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The Role of HER3 Expression in Advanced Solid Tumors

*Since the recording of this activity, clinical trial NCT04479436, patritumab deruxtecan in colorectal cancer, has been terminated early. To learn more about this trial, search for NCT04479436 on ClinicalTrials.gov.

Announcer:
Welcome to CME on ReachMD. This activity, entitled “The Role of HER3 Expression in Advanced Solid Tumors” is provided by Prova Education.

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[CHAPTER 1]

Dr. Ritterhouse:
Welcome to this activity about HER3 expression in advanced solid tumors. In this first chapter, we’ll be setting the stage for the rest of the chapters in this activity. This is CME on ReachMD, and I’m Dr. Lauren Ritterhouse, associate director at the Center for Integrated Diagnostics at Massachusetts General Hospital and assistant professor of Pathology at Harvard Medical School.

Dr. Jänne:
And I’m Pasi Jänne, from the Dana-Farber Cancer Institute. I’m a thoracic medical oncologist, a professor of medicine at Harvard Medical School, and the Director of the Chen-Huang Center for EGFR-Mutant Lung Cancers at Dana-Farber Cancer Institute.

Dr. Raghav:
And I’m Kanwal Raghav, one of the associate professors in GI Medical Oncology at the University of Texas MD Anderson Cancer Center in Houston.

Dr. Ritterhouse:
Great. Let’s get started with Chapter 1. So what does HER3 do? Dr. Jänne, can you give us some background on the role that HER3 plays in non-small cell lung cancer?

Dr. Jänne:
Sure. So HER3 is one of the ErbB family members – 1 of the 4 family members, and unlike the other 3 family members, it does not have an active kinase domain, so it’s not, by itself, an active oncogene. HER3 is often co-expressed with other ErbB family members, for example, in EGFR-mutant lung cancer, it’s co-expressed with EGFR. And ErbB3 can form a heterodimer with other ErbB family members such as EGFR or HER2, and as such, can be an active signaling molecule in a heterodimer sense, and a very potent one, especially when dimerized with HER2. Now, in EGFR-mutant lung cancer, as I mentioned, HER3 is often co-expressed. And biologically, mutant EGFR transphosphorylates HER3 to activate downstream signaling pathways, most notably the PI3 kinase AKT signaling pathway.

And in EGFR-mutant lung cancer, as I mentioned, HER3 is almost ubiquitously expressed, and there is some data across cancers that higher expression of HER3 is associated with worse outcome than in cancers without HER3 expression. This has not really been

specifically looked at in EGFR-mutant lung cancer, but in cancers in general.

Dr. Ritterhouse, what role does HER3 play in metastatic breast cancer?

Dr. Ritterhouse:
Well, the role of HER3 in breast cancer has some overlaps with what we just heard about its role in non-small cell lung cancer and the ErbB family. Includes a role in genesis and growth of these tumors. Additionally, HER3 activation has been implicated as a molecular mechanism, inducing both inherent and acquired de novo resistance to anti-HER2 therapy, and endocrine therapy. In addition to HER2-positive breast cancers, therapeutic targeting of HER3 receptors has also been suggested in the treatment of HER3-dependent, but HER2-negative, breast cancers, so hormone receptor-positive tumors. And HER3-targeting molecules have been developed as therapeutics, many of which are currently being tested in clinical trials.

The prognostic value of HER3 expression and either the protein or the RNA level in breast cancer is a bit tricky, as there's some conflicting studies. Generally speaking, overexpressed HER3 is thought to portend a worse survival, although there have been conflicting studies and reports that have been published. And so many studies have actually not shown a relationship between HER3 and patient survival in this tumor type, so HER3's use as a prognostic marker in breast cancer isn't totally clear.

So, Dr. Raghav, what you tell us about the role of HER3 in colorectal cancer?

Dr. Raghav:
So I think the issues with HER3 in colorectal cancer are very similar to what has been seen in other tumor types.

On a preclinical front, there is definitely oncogenic value to HER3, where HER3 knockout has been shown to decrease colorectal cancer cell survival, as well as proliferation and metastases, and increase cell cycle arrest. So I think that there is clearly a role of this this molecule, but mostly like you guys mentioned, in concert with other pathways. And, you know, as the therapeutics improve, we can double up, you know, more and more interest in this target.

Dr. Ritterhouse:
Thanks, this has really been great. Before we wrap up, Dr. Jänne, can you provide us with one key takeaway from this chapter?

Dr. Jänne:
Sure. So where ErbB3 or HER3 is a kinase-dead family member of the ErbB super family that, in conjunction with other ErbB family members, clearly has important roles in lung cancer, breast cancer, as well as in colorectal cancer.

Dr. Ritterhouse:
Thank you. In Chapter 2, we'll be discussing emerging concepts on the role of HER3 expression across different solid tumor types. Stay tuned.

[CHAPTER 2]

Dr. Ritterhouse:
In the first chapter, we covered the role of HER3 in non-small cell lung cancer, colorectal cancer, and breast cancer. In Chapter 2, we're discussing emerging concepts about the role of HER3 expression across different solid tumor types. Dr. Jänne, how does HER3 influence tumor progression and drug resistance across different tumor types?

Dr. Jänne:
Thank you. So HER3 is expressed in a vast or wide variety of solid tumors and has been associated with disease progression and metastatic events in a variety of cancers. There was a metanalysis that looked at the expression of HER3 – or whether expression of HER3 was associated with poorer prognosis in cancers that had expression of HER3, had a worse overall survival compared to patients with cancers that did not express HER3. However, the specifics of each individual cancer, I think, are still not perhaps as clearly defined. As mentioned before, most EGFR-mutant lung cancers do co-express HER3. As to HER2-mutant lung cancers, and HER2 and HER3 of course heterodimerize and are very potent signaling molecule. In terms of drug resistance, HER3 is really kind of an intermediary, for example, an EGFR-mutant lung cancer. So in EGFR-mutant lung cancer, EGFR transphosphorylates HER3 to activate downstream signaling, but you can also have other oncogenes kind of feed in to the same pathway by transphosphorylating HER3. So for example, in the case of MET amplification which is a known mechanism of resistance to EGFR inhibitors, MET can transphosphorylate HER3, and EGFR can be inhibited. And in this way, you can have the resistance mechanism essentially plug into the same pathways that are used by the primary oncogene, and in this case using HER3 as the intermediary. So clearly a role there, and clearly an important potential therapeutic target.

Dr. Raghav, do you have any additional insights you'd like to add from a colorectal cancer perspective?

Dr. Raghav:
So yes, I mean, in colorectal cancer, as far as HER3 is concerned, there is good preclinical evidence that it plays an established role in oncogenesis with, you know, knockouts showing decreased proliferation, decreased metastases, and consequently, you would come to the conclusion that a higher HER3 expression is important for cancer progression and survival in these patients. It has been partly supported with clinical observations, where some meta-analysis and studies have shown that HER3 expression can have, you know, sometimes a poorer prognostic or a good prognostic impact, which really depends on the kind of study that you're looking at and how that expression level is looked at. What's more interesting is the therapeutic drug resistance profile. Preclinically, it has been shown that HER3 expression is a negative predictive biomarker for anti-EGFR. Efficacy and some retrospective clinical data also supports this, where response rates in HER3-expressing tumors is lowered. Unfortunately, some of the other analysis with larger clinical trials, which has been done not with particularly protein expression but mRNA expression, failed to show these associations. So it's really unclear whether it plays a strong role in anti-EGFR resistance or not, but what's more important – and I think which is an active area of interest – is whether adaptive responses that acquired increased expression of HER3 can play a role in this resistance, and I think that that needs to be explored further.

Dr. Ritterhouse:
Thanks to you both. Those are some really great insights. Before we wrap up, Dr. Raghav, can you provide us with one key takeaway from this chapter?

Dr. Raghav:
Yeah, so I think, you know, clearly some oncogenic role here, across tumor types which has certain data backing it up, but we need more preclinical data, I think, across tumor types in general. With regards to context dependency or as far as tumor dependency is concerned, HER3 may play different roles in different tumor types and across different treatment strategies, such as, you know, EGFR/TKI has been used in lung cancer, or EGFR monoclonal antibodies have been used in colorectal cancer. But I think it would be an exciting target to exploit.

Dr. Ritterhouse:
Great, thank you. In Chapter 3, we'll address the genomic and molecular testing techniques for identifying HER3 alterations. Stay tuned.

[CHAPTER 3]

Dr. Ritterhouse:
In Chapter 2, we discussed emerging concepts on the role of HER3 expression across different solid tumor types. Now, in Chapter 3, we're going to address the genomic and molecular testing methods for identifying HER3 expression and alteration. So, Dr. Raghav, our knowledge of the role that HER3 plays in advanced solid tumors has been evolving in recent years. Can you tell us about the relevant guidelines and strategies for targeting, identifying, and other important considerations for HER3?

Dr. Raghav:
Yeah, I think, you know, this is definitely an evolving target. You know, we have knowledge of trials where single-agent HER3 inhibition has been met with some optimal success when you're targeting it purely from an oncogenic addiction perspective, right? Like if you think that a tumor is completely dependent on HER3 expression and its signaling only, without concomitant MET amplification, EGFR amplification, or HER2 overexpression. Single-agent studies of patritumab, were you know, not helpful There have been some bispecific antibodies against EGFR/HER3 that have shown some optimal activity in clinical trials, and certain other monoclonal antibodies. That does not mean that HER3 cannot be you know, challenged with regards to newer and evolving therapies, especially other bispecific antibody or antibody-drug conjugates. But as of now, there is no uniform role that I see for HER3, at least testing or targeting, in any of the tumor types, to the best of my knowledge. At least in colorectal or in other GI tumors, it is not standard of care to test this. As for the guidelines, even though there is some predictive impact on standard of care therapies, it is not a part of routine assessment for patients and is not used in management. So, you know, there will be definitely some barriers, even if we perform this as a part of routine assessment because, you know, if it's not actionable and we cannot really alter patient management, it's hard to get them on guideline recommendations. Now that could change as the therapies evolve and we get better and better at targeting this alteration.

Dr. Ritterhouse, by the way, what insights do you have into other mutations that have relationship with HER3 or ErbB3?

Dr. Ritterhouse:
Yeah, so in addition to looking at HER3 expression, either at the RNA or protein level, from an RNA expression assay or immunohistochemistry, we can also look at hot spot or activating ErbB3 mutations that are seen across a wide variety of tumor types, with some of the most common ones being urothelial cancer, a variety of different gastrointestinal cancers, gynecological tract, adenocarcinomas, as well as breast cancers and many others. And co-occurring HER3 mutations have previously been found in HER2-

mutant tumors, so co-mutated tumors, in several different tumor types. And in the case of breast cancer, for example, these co-occurring mutations are associated with lower clinical response to inhibitors. And so, the extracellular domain of HER3 harbors the largest fractions of these mutations seen across tumor types, whereas the tyrosine kinase domain, on the other hand, harbors fewer of them overall, and really just in the form of 3 different hot spots. However, the role of these ErbB3-mutated tumors in cancer is still evolving, and we're still collecting data.

Dr. Jänne, do you have any additional insights into the pertinent guidelines around biomarkers for HER3?

Dr. Jänne:
I would agree with both of you. At the moment, we don't have a standard of care assay to test for HER3, either by immunohistochemistry or by RNA-Seq or other expression methods.

We do test for HER3 mutations as part of our own larger NGS [next-generation sequencing] panel, but in lung cancer they are – and perhaps some other cancers – fairly rare, and I'm not sure that we know yet what to do optimally therapeutically in an individual who has a HER3 mutation.

As we wrap up this chapter, Dr. Raghav, can you provide us with one key takeaway?

Dr. Raghav:
Yeah, I think the key takeaway here is that whether it is expression, amplification, or mutations, we'll have to deal with these separately in different tumor types, and we still need to demonstrate clinical actionability on this to be a part of the guidelines, which it is not currently.

Dr. Ritterhouse:
Great, thank you. In Chapter 4, we'll highlight recent clinical trial data on the use of antibody-drug conjugates, and HER3-expressing advanced solid tumors as well as a look towards the future.

[CHAPTER 4]

Dr. Ritterhouse:
In Chapter 3, we discussed testing for HER3 expression. Now in the final chapter, we're going to give you some highlights from the data presented throughout the year on HER3 in lung cancer, breast cancer, and colorectal cancer.

With the ever-evolving landscape of precision medicine and the genetic alterations that these novel therapies target, it is imperative to stay up to date and even ahead of the curve.

Dr. Jänne, can you talk about some of the clinical trials in HER3 non-small cell lung cancer?

Dr. Jänne:
Sure, thank you, Dr. Ritterhouse. There've been a couple of studies that have looked at this, and I'll review some of the older ones first. First of all, with an agent called seribantumab, which is an anti-HER3 antibody. And this agent was tested in combination with erlotinib in EGFR-mutant patients compared to erlotinib alone and did not demonstrate an improvement in progression-free survival [PFS]. However, there was a suggestion that in patients that express high levels of heregulin, the ligand for HER3, there was a potential improvement. It subsequently led to a randomized phase 2 clinical trial comparing seribantumab/docetaxel to docetaxel alone in the second-line setting in patients that expressed high heregulin, but this also failed to improve progression-free survival. A second antibody, lumretuzumab, plus carboplatin and paclitaxel has also been tested in a phase 1 trial and additional data not available at this point.

The patritumab deruxtecan or HER3-DXd trial in advanced non-small cell lung cancer patients was focused initially on EGFR-mutant patients that have developed resistance to prior EGFR inhibitors. And the rationale for this is that HER3 is essentially ubiquitously expressed in EGFR-mutant cancers. However, it is not a known resistance mechanism to EGFR inhibitors, and as such, could be leveraged to deliver an antibody-drug conjugate, like the HER3 DXd.

So the lung cancer trial was a phase 1 trial with a dose escalation and a dose expansion. And the dose expansion focused specifically on EGFR inhibitor-resistant patients that had been treated with prior generation EGFR inhibitors. Many of them included osimertinib as well as platinum-based chemotherapy for a large number of the individuals. And there was significant clinical activity here with a confirmed overall response rate of 39% with a median PFS of 8.2 months. And the duration of response was 7 months, and the disease control rate was about 70% in this trial. What was also important was to evaluate the efficacy across the different resistance mechanisms to osimertinib and other EGFR inhibitors. And as predicted, from the preclinical hypotheses there was activity seen in patients regardless of their specific resistance mechanism. So patients could have had an osimertinib resistance mechanism such as C797S and still responded to HER3-DXd, or they could have had no detectable resistance mechanism and could have still responded to

HER3-DXd because, again, the activity and the expression is independent of the specific resistance mechanism. There were some adverse events associated with HER3-DXd including rare cases of interstitial lung disease, and serious treatment emergent adverse events were seen in about 20% of individuals, and dose reductions were seen in about 20% of individuals, and adverse events leading to dose discontinuation were seen in about 10% of individuals.

So there are additional studies ongoing, including the HERTHENA-1 lung trial, which evaluates HER3-DXd now in patients that have progressed on frontline osimertinib and chemotherapy and with a primary endpoint of looking at, again, response rate in this more unified patient population, unlike the phase 1 clinical trial, which had a more heavily pretreated patient population. And we look forward to these results from this trial and hope that this will emerge as a treatment option for our patients that have developed resistance to EGFR inhibitors.

So to date, targeting HER3 has met with challenges as the efficacy of naked antibodies, such as seribantumab or even patritumab by itself, have not really translated into significant clinical activity. That's in contrast to the HER3 antibody-drug conjugate, patritumab deruxtecan, where you're leveraging the presence of HER3 as a way to deliver a targeted chemotherapy to different tumor types. And so far, we've seen activity in EGFR-mutant lung cancer, in colon cancer, as well as in breast cancer, and the hope is that as we study this agent further, the degree of activity will continue. And of course we'll need to evaluate whether this extends to other disease settings and other tumor types as additional development of patritumab deruxtecan takes place. So some exciting developments there in the HER3 targeting space.

So, Dr. Raghav, what have been the updates for HER3 in colorectal cancer?

Dr. Raghav:
Thank you, Dr. Jänne. So, you know, as we have discussed in, I think, the last chapter, that HER3 has been seen to be expressed in colorectal cancer. There have been analyses which have shown that there is some prognostic significance of this marker, and at least in preclinical studies, it is very clear that it plays a significant role in tumor growth, development, and metastases as far as colorectal cancer is concerned. Another area which is specifically of interest when it comes to targeting of HER3, is the potential resistance to EGFR antibodies since HER3 is a part of the HER family of receptors, EGFR being HER1. There is significant crosstalk between these members, and it is seen that HER3 overexpression could potentially blunt response to anti-EGFR therapy. Therefore, most of the targeting for HER3 has been either as a single agent or in combination with EGFR to try to improve those responses. This has been predominantly done by either naked antibodies or antibody-drug conjugates. Unfortunately, so far, the success of HER3 targeting in colorectal cancer in clinical settings has not mirrored what was seen in preclinical settings. So for example, patritumab, which is a HER3 antibody, was tested in a phase 1 study with advanced solid tumors in about 57 patients across multiple cohorts. 29 of these were colorectal cancer patients. The best response that was seen was usually stable disease, and no single partial response was seen in the colorectal cancer cohort. And this really put a wrench in direct targeting of HER3. Similarly, antibody called seribantumab, which is a HER3/EGFR antibody, was tried in combination with cetuximab and cetuximab/irinotecan in a phase 1 study with 20 colorectal cancer patients. One colorectal cancer patient had an unconfirmed partial response, but no other significant activity was seen, irrespective of prior EGFR status or prior irinotecan status. In addition to this, another antibody which is called duligotuzumab, which is an EGFR/HER3 antibody inhibitor, was tested in combination with FOLFIRI, which is the standard of care chemo, against cetuximab/irinotecan. So this was a randomized phase 2 study based on the principle that EGFR alone versus EGFR/HER3 would be better. However, in the 98 patients that were randomized in the RAS wild-type population, there was no benefit of either PFS, objective response rate, or overall survival. As a result, it is very clear that clinically there is something more going on than simply EGFR inhibition.

Dr. Ritterhouse, what new data have been presented for HER3 in breast cancer?

Dr. Ritterhouse:
Thanks a lot, Dr. Raghav. For seribantumab, again, one of the antibody drugs that was discussed in the other tumor types, the phase 1 dose escalation trial in patients with solid tumors included 21% of patients with advanced or metastatic breast cancer. So to be eligible for this study, patients had to either have triple negative breast cancer or advanced or metastatic hormone receptor-positive / HER2-negative breast cancer. And the patients included in the trial were a heavily pretreated patient population, all having received prior systemic therapy. Almost all of them had received at least 3 prior lines, and over half reported receiving at least 6 prior lines of therapy. And unfortunately, no patients in the study achieved a complete or partial response. The best response of stable disease was achieved by 24% of patients in the dose escalation arm and 39% in the dose expansion arm. Among these patients, 3 had breast cancer. And so clinical benefit was 0% in the dose escalation portion and 11% in the dose expansion portion.

So another therapy that is also being looked at in breast cancer, again, is the antibody-drug conjugate patritumab deruxtecan, aka, HER3-DXd. And the patients in the ICARuS breast phase 2 study have unresectable locally advanced or metastatic breast cancer with high expression of HER3, which was defined as 75% or more of the tumor cells expressing HER3. And the tumors were hormone

receptor-positive and resistant to endocrine therapy as well as CDK4/6 inhibitors. And patients may have received multiple lines of endocrine therapy, with or without targeted therapies, and must have only had 1 prior line of chemotherapy. And so this trial is currently enrolling patients with a planned enrollment of a hundred participants who will receive the drug every 3 weeks until progression or until unacceptable toxicity, so we're looking forward to seeing the results from this study.

Another phase 1 trial of the same drug, which was conducted in Japan, was in combination with trastuzumab and resulted in an overall response rate of 38.9%, including 2 complete responses and a median progression-free survival of 274 days among 18 patients that had HER2-overexpressing metastatic breast cancer.

And finally, there's another study looking at patritumab deruxtecan that is currently enrolling patients with early breast cancer who are hormone receptor positive and HER2 negative and treatment naïve, and this study is also currently ongoing, and we look forward to seeing those results.

This has been a really nice summary, I think, of this new treatment class and these different tumor types.

So before we wrap up, Dr. Jänne, can you provide us with one key takeaway for this chapter?

Dr. Jänne:
Sure, thanks, Dr. Ritterhouse. Yes, I think despite the lack of success of naked HER3 antibodies as anti-cancer therapies, the antibody-drug conjugates, namely here, patritumab deruxtecan appears to have clinical activity across multiple tumor types.

And Dr. Raghav, can you provide us with one key takeaway from this chapter as well?

Dr. Raghav:
Thank you, Dr. Jänne. I think, you know, one of the key takeaways here is that even though preclinical data across tumor types that we have discussed shows oncogenic signaling, it seems like modulation of this pathway is a little bit more complex than just inhibiting the receptor and can be dependent on tissue and tumor type, I think. So, you know, the same studies and the same drugs are showing some sort of variable activity across, but I agree with you completely that an antibody-drug conjugate strategy is very novel and very exciting, and we look forward to the results of these trials.

As a close of this chapter and activity, Dr. Ritterhouse, can you provide us some final key takeaways?

Dr. Ritterhouse:
Yeah, I think I'll echo the sentiments from Dr. Jänne and Dr. Raghav in that although the development of drugs targeting HER3 have seen some difficulties and early failures, some of these newer antibody-drug conjugates are being evaluated in trials and in at least some tumor types shows promise. And upcoming trials and data include various combination regimens as well as monotherapy in several different tumor types, and so we'll anxiously await the additional results from these studies.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank both Dr. Jänne and Dr. Raghav for joining me and sharing their valuable insights today. It was great speaking with you all.

Dr. Jänne:
Thanks, Dr. Ritterhouse, and thank you to you and to Dr. Raghav for the discussion and for all of you for listening, and goodbye.

Dr. Raghav:
Thank you all. This has been incredibly exciting and hopefully we'll have future developments that can help these patients. Thank you.

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