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Advancing Care and Improving Survival for Patients With HER2-Positive Breast Cancer

Announcer Open:
Welcome to CME on ReachMD. This activity titled, Applying Novel Strategies to the Treatment of Advanced Renal Cell Carcinoma, is provided by Partners for Advancing Clinical Education, PACE, and supported by educational grants from Exelixis Incorporated and Merck Sharp and Dohme LLC. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Ms. Sims:
So, our first speaker today is Dr. Jeremy Force. He's Assistant Professor in Department of Medicine, and the Division of Medical Oncology in the Breast Oncology Program at Duke University in Durham, North Carolina. And I think you will find that he's an excellent speaker, and he's going to give us a lot of good information. We're going to do a few questions first to get everyone ready here.

These are his disclosures.

And these are our learning objectives today. These are also in your handouts to remember that he's going to summarize data supporting the recommended role of newer evidence-based treatments for care of patients with HER2 positive breast cancer, and integrate new therapies into patient care using evidence-based guidelines and sequencing for individual treatment plans for patients, and to implement strategies to recognize treatment-related AEs and support improved treatment adherence.

Alright, I'm going to turn this over now to Dr. Force and let him answer some of those questions for us. Dr. Force, welcome.

Dr. Force:
Yeah, thank you. Thank you for the opportunity to speak with you guys. Really appreciate this and have really enjoyed this venue with PCE and thanks for the invitation to come back and talk again, I really do greatly appreciate it.

Well, let's get started. We've got a lot to cover today, you will learn a lot. There's been a lot of really great changes for our patients in the HER2-positive breast cancer landscape. And so just by virtue of just a brief introduction, and then we'll really get into the data with HER2, focusing on HER2-positive breast cancer for this lecture. Just to reiterate that 15% of women with invasive breast cancer have the HER2 protooncogene being enriched or amplified in their situation, that is the oncogene that is driving the cancer growth. These can be driven by amplification, not necessarily mutations. There's a small proportion of patients that have mutations without amplifications, but we're not going to get into that. This is an aggressive phenotype. Thankfully, it was discovered, and we now have drugs that target this in this subgroup of women. About 50% of the HER2-positive breast cancers will have hormone positivity in it. So, we're not going to really dive into that too much. But endocrine therapy is needed in many situations to be given concomitantly. However, there's many drugs that we're going to talk about today where we don't have safety data with endocrine therapy, and anti-HER2 therapy. And so that's, again, something that's not really addressed today, but I just wanted to point that out at the beginning, just so you're aware that just because it's HER2-positive, and if it's hormone-positive as well, you don't necessarily ignore the endocrine therapy backbone, it's just sometimes we might not have safety data for the combination.

And so, one thing that is really disturbing about HER2-positive disease as well as triple-negative breast cancer is that a significant portion of these patients will go on to develop CNS relapses and, in part, that's because it seems to be a sanctuary for brain metastases in general, those specific subtypes. And the treatments that we're now – which we'll go through today, have now kept people alive for years. Years later, there's a higher chance of intracranial disease developing. And you can see here that the cumulative incidence of CNS relapses in patients with HER2-positive early-stage breast cancer. So, these are patients who had early-stage breast cancer, we

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don't know what their stage was, but you can see that they received trastuzumab and died, you know, without CNS relapse, that's the blue line on the bottom. But those who had observation alone who didn't have the necessary, you know, HER2 – anti-HER2 therapy, you can see that they're, you know, they had CNS relapse, and there's a higher rate of death. And that's really in pretty, you know, short timeframes, of 1 year of trastuzumab versus not. So, what you should take home from that is that trastuzumab, which if you didn't know this, trastuzumab, is on the WHO list of necessary medications in the world. So, it is a good drug that should be offered to patients, regardless of where you live. I think in third-world countries, it just becomes more challenging due to access to care. And well, there's just a whole slew of things that we're not going to be able to get to today.

Here's a really nice slide on the evolution of HER2-targeted agents, starting with, you know, 1984 when the HER2 gene was identified out of MIT, and looking at how this is implicated in amplification of breast cancer about a year later, and then HER3 being discovered, which does crosstalk with HER2 as a mechanism of resistance, all the way to, you know, when having trastuzumab approved in 1998, mainly out of much of the work out of UCLA, and then leading to further drug development in 2007, lapatinib, that was actually fostered by Neil Spector here at Duke University, and, you know, pertuzumab, trastuzumab, emtansine, that was also Kim Blackwell helped to move that forward from Duke University, and all the other slew of drugs that have now really ramped up that have changed the face of HER2 positive breast cancer. So, we have all this huge repertoire now of, you know, 5, 6, 7 drugs that we can provide patients. So that's great. And there's actually a lot more coming down the line that will change this disease entity.

So, recommended biomarker molecular testing for patients with breast cancer in general. Obviously, we always want to know, breast cancer is unique in the sense that we will commonly rebiopsy disease to recheck biomarkers; it's not - this is not commonly done in other cancer subtypes. Usually it's - there's a single, you know, target that's known to be amplified, whether it be BCR-ABL like in CML, or, well, there's just various different targets. In breast cancer, we can see the switching of these receptors about 15 to 20% of the time. So, even at the time of progression, it's been shown also that tumor heterogeneity, it's real in breast cancer, and it's probably real in many other cancers, it's just we haven't identified targets for them. But these subtypes can switch about 15 or 20% of the time, so it is important to rebiopsy over time. That's going to be patient dependent, and many different factors play into when you would want to rebiopsy. But looking at estrogen receptor, progesterone receptor in HER2 are important. Usually it's by IHC initially, and then the HER2 gene, you need to use dual probe fluorescent in situ assays that are well standardized across the ASCO CAP, the College of Pathologists, showing that there's amplification based on specific criteria.

Triple-negative breast cancer is the only one that we test for PD-L1 expression using IHC, that's with a 22C3 antibody; that's not going to be really covered here. And at recurrence or metastatic disease, germline sequencing and next generation sequencing for actual mutations is always recommended. Now that could be, you know, from a tumor biopsy or from circulating tumor DNA. So those are all options that – but should be considered at anytime that a patient is progressing or newly developing metastatic disease.

For - in terms of the classification, again, this is for those who don't know this, but this is actually very important, and this actually translates because breast cancer is leading the way in HER2-positive breast cancer and now that HER2-positive disease is applicable to GI malignancies and others. But if you're HER2 2+, then it reflexes to fluorescent in situ and you would need to have a copy number to CEP-17 ratio of greater than 2 to be considered amplified, or a copy number greater than 6 would be considered amplified for HER2 positivity. And then if it's HER2 low, which is a new – I want to just emphasize this, this is not a new biologic subtype, it is a target that allows for drugs to get to the cancer cell and deliver chemotherapy. HER2 low is not a new biology, it just means that HER2 is not driving the cancer, it's just present on the surface of the cell. And this is where it's 1+ or 2+ and fluorescent in situ not amplified.

And then we have HER2-negative. So HER2 low is still considered HER2-negative, it's just there's a protein on there but it's not driving the cancer. So, that's – I just want to emphasize that home. But HER2 low is a new entity that has revolutionized the face of HER2-positive, or breast cancer in general. And we'll get into a little bit of that later. But HER2-negative, stone-cold negative, is IHC 0 and fluorescent in situ not amplified. I just want to emphasize this is a confusing topic and we're still working through a lot of this but HER2 low will probably work its way into other disease entities. So, you probably - it would be worthwhile knowing this.

Alright, so back to you for a case study.

Ms. Sims:
Great. So, here's our first case study. Julie, a 57-year-old woman with right flank pain, headache, and a 4-cm mass in her right breast. She has no relevant family history or past medical history, no existing CVD, diabetes, or hypertension. She gets a core biopsy and it shows invasive ductal carcinoma. Her molecular testing shows ER-positive, PR-negative, and HER2-positive IHC 3 positive. Her PET and CT scans show three lesions in the right lobe of the liver with the greatest lesion diameter 1.5 cm, and the brain MRI shows two brain lesions both less than 1 cm. She underwent stereotactic radiosurgery to treat the brain lesions. She received the recommended THP for 6 cycles, and then HP with endocrine therapy. She achieved partial response at 3 months in metastatic sites and one lesion no longer measurable. She remained stable on follow-up now for 18 months. And at 24 months, her PET reveals progression in the liver,

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growth in one existing lesion, plus one new lesion. And then the brain MRI shows lesions are now stable.

Dr. Force:
Well, let's go through initially, you know, what this patient had, which was we would fondly refer to as the CLEOPATRA regimen. So, Sandy Swain and others put together docetaxel, trastuzumab, and pertuzumab. And they wanted to compare this to really see what the benefit of the pertuzumab would be in metastatic disease, and this was a landmark study. You can see here, compared to placebo, these are all patients with HER2-positive metastatic disease, they received pertuzumab, trastuzumab, and docetaxel versus docetaxel, trastuzumab, and placebo. So, the pertuzumab was the additional thing. So pertuzumab is a – I commonly use this Lego analogy and just bear with me for one second, I'll make it brief. So, imagine with me there's, you know, different, you know, red and orange Legos on the surface of the cell so, and there's a tail that goes onto the inside of the cell. And as the two red Legos come together, that's called homodimerization of the HER2 and HER2 protein coming together. Well, trastuzumab – and once those bind together, those Legos bump into each other, then the tail wags and it tells the cells to divide. If you have – that's called the homodimerization, and that's the HER2 and HER2 communicating. Where if you have the orange Lego and the red Lego bumping together, that's heterodimerization. And that also – that would be representing HER3 and HER2 bumping together and causing those tails to wag on the inside of the cell to allow the cancer cells to grow. So, trastuzumab will bind to the red Lego, so it allows no red-to-red connection. So, it stops the homodimerization. The pertuzumab binds to the HER3, the orange Lego, and it stops the orange Lego from binding to the red Lego. HER3 was identified shortly after HER2 from that previous slide showing the timeframe when things were identified, but HER3 was shown to be a known mechanism of resistance. And so, that's how pertuzumab came onto the market, because let's try to block the mechanism of resistance at the beginning.

And so, this CLEOPATRA study was saying, well, there was lots of safety data showing that this was safe, and safe to give in patients with refractory breast cancer. So, they came up with a study where at the time there was really no – it was just trastuzumab and chemotherapy as the first-line agent. And so, this study was the first to put a triplet combination. And pertuzumab is very well tolerated. And you can see here that pertuzumab added significant benefit, and overall survival is about 17 month or 1.7 in a month, and so a 17-month benefit of overall survival, which at the time was astronomical and it still is, in a lot of ways.

And so, this became the standard treatment to offer patients as a first-line setting and it still is today. And honestly, I don't know if this will really go away because it is pretty well tolerated. Patients get docetaxel, trastuzumab, and pertuzumab for 6 cycles of induction treatment, and then they go on to receive trastuzumab and pertuzumab indefinitely, which is super well tolerated. And I have patients who are on, you know, cycle 131, doing very well with no evidence of disease. So, when thinking about toxicity profile, there's going to be - this a very high bar for this to go away anytime soon. And that's important. I just want to hear that, because this is – there's newer drugs that we're going to get into with these antibody drug conjugates which are completely changing the face of HER2-positive and triple-negative breast cancer in very positive ways.

For those who aren't aware of antibody drug conjugates, just to briefly go over what they are, they have an antigen binding site, they have usually very high affinity and avidity for a specific antigen; in our case, that antigen is HER2. They are internalized and usually they can have a linker that is either stable or it allows for it to be cleaved. So, a cleavable or an uncleavable linker. That's super important for what's called this bystander effect. I'll get to that later. And then the payload is usually a cytotoxic agent that allows for it to get internalized and bind to either parts of the DNA and be able to cause, you know, cell death. They do have reduced toxicity. So, many of these chemotherapy backbones, if you were to give similar doses IV, would quite literally kill somebody. So, these have incredibly potent cytotoxic payloads that would otherwise not be able to be given to patients safely without this antibody drug conjugate.

There's two that we have. There's T-DM1. And then there's T-DXd. T-DXd is a much more potent agent in terms of its – you can see here, T-DM1 is a microtubular inhibitor, that's the DM1. And the deruxtecan is a topoisomerase I inhibitor. The EMILIA study and TH3RESA study were the studies that looked at T-DM1 in the EMILIA-1, which Duke was the lead site on, lead to T-DM1 being the standard second-line agent. That's all changed now. And T-DXd has been compared to that and we'll get to that data in a second. We're looking at this in the DESTINY – so whenever you hear like the DESTINY studies, that's always going to be with trastuzumab deruxtecan, and there's going to be a whole slew of these. We're up to like DESTINY-13 at this point, with ongoing studies, and I imagine this will continue to move forward.

So, let's start with one of the first ones that came out, the DESTINY-03, that's relevant for us. This was looking at so if T-DM1 was the standard second-line agent after THP, based on the CLEOPATRA data that I just showed, one of the first studies came out looking at – was the DESTINY-01, but that just showed that it was – T-DXd had really great efficacy in refractory HER2-positive breast cancer, like median lines of therapy was something like five lines or more of therapy. And patients were having, you know, great responses for long periods of time. So, it's natural now with the drug development strategy to move forward into an earlier metastatic disease setting. And so, they wanted to compare this head-to-head versus T-DM1, which was the standard of care, all given HER2-positive metastatic breast cancer, previous trastuzumab and a taxane in the metastatic setting or neoadjuvant with recurrence, clinically stable, previously treated

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brain mets were permitted, good ECOG status, had a median of two prior lines of therapy. And the primary endpoints being progression-free survival and secondary being overall survival and other ones that you can see here.

And the data was fundamentally practice changing, where you can see that T-DXd, based on primary progression-free survival, which was the primary endpoint, was far superior compared to T-DXd. This is again - like so the other one was 17 months. I mean, this is like a whopping 22 months of progression-free survival, and also improved overall survival, where actually the median overall survival in this study hadn't been reached, whereas T-DM1, it already had. So, clearly statistically significant. But more importantly, clinically, really clinically meaningful for our patients. And so, this became now, trastuzumab deruxtecan became now the standard second-line option for patients with HER2-positive metastatic breast cancer after THP.

So, you can see here, there were some patients who, they had stable brain mets, right, so they were allowed. So, they looked back and said, like, 'Oh, so of those patients who had brain metastases, how many had responses?' And because they were stable going into it, so they weren't – they were still present, just not growing. And so, T-DXd, we can see that there was great intracranial response, with 23 patients having a complete response or partial response. And then there was a smattering of patients who had some stable disease, and one with progression. Whereas T-DM1 still can penetrate the intracranial space, but clearly not as much CRs or about the same amount of PRs but more with stable disease and more with progression. So, something about the maybe the topoisomerase backbone, like the chemotherapy drug, or how this drug is delivered.

One key component between the two of them is that T-DXd has a cleavable linker, which allows for it to be cleaved. And what that means is as it's gaining sort of, endocytosed into the cell, it's simultaneously having those balls of chemotherapy cleaved that they can direct that payload into the cancer cell or to the adjacent cancer cell. So, if there's like a HER2 low or HER2-negative cancer cell that that antibody isn't binding to, it's delivering the payload of chemotherapy just next to it. T-DM1 does not have a cleavable linker, so the bystander effect is a lot less with that situation. And so, you could – that's part of the hypothesis of why maybe this was a lesser drug, because taxanes which emtansine is one, it's a microtubule inhibitor, it's a taxane backbone, and a really potent one it that, it showed it just wasn't as effective. And so, it should be effective, but part of the reason that we think it wasn't, it's just because it wasn't cleaved off and there was less bystander effect.

So, the TUXEDO study was looking at patients with – again, it's a small phase 2 trial of trastuzumab deruxtecan. This is in patients with HER2-positive metastatic breast cancer with active brain metastases. And that's important because there's the HER2CLIMB regimen that looked at tucatinib, and we'll get to that later. But we – and we don't have a bonafide study that's been large, focusing on brain mets for trastuzumab deruxtecan yet; it is ongoing, so we will have that data soon. But you can see intracranial response rate, 73%, small numbers. That's huge. That's on par with what we're seeing in the HER2CLIMB regimen, if not better, but again, small numbers so don't know if it's really directly comparable. But this is in patients with progressing disease after local therapy. So, something to consider and actually it's been still my go-to using this data to give trastuzumab deruxtecan in patients with progressing or active brain metastases.

Alright, so back to you for another question it looks like.

Ms. Sims:
Dr. Force, I'll turn it back over to you.

Dr. Force:
There are dose reductions that can be given. Just know that T-DM1 starts at 3.6 mg/kg, both of these are given every 3 weeks. And then you can go down to 3 and 2.4 mg/kg in T-DM1. In T-DXd, it starts on a 5.4. In GI, which this is also approved, it's at a higher dose, I forget the dose, I think it might be 6.2 but don't quote me on that. It's a high - they start out at a higher dose in GI malignancies for trastuzumab deruxtecan. But in HER2-positive breast cancer, it's 5.4, and then we can dose reduce to 4.4 and 3.2.

Things to consider with both when monitoring, especially with T-DXd, you need to get CT scans in HER2-positive breast cancer or HER2 low if this is being given to them, to monitor for interstitial lung disease. And we need to – you need to do those that really 9 weeks from initiating it to look for asymptomatic pulmonary infiltrates for concern of developing interstitial lung disease and pulmonary fibrosis.

So, the optimal sequence of HER2-targeted agents is now becoming controversial. I think, you know, the 03 study demonstrated significant overall survival. While the primary endpoint was progression-free survival, I could have probably highlighted that more, that it was approved because it met its primary endpoint, but primarily it was approved because it made people live longer. This was approved in May 2022 for HER2-positive metastatic breast cancer in patients who received one prior treatment to anti-HER2 therapy in the metastatic setting or in neoadjuvant therapy that then had a disease recurrence within 6 months of completing that therapy. And then based on the DESTINY-03 study, T-DXd was associated with significant improvement of PFS and OS compared to T-DM1, allowing for its approval.

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And the small TUXEDO-1 study reported that T-DXd has intracranial activity against active brain metastases. Whereas in the DESTINY-03, those patients had stable disease. And so, there is a question of, you know, whether or not a drug can decrease growth in something that's growing versus it's already stable. We know that many times that that stable disease can remain stable for many, many months. So, now the TUXEDO study was an important, yet small study. So, just considering T-DXd for eligible patients after one line of therapy – of anti-HER2 therapy.

So, here's the proposed strategy for managing patients with HER2-positive breast cancer. And first I just want to highlight it's great to see options and I know patients love it, that we have options for them. And I commonly tell them that. I mean, we don't want patients to give up hope, we want to be realistic. At least I am always trying to be realistic and have goals-of-care conversations with them from the beginning. But at the onset, these options can work, and as you saw, you know, it's, you know, 22 months of overall survival advantage, so above and beyond, you know, T-DM1. And then there's other options now that go beyond T-DXd. So, this this field is shifting really rapidly.

But you can see here, still, the CLEOPATRA study is still queen or king, however you want to look at it. That's a taxane, trastuzumab, and pertuzumab. And the reason why it's a taxane – sorry, just real quick – is that it is common that we will give weekly paclitaxel instead of docetaxel every 3 weeks with trastuzumab and pertuzumab. It's a little bit more tolerable, less neuropathy, less myelosuppression, and then but after 6 treatment cycles, the taxane is stopped. And sometimes we'll even do 2 weeks on, 1 week off, especially for more frail patients are ones, so you can't mess around. So, that's why it's a taxane, and paclitaxel, Abraxane, or nabpaclitaxel rather, or docetaxel, any of those three are reasonable options to combine and we have lots of data for the combination of those. So just want to highlight that so it's not always docetaxel, Herceptin, and Perjeta, it's other chemotherapy options, as long as they're a taxane. And then trastuzumab and pertuzumab in the maintenance setting, and again, have lots of patients who are on that for years without evidence of disease. So, high bar to hit for these other drugs that have toxicity to overtake that.

Second-line agent now it'd be T-DXd. How T-DM1 now falls into this, it's technically maybe like a third-line option. Many might skip over it though, and go straight to tucatinib, trastuzumab, and capecitabine, especially with 50% of patients developing brain metastases. And this is where, you know, that third-line option, you know, in patients who are complaining of like a little bit of excessive nausea, they have excessive fatigue, they have maybe like a little bit of a headache, you know, you should have a really low threshold to do imaging of the intracranial space and have a high degree of suspicion for brain metastases. So, I just want to just point that out.

So, but yeah, so here's some other agents. We're going to go into some of the data, not all of these different ones, you can read here, but even I believe some of you had, you know, chosen neratinib and capecitabine, that still is a bonafide option. And we've got good data for that still. So, there are options that we can use in this disease. And it's great to see that we have these options and can really personalize care based on side effect profile, patient's needs, and what their wishes are. So that's - it's great that we're at that point, many diseases aren't and so we're lucky for that.

So going on to tucatinib, this tyrosine kinase inhibitor. This has been, you know, I mentioned the HER2CLIMB study, you know, this is a well-tolerated tyrosine kinase inhibitor. It's active in combinations with capecitabine, trastuzumab, T-DM1. The key thing about this drug is that is has – so EGFR is considered HER1, and then there's HER2, HER3, and HER4. EGFR, it's not been clear, like how does that play a role in breast cancers with lots of studies looking at EGFR antagonism. To date, they've been negative. And so, it's really - that's not a standard practice for us and obviously, in colorectal cancer that's a very standard and in many other components but not so much for breast cancer. So, this has been thought, you know, if you have these Pan-HER inhibitors like neratinib, for instance, which binds and extremely inhibits EGFR, leading to lots of GI toxicity, is that really beneficial or not? And it's been shown that it probably isn't. So, this has a lower affinity for EGFR, less EGFR-associated toxicity than other HER2-targeted tyrosine kinase inhibitors. And most importantly, has excellent, excellent CNS penetration. So much so that Seattle Genetics, which I think they just got bought out by Pfizer, but they came together for the HER2CLIMB study, which had an emphasis on patients with – had brain metastases, like well over 40 – well over 50% of the population had active or untreated, and some with stable brain metastases. So, it really, like brain metastasis-focused study. Carey Anders here at Duke was one of the primary principal investigators on that study, and we enrolled heavily on it. Primary endpoint was progression-free survival and overall survival in the brain mets only, because they had such a large population, became a key secondary endpoint.

And as you can see here, progression-free survival being the primary endpoint, you can see that tucatinib, trastuzumab, and capecitabine was superior. You see that the addition of tucatinib improved progression-free survival across all subgroups; didn't matter on age, race, hormone receptor status, so I alluded to that earlier, we don't necessarily give endocrine therapy with this strategy, and the presence of brain metastases, so improved overall progression-free survival. Overall survival also was improved. You can see here that there was a 27% reduction in the risk of death. So, addition of tucatinib improved overall survival across all the subgroups, again, including the hormone receptor status and brain metastases.

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These were – the HER2CLIMB study and the DESTINY studies were kind of ongoing when these were, you know, being reported and 2020. So, at the time, it was kind of unclear, well, should we give the HER2CLIMB regimen or trastuzumab deruxtecan for brain metastases? And then the TUXEDO study came out shortly after all this, and we realized that, you know, there's – while this is a great option, the HER2CLIMB regimen, it's a lot of pills, they're taking a lot of tucatinib, they're taking a lot of capecitabine which is BID, and then they're coming in with Herceptin. And co-pays could be high, so you have to look for an insurance, what's going to be out-of-pocket costs, we certainly don't want financial toxicity to impact our patients. And so, that's just things that you need to think about. But when you look at intracranial activity, you know, 48.9% are having, you know, overall survival. So median overall survival with tucatinib was 9, and I'll just round up and say 10 months longer than with placebo. So, you know, active brain metastases. Now it's not really fair to look at a cross-trial comparison of like 13 patients, which is what they did in the TUXEDO study, you know, response rates were 73%. That's not the same thing as overall survival. So, we don't know truly if there's going to be the same degree of overall survival with trastuzumab deruxtecan compared to the HER2CLIMB regimen, actively being studied. But similar response rates not shown here, response rates are about 68% for the tucatinib regimen, and it was like 73% in trastuzumab deruxtecan, so similar response rates, I'd say across the board. You can see here basically 30 months of follow-up time. You can see the numbers here all still favoring benefit of tucatinib.

There's other TKIs, as I mentioned, neratinib and lapatinib. Lapatinib, it's a reversible dual HER2 and EGFR inhibitor. It's very, very specific. You know, this - there was phase 3 trial comparing this, lapatinib and capecitabine, versus capecitabine alone, and there was, you know, benefit. So, still an option. And neratinib, it's an irreversible Pan-HER inhibitor, where you get CNS penetration. The NALA study is really what led to its approval, and still can be used. And so, in patients who have progression after these drugs, trastuzumab deruxtecan, HER2CLIMB, these are still bonafide options to consider in your patients, assuming they can tolerate it.

Here's the NALA study. Not as robust as you can tell from the HER2CLIMB or trastuzumab deruxtecan, but nonetheless it is – there is a benefit of about 2.2 months in progression-free survival. This is neratinib or lapatinib added to capecitabine in metastatic breast cancer for two lines of prior HER2-directed therapy. PFS and OS, and you can see here that the overall survival was really not met when looking at the co-primary endpoint. Still based on two prior lines of therapy, you know, looking at even just progression-free survival over a couple of months, is still beneficial for patients. And here is just the focus of the CNS benefit. And you can see here, you know, some time to intervention for CNS disease, this is, you know, I think, an important clinically meaningful endpoint where patients might have like stable disease, and they're starting on lapatinib or neratinib. And you can see here that there's a little bit longer time to intervention with the use of neratinib and capecitabine. And there is a – CNS progression-free survival was improved with neratinib and capecitabine. But these were really small numbers and not statistically significant. So, still both options for patients though.

Here's some dosages, just briefly to go through this. This will be in your handout. But know that tucatinib 300 mg twice daily, neratinib – neratinib is important that you start out at sort of a dose – you start at the lowest dose and you'll increase it over the month, or a couple of weeks. And so, it starts out – you start out with the 40-mg tablets and then you can work your way up to the 240-mg once-daily, giving it on a 21-day cycle. So, do want to start at the low dose and go up, and then provide an intensified Imodium regimen. And that can really decrease the rates of diarrhea significantly with that approach. So, do remember that strategy if you're going to ever use neratinib. And it's given with capecitabine as in the NALA study. And then this is the neratinib dose escalation schedule, as I just mentioned, you know, starting with using the 40-mg tablets. So, they take 3, and then 4, and then they'll go up to 240 mg over 3 weeks, and then giving the Imodium regimen over that time, that will really help with minimizing diarrhea. And then lapatinib 1,250 mg once daily, and then you can go down to 1,000 and then 750.

So, the optimal use of HER2-targeted tyrosine kinase inhibitors for patients with HER2-positive metastatic breast cancer and brain metastases. So, the HER2 tyrosine kinases have known CNS penetration. Data from clinical trial shows systemic CNS benefit. Standard of care for patients with single or limited brain metastases continues to be radiotherapy, surgery and radiotherapy if possible, of CNS lesions. We have a brain and spine metastasis center completely dedicated to this here at Duke, where we're very aggressive with SRS. So, for the record, patients with, you know, upwards of 15-20 brain metastases, most centers will offer whole-brain radiation; here, we may actually consider stereotactic radiotherapy to salvage and use whole-brain radiation later. So, I think that's a really key point, to push your radiation oncologists to think about SRS more often, even with large degrees of tumor burden, because we have seen, in our hands, that we're able to salvage and keep those patients alive with good quality of life because there's less cognitive decline when you don't have to provide whole-brain radiation.

In light of time, I'm going to skip over some of these other things, but just to, you know, emphasize that for patients with progressive brain metastases, consider treatment with a HER2 tyrosine kinase inhibitor.

Alright, so I'm going to breeze through this because, margetuximab, it's an interesting drug we've been focused on, you know, as I mentioned, with those Legos binding into each other and stopping, you know, those from binding together. One thing that is a mechanism of action of HER2-targeted agents, specifically the monoclonal antibodies as there's upregulation of the immune system, not

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like immunotherapy, but it's an innate immune component and that allows for antibody drug, a cellular cytotoxicity, that's what ADCC stands for, it allows for basically just the innate immune system like an inflammatory response at the tumor site, and potentially natural killer cells to come in and target the HER2 protein in the cancer cell, as you can see by this cartoon figure here on the right. And so, they realized that CD16, which is an area that natural killer cells bind to, could we create an antibody that allows for helping the immune system to see that HER2 cancer cell is being present? And so margetuximab was created with the thought that there might be specific alleles that patients have with this Fc gamma R3A component and can it – can we increase affinity for this target, allowing for natural killer cells to get to that tumor cell more readily as the essentially the trastuzumab, or in this case margetuximab, is able to bind and help to decrease cancer growth.

So, the SOPHIA study, patients who had, you know, lots of therapy and this situation is greater than two lines. And they did a lot for stable brain mets. And you can see here there was 5.7 versus 4.4 months of benefit, 27% reduction risk of progression, probably clinically meaningful, especially given that many of these had several different treatments. So, it led to the SOPHIA margetuximab being approved. They looked at this allele, where if they were heterozygotes, or they are homozygotes, if there was differences and you can see those in numerically and statistically significant in margetuximab group if they had this allele present, it's not something that you would look for because all patients benefited. And, but nonetheless, it seems like you could get the allele; it seems like historically, about 80% of people will have this allele. So, you can send it as a send-out test, but it doesn't change management. This is like now a, you know, fourth-line or fifth-line agent. So, you know, patients are going to be anticipating less responses due to tumor heterogeneity. But you can send out this CD16A 158F to look for if this allele is present. This is more important. I want to just emphasize some of this. I'll quickly pass it back to you and then hopefully give enough time to answer, to go through the side effects.

Ms. Sims:
So, here's our case study again, Julie, 3 months after starting T-DXd for her progressive HER2-positive metastatic breast cancer, and she reports new shortness of breath. Her chest CT shows new pulmonary infiltrates. Bronchoscopy shows that inflammation process but not lymphangitic spread. And she's diagnosed with grade 2 interstitial lung disease, or ILD. And I'll turn it back over to Dr. Force.

Dr. Force:
So, for HER2CLIMB regimen, just to emphasize that what you can see here on the far right, there's a significant increase in hepatotoxicity with tucatinib. There is increases in diarrhea and hand-foot syndrome, or that's palmar-plantar erythrodysesthesia. But just to emphasize that you need to monitor for LFTs with tucatinib. And I'm not going to read through this, but just to emphasize that this can cause diarrhea and hepatotoxicity, and you can manage – and monitor and manage and that's located here.

Back to you for the question.

Ms. Sims:
And Dr. Force, I'll turn it back over to you.

Dr. Force:
Yep. And then based on the NALA data, and I've highlighted this, you can see the overwhelming – I mean, look at all-grade diarrhea at 83%. So, it's very important. Same thing was 66% with lapatinib and capecitabine. So, there was thankfully no grade 4 diarrhea, but just to put it in perspective, grade 2 diarrhea is having bowel movements 4 to 6 times a day. Grade 3 is over that. So, making sure that we're minimizing the time that patients – I mean, you can't like leave your house with that degree of diarrhea. That's a quality-of-life issue. That's, you know, big time. So, dose escalation for neratinib is key to minimizing this and we can get this to under 20% with all-grade diarrhea. The preventative strategy is really the dose escalation and giving patients the intensified Imodium regimen can minimize things dramatically. Loperamide, colestipol, and the neratinib dose all can be helpful.

I'll let you guys read through this. For the adverse events with neratinib, I really want to get to this. So, the pneumonitis, this is a major issue with interstitial lung disease, needs to be monitored. You can see here that there's significantly higher rates of interstitial lung disease. We don't know why. But things that really need to be monitored for ILD and pneumonitis with patients receiving trastuzumab deruxtecan. You can see here that there's higher degrees of lung toxicity, and that's frequent amongst oncology drugs. There is lung toxicity across – that's frequent across oncology drugs. ILD is characterized by ineffective gas exchange, and it can cause fibrosis, essentially hardening of the alveoli where they just can't exchange oxygen and they can die. I've had two patients have this happen and it can be very abrupt, quick, and progress quickly. So, you need to take action, need to follow with CT scans, like I said, and they initiate trastuzumab deruxtecan, and then they will follow with CT scans every 9 weeks initially, and then you can go out to really every 3 months after a few cycles. But you do need to monitor and if you do see somebody with just fluffy infiltrates and they're completely asymptomatic, you need to stop T-DXd immediately and put them on steroids. I think the next slide has this.

So, these are the strategies for ILD. If you suspect it, again, could be if they have a cough, like literally they have a new cough, even if they've been exposed to somebody who's sick, you need to suspect ILD. Get a CT with ILD protocol, and promptly investigate interstitial

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lung disease. Involve a pulmonologist immediately. A CT with ILD protocol is a high-resolution CT. But definitely get a pulmonologist involved, if indicated. I would develop a close relationship – we have a great one here at Duke and we'll, you know, commonly bronch these patients to rule on inflammation versus infection, and, you know, help us understand what we can do. Pulmonary function tests may be helpful, they have yet to really demonstrate a real need. The grade 1 toxicity, hold until it's resolved under 0, give them either 0.5 or 1 mg/kg of prednisone and then follow with a CT scan in 28 days. If resolved, you can go to the first dose reduction. That's in patients who have grade 1, that's somebody who is clinically asymptomatic. If they have a cough, that's considered grade 2, and in that situation, you want to permanently discontinue and still promptly initiate systemic therapy with steroids at 1 mg/kg or equivalent for at least 14 days and then a taper over 4 weeks and follow up with another CT ILD protocol to ensure that it's not progressing. So please, please, please follow with another CT scan to show that it's not progressing. If it is, you may need to have them admitted to the hospital for further workup and management with pulmonary involved.

So, here's a resuming T-DXd after withholding for grade 1 ILD. So, this is usually somebody that you just detected fluffy infiltrates on a CT scan and they're clinically asymptomatic. In those patients, the first published data on T-DXd rechallenge came from this pooled analysis is 9 phase 1 studies all from basically the DESTINY studies, of 76 patients with grade 1 ILD, 47 resumed T-DXd as recommended and 3 had a second ILD event. So, many patients for reasons that we don't know, if you have grade 1, you catch it early, treat it so it's grade 0, you can resume. You'd want to give them a dose reduction, but you can resume. And only a small proportion would have a second ILD event. If they have a second ILD event, it's over and you need to permanently discontinue. I just want to really emphasize that because that's a hot topic and hopefully that was helpful.

Last couple of minutes, SOPHIA with margetuximab, starting dose is 15 mg/kg every 3 weeks. I'll let you guys go through this. This is something you'll be using in the fifth line. Fatigue, nausea, diarrhea are more prevalent in this. I think many of you know how to manage those, so I won't go through that. And cardiotoxicity, you know, trastuzumab-based therapies always associated with LDF decline and heart failure, so monitoring appropriately in all of the different agents. And for what reasons, the tyrosine kinase inhibitors appear to have less cardiomyopathy compared to the antibodies or antibody drug conjugates. But nonetheless, still need to monitor periodically. And the ADCs in margetuximab have not been studied in patients with LVF of less than 50% at baseline. I still think it's reasonable to offer, just need to monitor. And lapatinib, you need to follow with QTC prolongation.

Here's the cardiac safety from all of these HER2-targeted direct therapies. The SAFE-HEaRt study, and just in light of time, I'll let you guys read this on your own. And same here with the approach to cardiovascular monitoring. I mean, you do need to monitor really with echocardiograms, and then a baseline EKG and then withholding treatment if you see that there's a decline in their EF or if there's QTC prolongation that's happening. And this is all labeled here for you to read. And obviously neutropenia, LV dysfunction we've gone through, there is embryofetal toxicity and hepatotoxicity specifically with like tucatinib for instance. And then the interstitial lung disease, please don't forget about that and how to monitor with respect to trastuzumab deruxtecan.

So, treatment-related toxicities vary depending upon therapy used. Diarrhea, quality of life's a major issue, it can be severe. Up-titrating the dose of neratinib with anti-diarrheal prophylaxis is successful. Monitoring for hematologic toxicities with T-DXd and ILD with T-DXd. Cardiac toxicity can occur across the board, so EKG and treatment interruption if needed. And then the ILD pneumonitis was more frequent with T-DXd compared to anything, and initiation of corticosteroids until grade 1. So, educate patients on unique adverse events associated with HER2-targeted therapies. And managing expectations should be at the key for everything. And we are running over by 1 minute, so I'll let you guys kind of read this over at your own time. Okay, so consider T-DXd for eligible patients after one line of therapy, for patients with progressive brain mets, consider HER2 tyrosine kinase inhibitor versus T-DXd, educate patients on unique adverse events.

And then the post-test questions.

Ms. Sims:
I think Dr. Force got that through to us today. And as I said, we really had questions about adverse side effects, but I think they were answered by our speaker today. And Dr. Force, I want to thank you for such a wonderful session this morning on HER2-positive breast cancer. I certainly learned a lot and I know our audience did too. Thank you again.

Announcer Close:
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