss of expression that we have for the current time, and at some timepoint, the driver of the disease usually comes back, right? So I fully agree that, you know, from a scientific point of view, it would be clear that looking again for HER2 would be an acceptable option.

Dr. Correa:
Thank you. Excellent talks. I'm Peter Correa from the UK. If a patient is on trastuzumab deruxtecan and develops brain metastases and is mildly symptomatic and you have to consider radiotherapy, SABR radiotherapy or whole-brain radiotherapy for the brain metastases, how long will you interrupt the trastuzumab deruxtecan for?

Dr. Lonardi:
Well, I don't add variance based on that, but based on common sense, I don't think that we need a long interruption of treatment because, especially if you are delivering stereotactic radiation, I don't think that we need to interrupt treatment. I usually don't like whole-brain radiation for metastasis in GI cancer because I don't think that we are giving a really useful treatment. And so I don't think that with the stereotactic radiation, we need to interrupt for long.

Dr. Wainberg:
I agree. I also will point out that – and I agree with that. I don't think there's a big interruption of antibody-drug conjugate. The interesting thing about the brain metastasis, that's one of the reasons why the tucatinib was interesting because it's one of the few drugs, the HER2 blockers, that crosses the blood-brain barrier. So sometimes if you happen to see that situation, it's something to consider.

Dr. Correa:

Thanks very much. Thank you.

Dr.Tabernero:
Thank you. We have one final question. Thanks.

Question:
Hello. I am from Switzerland, and I have a clinical question. We have a very young patient with advanced gastric cancer, and we want to do neoadjuvant therapy and she's 3+. What do you recommend? FLOT? We have this negative trial, or other data for trastuzumab deruxtecan in a neoadjuvant setting?

Dr. Lonardi:
I think that in the clinical practice, FLOT, for now, is the only one new adjuvant chemotherapy, even in the case of HER2 overexpression. Otherwise, if there is the possibility to enroll a patient in a trial, I think that it might be a good solution.

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