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Utilization and Management of Antibody-Drug Conjugates in Metastatic Breast Cancer: The Relationship Between ADCs and HER2

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[CHAPTER 1]

Dr. Gradishar:
Antibody-drug conjugates [ADCs] have transformed the treatment of HER2-positive breast cancer. There are now 2 anti-HER2 ADCs approved with different indications. Do you know how to sequence these drugs in your patients?

This is CME on ReachMD, and I'm Dr. Bill Gradishar. Here with me today are Drs. Hope Rugo and Dr. Javier Cortés.

Dr. Rugo:
Hi, Bill, and thanks for having me.

Dr. Cortés:
Thank you very much, William, for having me here with you today.

Dr. Rugo:
I'll get our conversation started today. And, Bill, in your role as the [Panel Chair] of the NCCN breast guidelines, the most up-to-date guidelines, really, for breast cancer in the world, and to set the stage for our chapterized course, could you discuss and review the NCCN guidelines for HER2-positive metastatic breast cancer and how the NCCN guidelines deal with the potential sequencing of ADCs for HER2-positive metastatic breast cancer?

Dr. Gradishar:
Sure, thanks Hope. And I think if you look at the NCCN guidelines, we try to make our decisions based on level of evidence. Is there compelling randomized clinical trial data that supports the position of a given drug or combination of drugs for therapy?

So in the case of HER2-positive breast cancer, we still have the CLEOPATRA-like regimen still standing as the first-line therapy of choice for the majority of patients. And that is a dual HER2-targeting strategy with pertuzumab, trastuzumab, and a taxane. After a disease progression for most patients, we would now consider trastuzumab deruxtecan as displacing T-DM1 [trastuzumab emtansine] as the best preferred regimen following progression on a CLEOPATRA-like regimen. And I'm sure we'll talk about the DESTINY data in subsequent chapters.

Thereafter we have the HER2CLIMB regimen, which is a combination of the TKI [tyrosine kinase inhibitor] tucatinib, trastuzumab, and capecitabine. And in certain circumstances, both trastuzumab deruxtecan and the HER2CLIMB regimen could be considered options for

a given patient. Both of the data are based on randomized phase 3 trial that showed very compelling data to support their use in improving outcomes.

But thereafter, it's still a bit of the Wild West with many different options. And I think that really reflects the explosion of new data and options that we have for patients in the HER2 space. Obviously, the newest drugs, the newest combinations gain the most attention, but we do know that continuing to
leverage the HER2 positivity of a tumor is important. So even after disease progression with what we view as the best therapies available, we would continue targeting HER2, whether it's with trastuzumab and different chemotherapy options, and even older drugs in select cases like lapatinib, neratinib can be used, another TKI, and most recently, another antibody, margetuximab, may be used in later lines of therapy as well.

So I think the explosion of new data has really benefited our patients and provided extended options, but we do look at the level of evidence leading us to go from the CLEOPATRA regimen, then to the ADC trastuzumab deruxtecan or the HER2CLIMB regimen as the first therapies we choose.

Dr. Rugo:
That's so interesting and really helpful to hear how the NCCN guidelines deal with the now increasing number of very effective treatments for HER2-positive metastatic breast cancer.

Javier, what clinical data do we have for trastuzumab deruxtecan, or T-DXd, in HER2-positive metastatic breast cancer?

Dr. Cortés:
We have many of impressive data we have known the last year and also this year at ASCO and at San Antonio. So basically, if we remember the DESTINY-Breast01, that was a large phase 2 study in the late-line setting of HER2-positive metastatic breast cancer patients. We have an impressive overall response rate in the range of 62% with T-DXd and a median PFS [progression-free survival] in the range of 19.4 months. And based on this trial, T-DXd got approval by the FDA. But of course we needed the DESTINY-Breast02, the randomized phase 3 trial in that setting, that was presented by Ian Krop at San Antonio 2022. And in brief, we observed a very nice improvement in progression-free survival with a hazard ratio of 0.36, of course in favor of T-DXd, with a median PFS 17.8 months, compared with about 6.9 months, which I think was absolutely impressive. And also, the overall survival was improved, with a hazard ratio of 0.66; the median was also nicely improved, from 26.5 months with physician's choice to 39.2 months. And this was very important that we did not have any specific or new safety concerns. Of course, it's important to highlight the ILD [interstitial lung disease] pneumonitis; 2 patients did have grade 5 events. And also, we knew from San Antonio, the updated data in DESTINY-Breast03 – remember this was the face-to-face against T-DM1 in the second-line setting, and we knew that the median PFS was nicely improved. Hazard ratio 0.28, when it was presented and published in The New England Journal of Medicine, and the updated analysis showed a median PFS of in the range of 29 months with T-DXd, and about 7.2 months. According to the investigators, there has been 28.8 months, according to the central review, compared with 6.8 months according to the central review with T-DM1. And overall survival was also achieved. The hazard ratio was 0.64, P value 0.0037, and of course, neither the median overall survival with the T-DM1 nor the T-DXd arms were achieved. So overall response rate 78%, and about 21% of patients achieved complete responses. So I think that these are great data. In my opinion, established T-DXd as the standard of care in the second-line setting.

Dr. Rugo:
And in Chapter 2, we'll be discussing the use of antibody-drug conjugates in yet another setting in HER2-low metastatic breast cancer. Stay tuned.

[CHAPTER 2]

Dr. Gradishar:
Welcome back, we're just talking about ADCs in HER2-positive metastatic breast cancer, and now we're turning to their use in HER2-low metastatic breast cancer.

Javier, can you start us out by outlining the NCCN guidelines and, for that matter, the European guidelines for HER2-low metastatic breast cancer and the sequencing of ADCs?

Dr. Cortés:
Well, as we all know, HER2-low metastatic breast cancer has got more of our attention based on the data that we knew this year, with trastuzumab deruxtecan optimizing and increasing the median PFS and also overall survival. And just after these data were announced and presented by Shanu Modi at ASCO 2022, the NCCN guidelines have incorporated T-DXd as one of the options to treat these patients. And I think it's very, very interesting to remark that basically, this is one of the – not only is available, but also one of the preferred regimens to use in patients with metastatic disease, if they express HER2, but in the low level. So I think that it is important to

remark once again that trastuzumab deruxtecan, according to the NCCN guidelines, is not only recommended to treat patients with HER2-positive breast cancer, but also now for the group of patients with low HER2 expression. So very good news for our patients, in my opinion.

Dr. Gradishar:
Thank you, Javier. Hope, what data do we have for trastuzumab deruxtecan and HER2-low metastatic breast cancer?

Dr. Rugo:
So this is actually a very exciting area. You know, I don't think any of us would have thought that you could take an ADC with the antibody, using trastuzumab in this case, a trastuzumab biosimilar for a T-DXd, and target cancers that we don't call HER2 positive. You know, we had done previous studies in the metastatic setting with T-DM1, and in the early-stage setting with trastuzumab, looking at patients whose tumors had a little bit of HER2 expression or a gene amplification, but not meeting that criteria for being HER2 positive, based on all of our prior trials in the metastatic and early-stage setting.

But none of those treatments seemed to work. They weren't better, and sometimes they didn't work at all. But in the early phase 1 trials looking at trastuzumab deruxtecan, they thought that because this had a high drug-to-antibody ratio of 8:1 and because there's this hypothesis of the bystander effect, where the hydrophilic or membrane-permeable toxin could leak out of the cancer cell and kill neighboring cells, and understanding that tumor cells like to hang out together, that you might be able to see efficacy, they explored the effectiveness of T-DXd in patients who had HER2-low, in other words, 1+ or 2+, but without gene amplification, now referred to as HER2-low disease.

So in 54 patients who had so-called HER2-low disease and were heavily pretreated, with metastatic disease, the median progression-free survival was 11 months, quite remarkable. And the response rate was 37%. And that led to the design of DESTINY-Breast04, which randomized patients with metastatic centrally confirmed HER2-low metastatic disease to receive T-DXd every 3 weeks or treatment of physician choice. Again, the sort of standard menu of chemotherapy agents we see in this setting where eribulin is often one of the more common agents given. The randomization was 2:1, and patients had to have received at least 1 line of chemotherapy for metastatic disease but not more than 2, and at least 1 line of endocrine therapy of hormone receptor positive.

The primary endpoint of DESTINY-Breast04 was the progression-free survival in patients who had hormone receptor-positive metastatic breast cancer. And then they allowed a small number of patients with triple-negative disease as an exploratory endpoint. And triple-negative, again, all had to have centrally confirmed HER2-low disease.

So as I think the audience is familiar with, and presented at ASCO 2022 to a standing ovation, trastuzumab deruxtecan improved progression-free survival, as well as overall survival not only in the population for the primary endpoint, hormone receptor-positive HER2-low disease, but also in all patients. And in an exploratory analysis looking at patients who had triple-negative disease – this was, again, a very tiny number of patients – 40 received T-DXd and 18 treatment of physician choice, progression-free and overall survival was also markedly improved. So this was quite encouraging. The hazard ratios were all just below 0.5 in that subset of the population. But where, of course, the primary data came was in this patient group who had HER2-low hormone receptor-positive disease, median of 1 line of prior chemotherapy, and a little, about 85% had visceral disease. So really intriguing results. And the toxicity we'll talk about more, but nausea is the primary toxicity for trastuzumab deruxtecan. And there was no difference in the toxicity seen in DESTINY-Breast04, compared to the other phase 3 studies in HER2-positive disease, but interstitial lung disease remains a problem that can be life threatening and needs to be identified early and treated appropriately.

There are other studies which have continued to suggest that T-DXd is very effective in HER2-low disease, including studies combined with immunotherapy that are in small numbers of patients, you know, single-arm trials but quite intriguing.

And then, of course, patient-reported outcomes are also very important. And data looking at patient-reported outcomes in DESTINY-Breast04 was presented at ESMO 2022 and showed that T-DXd doesn't result in deterioration of quality of life endpoints reported by patients. And also in some cases represents an improvement, for example, in pain and other patient-reported endpoints. There is, of course, ongoing fatigue with all of these agents, nausea, which can be delayed and needs active management.

Dr. Gradishar:
I think that was a nice summary of the data we have from the DESTINY trial looking at HER2-low. And to state that there was a lot of excitement surrounding this data, I think, would be obviously minimizing it. From the point of the presentation to the time to get in clinic, I think people were all thinking, who are the patients that I currently have under treatment where they may be a candidate for this drug? And I think one of the things that subsequently happened is people have now gone back, they're looking at the original reports from patients who were viewed as HER2-negative by the classical sort of binary decision-making to determine whether they may have had 1+ or 2+, FISH negative, and may be candidates for this drug. So I think that if you look at the universe of patients with breast cancer,

it's a significant fraction that actually have HER2-low disease and will be candidates for drugs that target this.

And as Hope pointed out, you know, previous experiences trying to use trastuzumab as a therapy for HER2-low disease was sort of a bust. There was no advantage in that setting, which really speaks to the novelty of how this drug delivers its toxin, in this case, deruxtecan. And by doing so, we may have the bystander effect that leads to the efficacy of the drug. So it's clearly dependent on the drug that's used.

In Chapter 3, we'll be discussing the use of ADCs for hormone receptor-positive HER2-negative metastatic breast cancer. Stay tuned.

[CHAPTER 3]

Dr. Gradishar:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Bill Gradishar, and here with me today are Drs. Hope Rugo and Javier Cortés. We're discussing the use of antibody-drug conjugates in metastatic breast cancer.

Welcome back, we've just covered the use of ADCs in HER2-low metastatic breast cancer. And now we're going to discuss their use in hormone receptor-positive HER2-negative metastatic breast cancer.

Dr. Rugo, what do the clinical data tell us about the use of sacituzumab govitecan in hormone receptor-positive HER2-negative metastatic breast cancer?

Dr. Rugo:
Thanks so much, Bill, for asking this question. And I will say just in response to some of your comments earlier, the NCCN Guidelines were updated in lightning-fast time after the presentations at ASCO 2022, adding the HER2-low indication for trastuzumab deruxtecan in the HR-positive, heavily pretreated population for sacituzumab, which I think is quite well done and remarkable because it helps us all in practice to prescribe these drugs and better understand how we can utilize them in our patients with metastatic disease, where we're really often desperate for therapies that can improve outcome with tolerable toxicity.

But also I think that, you know, sacituzumab govitecan was studied in hormone receptor-positive HER2-negative disease, so HR positive. There are some striking differences between this trial and DESTINY-Breast04. One, we didn't do central confirmation of HR positivity; it was done locally. And we didn't look at HER2 except for in a post hoc analysis, whereas DESTINY-Breast04 was really designed for a centrally confirmed HER2-low population. And then of course, hormone receptor-positive was a primary endpoint as well, so 2 indicators.

The other thing is that TROPiCS-02, the randomized phase 3 trial that evaluated sacituzumab in HR-positive HER2-negative disease, was designed as a study to treat patients who were more heavily pretreated based on phase 1 data from an expansion study, a phase 1/2 trial that looked at sacituzumab govitecan in patients who had heavily pretreated HR-positive disease and, again, showed this very nice response rate in patients who had hormone receptor-positive, heavily pretreated disease. So that led to the concept of studying sacituzumab govitecan in HR-positive disease, particularly after we got the results from ASCENT that showed the activity of sacituzumab govitecan in patients who had metastatic heavily pretreated triple-negative disease. So in contrast to DESTINY-Breast04, where patients received 1 line of prior chemotherapy for metastatic disease, patients treated on the TROPiCS-02 trial had received a median of 3, so the majority of patients received 3 or more prior lines of chemotherapy for metastatic disease.

Also, in contrast, all patients had received CDK4/6 inhibitors, and 95% of patients had visceral disease. And they had a median of 4 years from diagnosis of metastatic disease to randomization and treatment on study. Sacituzumab govitecan, compared to treatment of physician choice, improved progression-free survival with a hazard ratio of 0.66. There was an absolute difference, so looking at the medians of 1.5 months, but that is in large part because of this rapid progression in patients who had heavily pretreated resistant disease. And when we looked at landmark analyses at 1 year, 3 times as many patients were alive and free from progression who received sacituzumab compared to chemotherapy.

And now that data is now published in the JCO [Journal of Clinical Oncology]. But we were also able to show in the second interim analysis that sacituzumab significantly improved overall survival in this heavily pretreated patient population, with a median improvement to 3.2 months and a hazard ratio 0.79, also statistically significant. And this was true across different subgroups for overall survival.

We were able to show there was also a significant improvement in overall response rate and duration of response. And then a significant delay in time to deterioration in global health status quality of life, which I think is also very important for our patients. And that data was presented in more detail at ESMO in 2022.

And then, because of the interest in HER2-low, we evaluated in a post hoc analysis whether there were differences in the efficacy of

sacituzumab, and that's presented in relationship to PFS and not OS [overall survival], because we didn't have the OS data when we did that. We showed that sacituzumab maintained efficacy across the HER2 subgroups, so 1+, 2+, and 0. Now this was also determined locally and not centrally. So it is a different population and it was post hoc, but I think it's quite intriguing.

So based on the data from TROPiCS-02 the indication for hormone receptor-positive HER2-negative disease in the heavily pretreated patient population was submitted to the FDA and accepted for priority review in October of 2022, with a PDUFA date of February 2023.

Dr. Gradishar:
So I think that's great, Hope, just discussing the nuances between these trials and the datasets and what they tell us. And I think, for the listeners, you have to be aware of these trials and understand the eligibility of the patients in the trial, what prior therapy they had, because there are distinctions with one population being more heavily pretreated than another. And we'll see how this data pans out over time.

But I think the bottom line is we have a couple of drugs now that are very active that have shown significant activity in randomized clinical trials, and how we sequence them will be what we have to pay attention to going forward. Thank you.

In Chapter 4, we're going to look at regional considerations in treating hormone receptor-positive HER2-negative metastatic breast cancer. Stay tuned.

[CHAPTER 4]

Dr. Gradishar:
Welcome back. We just talked about using sacituzumab govitecan in hormone receptor-positive HER2-negative metastatic breast cancer. And now we're going to close with a look at regional considerations.

Javier, what are some of the HER2 testing challenges outside of the United States?

Dr. Cortés:
The first one, my opinion is that the HER2 analysis is based usually in immunohistochemistry, very similar to the United States, but that's different companion diagnostics. And we know that depending on this companion diagnostics, the HER2 positivity could be higher or lower. Indeed, when we look at the differentiation between HER2 1+ and 0, across different pathologies, could be very discordant. The concordance could be only in the range of 20%-30% sometimes. Now this could be even higher, outside of the United States.

Another important aspect is that, unfortunately, trastuzumab deruxtecan is not approved outside the United States, so we do not have the report of HER2 1+, 2+, in many of our patients. So we just know that patients do have HER2-negative cancer, or HER2-positive cancer, but not if either has HER2 0, 1+, and 2+. And we have another caveat. What happens in many, many countries outside the United States, maybe also in some hospitals in the US, which is that in some patients, the report of the HER2 is just made by each directly, without the immunohistochemistry. So I think that these are important caveat, if we want to use [trastuzumab] deruxtecan in the future in the HER2-negative patient population, because I said before, in many patients, this is not reported.

Dr. Gradishar:
Well, this certainly has been a fascinating conversation. I'd like to get Hope's takeaway from the discussion we've had.

Dr. Rugo:
You know, I think there are so many different points to cover. But just briefly, I think that we're very excited about the role of antibody-drug conjugates in treating the most common population of patients with metastatic breast cancer worldwide. Hormone receptor-positive disease represents about 70% of the patients we see. And the HER2-low group is so fascinating. An ongoing trial, DESTINY-Breast06 in the first-line setting, is evaluating trastuzumab deruxtecan as first-line therapy compared to chemo in patients who have centrally confirmed HER2-low disease. But it's a large trial, over 800 patients, and a subset of these patients will have disease that's so-called HER2-ultra low, so not zero, but not meeting the ASCO CAP criteria for [HER2] 1+. So this is going to be fascinating to see how that drug works. There's some tiny bit of data and HER2-0 disease that suggests that the drug may not work quite as well in true [HER2] 0 disease. But there's so many controversies about when you should test, like if you were [HER2] 1+ in early stage and [HER2] 0 in metastatic, could you still use the drug? We have no idea because that, really, data hasn't been generated.

And then for hormone receptor positive-disease, is there a subgroup of patients where sacituzumab may work more effectively, for example, where we don't have an indication for T-DXd and HER2-0 disease, sacituzumab is now the ADC of choice, even while we wait to see the FDA's ruling as listed in the NCCN guidelines.

And I think that understanding how we should sequence these agents and efficacy in sequencing is going to be incredibly important, and a number of studies will look at this, both in a prospective manner as well as in a registry approach as we move forward and will really

help us understand how we should be using these agents in metastatic disease, even as we move all of these agents into the early-stage setting.

Dr. Gradishar:
Thanks, Hope. And I would echo much of what you've already said, but I won't. What I will say is that if you think about how we would approach patients who are hormone receptor-positive, and then run out of endocrine options, they would revert to chemotherapy. And we know that in that setting, the probability of getting great benefit from chemotherapy certainly is not high, and with each subsequent therapy, it diminishes. Now with antibody-drug conjugates as a potential tool in this setting, we have from the results that have been presented thus far, shown that compared to chemotherapy, using antibody-drug conjugates in this setting are better than chemotherapy as monotherapy. So again, chemotherapy is not going away, but at the point where you're making the transition from a patient who is viewed as endocrine refractory to what would have been the reflex of chemotherapy, we now have some other options with better results based on the data we have to date.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening and thank both Hope and Javier for joining me and sharing all of their valuable insights. It was great speaking with you today.

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