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Virtual Case Clinic: ADCs Across the Spectrum of HER2 Expression in Metastatic Breast Cancer

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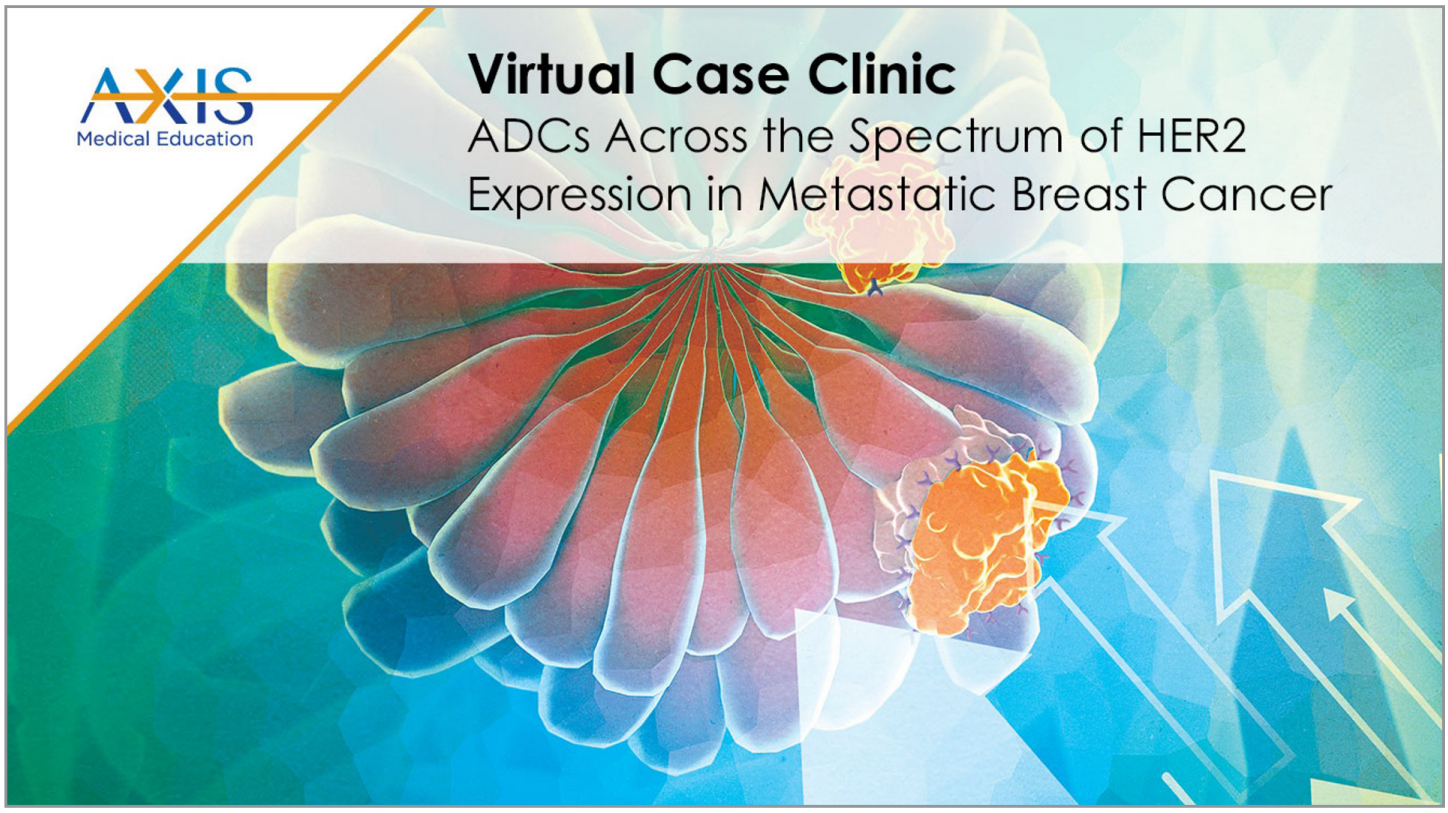
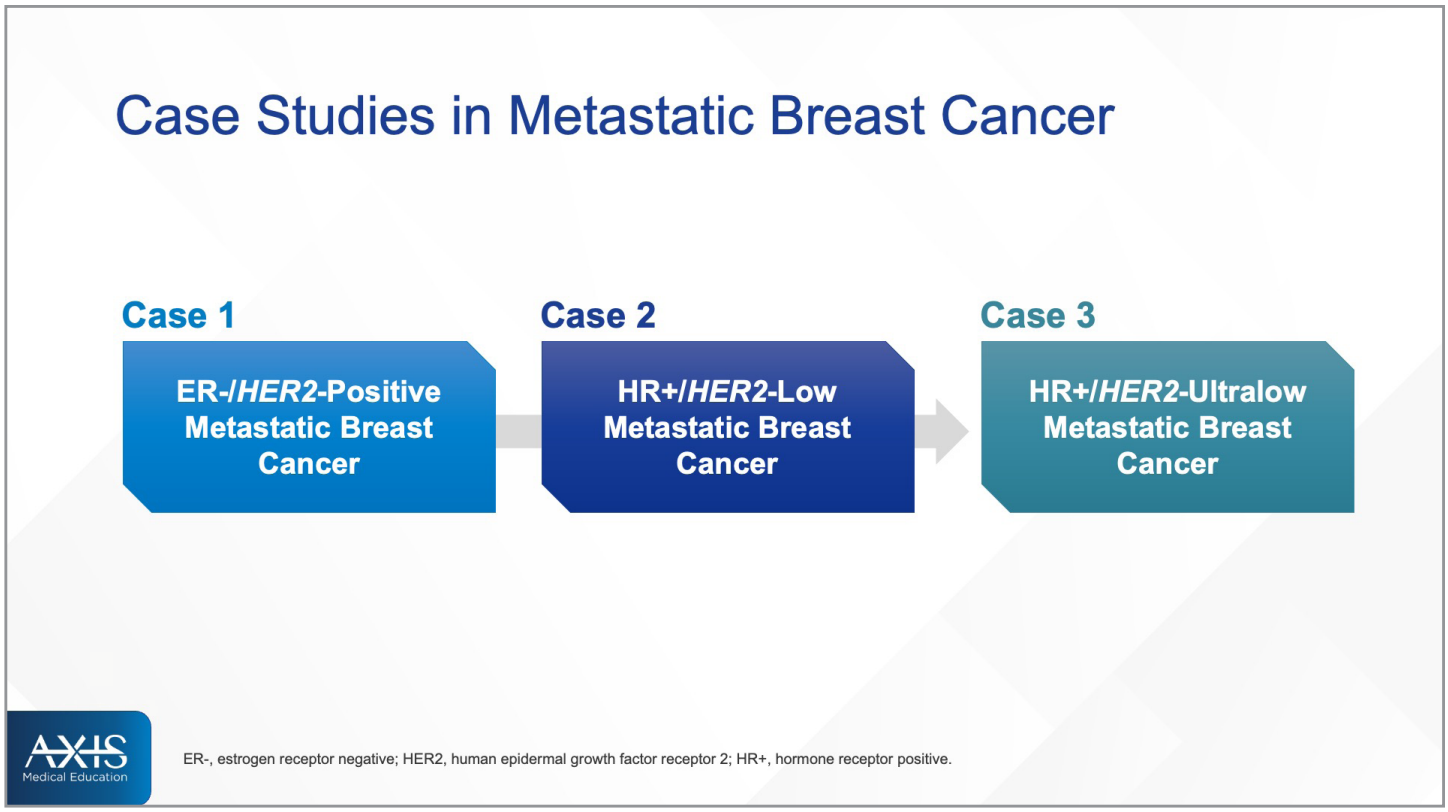
Virtual Case Clinic: ADCs Across the Spectrum of HER2 Expression in Metastatic Breast Cancer

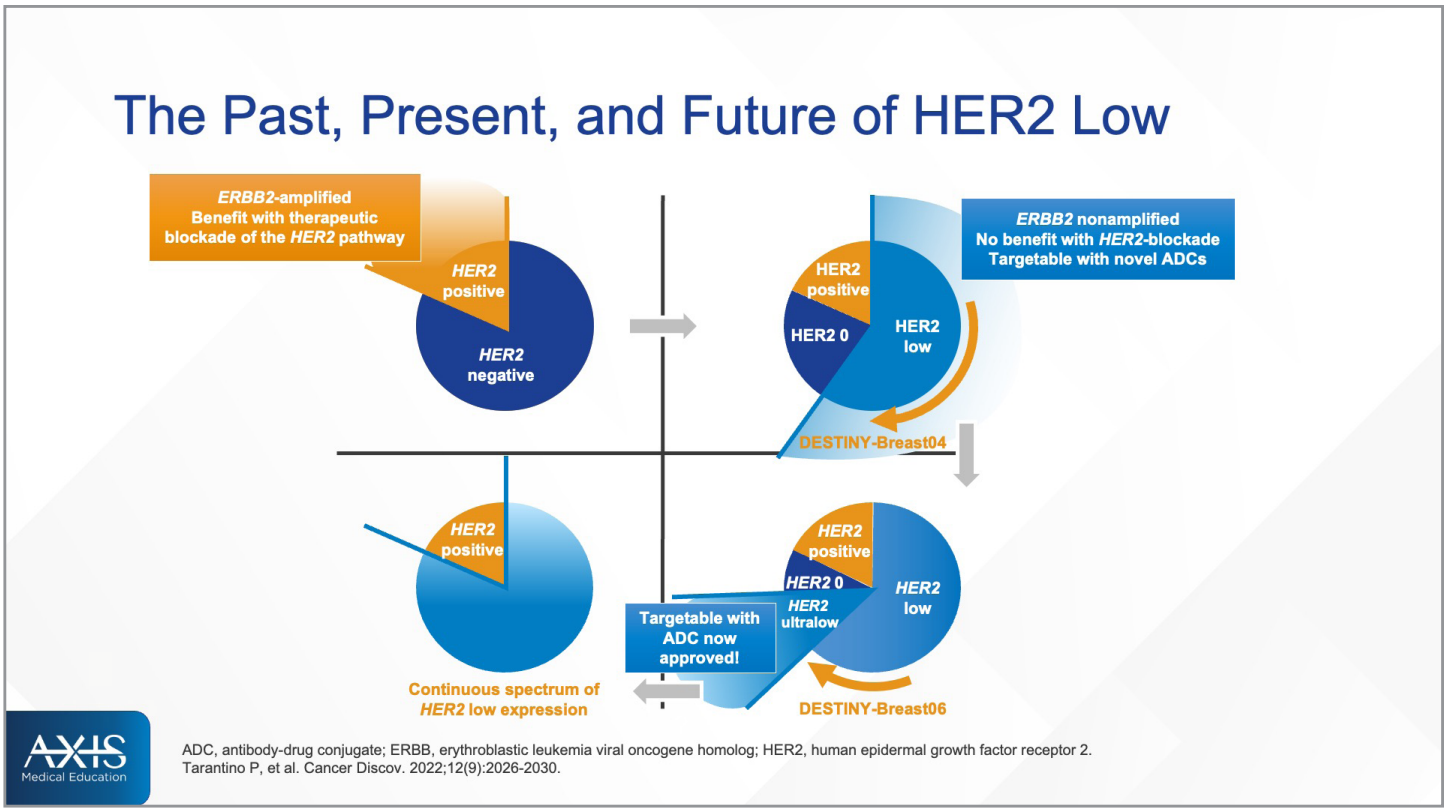
Reshma L. Mahtani, DO



Reshma L. Mahtani, DO:
Hello, and welcome to this educational activity. My name is Dr. Reshma Mahtani, and I'm Chief of Breast Medical Oncology at Miami Cancer Institute, Baptist Health, South Florida.



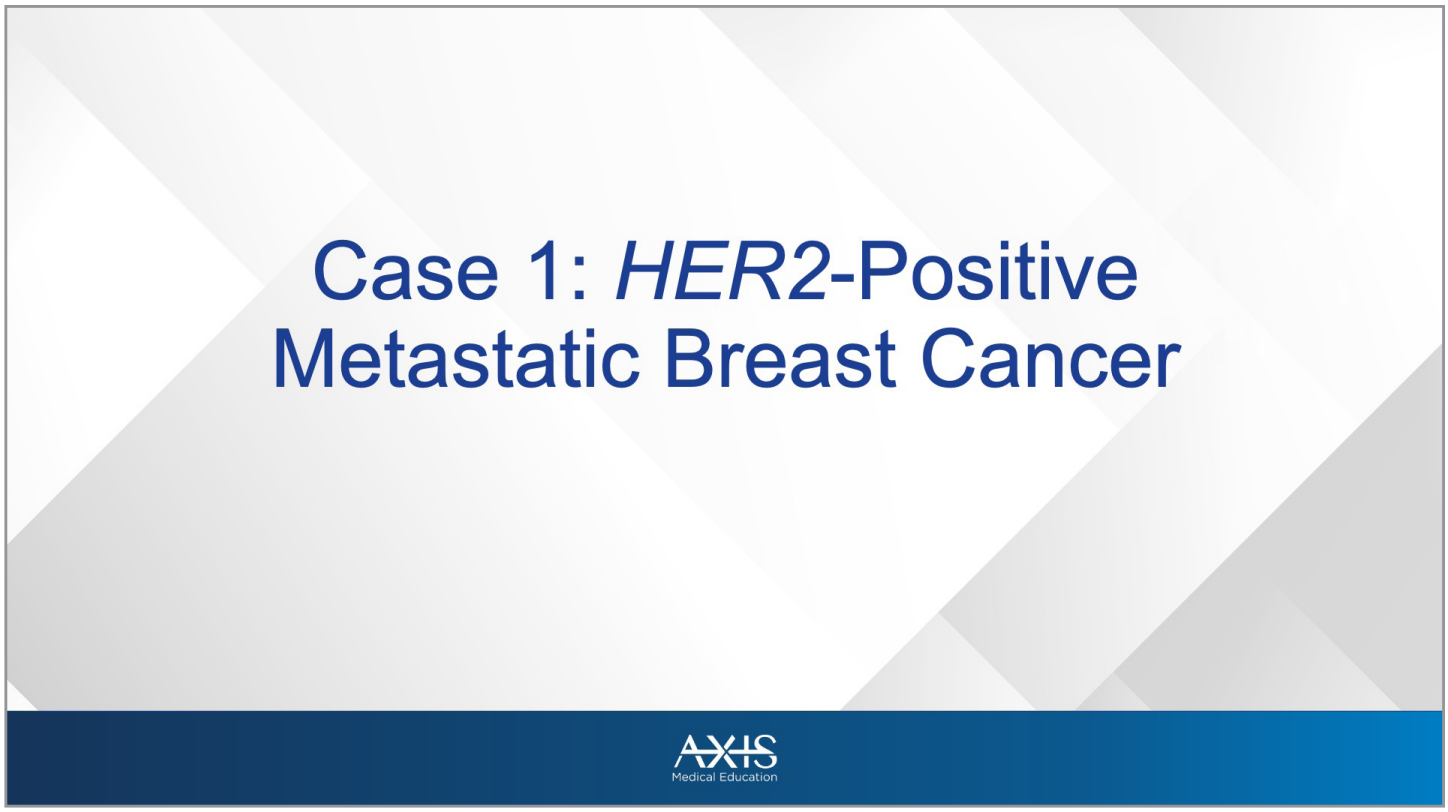
- Today, I will be reviewing three cases to demonstrate the application of antibody-drug conjugates across the spectrum of HER2 expression in metastatic breast cancer. Let's begin.



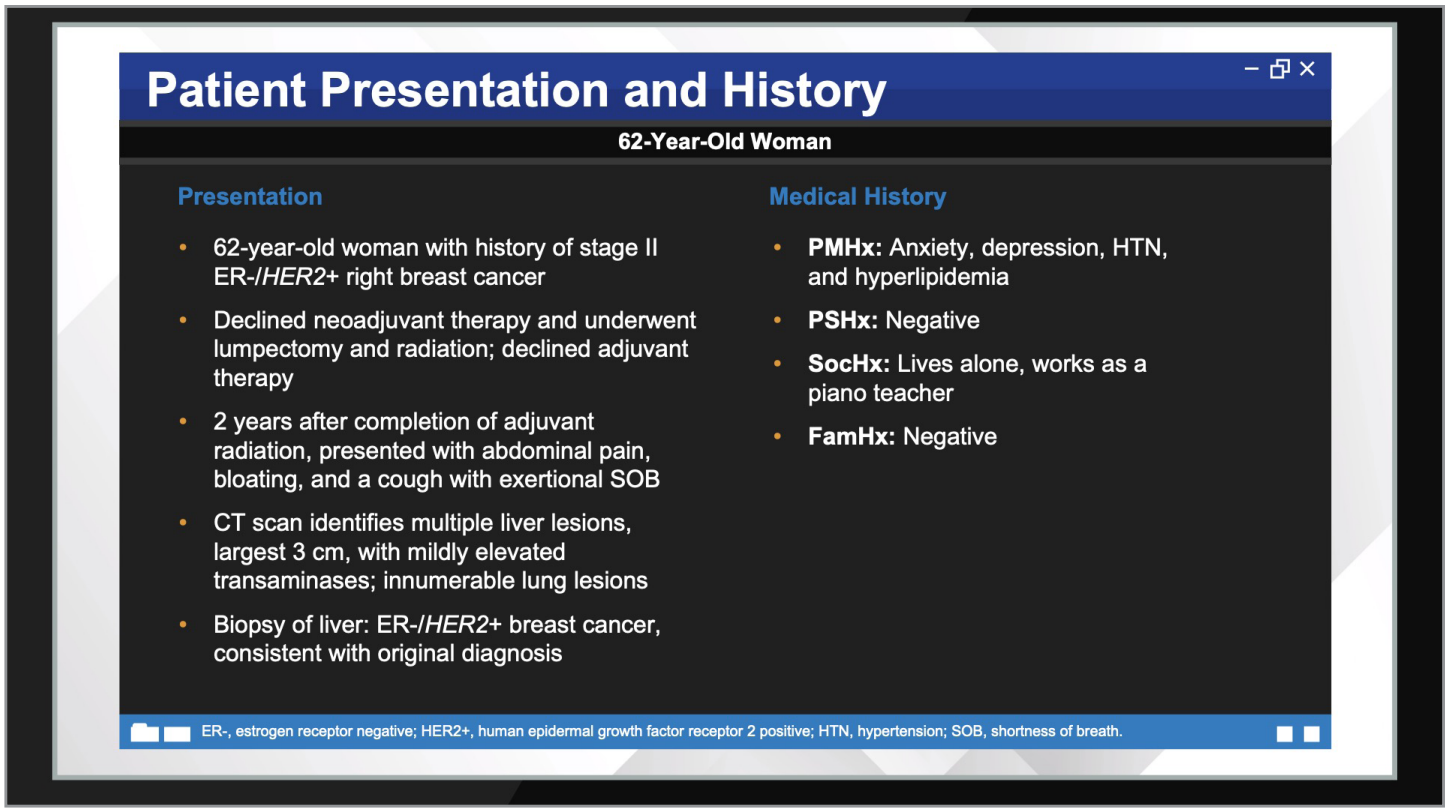
- It's always great to start with a general overview of the past, present, and future of HER2 testing and how we classify these tumors. We used to consider tumors as either HER2-positive or HER2-negative. HER2-positive being those that are HER2 amplified or with HER2 protein overexpression, really trying to identify these tumors that can benefit with therapeutic blockade of the HER2 pathway.

And it was initially the intent of our assays to identify these tumors that were going to benefit from these targeted treatments. And then with more recent data sets, we've started to segment the HER2-negative tumors into HER2-low and even now HER2-ultralow tumors, recognizing that we now have an antibody-drug conjugate that can target these lower levels of HER2 expression.

And so with that, we still have tumors that are clearly HER2-positive, but the rest are at a varying expression, or continuous spectrum of HER2-low expression. And the cases that we'll go through will nicely highlight these nuances.



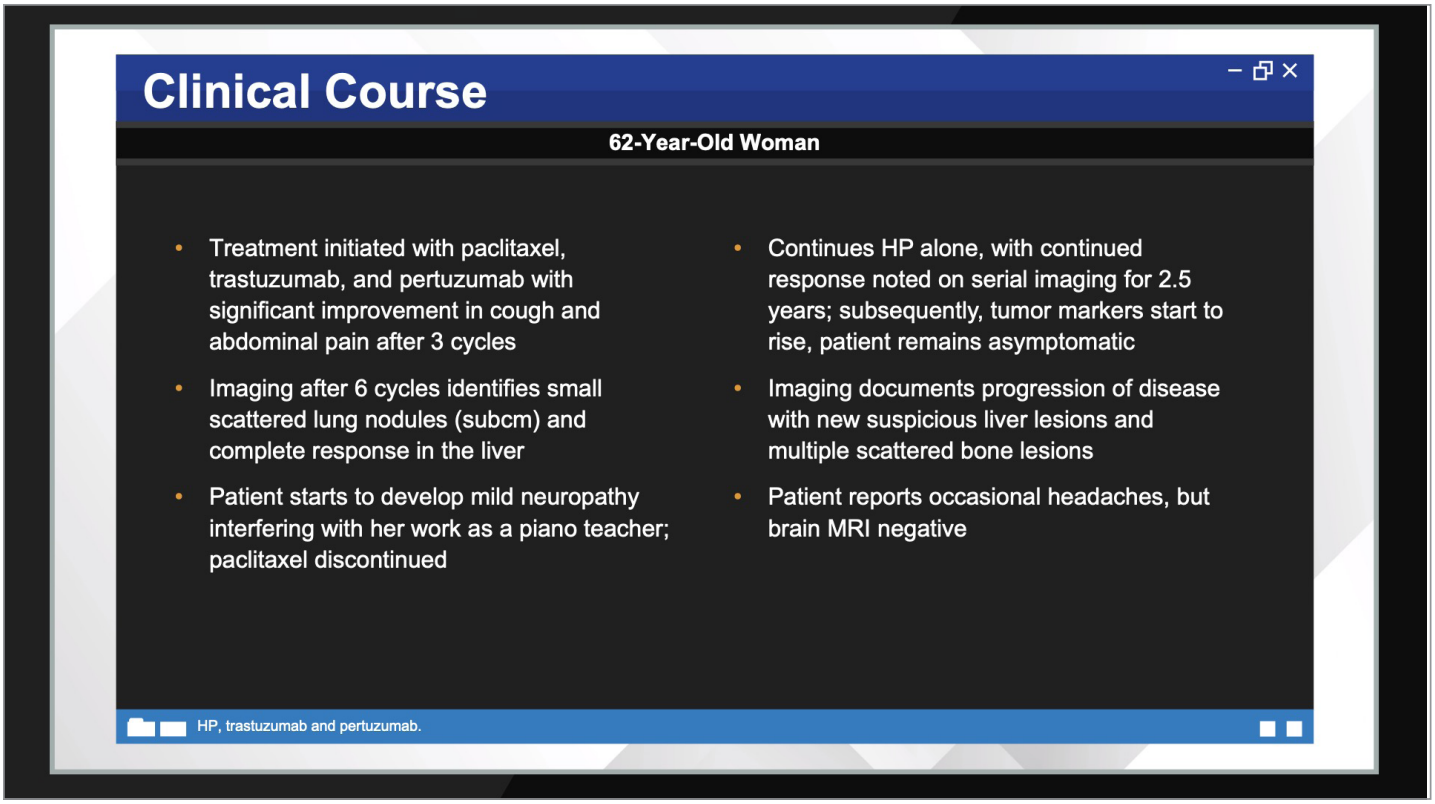
- So let's start with the first case, a HER2-positive metastatic breast cancer case.



This is a 62-year-old woman with a history of stage II ER-negative, HER2-positive right breast cancer. She declined neoadjuvant therapy and underwent upfront surgery with lumpectomy and radiation, and then she declined adjuvant systemic therapy.

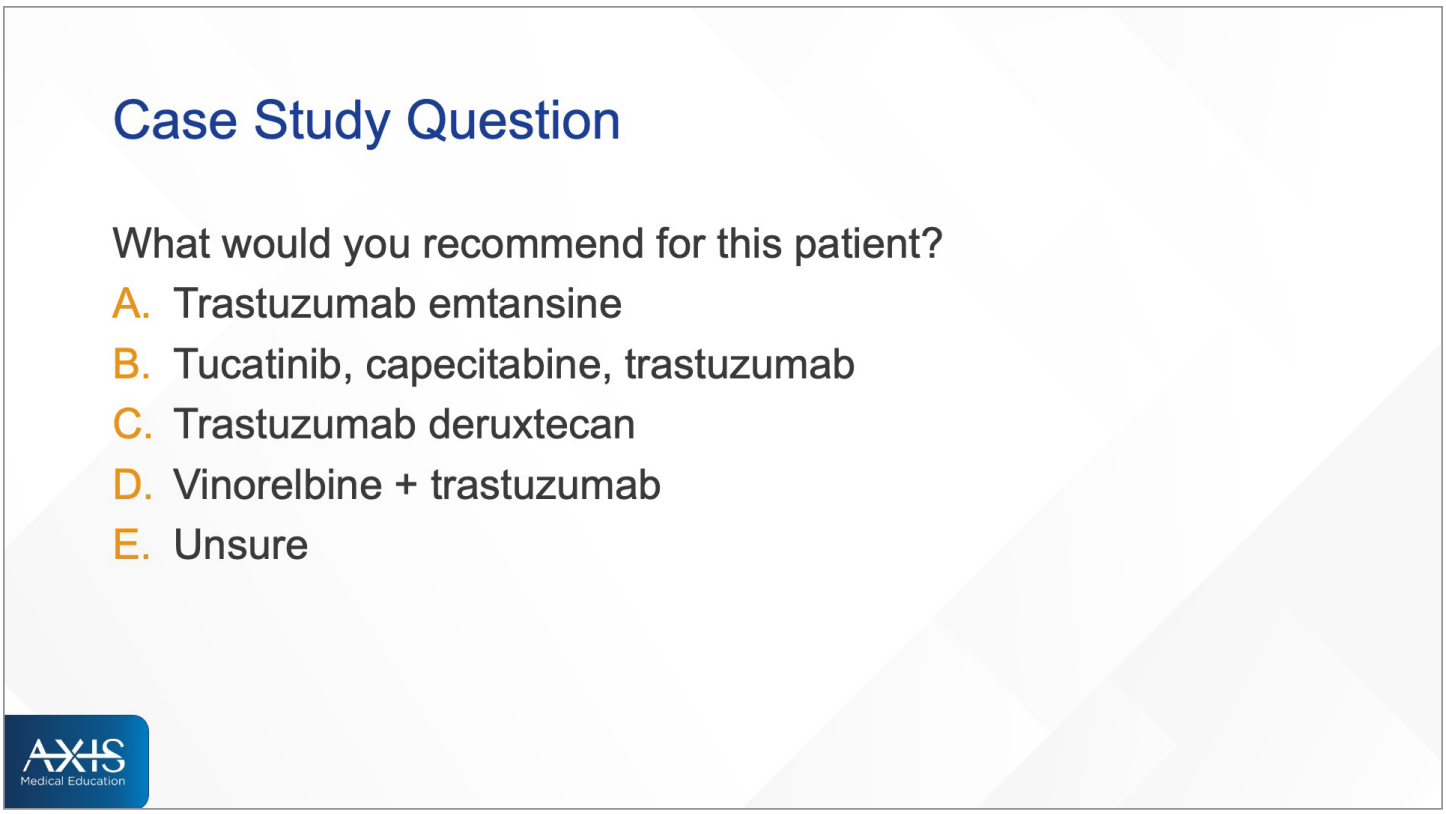
Two years after completion of local treatment, she presents with abdominal pain, bloating, and a cough associated with exertional shortness of breath. On imaging, there are multiple lesions in the liver. The largest is 3 cm. Transaminases are mildly elevated, and there are innumerable lung lesions on imaging. Biopsy of a liver lesion confirms the diagnosis of metastatic breast cancer with those same markers, ER-negative, HER2-positive. These were consistent with the original diagnosis.

And in terms of her past medical history, she has anxiety, hypertension, depression, and hyperlipidemia. These are common comorbidities that we see in our patients in clinic. Negative surgical history. She lives alone. She works as a piano teacher. And her family history is negative.

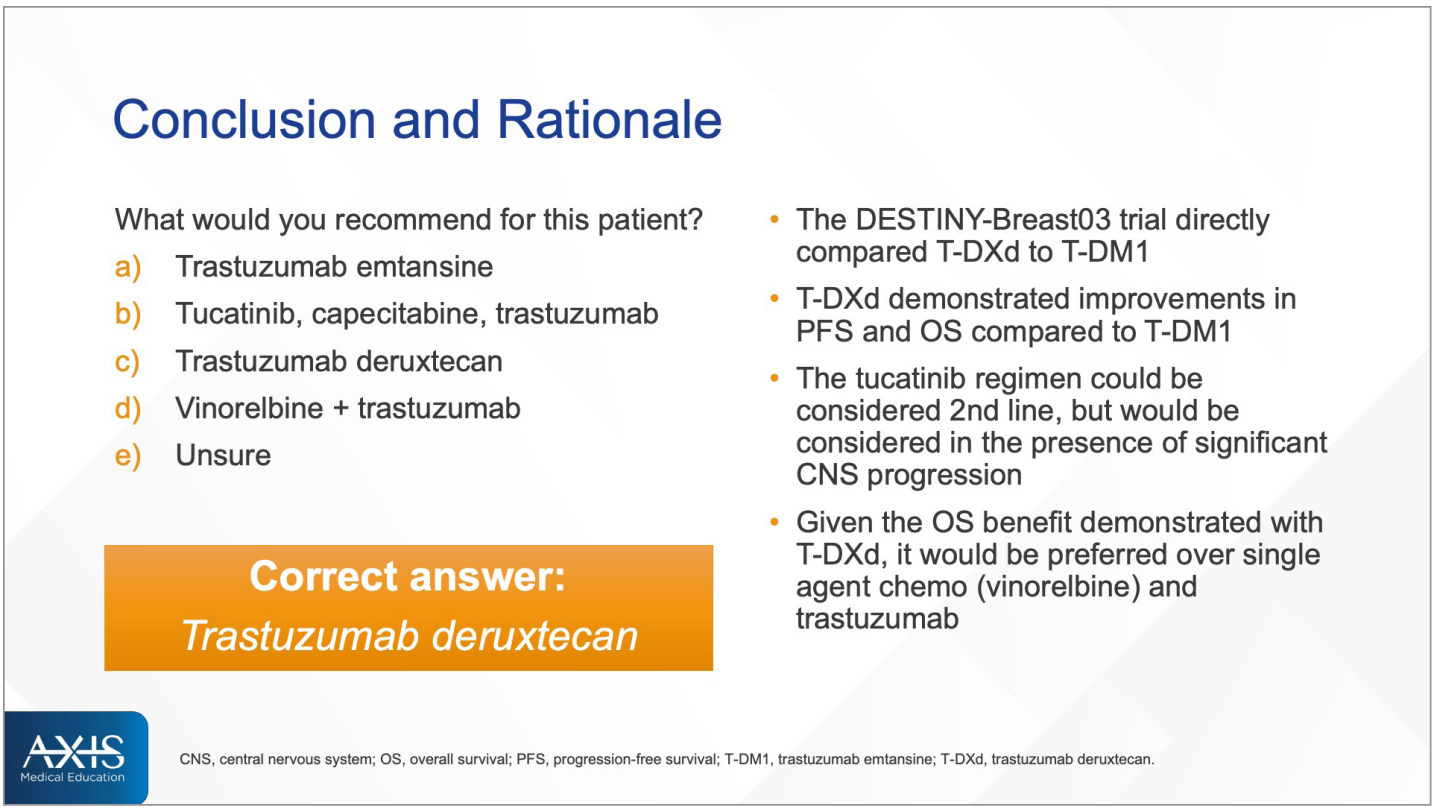


In terms of her clinical course, she initiates treatment with first-line paclitaxel, trastuzumab, and pertuzumab. And at the time that she was treated, this was considered the standard of care as first-line therapy based on the CLEOPATRA trial. Of course, we heard the exciting new data at ASCO this year, the DESTINY-Breast09 trial, where we saw the remarkable median PFS associated with T-DXd and pertuzumab in combination. But in any case, this patient received what had been standard at that time, the CLEOPATRA regimen, and she reported significant improvement in cough and abdominal pain after three cycles of therapy. And after six cycles, imaging identified small, scattered lung nodules that were all subcentimeter. She had a complete response in the liver. And I would say that this is not unusual, as we see these ER-negative, HER2-positive tumors responding remarkably well to our chemotherapy and targeted therapy options, as shown here.

So after that induction chemotherapy time period that she was on the taxane, she then stops after a period of time and continues on dual antibody therapy alone, and has a continued response noted on serial imaging lasting 2.5 years. And then subsequently she develops asymptomatic progression. She has tumor markers that are rising, and imaging documents progression of disease with new suspicious liver lesions and multiple scattered bone lesions. She does report occasional headaches. And on that basis, an MRI is ordered. As we know, patients with HER2-positive breast cancer are not infrequently diagnosed with brain metastases. Fortunately, her brain MRI is negative.



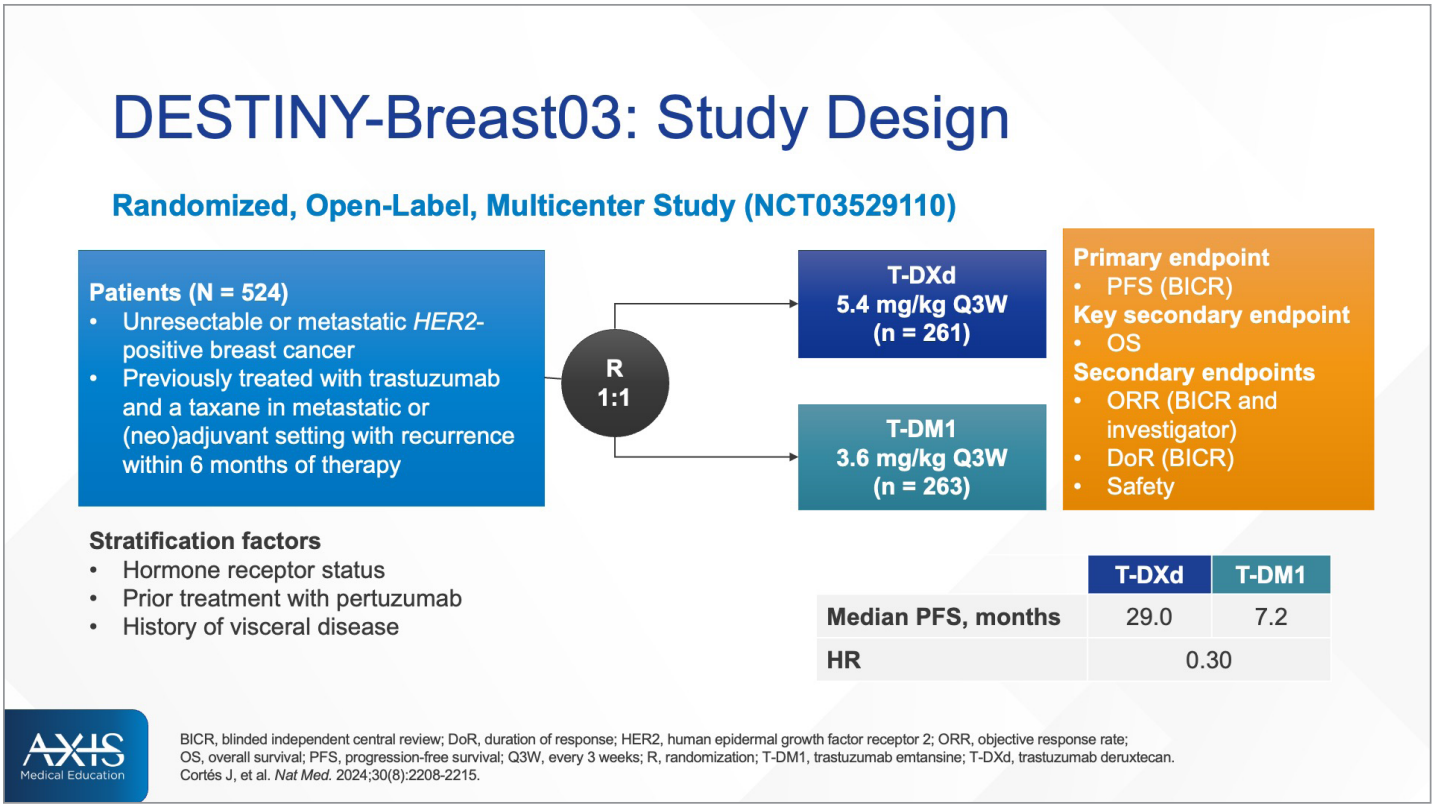
- What would you recommend for this patient?



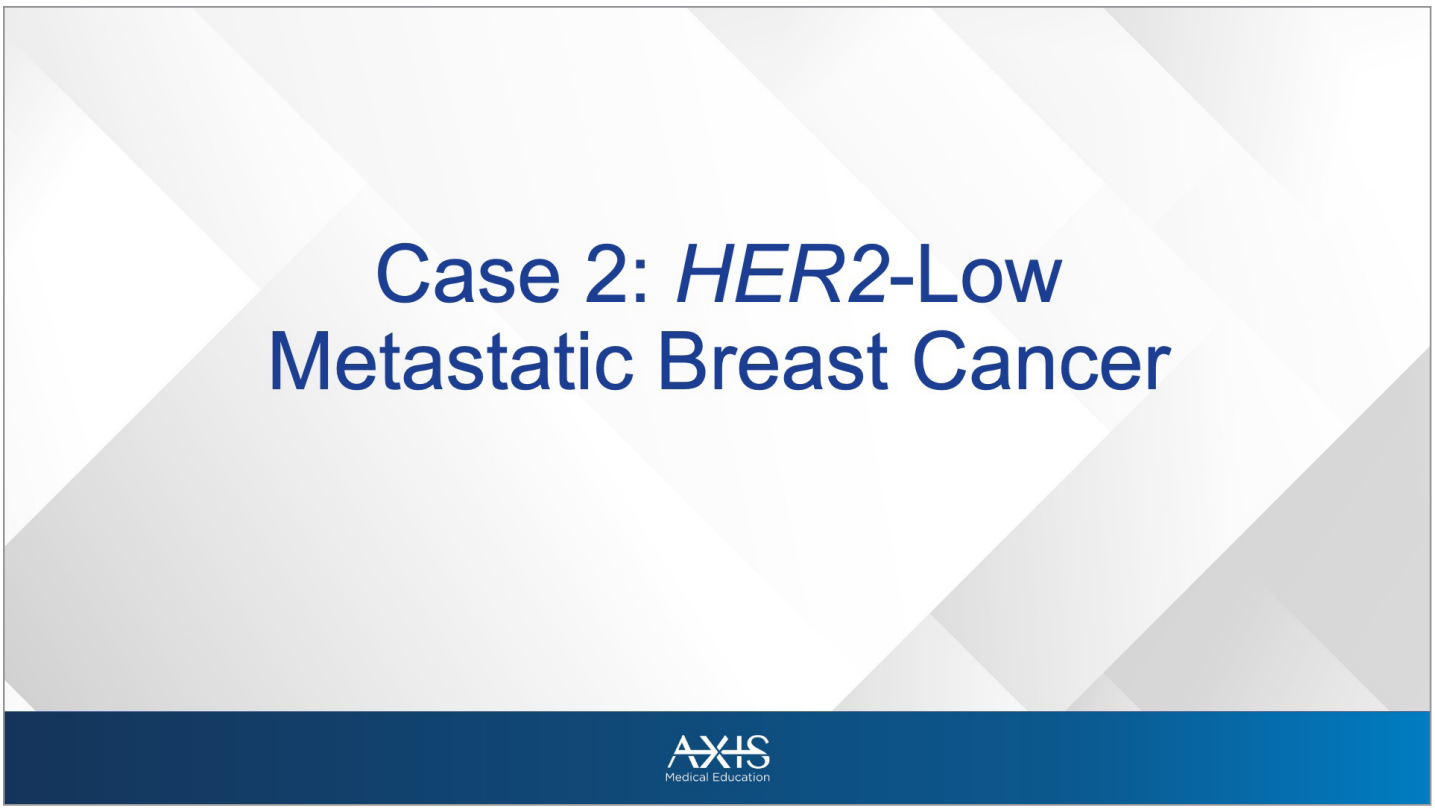
So the correct answer with this case is trastuzumab deruxtecan. And this is on the basis of the DESTINY-Breast03 trial, which directly head-to-head compared the two antibody-drug conjugates, T-DXd and T-DM1. As you may recall, prior to this trial, T-DM1 had been our standard second-line therapy based on the EMILIA trial, where T-DM1 was compared against capecitabine and lapatinib, and shown to be superior in terms of progression-free and overall survival.

And in the DESTINY-Breast03 trial, these two ADCs were compared head-to-head, and T-DXd demonstrated improvements in progression-free and overall survival compared to T-DM1, quickly becoming our go-to second-line regimen.

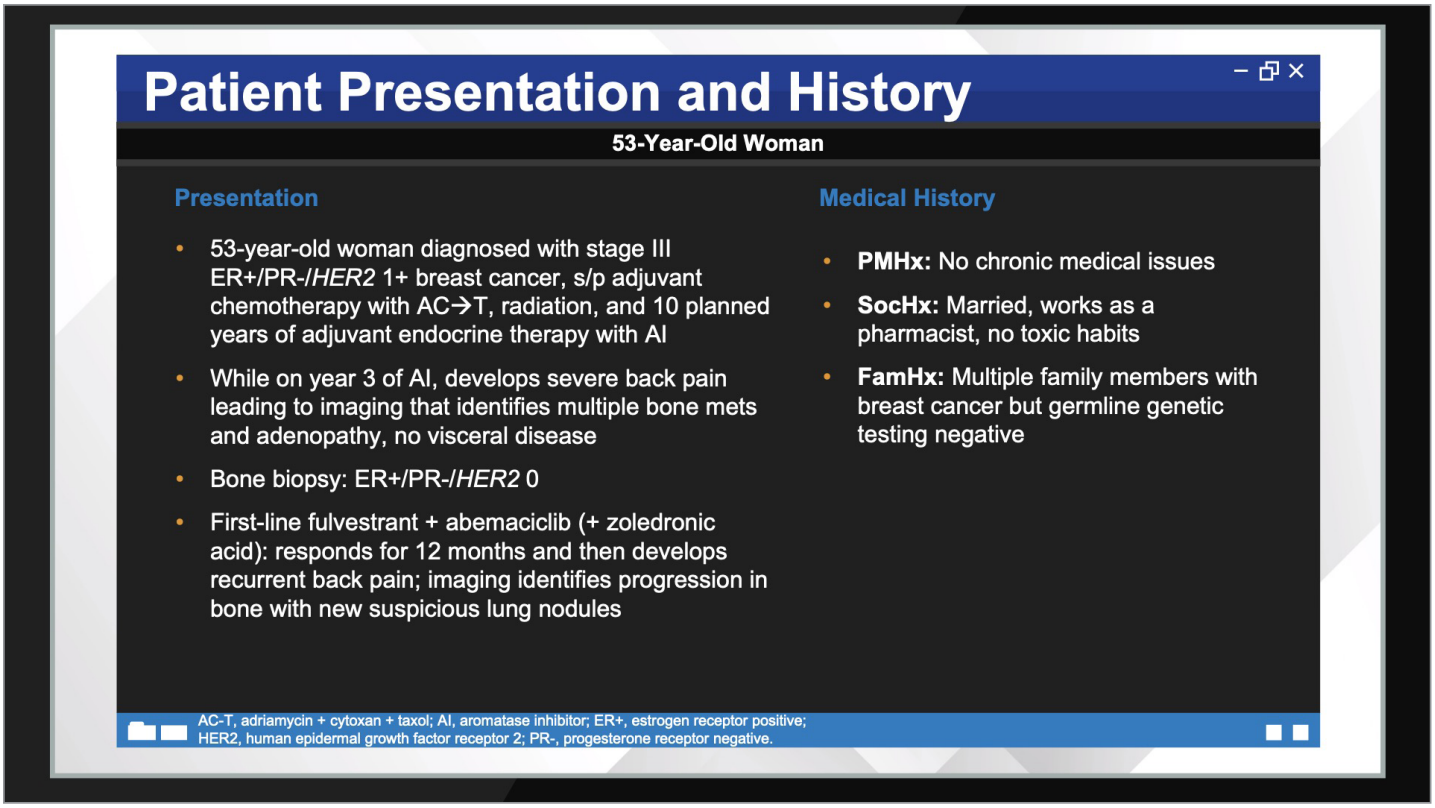
It should be mentioned that the tucatinib regimen, meaning tucatinib, trastuzumab, and capecitabine, per guidelines, can be considered in the second-line therapy, but we would usually consider this triplet regimen in the presence of significant CNS progression, and this patient did not have progression in the brain. Given the overall survival benefit demonstrated with T-DXd, again, it would be preferred over single-agent chemotherapy with vinorelbine and trastuzumab.



So as a reminder, the study design for the DESTINY-Breast03 trial. This was a randomized, open-label, multicenter trial in which patients with HER2-positive metastatic breast cancer who were previously treated with trastuzumab and a taxane in the metastatic or early stage setting and developed recurrence within 6 months, were randomized 1:1 to T-DXd versus T-DM1. And you see that remarkable improvement in median PFS, 29 months versus only 7.2 months with T-DM1. And subsequently a survival benefit was also reported. So our second-line therapy of choice.



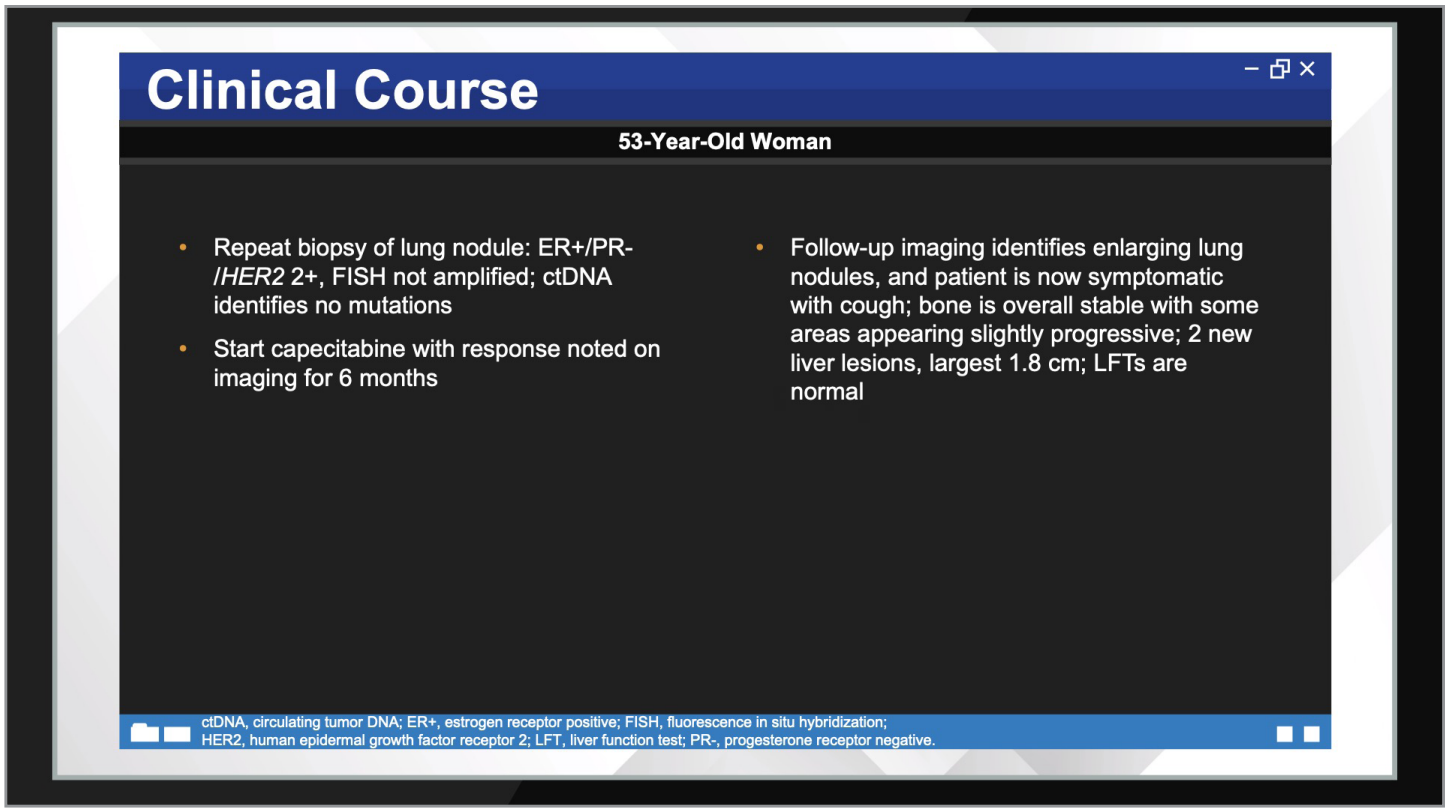
- Now, let's move to a case that is demonstrating the activity of ADCs in HER2-low metastatic breast cancer, as we continue the discussion of HER2 expression across the continuum.



This is a 53-year-old woman who's diagnosed with stage III, ER-positive, PR-negative, HER2 1+ breast cancer, so HER2-low. She undergoes adjuvant chemo with anthracycline and taxane-based treatment, along with radiation, and had planned 10 years of adjuvant endocrine therapy with an aromatase inhibitor.

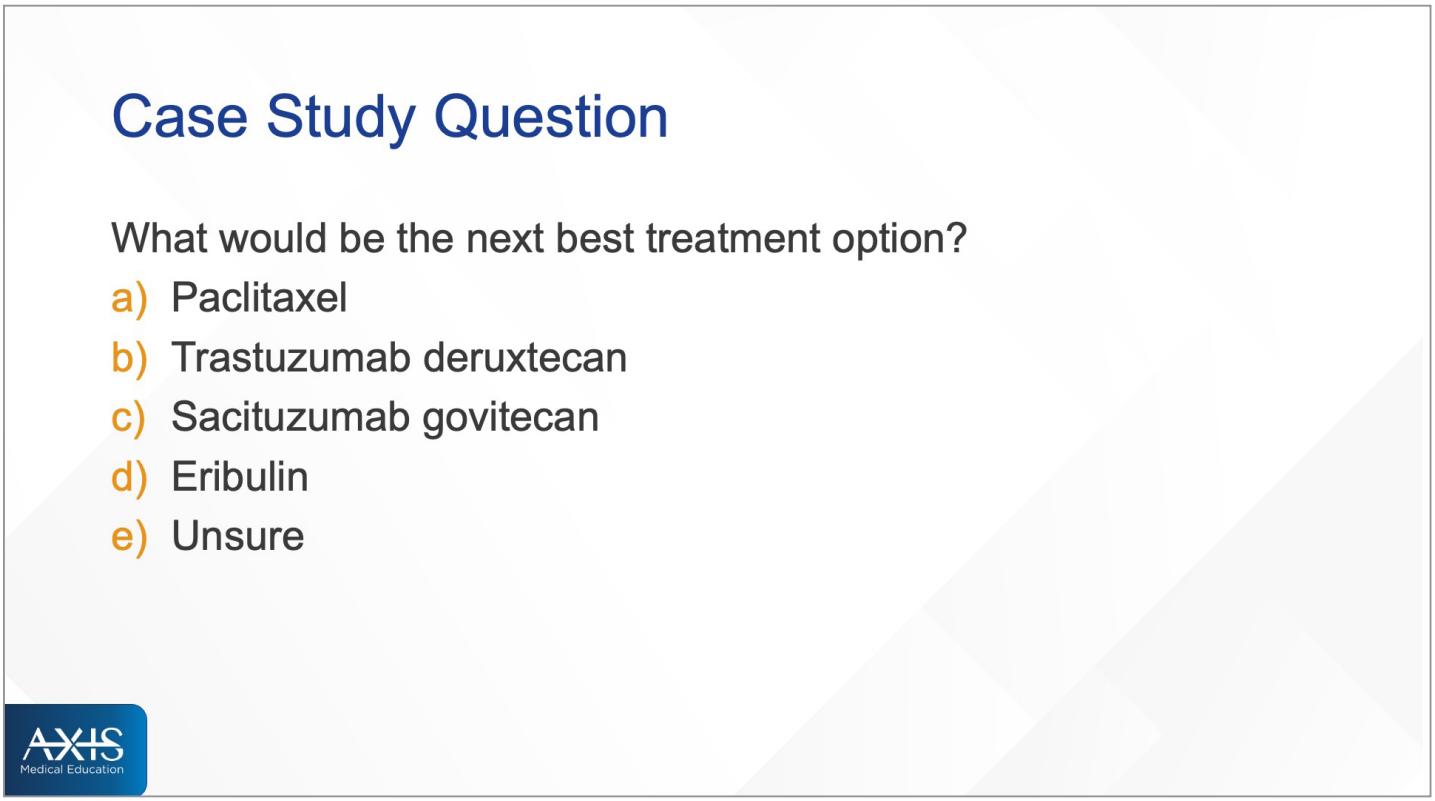
While on year 3 of adjuvant AI therapy, she becomes symptomatic with back pain that then leads to imaging, unfortunately identifying multiple bone metastases and malignant adenopathy, no visceral disease. The bone biopsy is done and shows invasive ductal cancer consistent with breast cancer, ER-positive, PR-negative. HER2 is reported simply as 0. She is started on first-line endocrine therapy and a CDK4/6 inhibitor, along with supportive therapy to reduce the risk of skeletal-related events with zoledronic acid, and responds for 12 months, and then develops recurrent back pain and imaging identifies progression in bone with new suspicious lung nodules.

In terms of her other medical issues, she has no chronic medical conditions. She's married, works as a pharmacist, has no toxic habits, and does undergo germline genetic testing as she has multiple family members with breast cancer. And even if she didn't, per guidelines, any patient with metastatic breast cancer should be undergoing germline genetic testing.

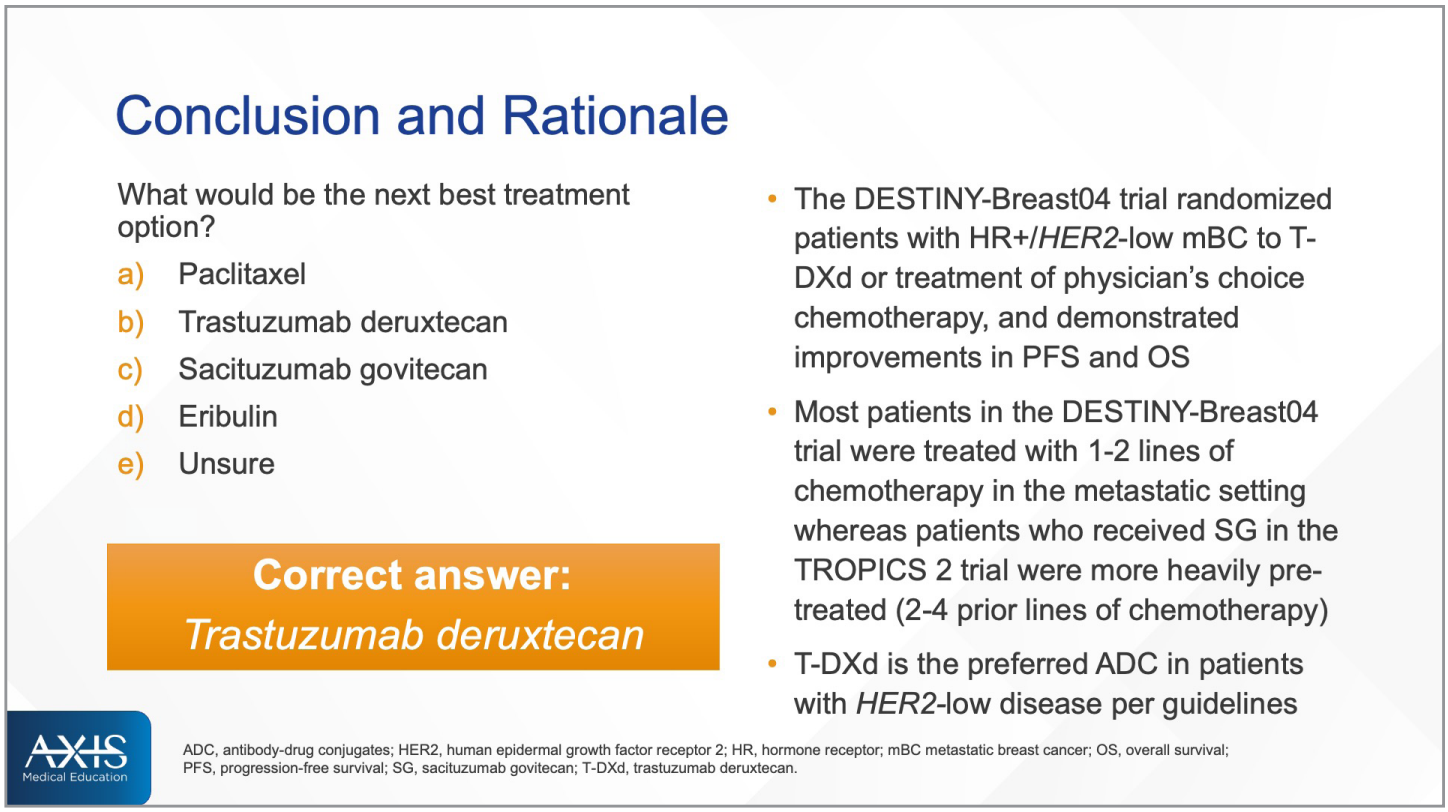


So repeat biopsy of the lung nodule after progression on fulvestrant and abemaciclib for 12 months again shows evidence of carcinoma. This time, the tumor is HER2 2+, FISH not amplified, again, HER2-low. And ctDNA testing is done to identify any further mutations that could be helpful in identifying biomarker-directed therapy, such as a PIK3CA inhibitor or the AKT inhibitor, capivasertib. But no mutations or alterations are identified.

So she then goes on to receive capecitabine with response noted on imaging for 6 months, but then, unfortunately, afterwards, has follow-up imaging that shows further enlarging lung nodules. She's now symptomatic with cough. Bone disease is overall stable, with some areas appearing slightly progressive, and there are two new liver lesions, the largest 1.8 cm. LFTs are again normal.

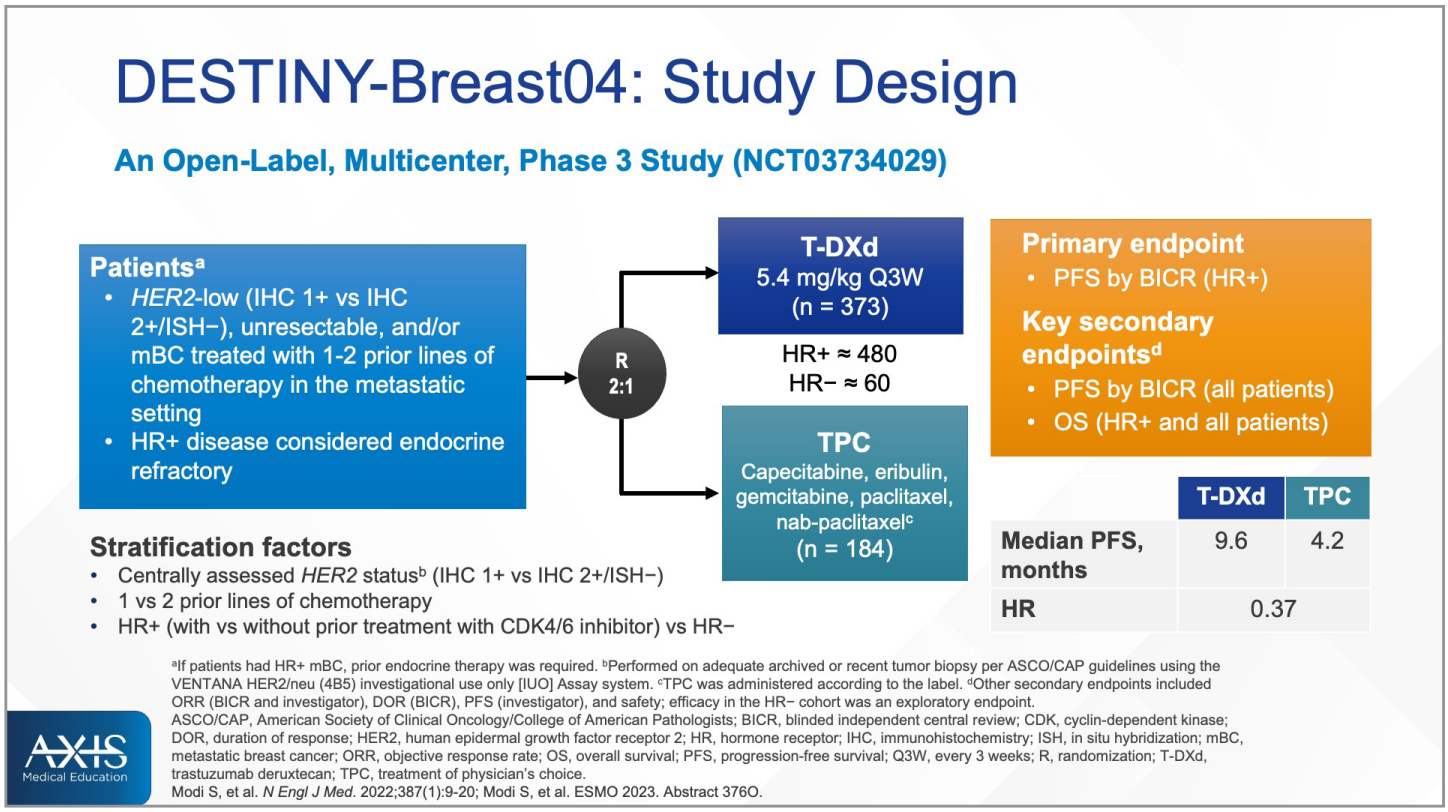


- So what would the next best treatment option be? Again, to summarize, this patient had fulvestrant and abemaciclib for about a year, then went on to get capecitabine, and is now progressing.



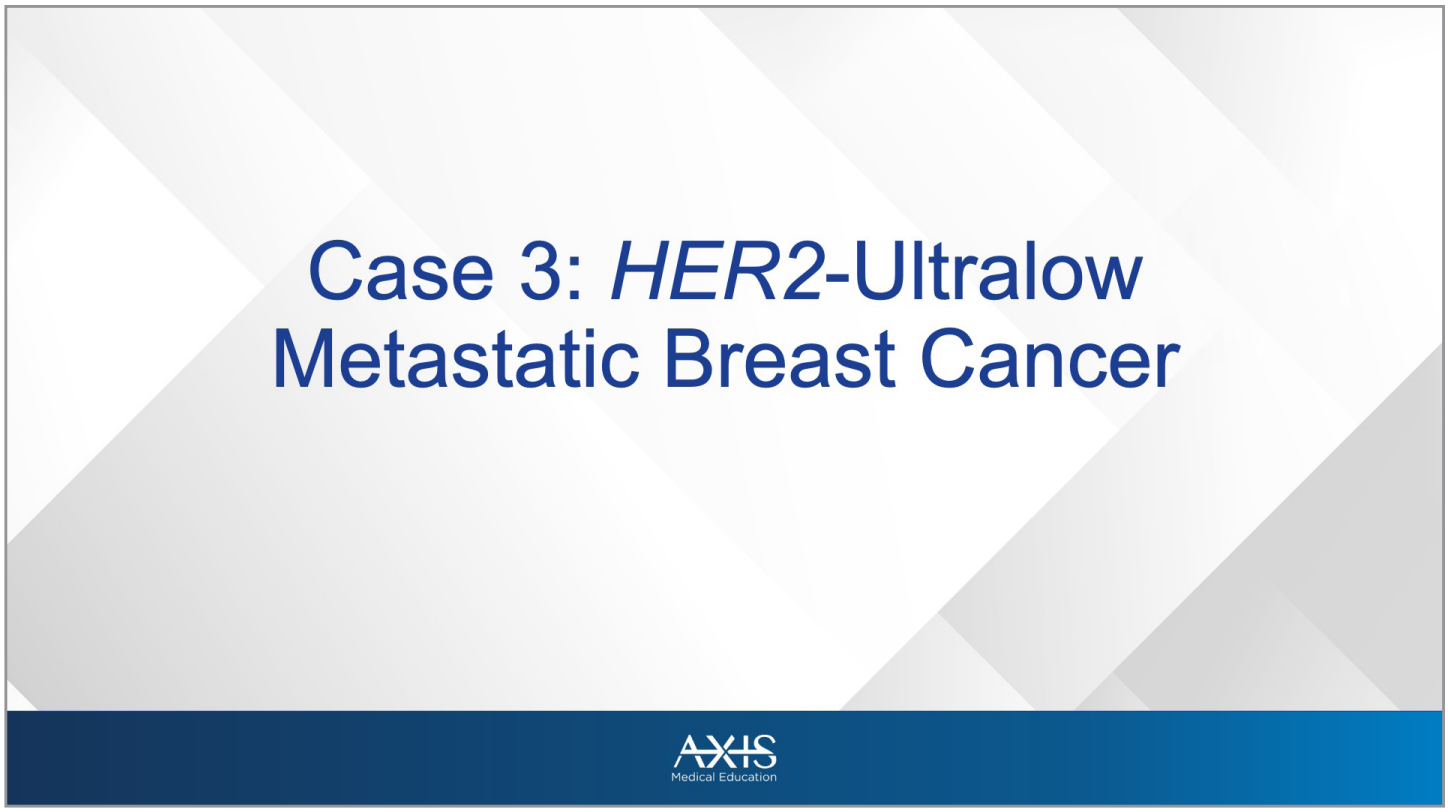
So here, the correct answer would be trastuzumab deruxtecan, on the basis of the DESTINY-Breast04 trial, which randomized patients with hormone receptor-positive HER2-low metastatic breast cancer to treatment of physician's choice or the antibody-drug conjugate, T-DXd. And showed improvements in progression-free and overall survival favoring the use of the ADC.

Most of these patients were treated with one to two prior lines of chemotherapy in the metastatic setting, whereas patients who received sacituzumab govitecan in the TROPiCS-02 trial (which was also an option in terms of the ADCs that you could have selected), these were more heavily pretreated patients who had received at least two to four prior lines of therapy. And as such, T-DXd is the preferred ADC in patients with HER2-low disease, per guidelines. And again, this patient has hormone receptor-positive, HER2-low disease, not hormone receptor-negative, HER2-low or triple-negative, where one might consider utilizing sacituzumab before T-DXd.

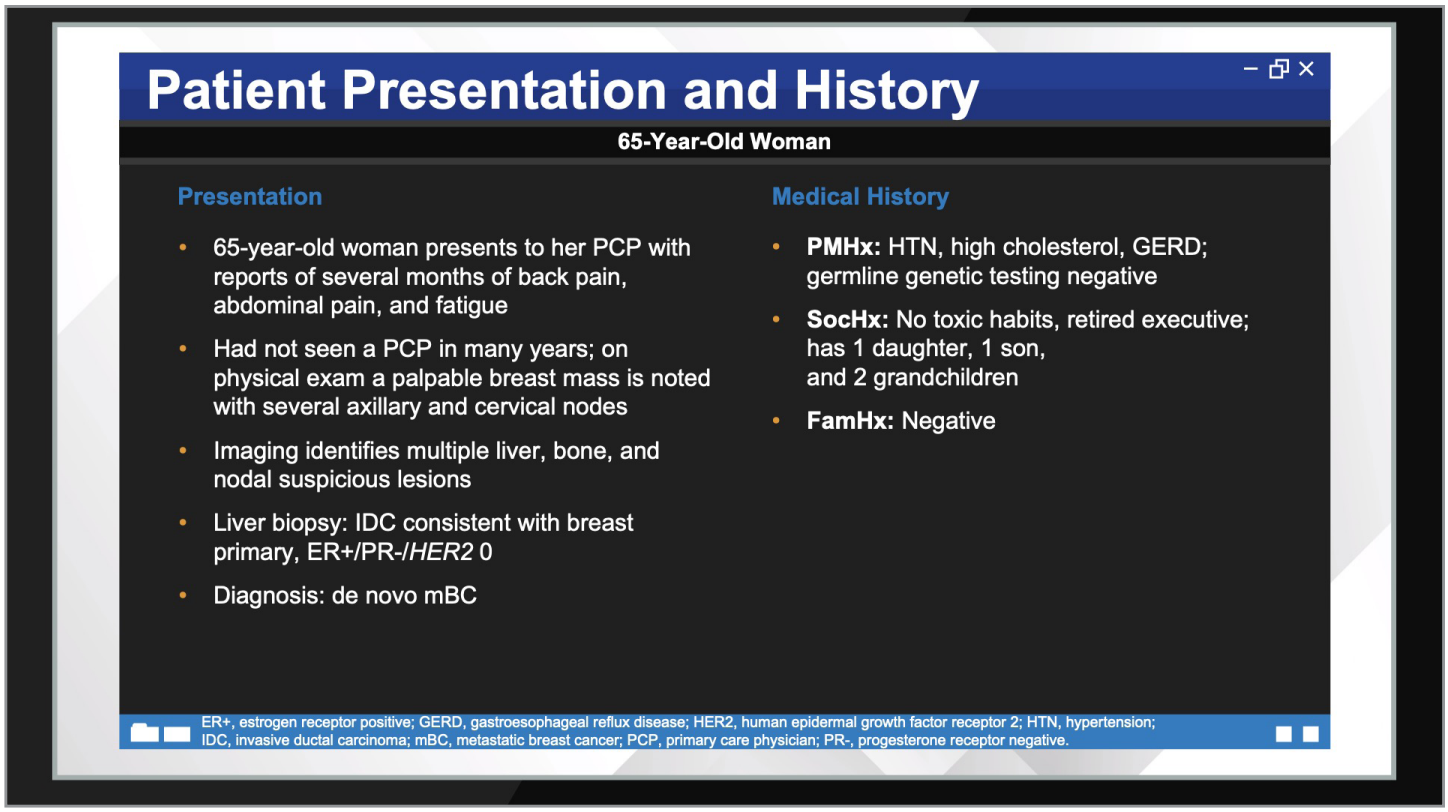


So in any case, here we see the schema for the DBO4 trial. Again, these patients had HER2-low disease, defined as 1+ or 2+, and FISH not amplified, having been treated with one to two prior lines of chemo in the metastatic setting.

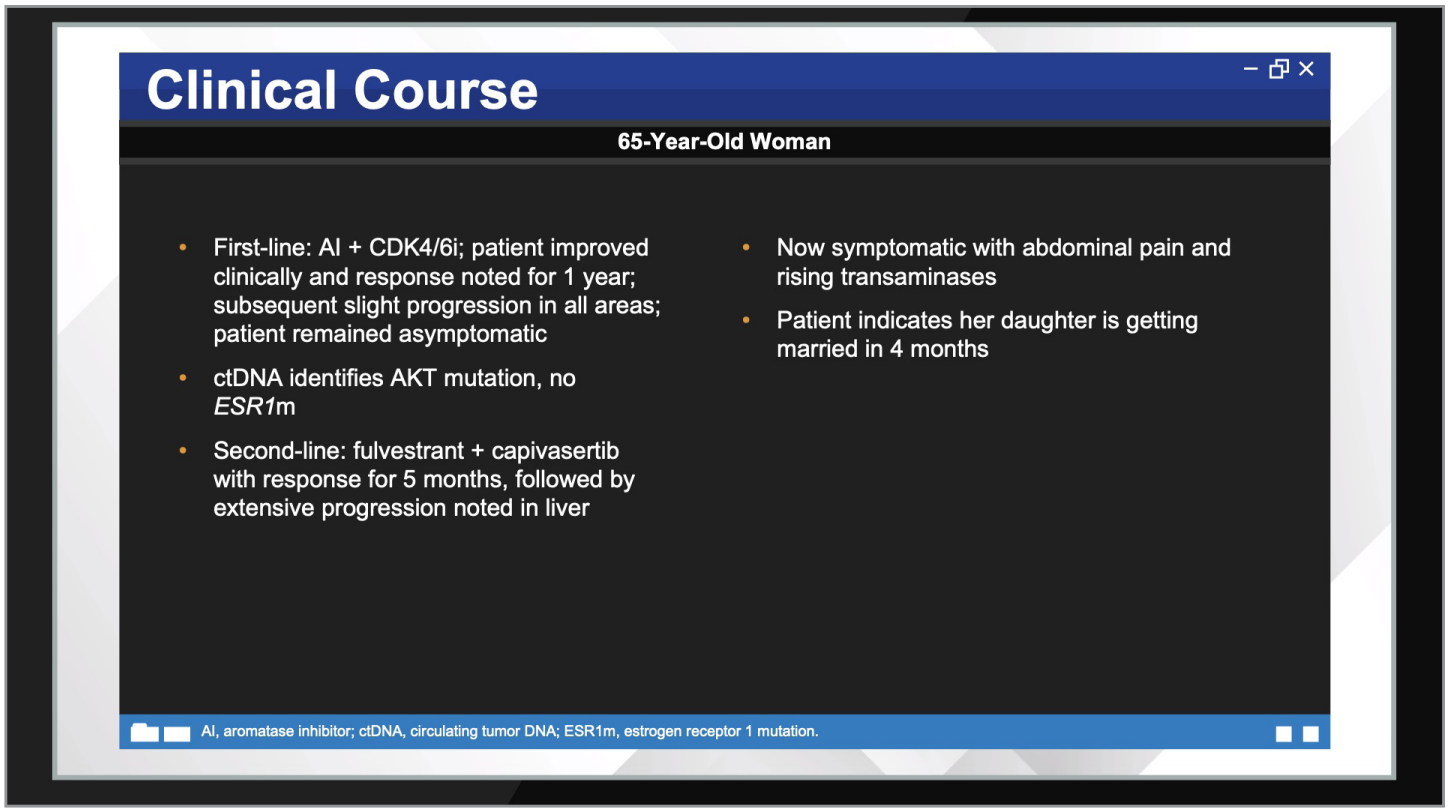
Notice the majority of these patients, as I mentioned a moment ago, had hormone receptor-positive HER2-low disease. Only 60 patients had hormone receptor-negative HER2-low disease. The randomization was to T-DXd versus treatment of physician's choice. And the primary endpoint was progression-free survival. Again, as we see summarized in the box on the right part of the slide, the median PFS favored the use of T-DXd, 9.6 months versus 4.2 months. And not shown is also the data that's documented in overall survival benefit as well.



- And then finally, let's finish with a case of HER2-ultralow metastatic breast cancer.



This is a 65-year-old woman who is symptomatic with back pain and abdominal pain and fatigue, and goes to her primary medical physician who she had not seen in many years. And on physical exam, there's a palpable mass, several areas of adenopathy. On imaging, there's widespread metastatic disease involving bone, liver, and nodal lesions. A liver lesion is biopsied and does show metastatic breast cancer, ER-positive, HER2-0. This patient has de novo metastatic breast cancer. As far as other medical issues, she has hypertension, high cholesterol, GERD, undergoes germline genetic testing and it is negative. She has no toxic habits, no pertinent family history.



In the first-line setting, she receives an AI and a CDK4/6 inhibitor, and has a response for a year, but then develops progression. She's asymptomatic. There is an AKT mutation noted on ctDNA, no ESR1 mutation. And on this basis, she receives fulvestrant and capivasertib, with a response lasting for 5 months, but then develops pretty widespread progression in the liver, and she's now very symptomatic. LFTs are rising, and she says, 'I really want to feel well and be around for my daughter who's getting married in 4 months.'

Case Study Question

What would be the next best option?

A. Rebiopsy a metastatic site, and if HER2-low, T-DXd
B. Ask pathologist to quantify any faint HER2 expression, and if present, T-DXd
C. Refer to hospice
D. Eribulin
E. Unsure

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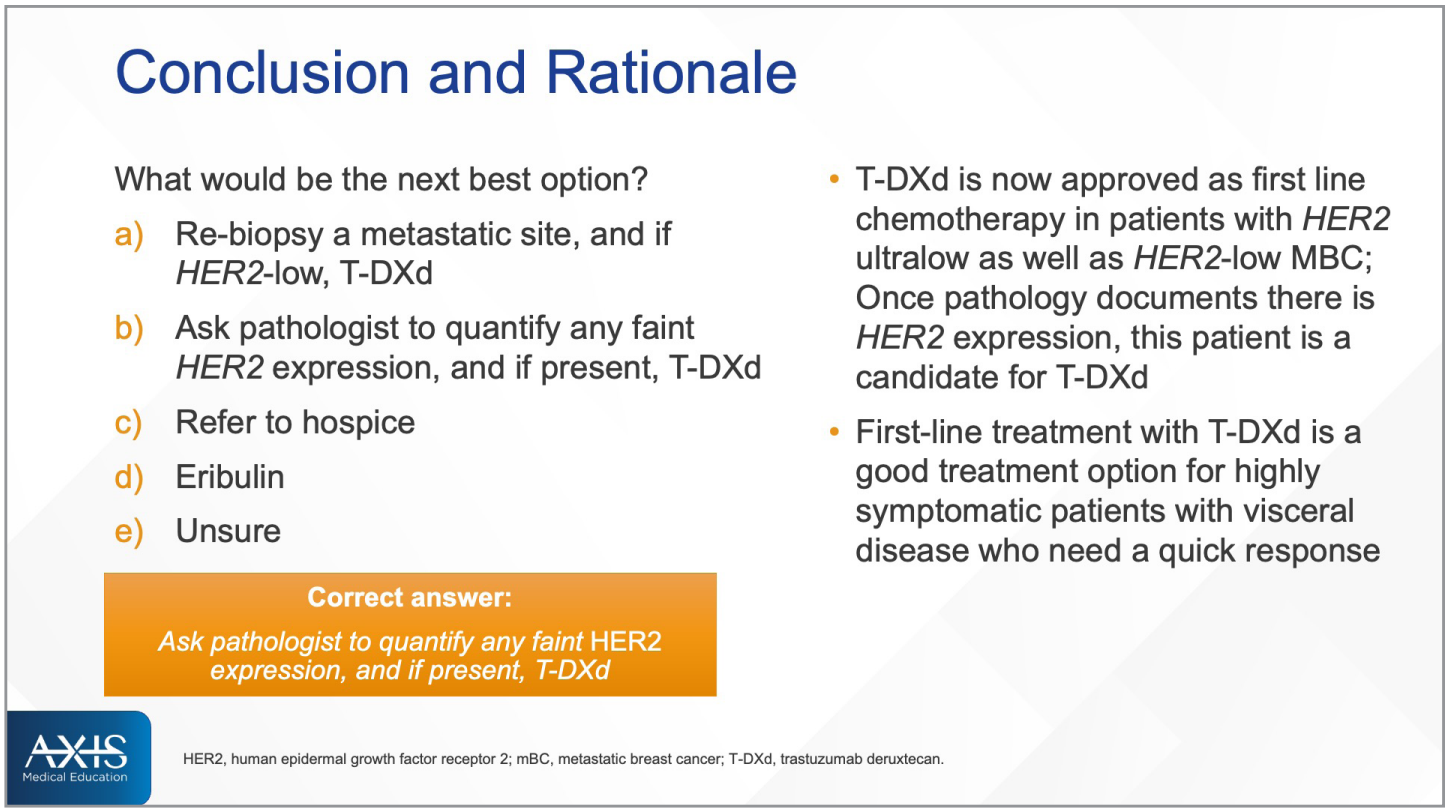
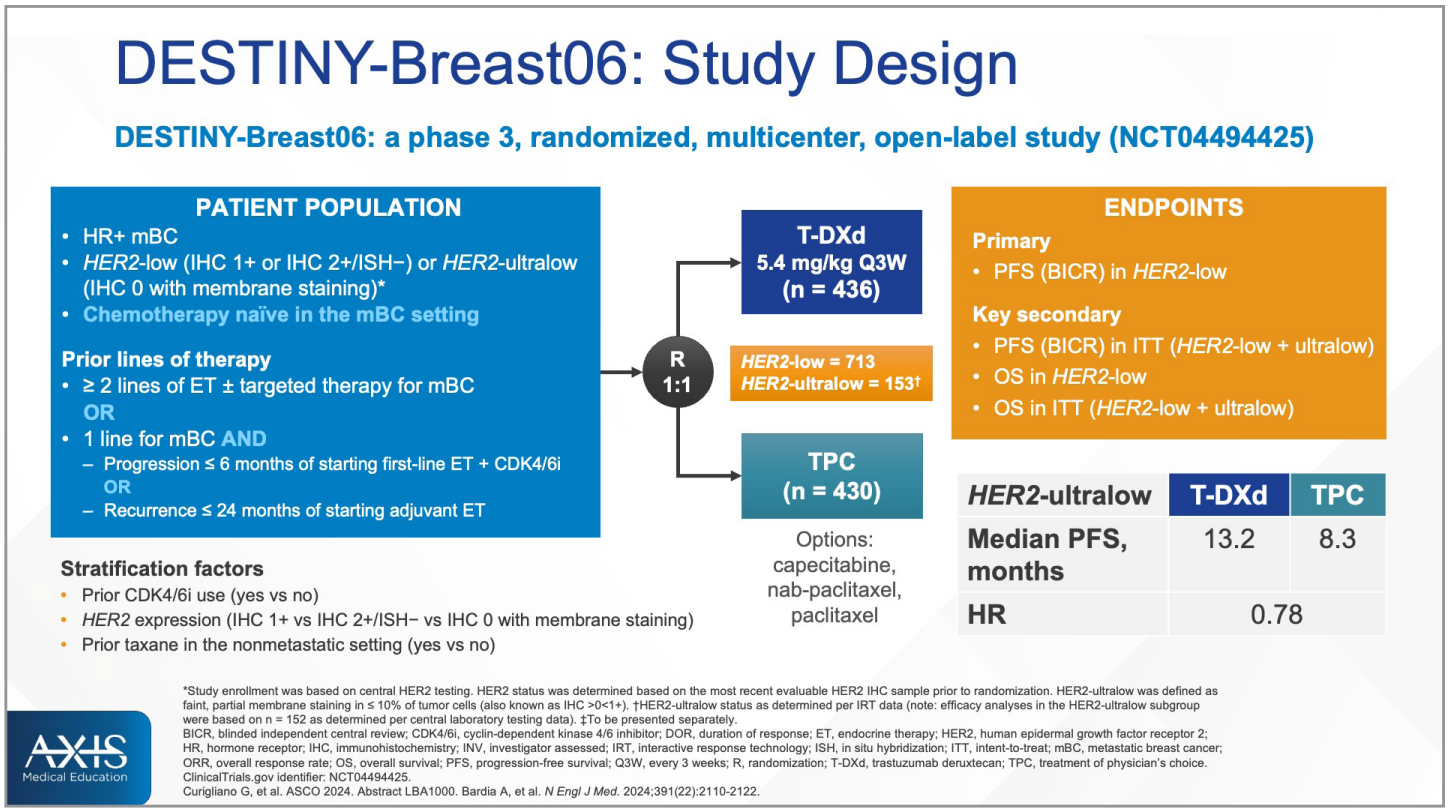
HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.

- So what would the next best option be?



So here, remember we had a liver biopsy that showed IHC simply reported as 0, and we now know that a certain subsegment of these IHC-0 tumors will be considered HER2-ultralow, meaning faint staining up to 10%. These were patients that were treated with T-DXd in the first-line setting as part of the DESTINY-Breast06 trial; 150 of these patients were enrolled on this trial. And T-DXd is now available as a first-line chemotherapy option, not only for HER2-low, but now also HER2-ultralow. Once pathology documents that there is HER2 expression up to 10%, we would then be able to offer this patient T-DXd. And I would say that this is an excellent treatment option for her, as she's highly symptomatic and she needs a quick response.



▶ Here you see the study schema of the DBO6 trial. Notable differences as compared to the DBO4 trial that we reviewed earlier is that these are patients that are receiving T-DXd or treatment of physician's choice as first-line chemotherapy in the metastatic setting. And again, HER2-low tumors, as well as 150 or so HER2-ultralow tumors, IHC-0 with faint staining up to 10%, were allowed on this trial. And the primary endpoint was progression-free survival, again favoring T-DXd, 13.2 months versus 8.3 months. And we await overall survival data to be reported.

FDA Approval Summary: ADCs in mBC

ADC	*HER2*-positive (IHC 3+ or ISH positive)	*HER2*-low (IHC 1+ or IHC 2+/ISH-)	*HER2*-ultralow (IHC 0 with membrane staining)	HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH–)
Trastuzumab emtansine (T-DM1)	EMILIA: patients who previously received trastuzumab and a taxane, separately or in combination			
Trastuzumab deruxtecan (T-DXd)	DESTINY-Breast03: patients who have received a prior anti-*HER2*-based regimen	DESTINY-Breast04: patients who have received a prior chemotherapy		
		DESTINY-Breast06: HR+ patients that have progressed on one or more endocrine therapies (chemotherapy-naïve in mBC)		
Sacituzumab govitecan (SG)				TROPiCS-02: HR+ patients who have received endocrine-based therapy and at least two additional systemic therapies
Datopotamab deruxtecan (Dato-DXd)				TROPION-Breast01: HR+ patients who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease

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ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Kadcyla. Prescribing information. Genentech, Inc; 2022. Enhertu. Prescribing information. Daiichi Sankyo, Inc; 2025. Trodelvy. Prescribing information. Gilead Sciences, Inc; 2025. Datroway. Prescribing information. Daiichi Sankyo, Inc; 2025.

- Here you see an FDA approval summary of ADCs in metastatic breast cancer. This is not meant to be comparative. Remember, these trials all enrolled somewhat different populations. But just to summarize the data, we have T-DM1 for HER2-positive tumors. We have T-DXd across a broad range of HER2 expression, HER2-positive, HER2-low, HER2-ultralow. And then we have sacituzumab govitecan. And more recently, datopotamab deruxtecan in patients that are hormone receptor-positive, HER2-negative as well, with sacituzumab govitecan being available in the triple-negative setting as well.

  Thank you so much.

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