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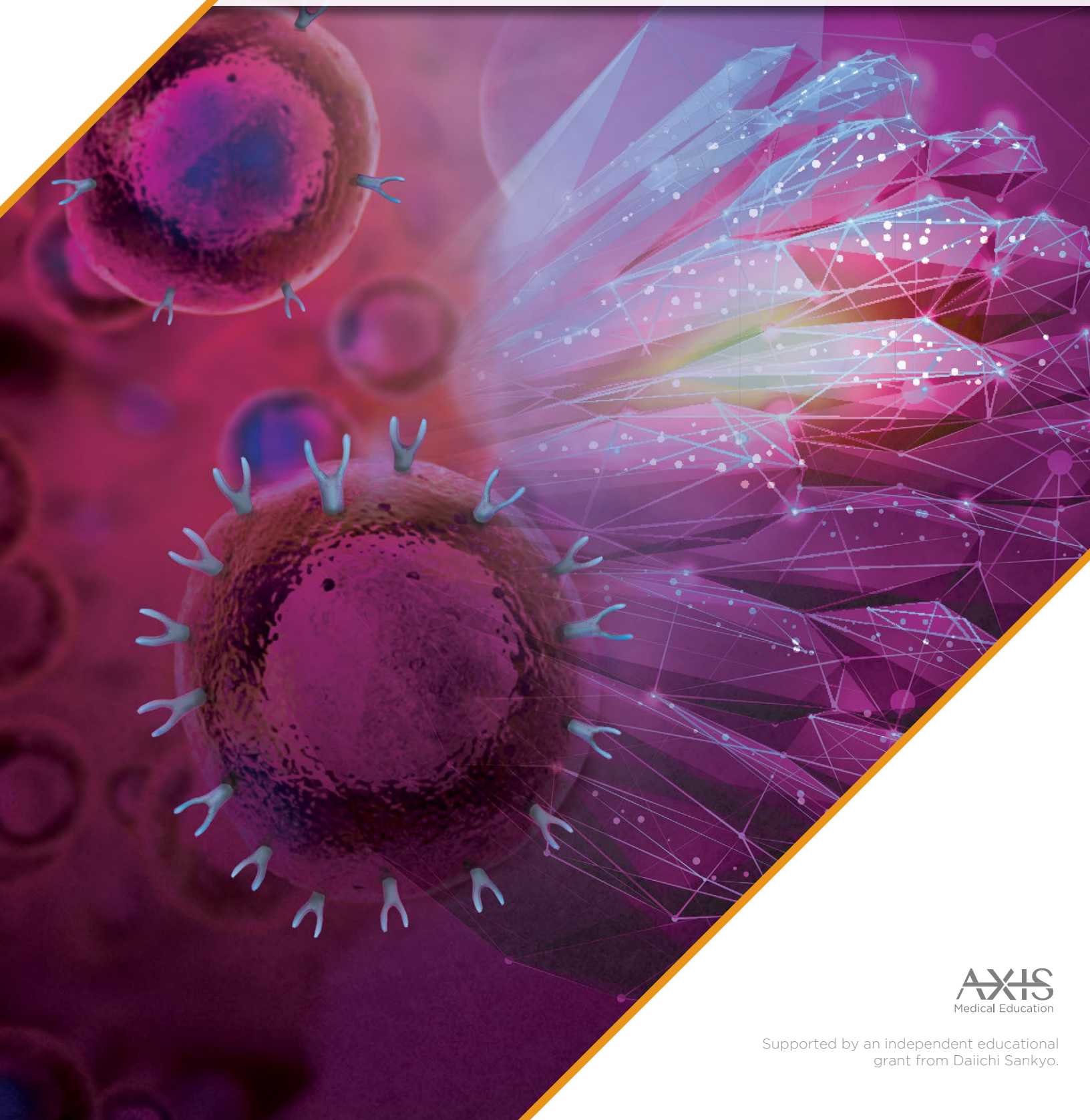
UsHERing in New Standards of Care on HER2+ and HER2-low MBC

This transcript has been edited for style and clarity and includes all slides from the presentation.



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Supported by an independent educational grant from Daiichi Sankyo.

UsHERing in New Standards of Care on HER2+ and HER2-low MBC

Reshma L. Mahtani, DO

Reshma L. Mahtani, DO: Hello and welcome to this educational activity on HER2+ and HER2-low metastatic breast cancer (MBC), focusing on antibody-drug conjugates (ADCs).

My name is Dr. Reshma Mahtani, and I'm chief of breast medical oncology at Miami Cancer Institute Baptist Health South Florida.

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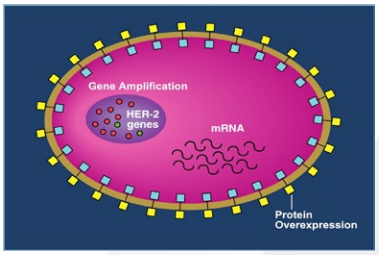
FDA, US Food and Drug Administration.

- First, a disclaimer and disclosure indicating that we may be discussing off-label use of approved agents or agents that are in development.

HER2+ Breast Cancer

- 1980s: HER2+ breast cancer denoted an aggressive phenotype with increased risk for recurrence and death; median survival 2-3 years; very difficult to treat
  - 1982-1984: Oncogene for HER2/neu discovered
  - 1986: *ERBB2*/HER2 cloned; mutated gene stimulates excess cell growth and division
- Better understanding of molecular mechanisms underlying pathogenesis of HER2+ disease has generated targeted therapy options to combat this poor-prognosis disease
- 1989-2020: Deaths per year from breast cancer decreased 42% due to advances in early detection and better treatment



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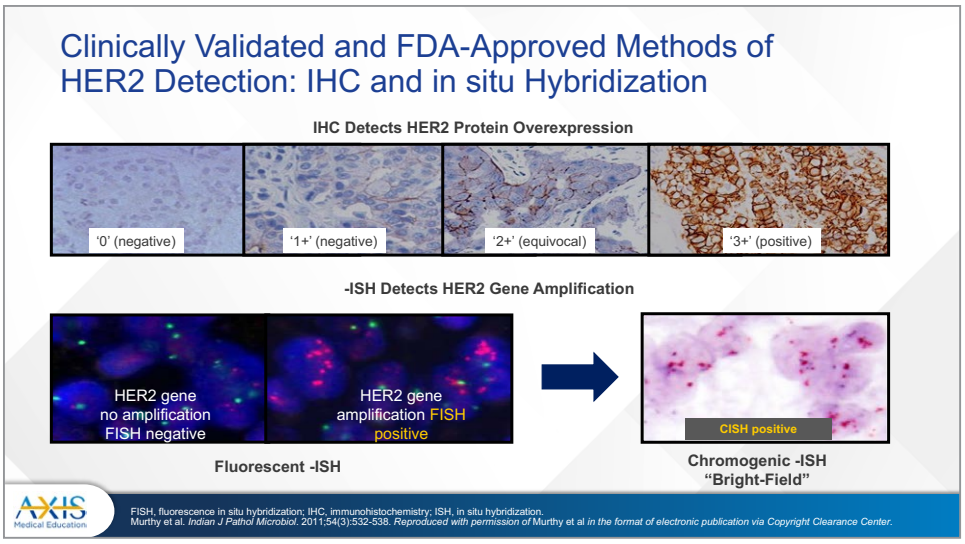
NCI SEER, 2022.

- So as we start, I'll just point out that HER2+ breast cancer is one of our greatest success stories in oncology. It's been nearly 40 years since we've identified the amplification of the HER2 gene is associated with an aggressive phenotype and an increased risk of recurrence and death, with a median survival of about 2 to 3 years, a very difficult type of breast cancer to treat. And over the ensuing many years that followed, we've made significant progress in our understanding of molecular mechanisms and the underlying pathogenesis of HER2+ disease. And this has generated several targeted therapy options to combat this poor-prognosis disease.

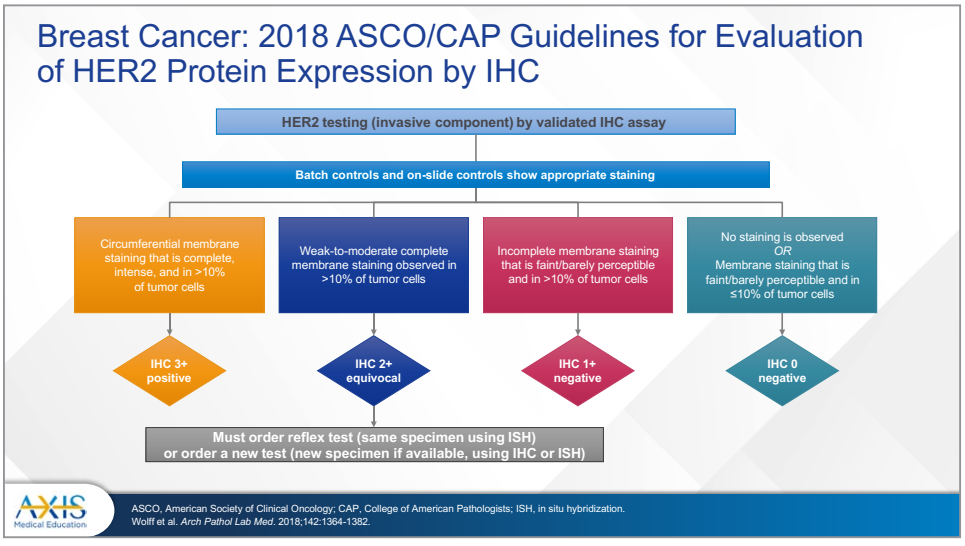
  In fact, it's the development of several targeted agents that has significantly contributed to the declining death rate for MBC. From 1989 to 2020, deaths per year from breast cancer decreased 42% due to advances in early detection as well as better treatments, including HER2-targeted therapies.



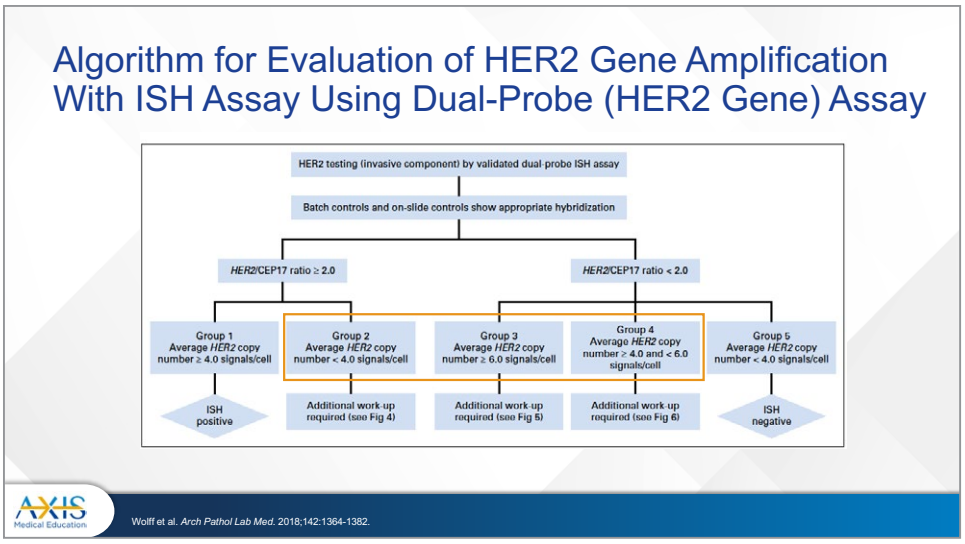
- This slide shows the currently clinically validated and US Food and Drug Administration (FDA)-approved methods for HER2 testing for overexpression and those include immunohistochemistry (IHC) and gene amplification by fluorescence in situ hybridization (FISH) and chromogenic in situ hybridization. It's important to recognize that the presence of HER2 amplification determines a patient's eligibility for anti-HER2 targeted therapy. And because HER2 test results inform treatment decisions, the need for accurate testing is paramount.

  IHC expression is a continuous variable: IHC 0, which means ≤ 10% staining, and IHC 3+, which denotes circumferential membrane staining that's complete, intense, and in >10% of tumor cells, with 1+ and 2+ being in between that continuum.

  On the bottom part of the slide, you see in situ hybridization techniques, including FISH and CISH, or chromogenic in situ hybridization. These techniques look to identify gene amplification.

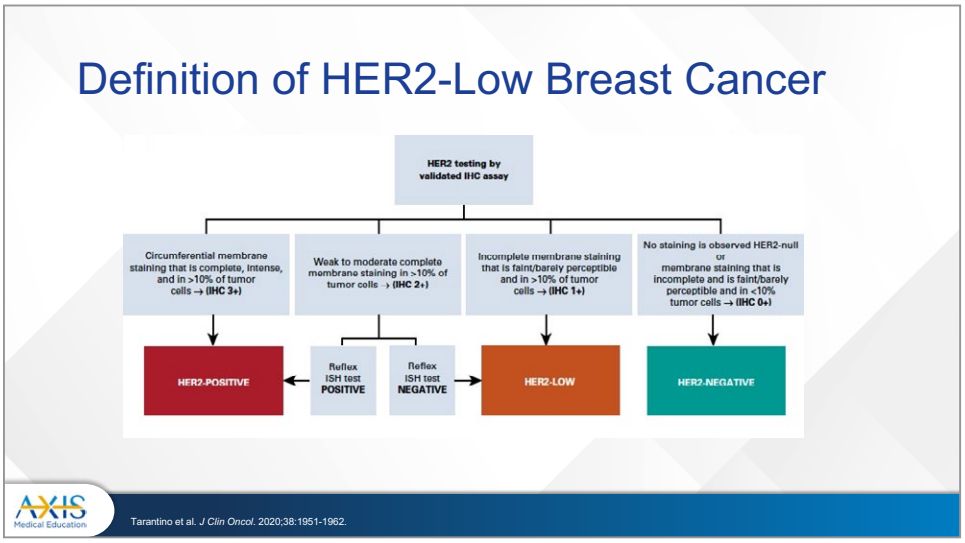


- The 2018 ASCO/CAP Guidelines are the latest iteration of the guidelines that are intended to help us identify patients that may benefit from HER2-targeted approaches. As I alluded to a moment ago, HER2 testing by IHC is a continuous variable, 3+ referring to circumferential membrane staining that's complete, intense, and in >10% of tumor cells. For IHC 0 tumors, this refers to no staining being observed or membrane staining that's faint or barely perceptible and in ≤10% of tumor cells. There is a recommendation to proceed to in situ hybridization testing, reflex testing, in tumors that are considered equivocal or 2+ for IHC testing to adjudicate results.

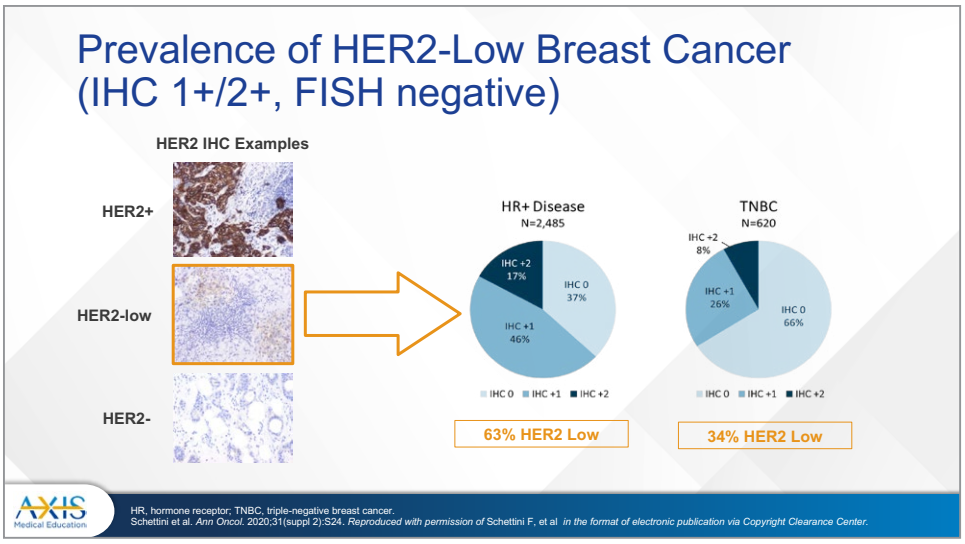


- In terms of patients who do require in situ hybridization analysis, we look at the HER2-to-CEP17 ratio and the HER2 copy number to put them in 1 of 5 groups. And in the latest iteration of the ASCO/CAP Guidelines, this focused on what to do in these less-common results groups 2, 3, and 4, where additional workup is required. Fortunately, these results are an issue in <5% of cases. But I would say these rare cases do account for a large majority of the confusion when it comes to HER2 testing results. Additional workup is required in these situations, and I would refer you to the guidelines for the additional workup that's required.

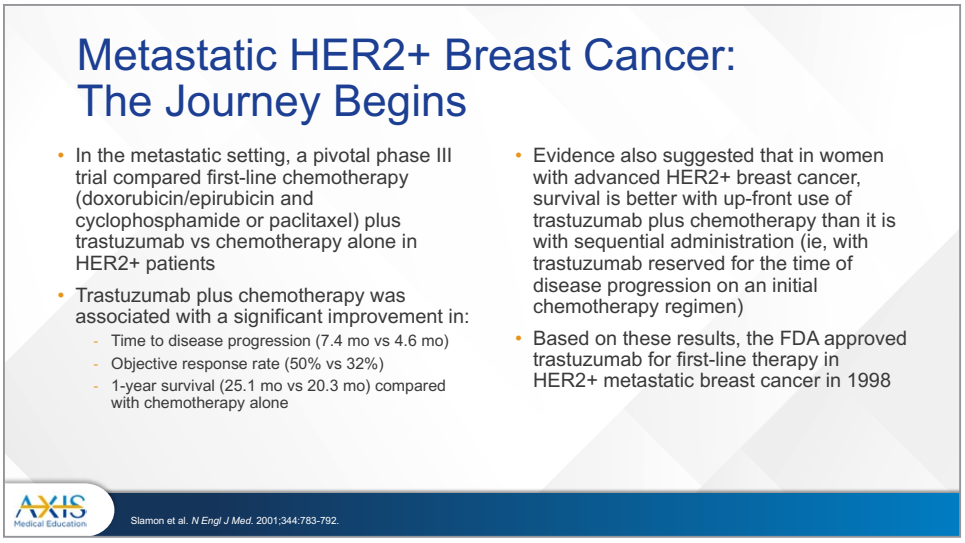
  And then on the far right and far left of this slide, you see the patients that are clearly in group 1, being ISH positive based on ratio and copy number, and those in group 5 that are clearly negative, with the ratio of <2 and a copy number of <4.



- And then more recently, we've developed a new nomenclature in breast cancer based on some data that I'll be reviewing with you shortly, HER2-low breast cancer. And so what do we mean by HER2 low? Again, I showed you this slide a moment ago where patients that are HER2+ based on IHC staining 3+ are clearly identified. And then those that have <10% or no staining being HER2 negative. But this group in the middle, these patients that have tumors that are 1+ or 2+ and then require ISH testing for confirmation and those are negative; those tumors would now be called HER2 low. Of course, if the ISH testing on a 2+ tumor reveals that the tumor is HER2+ for gene amplification, then those tumors are considered HER2+.



So as we look at this new definition of HER2 low again, IHC 1+ or 2+ and FISH negative, what is the prevalence here in terms of our patients that have breast cancer? Overall, those with MBC, approximately 50% of the total would be considered HER2 low. And as broken down in terms of the hormone-receptor–positive cases, about two-thirds would be considered HER2 low and about a third of triple-negative breast cancer patients would be reclassified as having HER2-low disease.



So now let's talk a bit about the journey that we've been on with the treatment of HER2+ breast cancer and where we started and what progress we've made. The pivotal study that was published in *The New England Journal of Medicine* back in 2001 by Slamon et al was a phase 3 study looking at the use of chemotherapy in combination with trastuzumab vs chemotherapy alone for patients with HER2+ MBC. The time to disease progression was longer, objective response rate was higher, and 1-year survival was longer compared with chemotherapy alone with the addition of trastuzumab. And we also identified that it was better to use upfront trastuzumab plus chemotherapy as opposed to sequential administration. Based on these results, the FDA approved trastuzumab for first-line therapy in HER2+ MBC. And the journey then began in terms of additional improvements that we've made on some of these efficacy data.

Timeline of FDA Approvals for HER2+ Breast Cancer

1998	2007-2008	2012	2013	2017	2019	2020
Trastuzumab (metastatic)	Lapatinib (metastatic)	Pertuzumab (metastatic)	T-DM1 (metastatic)	Neratinib (adjuvant)	T-DM1 (adjuvant)	Tucatinib (metastatic)
	Trastuzumab (adjuvant)		Pertuzumab (neoadjuvant)	Pertuzumab (adjuvant)	Trastuzumab deruxtecan (metastatic)	Neratinib (metastatic)
						Margetuximab (metastatic)

T-DM1, ado-trastuzumab emtansine.
FDA, 2023.

- And in that regard, you see this timeline of FDA approvals for several other agents that have come afterward, including tyrosine kinase inhibitors like lapatinib, neratinib, and, more recently, to tucatinib; monoclonal antibodies such as pertuzumab and then ADCs, which we'll be spending quite a bit of time talking about in the context of this program today, including T-DM1 and trastuzumab deruxtecan. So definitely a steady progress that has been made in the treatment of HER2+ disease, contributing to the significant gains that we've made in survival for our patients.

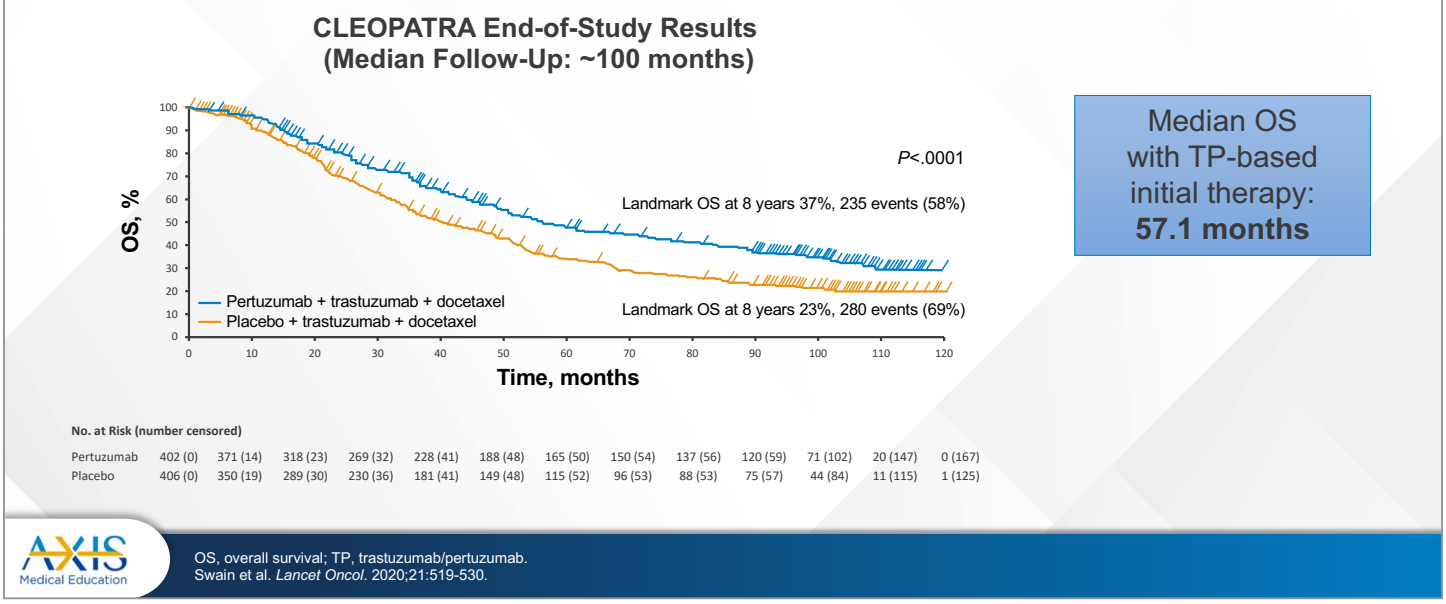
NCCN Guidelines®: HER2+ MBC (ER-/PR-)

Setting	Regimen	NCCN Category of Preference (Category of Evidence)
First-line	Pertuzumab + trastuzumab + docetaxel	Preferred regimen (1)
	Pertuzumab + trastuzumab + paclitaxel	Preferred regimen (2A)
Second-line	Fam-trastuzumab deruxtecan-nxki (T-DXd)	Preferred regimen (1) (May be considered in the first-line setting as an option for select patients, ie, those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens])
	Ado-trastuzumab emtansine (T-DM1)	Other recommended regimen (2A)
Third-line and beyond	Tucatinib + trastuzumab + capecitabine	Other recommended regimen (1) (May be used as a third- or fourth-line option; preferred in patients with both systemic and CNS progression in the third-line or beyond; and it may be given in the second-line setting)
	Trastuzumab + docetaxel or vinorelbine	Other recommended regimen (2A)
	Trastuzumab + paclitaxel ± carboplatin	
	Capecitabine + trastuzumab or lapatinib	
	Trastuzumab + lapatinib (without cytotoxic therapy)	
	Trastuzumab + other agents	
	Neratinib + capecitabine	
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)	

NCCN, National Comprehensive Cancer Network; ER, estrogen receptor; PR, progesterone receptor.
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. V.4.2022.

- This slide shows the NCCN Guidelines for treatment for HER2+ MBC. In the first line, the standard treatment is pertuzumab, trastuzumab, and a taxane-based chemotherapy, either docetaxel or paclitaxel. Second line, our preferred regimen based on NCCN Guidelines is T-DXd, or trastuzumab deruxtecan, with T-DM1 being another recommended regimen. And then in the third line and beyond, we see a variety of choices, including the tucatinib, trastuzumab, and capecitabine regimen, with a caveat that this therapy could be considered in the second line, especially in patients that have CNS metastases based on the FDA approval of that triplet combination. Beyond that, we have several other options, including chemotherapy in combination with trastuzumab, other tyrosine kinase inhibitors such as neratinib in combination with capecitabine, and the new monoclonal antibody margetuximab as well.

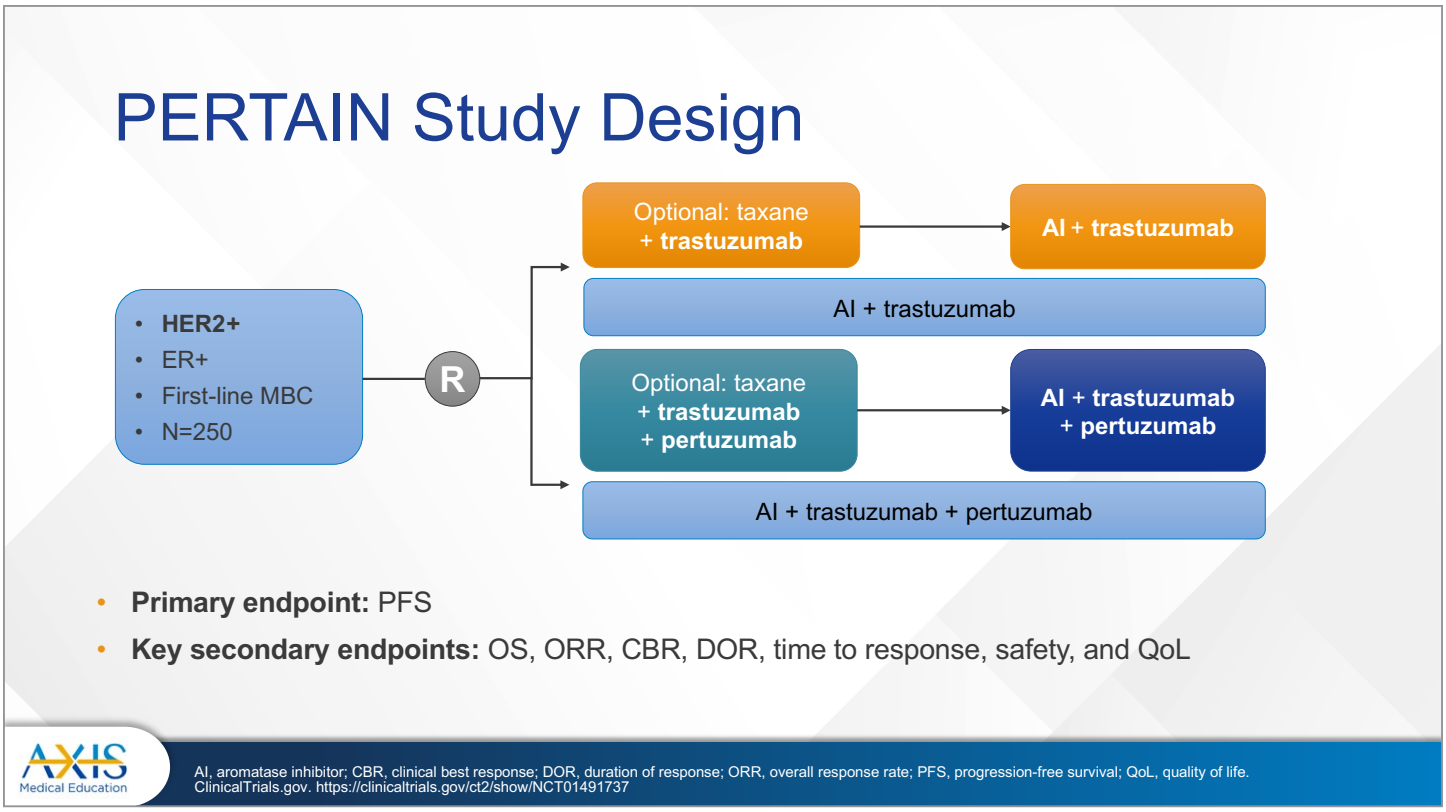
OS in Patients With Advanced HER2+ MBC



Median OS with TP-based initial therapy: **57.1 months**

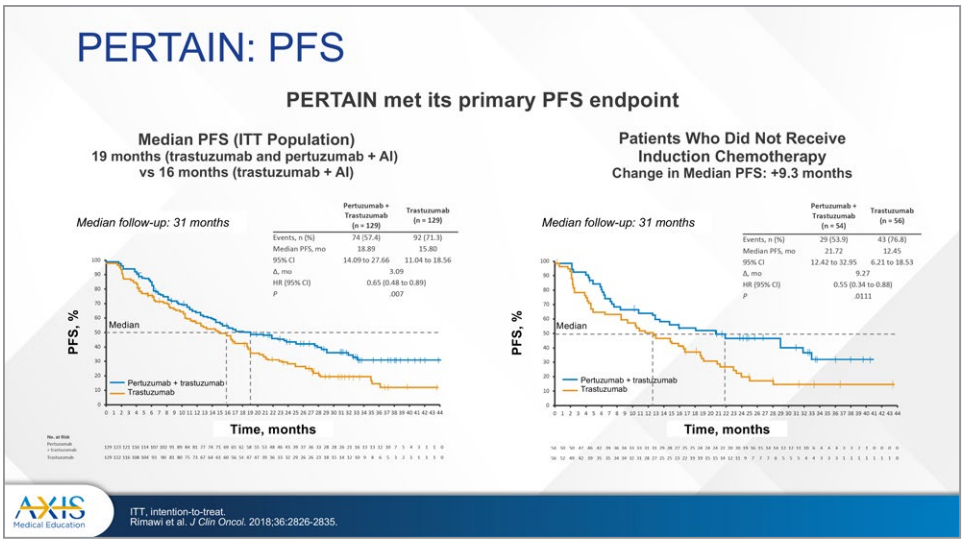
OS, overall survival; TP, trastuzumab/pertuzumab.
Swain et al. *Lancet Oncol*. 2020;21:519-530.

- In terms of our first-line data, the CLEOPATRA trial really established the standard for that first-line recommendation of trastuzumab, pertuzumab, and taxane-based chemotherapy. Here you see overall survival in patients at the end of this pivotal trial with a median follow-up of 100 months. The addition of pertuzumab to the backbone of trastuzumab and a taxane, as demonstrated in this study, was associated with dramatic improvements in both progression-free survival (PFS) and overall survival. The end-of-study analysis of the CLEOPATRA trial of pertuzumab plus trastuzumab and chemotherapy found that 37% of patients were still alive at 8 years vs 23% in the control arm. Median overall survival was 57.1 months in the pertuzumab arm and 40.8 months in the placebo arm, an absolute difference of 16.3 months favoring the pertuzumab arm.

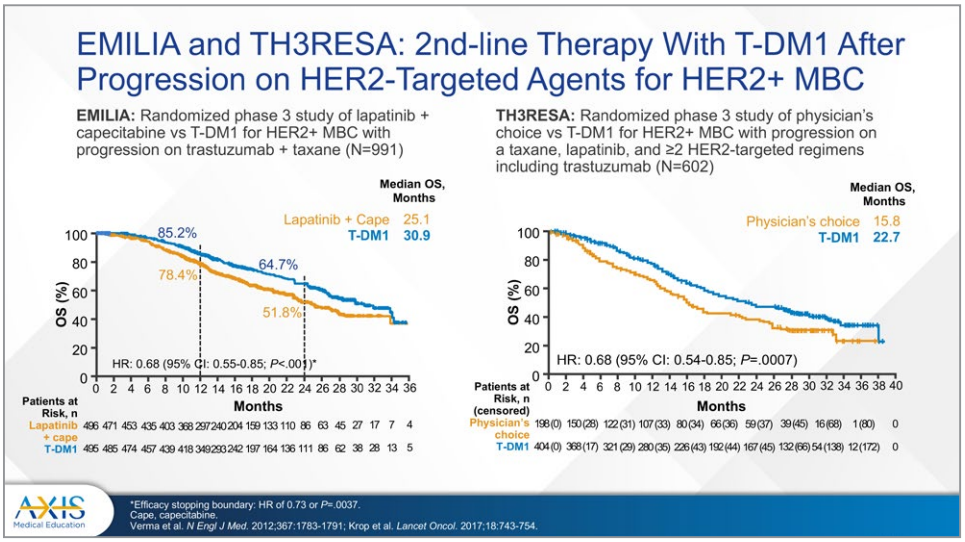


For some patients, the use of chemotherapy may not be appropriate based on concerns regarding tolerance or due to comorbid conditions. And particularly in those patients with triple-positive breast cancer, there is the thought of perhaps omitting chemotherapy in favor of endocrine therapy up front. So there is some support to this approach available based on the results of this trial, the PERTAIN study, which was a first-line, triple-positive study, with the aim of evaluating the benefit of the addition of pertuzumab to the backbone of an aromatase inhibitor or endocrine therapy and trastuzumab.

It should be noted that induction IV docetaxel every 3 weeks or paclitaxel every week could be administered for 18 to 24 weeks at the investigators' discretion. And this was decided before but given after a random assignment. The PFS, and patients were stratified by whether they received induction chemotherapy and their time since adjuvant hormonal therapy.



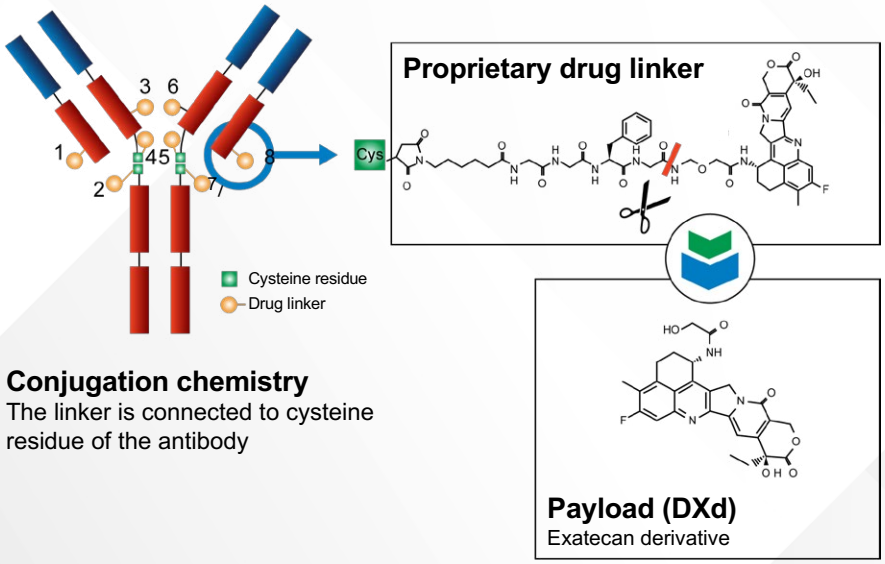
- These results were recently updated, and, with a median follow-up of now more than 6 years at the final analysis, the PFS benefit of adding pertuzumab to trastuzumab and an aromatase inhibitor was maintained. A potentially enhanced treatment effect was observed by the addition of pertuzumab and trastuzumab plus an AI in patients who did not receive induction chemotherapy after randomization. And that's what's shown on the right-hand part of the slide. Not shown is the fact that there were no new safety concerns at the final analysis. So certainly, some data to support this approach but our standard treatment would still be chemotherapy with a taxane plus trastuzumab and pertuzumab in the majority of our patients.



- For many years, T-DM1, the ADC, was our standard second-line treatment. And this was based on the EMILIA randomized phase 3 study of lapatinib and capecitabine vs T-DM1 for HER2+ MBC with progression on trastuzumab and a taxane. At that time, lapatinib and capecitabine was the standard second-line therapy. And in a head-to-head study comparing that combination with T-DM1, we saw an improvement of about 6 months in median overall survival with the use of T-DM1 as compared to lapatinib and capecitabine.

  And then in the TH3RESA trial, which was a randomized phase 3 study looking at T-DM1 vs treatment of physician's choice in patients that had received ≥2 prior therapies in the metastatic setting including trastuzumab, similarly, we saw an overall survival benefit with the use of T-DM1.

Trastuzumab Deruxtecan (T-DXd; DS8201a): A Novel HER2 ADC



	T-DXd	T-DM1
Antibody	Trastuzumab Anti-HER2 mAb	Trastuzumab
Payload	Topoisomerase I inhibitor	Tubulin inhibitor
DAR	7-8	3.5
Membrane Permeability	Yes (bystander effect)	No

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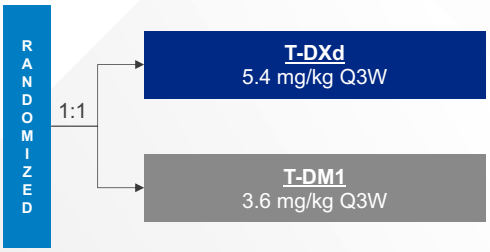
DAR, drug-to-antibody ratio.
Nakada et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185; Pondé et al. *Curr Treat Options Oncol*. 2019;20:37. *Permission requested from Chem Pharm Bull.*

- And then on the scene came newer, novel ADCs, and trastuzumab deruxtecan is one of these newer agents. These drugs are highly potent in that they have a clever design of a way to deliver chemotherapy directly to the cancer cells. Here you see the attributes of T-DXd as compared to T-DM1, the ADC that we had been using routinely prior. The antibody in both compounds is targeting HER2. The payload is different. T-DXd, that payload is a topoisomerase-1 inhibitor as opposed to a tubulin inhibitor for T-DM1. The DAR, or the drug-to-antibody ratio, is much higher with T-DXd, 7 to 8 as compared to 3.5 with T-DM1. And most importantly, we see this potent bystander effect, with T-DXd being able to target cells that are expressing some HER2, or so-called HER2 low, which we'll talk about in detail a bit more later in the presentation. And this is linked to the membrane permeability of this agent as compared to T-DM1, where we do not see this membrane permeability.

T-DXd vs T-DM1 in HER2+ MBC, Results From the Randomized Phase 3 DESTINY-Breast03 Study: Study Design and Patients

Key Eligibility Criteria

- HER2+ unresectable or MBC[a]
- Previous treatment with trastuzumab and taxane in advanced/metastatic setting[b]
- Clinically stable, treated brain metastases allowed



Primary endpoint: PFS by BICR
Secondary endpoints: OS, ORR (BICR and investigator), DOR (BICR), PFS (investigator), safety

Patient Characteristics		T-DXd (n=261)	T-DM1 (n=263)
Median age, years (range)		54.3 (27.9-83.1)	54.2 (20.2-83.0)
Region, Asia		57.1	60.8
HER2 status (IHC,[c] %)	3+	89.7	88.2
	2+ (ISH amplified)	9.6	11.4
	1+/NE/not examined	0.4/0.4/0	0/0.4/0
ECOG PS, %	0/1/Missing	59.0/40.6/0.4	66.5/33.1/0.4
Brain metastases, %	Yes/No	23.8/76.2	19.8/80.2
Visceral disease, %	Yes/No	70.5/29.5	70.3/29.7
Prior lines of therapy in the metastatic setting (includes rapid progressors as one line of treatment), n (%)	0	2 (0.8)	3 (1.1)
	1	130 (49.8)	123 (46.8)
	2	56 (21.5)	65 (24.7)
	3	35 (13.4)	35 (13.3)
	4	15 (5.7)	19 (7.2)
	≥5	23 (8.8)	18 (6.8)
Prior trastuzumab, %		99.6	99.6
Prior pertuzumab, %		62.1	60.1

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[a] HER2+ is defined as IHC 3+ or IHC 2+/ISH+ based on central confirmation. [b] Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane. [c] HER2 status as evaluated by central lab.
BICR, blinded independent committee review; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not estimable; T-DXd, trastuzumab deruxtecan.
Cortés et al. *Ann Oncol.* 2021;32(suppl 5):S1283-S1346; Cortés et al. *N Engl J Med*. 2022;386(12):1143-1154.

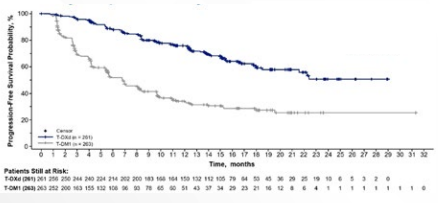
So as I mentioned, T-DM1 had been our standard second-line therapy for many years until this study was presented now almost 2 years ago at ESMO, where we saw a head-to-head comparison of T-DXd vs T-DM1 in patients with HER2+ unresectable or metastatic breast cancer who had received prior treatment with trastuzumab and a taxane. Of note, patients who had brain mets were permitted to enroll on this trial, but it was required that the brain metastases were clinically stable and treated, not progressive brain mets.

The primary endpoint in this important study was PFS. Secondary endpoints included overall survival, overall response rate, duration of response, and safety.

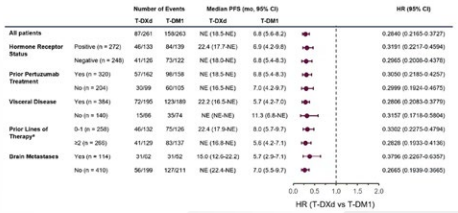
In the table here, you see patient characteristics broken down by both treatments. Patients had a median age of about 54. Almost all of them were 3+ by IHC. There were about 10% that were 2+ and ISH amplified with a good performance status. Again, patients with brain mets, they were permitted as long as they were stable and treated; they accounted for about 20% of patients enrolled. Not surprisingly, these patients had a heavy burden of visceral disease. And the majority of these patients, about half actually had received this therapy as second-line treatment, having received 1 line in the prior setting of metastatic disease. And then the other 50% were treated beyond that. All patients had received prior trastuzumab and about two-thirds, prior pertuzumab.

T-DXd vs T-DM1 in HER2+ MBC, Results From the Randomized Phase 3 DESTINY-Breast03 Study: PFS

Primary Endpoint: PFS Assessed by BICR



PFS in Key Subgroups



	T-DXd	T-DM1
mPFS, months (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-month PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37) $P = 7.8 \times 10^{-22}$	

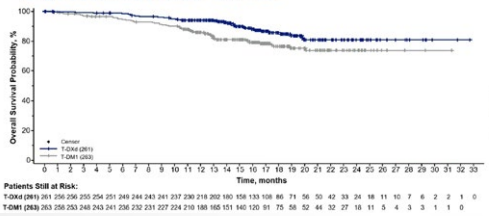
- Median PFS follow-up was 15.5 months for T-DXd and 13.9 months for T-DM1 (P<0.001)
- A consistent PFS benefit was seen across key patient subgroups

mPFS, median progression-free survival.
Cortés et al. *Ann Oncol*. 2021;32(suppl 5):S1283-S1346; Hurvitz et al, SABCS 2021. Abstract GS3-01; Cortés et al. *N Engl J Med*. 2022;386(12):1143-1154.

- So what did we see? We saw very impressive results in this head-to-head study looking at these 2 potent ADCs and comparison. When initially presented, the median PFS was 6.8 months in the T-DM1 arm compared to not reached initially in the T-DXd arm, and the 12-month PFS rates being drastically different as well. These results were highly statistically significant. In the forest plot, a consistent PFS benefit was seen across patient subgroups.

T-DXd vs T-DM1 in HER2+ MBC, Results From the Randomized Phase 3 DESTINY-Breast03 Study: OS and ORR

Secondary Endpoint: OS



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-month OS rate, % (95% CI)	94.1 (90.3-96.4)	85.9 (80.9-89.7)
HR (95% CI)	0.56 (0.36-0.86) P=.007172[a]	

Efficacy Endpoints	T-DXd (n=261)	T-DM1 (n=263)
Confirmed ORR n (%)[b] [95% CI]	208 (79.7) [74.3-84.4]	90 (34.2) [28.5-40.3]
	P<.0001	
CR, n (%)	42 (16.1)	23 (8.7)
PR, n (%)	166 (63.6)	67 (25.5)
SD, n (%)	44 (16.9)	112 (42.6)
PD, n (%)	3 (1.1)	46 (17.5)
Not evaluable, n (%)	6 (2.3)	15 (5.7)
CR+PR+SD (DCR), n (%)	252 (96.6)	202 (76.8)

[a]P=.007172 but does not cross prespecified boundary of P<.000265. [b]Based on BICR.
CR, complete response; DCR, disease control rate; mOS, median overall survival; PD, progressive disease; PR, partial response; SD, stable disease.
Cortés et al. *Ann Oncol*. 2021;32(suppl 5):S1283-S1346; Hurvitz et al, SABCS 2021. Abstract GS3-01; Cortés et al. *N Engl J Med*. 2022;386(12):1143-1154.

- And again, when initially presented, overall survival data were not mature. And you see the secondary endpoint of overall response rate broken down by complete response, partial response, stable disease, and disease control rate (DCR) rate as well in the table on the right. Again, very potent activity in the T-DXd arm, with 16% of patients being able to achieve a complete response.

DESTINY-Breast03: Updated Results

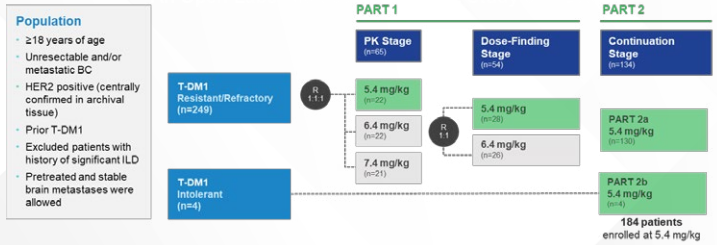
Efficacy Endpoints	T-DXd (n=261)	T-DM1 (n=263)
Median duration of study follow-up	28.4 months	26.5 months
Median PFS by BICR	28.8 months	6.8 months
HR	0.33	
nominal *p*	<0.0001	
Median OS	NR (95% CI 40.5 months–NE)	NR (95% CI 34.0 months–NE)
OS events, n (%)	72 (28%)	97 (37%)
HR	0.64	
p	0.0037	
Grade 3 or worse treatment-emergent adverse events, n (%)	145 (56%)	135 (52%)
Adjudicated drug-related interstitial lung disease or pneumonitis, n (%)	39 (15%)	8 (3%)

HR, hazard ratio; NR, not reached.
Hurvitz et al. *Lancet.* 2022;401(10371):P105-P117.

- This is hot off the presses at San Antonio Breast Cancer Symposium 2022. These data were updated and now we have a median duration of steady follow-up of about 26 to 28 months. Median PFS is now 28.8 months in the T-DXd arm compared to 6.8 months. This was highly statistically significant. And median overall survival is now significant as well. And Grade 3 or worse treatment-emergent adverse events, about 56% in the T-DXd arm vs 52%, with a 15% adjudicated drug-related interstitial lung disease (ILD) or pneumonitis rate. Again, this is all Grades; we'll talk about toxicity a bit later. Fortunately, none of these events were Grade 5 events.

Phase 2 DESTINY-Breast01: Study Design

T-DXd in Third-Line Setting, Previously Treated With T-DM1



Endpoints

- Primary: confirmed ORR by independent central imaging facility review per RECIST v1.1
- Secondary: investigator-assessed ORR, DCR, DOR, CBR, PFS, OS, PK, and safety

Median Duration of Follow-Up

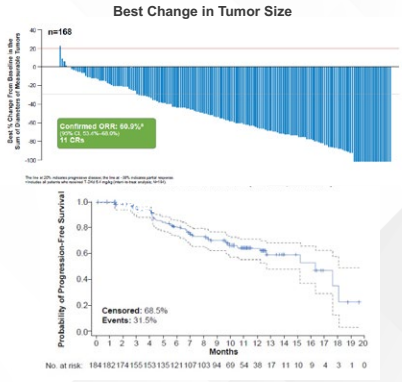
- August 1, 2019, data cutoff: 11.1 months (range, 0.7-19.9 mo)[1]
- June 8, 2020, data cutoff: 20.5 months (range, 0.7-31.4 mo)[2]
- March 26, 2021, data cutoff: 26.5 months (range, 0.7-39.1 mo)[3]

[a]All 184 patients received ≥1 dose of T-DXd. [b]HER2 status was centrally assessed on the most recent archival tissue according to the ASCO-CAP guidelines.
BC, breast cancer; CBR, clinical benefit rate; ILD, interstitial lung disease; ORR, objective response rate; PK, pharmacokinetics.
1. Modi et al. *N Engl J Med.* 2020;382(7):610-621; Modi et al, SABCS 2020 Virtual. Poster Spotlight PD3-06. 3. Manich et al. *Ann Oncol.* 2021;32(5):S485-S486.

- Our previous study where we had been very impressed with this agent was a nonrandomized phase 2 study. This was what led to accelerated approval of this potent ADC, the DESTINY-Breast01 trial. This nonrandomized phase 2 study looked to identify an appropriate dose, and this was in patients that had largely been resistant or refractory to T-DM1, a few that were intolerant.

Phase 2 DESTINY-Breast01 Study: T-DXd Efficacy

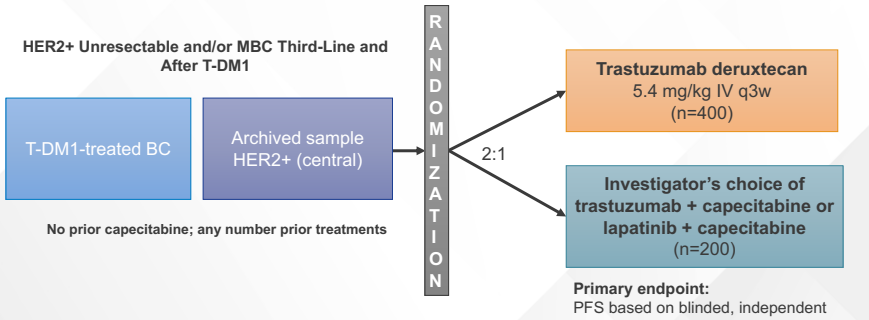
Endpoint (N = 184)	Result
Confirmed ORR (primary endpoint)	60.9% (n = 112)
CR	6.0% (n = 11)
PR	54.9% (n = 101)
DCR (CR+PR+SD)	97.3%
Median PFS, months	16.4
Median OS, months	Not reached
Median DoR, months	14.8
Median prior lines of cancer therapy	6 (range, 2-27)



Median follow-up: 11.1 months.
Krop et al, SABCS 2019. Abstract GS1-03; Modi et al. *N Engl J Med.* 2020;382:610-621.

- This trial had previously reported and had shown a really remarkable high confirmed overall response rate of almost 61%, including some complete responses in a group of patients that were quite heavily pretreated, median prior lines of cancer therapy, 6. And this waterfall plot made an indelible impression in everyone's mind, the potent activity of this agent, with a confirmed response rate of about 61%.

Phase 3 DESTINY-Breast02: Study Design
T-DXd in Third-Line Setting, Previously Treated With T-DM1



IV, intravenously; q3w, every 3 weeks; T-DM1, trastuzumab emtansine.
ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03523585; Krop et al, SABCS 2022. Abstract GS2-01.

- And our additional data with this agent was presented—again hot off the presses from San Antonio—this was the confirmatory phase 3 study, the DESTINY-Breast02 trial. Again, now our standard of care has changed in that we're using T-DXd in the second line. So the applicability of these data is somewhat questionable in terms of the fact that I think most of our patients will have already received T-DXd in the second line, but certainly these are important data to continue to lend support to utilize T-DXd in the patients that have not seen it yet and have perhaps already received treatment with T-DM1. These patients had archived sample HER2+ centrally confirmed disease and were randomized 2 to 1 to T-DXd vs treatment of physician's choice of trastuzumab and capecitabine or lapatinib and capecitabine.

Phase 3 DESTINY-Breast02: Efficacy

Efficacy Endpoints	T-DXd (n=406)	TPC (n=202)
Median follow-up	21.5 months	18.6 months
Median PFS	17.8 months	6.9 months
HR	0.3589	
P	<.000001	
Median OS	39.2 months	26.5 months
HR	0.6575	
P	.0021	
Confirmed ORR by BICR	69.7%	29.2%
P	<.001	

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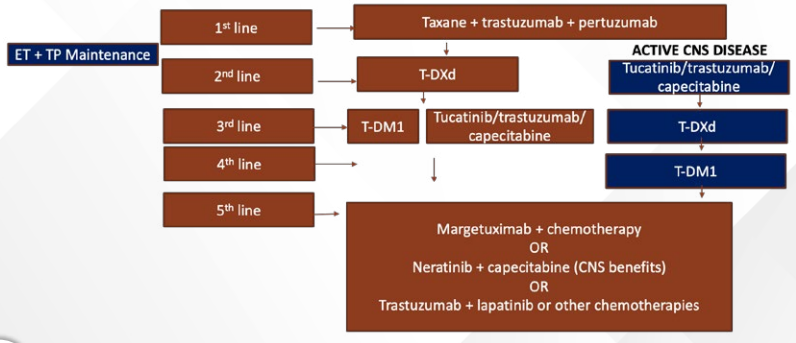
TPC, treatment of physician's choice.
Krop et al, SABCS 2022. Abstract GS2-01.

- Median follow-up was about 20 months and the median PFS: 17.8 months vs 6.9 months in the TPC arm, hazard ratio 0.3589, highly statistically significant. Certainly not surprising to see this remarkable efficacy in a larger randomized study. Again, building on the DESTINY-Breast01 nonrandomized single-arm phase 2 study, median overal survival is statistically significant and much higher response rate as well.

Post-ESMO 2021 Approach to Therapy

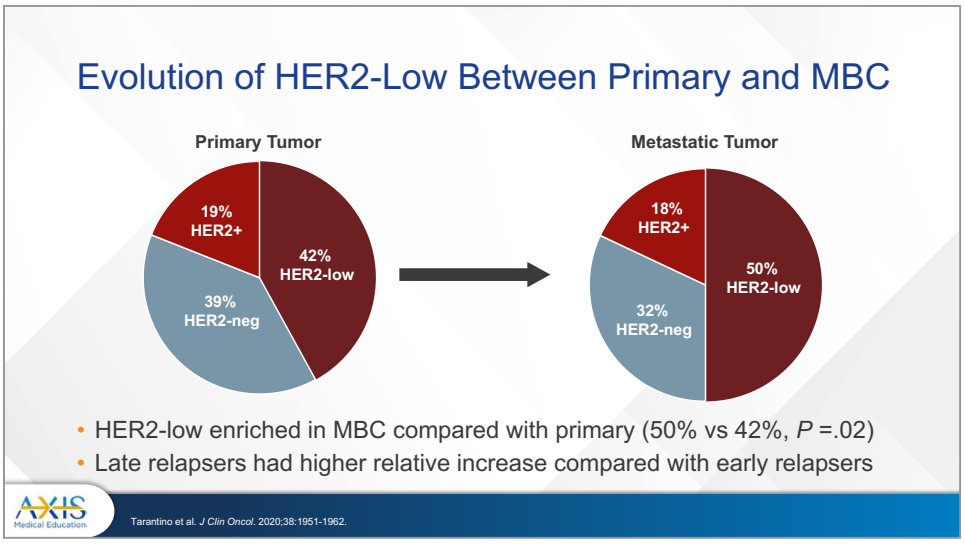


AXIS Medical Education

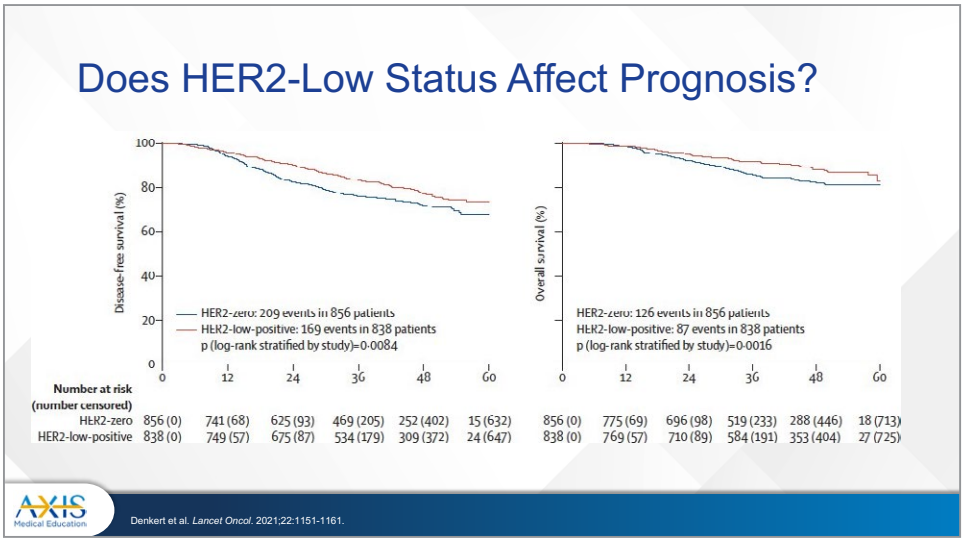
CNS, central nervous system; ESMO, European Society for Medical Oncology; ET, endocrine therapy.
Adapted from Modi et al. *N Engl J Med*;2020;382(7):610-621; Gennari et al. *Ann Oncol*. 2021;32(12):1475-1495.

- So as I mentioned, at ESMO in 2021, the DB03 data were first presented and that's why this slide says the post-ESMO 2021 approach to therapy. What hadn't changed is our first-line treatment with trastuzumab, a taxane, and pertuzumab based on the CLEOPATRA data. And in the second line, what really did change is the jump of T-DXd into the second line for the majority of patients, as we saw the remarkable efficacy of this highly potent ADC, a caveat being in patients who have active CNS disease, where tucatinib has been studied, especially in those with active brain metastases. The combination of tucatinib, trastuzumab, and capecitabine could be considered in the second line and beyond based on the FDA approved label of that triplet combination. And then in the third line, you see that for those patients who had not received T-DM1, it could be considered, or the tucatinib regimen.

  Of course, an unanswered question here is, what will the activity of T-DM1 be post T-DXd? We certainly still need to do a lot more to identify mechanisms of resistance and biomarkers of response to understand if there would be efficacy noted there. And then, of course, as we move further through this algorithm, we still have other targeted therapies, including the newly approved FC-engineered monoclonal antibody margetuximab, along with the neratinib-capecitabine combination, and other chemotherapy agents given in combination with trastuzumab.



Now, let's shift gears a bit. We talked about, at the beginning of this presentation, the definition of HER2+ and HER2 low. And as we move into the discussion regarding HER2 low, it's informative to look at the evolution of HER2 low between the primary and metastatic breast cancer specimens. At least in this analysis, it looked like HER2 low was enriched in MBC compared with the primary. We see when tested on the primary, 42% in the series were HER2 low as opposed to 50% in the metastatic sites. Late relapses also had a higher relative increase compared with early relapsers.



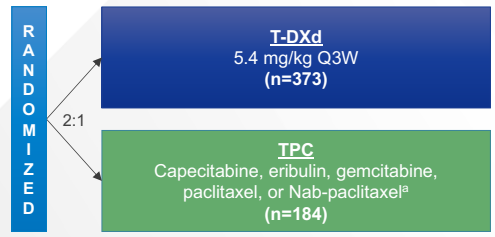
So certainly at San Antonio we heard a lot of debate regarding this question: Does HER2 low affect prognosis? And that was the subject of this current analysis, where the objective of the analysis was to characterize this new breast cancer subtype. The investigators compared the clinical and molecular characteristics of a HER2-low breast cancer and HER2-0 breast cancer, including response to neoadjuvant chemotherapy and prognosis.

So here in this analysis, patients with HER2-low tumors had significantly longer survival than in those with HER2-0 tumors, 3-year invasive-disease-free survival was 83.4% vs 76.1% and overall survival 91.6% vs 85.8%. And they concluded that HER2-low tumors had a specific biology and showed a difference in response to therapy and prognosis, which is particularly relevant in therapy-resistant, hormone-receptor–negative tumors. And I think we still have quite a bit to learn about this new subtype.

Results From the Phase 3 DESTINY-Breast04 Trial of Trastuzumab Deruxtecan in HER2-Low MBC: Study Design and Patients

Key Eligibility Criteria

- HER2-low (IHC 1+ or IHC 2+/ISH-) unresectable and/or MBC
- ≥1 prior line of chemotherapy in the metastatic setting or disease recurrence ≤6 months after adjuvant therapy
- ≥1 line of endocrine therapy if HR+ MBC



Primary endpoint: PFS by BICR (HR+)
Key secondary endpoints[b]: PFS by BICR (all patients), OS (HR+ and all patients)

Patient Characteristics		HR+		All Patients	
		T-DXd (n=331)	TPC (n=163)	T-DXd (n=373)	TPC (n=184)
Median age (range), years		57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
HER2 status (IHC), n (%)	1+	193 (58)	95 (58)	215 (58)	106 (58)
	2+/ISH-	138 (42)	68 (42)	158 (42)	78 (42)
HR positive,[c] n (%)		328 (99)	162 (99)	333 (89)	166 (90)
ECOG PS, n (%)	0	187 (56)	95 (58)	200 (54)	105 (57)
	1	144 (44)	68 (42)	173 (46)	79 (43)
Metastases at baseline, n (%)	Brain	18 (5)	7 (4)	24 (6)	8 (4)
	Liver	247 (75)	116 (71)	266 (71)	123 (67)
	Lung	98 (30)	58 (36)	120 (32)	63 (34)
Prior lines of chemo (MBC setting)	Median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
	≥3, n (%)	3 (0.9)	0	6 (1.6)	0
Prior lines of endocrine therapy (MBC setting)	Median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
	≥3, n (%)	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)	Targeted	259 (78)	132 (81)	279 (75)	140 (76)
	CDK4/6i	233 (70)	115 (71)	239 (64)	119 (65)

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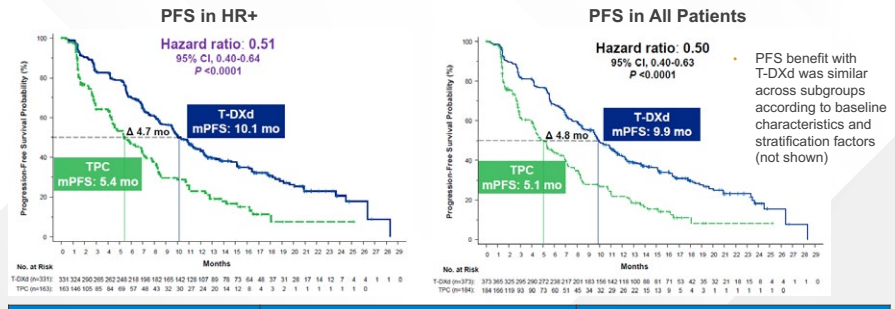
Data cutoff: January 11, 2022.
[a]TPC was administered according to the label. [b]Other secondary endpoints included ORR (BICR and INV), DOR (BICR), PFS (INV), and safety. Efficacy in the HR- cohort was an exploratory endpoint. [c]HR status was based on data collected using interactive web/voice response system at randomization, which includes mis-stratified patients.
Modi et al. *J Clin Oncol*. 2022;40(17):LBA3; Modi et al. *N Engl J Med*. 2022;387:9-20.

The study that really informed our utilization of the ADC, trastuzumab deruxtecan, in HER2-low disease was the DESTINY-Breast04 trial. This was a very important, pivotal study, which subsequently led to the approval of trastuzumab deruxtecan in HER2-low disease, remarkably changing the nomenclature of all of HER2+ and HER2-negative metastatic disease.

So in this trial, HER2 low was defined as 1+ or 2+ and ISH negative, unresectable, and/or metastatic disease, with patients having been required to receive at least 1 prior line of chemo in the metastatic setting. Or they could enroll if their disease had recurred ≤6 months after completion of adjuvant therapy. For those who were ER positive, HER2 low, and just to be clear, the majority of patients that were enrolled on this trial were hormone-receptor positive, HER2 low, they were required to have received at least 1 line of therapy with endocrine therapy if these patients had hormone-receptor–positive disease. And they were randomized 2 to 1 to T-DXd vs treatment of physician's choice, including capecitabine, eribulin, gemcitabine, or a taxane. And the primary endpoint was PFS in the hormone-receptor–positive group, with key secondary endpoints being PFS in all patients. So including that smaller subset that were ER negative, HER2 low and overall survival in the HR positive and all patients.

The patient characteristics broken down here: median age was mid-50s. HER2 status, almost 60% were 1+; the other 40% were 2+ and ISH negative. Again, as I mentioned a moment ago, the vast majority of these patients were ER positive with a good performance status. And not surprisingly, many of these patients had received several targeted therapies that are shown below and had significant burden of visceral disease in about two-thirds of these patients, with the median prior lines of chemo being, 1, so many of these patients were treated in the second line. And about 70% had received prior CDK4/6 inhibitor therapy.

Results From the Phase 3 DESTINY-Breast04 Trial of Trastuzumab Deruxtecan in HER2-Low MBC: Efficacy



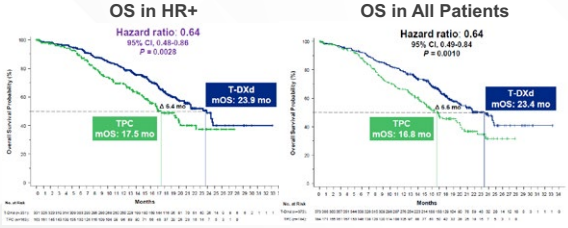
PFS benefit with T-DXd was similar across subgroups according to baseline characteristics and stratification factors (not shown)

PFS	HR+		All Patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n=373)	TPC (n = 184)
Median PFS, months	10.1	5.4	9.9	5.1
HR (95% CI); *P* value	0.51 (0.40-0.64); <.0001		0.50 (0.40-0.63); <.0001	

Modi et al. *J Clin Oncol*. 2022;40(17):LBA3.

- Here are the efficacy data from this pivotal study, where we see the PFS in the hormone-receptor–positive patients, T-DXd median PFS was 10.1 months as compared to the TPC arm of 5.4 months; that's hazard ratio of 0.51, highly statistically significant. And then including those ER-negative, HER2-low patients, the PFS in all patients a very consistent hazard ratio of 0.5, again statistically significant, with the median PFS being 9.9 months vs 5.1 months. And the benefit was similar across subgroups according to baseline characteristics and stratification factors, which is not shown on this slide.

Results From the Phase 3 DESTINY-Breast04 Trial of Trastuzumab Deruxtecan in HER2-Low MBC: Efficacy (cont.)



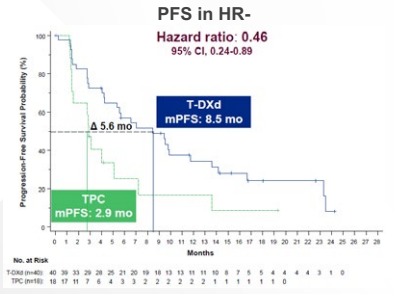
Response	HR+		HR-	
	T-DXd (n=333)	TPC (n=166)	T-DXd (n=40)	TPC (n=18)
Confirmed ORR, %	52.6	16.3	50.0	16.7
CR	3.6	0.6	2.5	5.6
PR	49.2	15.7	47.5	11.1
PD	7.8	21.1	12.5	33.3
NE	4.2	12.7	7.5	5.6
CBR, %	71.2	34.3	62.5	27.8
Median DOR, months	10.7	6.8	8.6	4.9

OS	HR+		All Patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Median OS, months	23.9	17.5	23.4	16.8
HR (95% CI); *P* value	0.64 (0.48-0.86); .0028		0.64 (0.49-0.84); .0010	

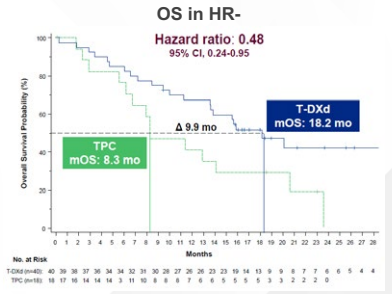
Modi et al. *J Clin Oncol*. 2022;40(17):LBA3.

- In terms of the endpoint of overall survival, again, the overall survival benefit in the ER-positive patients: about 6 months and including all patients, including the ER negative, HER2 low. And the confirmed overall responses being much higher in the T-DXd arm in both HR-positive and HR-negative patients.

Results From the Phase 3 DESTINY-Breast04 Trial of Trastuzumab Deruxtecan in HER2-Low MBC: Efficacy (cont.)



PFS	HR-	
	T-DXd (n=40)	TPC (n=18)
Median PFS, months	8.5	2.9
HR (95% CI)	0.46 (0.24-0.89)	



OS	HR-	
	T-DXd (n=40)	TPC (n=18)
Median OS, months	18.2	8.3
HR (95% CI)	0.48 (0.24-0.95)	

Modi et al. *J Clin Oncol*. 2022;40(17):LBA3.

- In this analysis, there was also an analysis of the smaller numbers of patients that were included that were ER negative or HR negative, hormone-receptor negative. The randomization was 2 to 1 so there were about 60 patients total, 40 and about 20 in the other group, that had had T-DXd as compared to TPC. And we see, again, very consistent hazard ratios but certainly much smaller numbers here. But pointing to a clear signal of activity, even in the ER-negative, HER2-low patients.

Trastuzumab Deruxtecan FDA Approved for HER2-Low MBC: August 2022

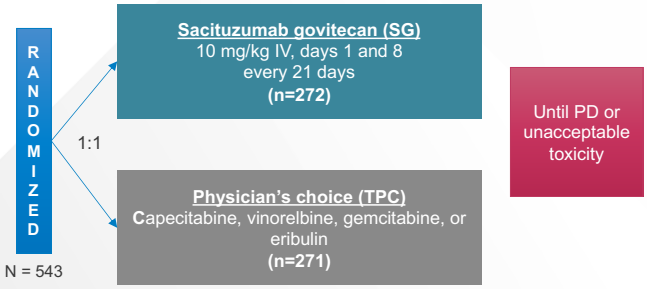
- Trastuzumab deruxtecan FDA approved for adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- Based on DESTINY-Breast04 trial
- Recommended dose: 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity

FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-her2-low-breast-cancer/

- And on the basis of this important study in August of last year, trastuzumab deruxtecan was FDA approved for adult patients with unresectable or metastatic HER2-low breast cancer in those patients that have received a prior chemotherapy in the metastatic setting or develop disease recurrence during or within 6 months of completing adjuvant chemotherapy. This approval was based on the DB04 trial, which I've just gone through with you. As a reminder, the dosing is 5.4 mg/kg as an IV infusion once every 3 weeks (21-day cycle) until disease progression or intolerable toxicity.

Primary Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2- Advanced BC: Study Design and Patients

Key Eligibility Criteria
- HR+/HER2- MBC (or locally recurrent inoperable) with PD after
  - ≥1 endocrine therapy, taxane, and CDK4/6i in any setting
  - ≥2 to ≤4 lines of chemotherapy for metastatic disease
  - Measurable disease by RECIST 1:1



Primary endpoint: PFS by BICR
Secondary endpoints: OS, ORR, DOR, CBR by LIR and BICR, PRO, safety

Patient Characteristics		SG (n=272)	TPC (n=271)
Median age (range), y		57 (29-86)	55 (27-78)
ECOG PS, n (%)	0	116 (43)	126 (46)
	1	156 (57)	145 (54)
Visceral mets at baseline, n (%)		259 (95)	258 (95)
Liver mets, n (%)		229 (84)	237 (87)
Median time from initial MBC diagnosis to randomization (range), months		48.5 (1.2-243.8)	46.6 (3.0-248.8)
Prior chemotherapy in (neo)adjuvant setting, n (%)		173 (64)	184 (68)
Prior endocrine therapy use in the metastatic setting ≥6 months, n (%)		235 (86)	234 (86)
Prior CDK4/6i, n (%)	≤12 months	161 (59)	166 (61)
	>12 months	106 (39)	102 (38)
	Unknown	5 (2)	3 (1)
Median prior chemotherapy regimens in the metastatic setting (range), n		3 (0-8)	3 (1-5)

AXIS Medical Education

LIR, local investigator review; PRO, patient-reported outcomes; SG, sacituzumab govitecan.
Rugo et al. *J Clin Oncol*. 2022;40(17):LBA1001.

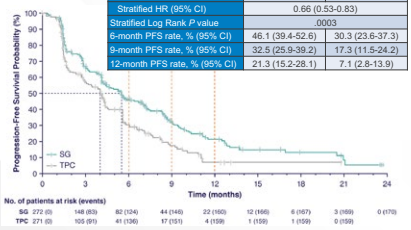
So we also have another ADC, sacituzumab govitecan. This is a highly potent ADC that is currently already approved for triple-negative breast cancer patients and has shown activity in a heavily pretreated population of HR-positive, HER2-negative patients based on the phase 3 TROPiCS-02 trial. So here, we see patients that are hormone-receptor positive, HER2 negative, not specifically HER2 low, but our prior definition of HER2 negative with progressive disease after at least 1 line of prior endocrine therapy, taxane, and a CDK4/6 inhibitor in any setting. Notice here that patients had to have at least 2 but no more than 4 prior lines of chemo for metastatic disease. So as compared to the DB04 data that we just went through, this patient population was more heavily pretreated. They were randomized 1 to 1 to the ADC sacituzumab govitecan vs physician's choice treatment, including the usual drugs that we would consider giving in the setting: capecitabine, vinorelbine, gemcitabine, or eribulin. Again, these patients were treated until progressive disease or unacceptable toxicity, and the primary endpoint was PFS.

The patient characteristics table is summarized. Most patients are in their mid-50s, very heavy disease burden in terms of visceral metastases: 95%, with 84% to 87% having liver metastases, many of these patients having received prior chemotherapy, and the endocrine therapy. Again, the patients would have received a prior CDK4/6 inhibitor, as shown here. This was broken down by their duration of response to that therapy, with the median prior chemo regimens being 3. So, most of these patients being treated quite later on with this agent.

Primary Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2− Advanced BC: Efficacy

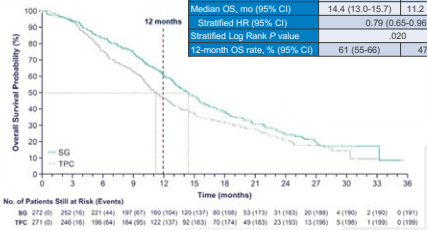
BICR-Assessed PFS in the ITT Population

PFS Analysis	SG (n = 272)	TPC (n = 271)
Median PFS, mo (95% CI)	5.5 (4.2-7.0)	4.0 (3.1-4.4)
Stratified HR (95% CI)	0.66 (0.53-0.83)	
Stratified Log Rank *P* value	.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4-52.6)	30.3 (23.6-37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9-39.2)	17.3 (11.5-24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2-28.1)	7.1 (2.8-13.9)



OS in the ITT Population (Second Interim Analysis)

OS Analysis	SG (n = 272)	TPC (n = 271)
Number of Events	191	199
Median OS, mo (95% CI)	14.4 (13.0-15.7)	11.2 (10.1-12.7)
Stratified HR (95% CI)	0.79 (0.65-0.96)	
Stratified Log Rank *P* value	.020	
12-month OS rate, % (95% CI)	61 (55-66)	47 (41-53)

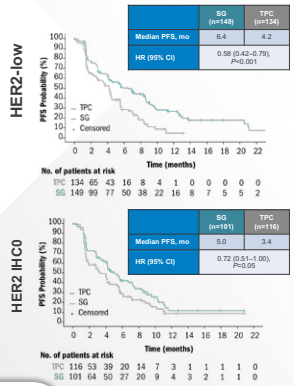


- SG resulted in a 34% reduction in the risk of PD/death
- SG resulted in PFS and OS benefit consistent across all subgroup analysis, including patients with
  - ≥3 prior chemotherapy regimens in the metastatic setting
  - Visceral metastases
  - Endocrine therapy for MBC ≥6 months

Rugo et al. *J Clin Oncol.* 2022;40(17):LBA1001.

And what we did see in this trial was a benefit in terms of median PFS; the hazard ratio was 0.66, 5.5 months in the SG arm compared to 4 months in the treatment of physician's choice arm, highly statistically significant, resulting in a 34% reduction in the risk of progression or death. And the results in terms of PFS were consistent across all subgroups, as detailed on the bottom. Initially, we did not have overall survival but subsequently updated results from last year at second interim analysis did show about a 3-month improvement in overall survival, which I would say is quite clinically meaningful, as these patients are heavily pretreated and certainly require additional treatment options that are efficacious.

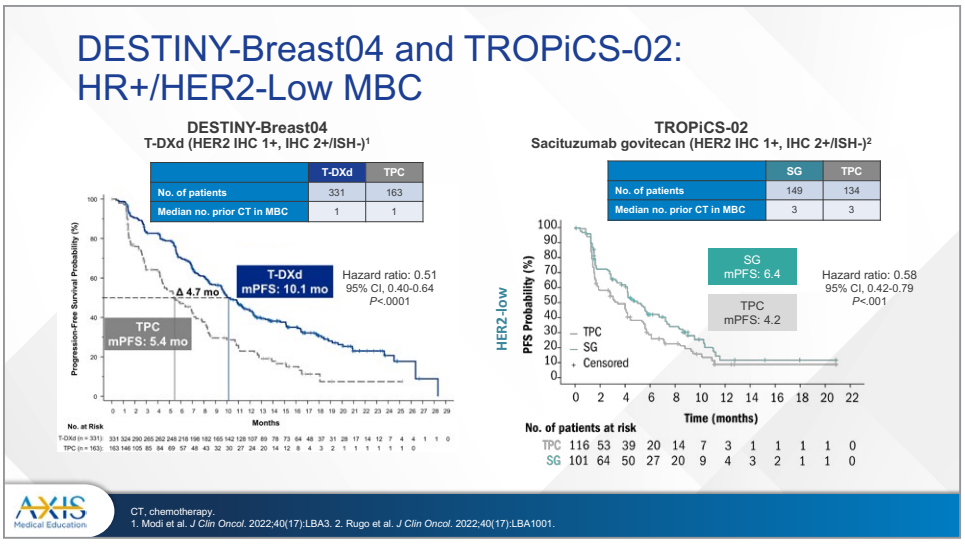
Primary Results From the Phase 3 TROPiCS-02 Trial of Sacituzumab Govitecan in HR+/HER2- Advanced BC: PFS and ORR by HER2 Status



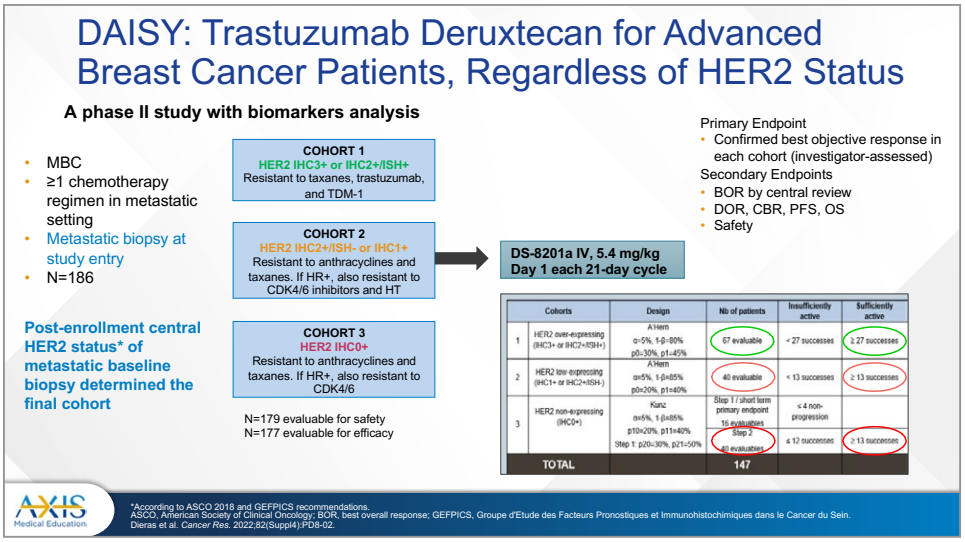
BICR Analysis		ITT		HER2-low		HER2 IHC0	
		SG (n=272)	TPC (n=271)	SG (n=149)	TPC (n=134)	SG (n=101)	TPC (n=116)
ORR, n (%)		57 (21)	38 (14)	38 (26)	16 (12)	16 (16)	17 (15)
Odds ratio (95% CI)		1.63 (1.04-2.55)		2.52 (1.33-4.78)		1.10 (0.52-2.30)	
Best overall response, n (%)	CR	2 (1)	0	2 (1)	0	0	0
	PR	55 (20)	38 (14)	36 (24)	16 (12)	16 (16)	17 (15)
	SD	142 (52)	106 (39)	73 (49)	61 (46)	56 (55)	39 (34)
	SD ≥6 months	35 (13)	21 (8)	18 (12)	10 (7)	15 (15)	8 (7)
	PD	58 (21)	76 (28)	29 (19)	36 (27)	23 (23)	38 (33)
	NE	15 (6)	51 (19)	9 (6)	21 (16)	6 (6)	22 (19)
CBR,[b] n (%)		92 (34)	59 (22)	56 (38)	26 (19)	31 (31)	25 (22)
Odds ratio (95% CI)		1.84 (1.25-2.69)		2.50 (1.46-4.30)		1.61 (0.87-2.97)	
Median DOR, months (95% CI)		7.4 (6.5-8.6)	5.6 (3.8-7.9)	7.4 (5.8-8.9)	4.1 (2.8-6.1)	8.1 (4.1-NE)	6.1 (2.8-8.3)

[a]Not formally tested because OS at interim analysis was not statistically significant. [b]CBR is defined as the percentage of patients with a confirmed best overall response of CR, PR, and SD ≥6 months.
Rugo et al. *J Clin Oncol.* 2022;40(17):LBA1001; Schmid et al. *Ann Oncol.* 2022;33:S88-S121.

So now this trial—there was an ad-hoc analysis looking at the benefit of sacituzumab govitecan in patients with HR-positive, HER2-negative advanced breast cancer broken down by HER2-low status. So, recall, these patients did not require HER2 low specifically to go on the trial, as opposed to the DB04 data where those patients exclusively had HER2-low disease. Here, some of these patients were HER2 IHC-0, and others were HER2 low. And the response rates were broken down by HER2 low and IHC-0 as compared to that intent-to-treat population. And so this ad hoc analysis basically showed that there were consistent results in patients with HER2-low disease, again giving us some assurance that, regardless of HER2-low status, this therapy could be considered.



Now we see the results of DESTINY-Breast04 and TROPiCS-02, looking specifically at this HER2-low ad hoc analysis that I just went through with you in the TROPiCS-02 trial, looking at that as well with the patients in the DB04 trial that were exclusively HER2 low. And this is not meant to be comparative because, recall that there were patients that were more heavily pretreated in the TROPiCS-02 trial. So when looking at the magnitude of benefit of these 2 highly potent ADCs, I would say that we can't draw any conclusions that one is better than the other knowing that the populations that they were studied in were different. But certainly good news for our patients in terms of options for further therapy.



Now, looking back at this agent, trastuzumab deruxtecan, we talked about the activity in HER2+ disease. I've shown you some data that led to the approval of this agent for HER2-low disease. This is an important study, the DAISY trial, because it was a phase 2 study with biomarker analyses with 3 cohorts. One was the clearly HER2+ patients, cohort 2 were the HER2-low patients, and cohort 3 were actually patients that would not have been eligible for DB04 because these were completely IHC-0, so not HER2 low. And this was tested centrally post enrollment; the central HER2 status of metastatic baseline biopsy determined which of the final cohorts.

DAISY: Results

Median follow-up: 15.6 months

	Total	Cohort 1 (HER2 over-expressing)	Cohort 2 (HER2 low-expressing)	Cohort 3 (HER2 non-detected)
BOR confirmed n/N [95%CI]	86 / 177 (48.6%) [41.0-56.2]	48 / 68 (70.6%) [58.3-81.0]	27 / 72 (37.5%) [26.4-49.7]	**11 / 37 (29.7%)** [15.9-47.0]
Median DOR (mo)	8.5 [6.5-9.8]	9.7 [6.8-13]	7.6 [4.2-9.2]	6.8[2.8-NR]
Median PFS (mo) [95%CI]	7.0 [6.0-8.7]	**11.1** [8.5-14.4] HR+=11 TNBC =12.2	**6.7** [4.4-8.3] **HR+=6.9 TNBC=3.5**	**4.2** [2.0-5.7] **HR+=4.5 TNBC=2.1**

Cohort 3
≥13/40 confirmed BOR needed to declare success

Dieras et al. *Cancer Res*. 2022;82:PD8.02.

- And what we saw, remarkably, in this study was that this agent trastuzumab deruxtecan, in this small group, had activity almost 30% in even those patients that were HER2-0, that's that cohort 3. So certainly thought provoking.

  And I would just remind you that, as we reviewed earlier, the definition of IHC-0, it doesn't mean no HER2 staining, it just means <10%. So if this is based on some HER2 expression or if there are issues with concordance in testing, it could certainly be related to that. But remember, in this situation, these patients were clearly centrally confirmed. So, a clear signal that there may be some activity of this agent even in IHC-0, which is certainly remarkable to see but needs to be further proven.

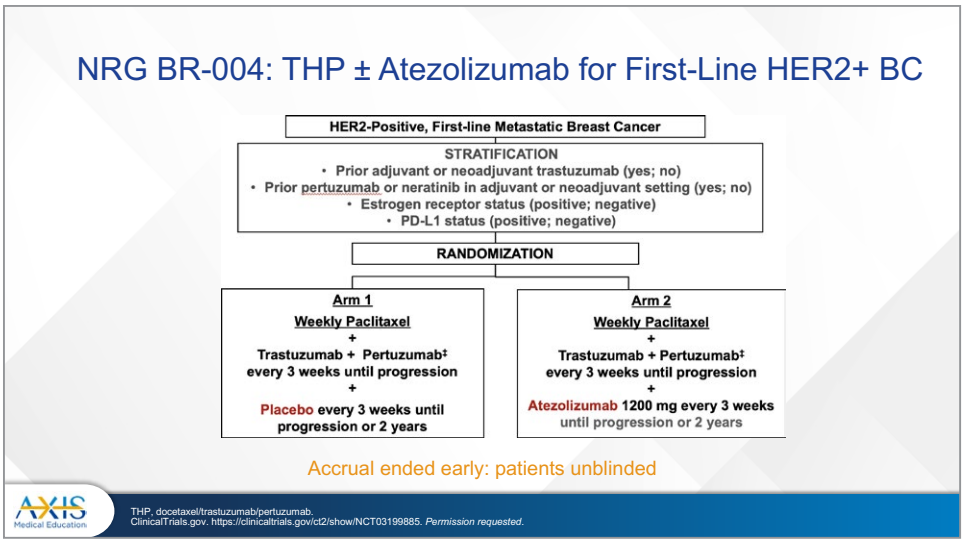
Immunotherapy for HER2+ Breast Cancer

	PANACEA[1]	KATE-2[2]	NCT02649686[3]	JAVELIN Sol Tum[4]
Study design	Phase 1b to 2, single-arm	Phase 2, randomized	Phase 1	Phase 1b
Patient Population	HER2+ ABC, progressed during trastuzumab-based therapy	HER2+ ABC, previously treated with trastuzumab and a taxane	HER2+ ABC, previously treated with trastuzumab and taxanes	MBC refractory to or progressing after standard-of-care therapy
N HER2+ pts (PD-L1+)	52 (40)	202 (84)	15 (0)	26
Treatments	Pembrolizumab + trastuzumab	Atezolizumab + T-DM1 vs placebo + T-DM1	Durvalumab + trastuzumab	Avelumab
ORR	15% of PD-L1-positive pts No objective responses among PD-L1-pts	54% vs 33% in PD-L1-positive pts; 39% vs 50% in PD-L1-negative pts	0/15	0/26
Median PFS	2.7 months (90% CI 2.6-4.0) in PD-L1-positive 2.5 months (90% CI 4.9-9.8) in PD-L1-negative	8.2 vs 6.8 months in ITT (HR 0.82, 95% CI 0.55-1.23) 8.5 vs 4.1 months in PD-L1-positive (HR 0.60, 95% CI 0.32-1.1)	--	--
Median OS	Not reached (90% CI 13.1 to NR) in PD-L- positive 7.0 months (90% CI 4.9-9.8) in PD-L1-negative	Not reached in ITT (HR 0.74, 95% CI 0.42-1.30) Not reached in PD-L1-positive (HR 0.55, 95% CI 0.22-1.38)	--	--

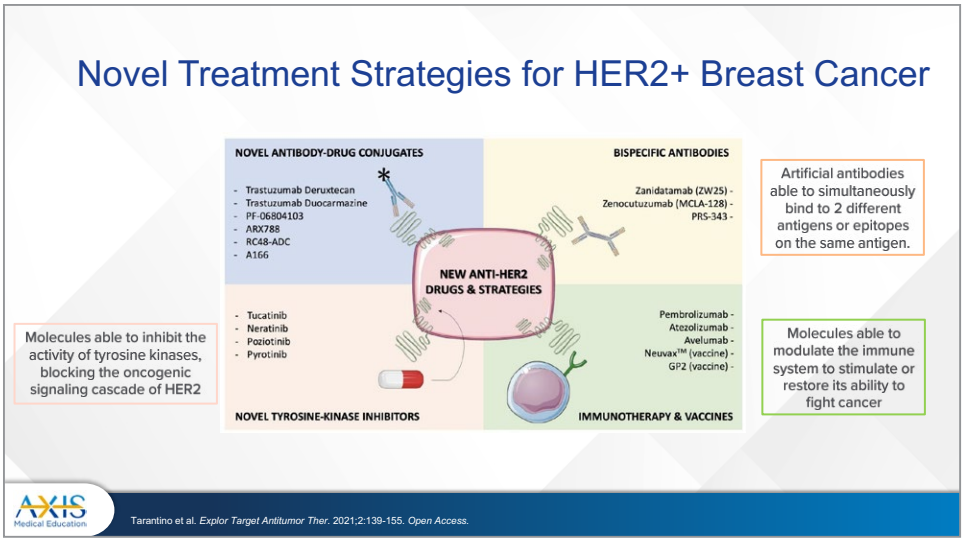
Low antitumor efficacy in unselected heavily pretreated patients with HER2+ MBC: Signal in PD-L1+

ABC, advanced breast cancer; PD-L1, programmed death ligand 1.
1. Loi et al. *Lancet Oncol*. 2019;20:371-382. 2. Emens et al. *Lancet Oncol*. 2020;21:1283-1295.
3. Azambuja et al. ESMO Virtual Plenary 2021. 4. Dirix et al. *Breast Cancer Res Treat*. 2018;167:671-686.

- What about immunotherapy for HER2+ breast cancer? Well, this is a nice summary slide that has illustrated some of the attempts that had been made to look at the utilization of various immunotherapy agents, including pembrolizumab, atezolizumab, durvalumab, and avelumab. And the summary, take-home message from all of these studies is that there overall has been low antitumor efficacy in an unselected, heavily pretreated patient population with HER2+ MBC, certainly perhaps a signal in those that are PD-L1 positive.



- I'll just point out that this is a study run through the NRG-B004, which was looking to identify whether there was a benefit of adding immunotherapy, in this case atezolizumab, to our standard backbone of THP, meaning that CLEOPATRA regimen that we've already gone through. This trial accrual ended early. Patients were unblinded; there were some safety issues of concern here. So certainly the story about whether or not there is a role for immunotherapy in HER2+ breast cancer remains not clearly answered at this point.



- In terms of novel strategies for HER2+ breast cancer, there are other agents under investigation, including novel ADCs, other tyrosine kinase inhibitors, bispecific antibodies that are able to simultaneously bind to 2 different antigens or epitopes on the same antigen and force that connection between the immune system and the tumor cells. And then, of course, as I mentioned, I think the story regarding immunotherapy and vaccines is still not fully answered and is certainly an area of interest moving forward.

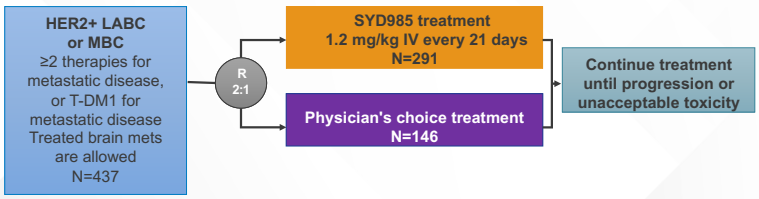
Select ADCs in Development for HER2+ Breast Cancer

ADC	Target	Antibody	Payload	DAR	Clinical Program
SYD985[1]	HER2	Trastuzumab	Duocarmycin	2.8	Phase 3
ARX788[2]	HER2	ND	Amberstatin269	2	Phase 1 /2 MBC
RC48 (disitamab)[3]	HER2	Hertuzumab	MMAE	4	Phase 3
A166[4]	HER2	Trastuzumab	Duostatin-5	ND	Phase 1 /2 BC
ZW49[5]	HER2	Bispecific	Auristatin	2	Phase 1
ALT-P7 (HM2-MMAE)[6]	HER2	HM2	MMAE	ND	Phase 1 MBC

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03262935; 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04829604; 3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03052634; 4. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03602079; 5. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03821233; 6. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03281824.

- This slide summarizes select ADCs that are in development for HER2+ MBC. And you see, many of these are just drugs without a name as yet, just letters and numbers, and they're certainly in various phases of clinical development, with different DARs, payloads, antibodies, with the target all being HER2 here.

TULIP: Phase III Trial Design



Stratification factors

- Region (EU + Singapore vs North America)
- Number of prior treatment lines for LMBC/MBC (1 to 2 vs >2)
- Prior treatment with pertuzumab (yes vs no)

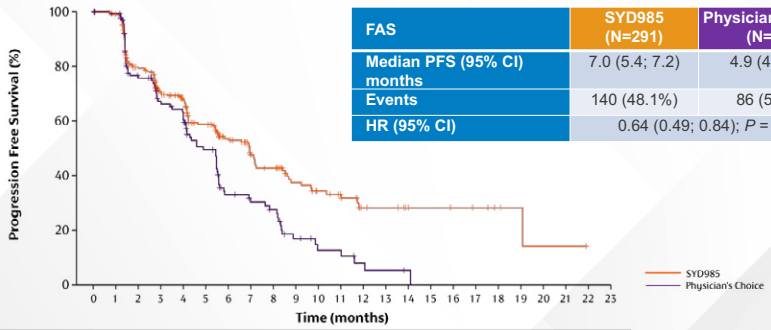
Physician's choice

- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + vinorelbine
- Trastuzumab + eribulin

LABC, locally advanced breast cancer.
Manich et al. *Ann Oncol.* 2021;32:S1283-S1346.

- One of these was investigated in a randomized phase 3 study called the TULIP trial, with SYD985. This was a therapy that was evaluated in patients that had received ≥2 prior therapies in the metastatic setting or T-DM1 for metastatic disease. Patients with brain metastases were permitted to enroll if they were treated. And the randomization was to SYD985 vs treatment of physician's choice.

TULIP: Centrally Reviewed PFS



FAS	SYD985 (N=291)	Physician's Choice (N=146)
Median PFS (95% CI) months	7.0 (5.4; 7.2)	4.9 (4.0; 5.5)
Events	140 (48.1%)	86 (58.9%)
HR (95% CI)	0.64 (0.49; 0.84); *P* = .002	

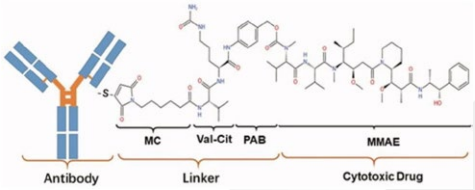
No. Patients at Risk																							
SYD985	291	278	208	167	150	109	83	59	51	35	28	24	13	12	9	8	6	5	3	2	1	1	0
Physician's Choice	146	125	86	69	64	44	26	22	19	10	6	6	3	2	1	0							

Manich et al. *Ann Oncol*. 2021;32:S1283-S1346.

- And what we did see was about a 2-month improvement in PFS, hazard ratio of 0.64, statistically significant with a *P*-value of 0.002 favoring the utilization of SYD985.

Disitamab Vedotin (RC48)

- Hertuzumab: mAb against a different epitope and better molecular affinity than trastuzumab
- Protease-cleavable linker
- MMAE payload
- DAR 4:1
- Bystander effect: YES
- Conditional approval in China for platinum-refractory HER2+ advanced urothelial cancer
- FDA granted breakthrough therapy designation for mUC in 2020



mAb, monoclonal antibody; MMAE, monomethyl auristatin E; mUC, metastatic urothelial cancer.
Jiang et al. *Toxicol Lett*. 2020;324:30-37; Deeks. *Drugs*. 2021;81:1929-1935. *Open Access*.

- Other ADCs under investigation include RC48. This is an agent that has MMAE as a payload; the DAR is 4 to 1. There is a bystander effect noted with this agent. And there is a conditional approval in China for platinum-refractory, HER2+ advanced urothelial cancer, and the FDA has granted this as breakthrough therapy for urothelial cancer in 2020.

RC48 Phase 1: Efficacy

Key Patient Characteristics

- 70% prior anti-HER2 therapy
- 35% ER+
- 40% in ER+ cohort had prior HT 89% visceral mets

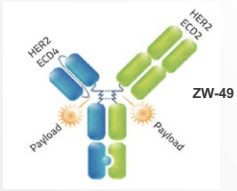
	HER2+ BC			HER2+ BC	HER2-low BC
	N = 18 (1.5 mg/kg)	N = 21 (2.0 mg/kg)	N = 25 (2.5 mg/kg)	N = 70	N = 48 (2.0 mg/kg)
BOR				BOR	
CR	0	0	0	CR	0	0
PR	4 (22.2)	9 (42.9)	10 (40.0)	PR	23 (32.9)	19 (39.6)
SD	12 (66.7)	11 (52.4)	13 (52.0)	SD	39 (55.7)	25 (52.1)
PD	2 (11.1)	1 (4.8)	0	PD	6 (8.6)	4 (8.3)
NE	0	0	2 (8.0)	NE	2 (2.9)	0
Confirmed ORR	4 (22.2)	9 (42.9)	10 (40.0)	Confirmed ORR	23 (32.9)	19 (39.6)
95%CI	6.4 to 47.6	21.8 to 66.0	21.1 to 61.3	95%CI	22.1 to 45.1	25.8 to 54.7
Confirmed DCR	16 (88.9)	19 (90.5)	22 (88.0)	Confirmed DCR	60 (85.7)	43 (89.6)
95%CI	65.3 to 98.6	69.6 to 98.8	21.1 to 61.3	95%CI	22.1 to 45.1	25.8 to 54.7
CBR	4 (22.2)	10 (47.6)	12 (48.0)	CBR	26 (37.1)	23 (47.9)
95%CI	65.3 to 98.6	25.7 to 70.2	21.1 to 61.3	95%CI	25.9 to 49.5	33.3 to 62.8
Median PFS, months	4	5.7	6.3	Median PFS, months	5.5	5.7
95%CI	2.6 to 7.6	5.3 to 8.4	4.3 to 8.8	95%CI	4.6 to 6.5	4.1 to 8.3

BOR, best overall response; HT, hormone therapy.
Wang et al. *J Clin Oncol*. 2021;39(5):1022.

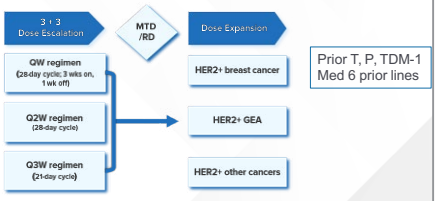
- In terms of efficacy in breast cancer patients, the patients that were studied with this agent in phase 1, in terms of their characteristics summarized on the left. And some promising activity noted in both HER2+ as well as HER2-low MBC patients, again, in phase 1.

ZW49: Bispecific HER2 ADC

- HER2-targeting bispecific antibody (ECD4 and ECD2)
  - Ab sequence identical to zanidatamab (ZW25)
- Proprietary auristatin toxin covalently linked via a protease cleavable valine-citrulline linker
- Average DAR=2
- Enhanced internalization and toxin-mediated cytotoxicity/immunogenic cell death



Ongoing Phase 1 FIH

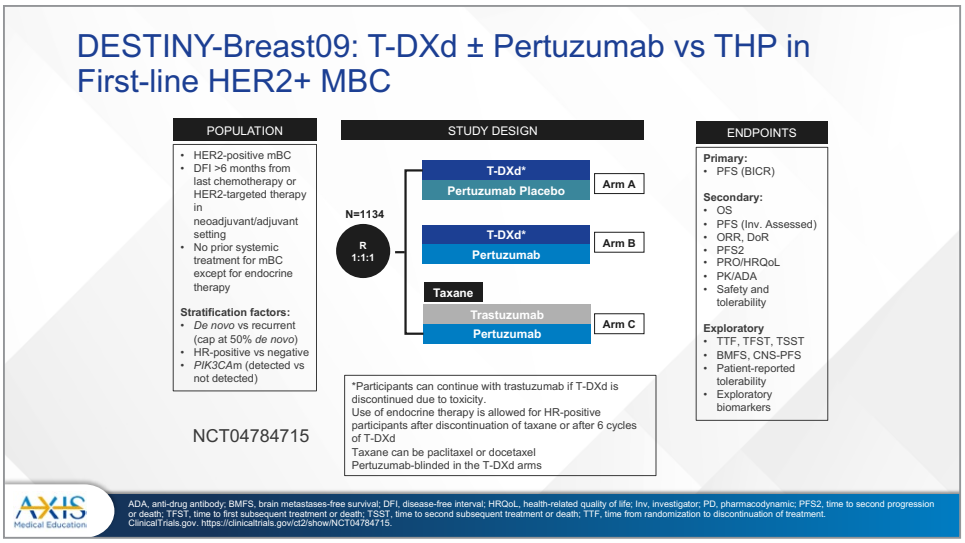


ESMO 2022 Preliminary results in 77 patients (DE+DX)

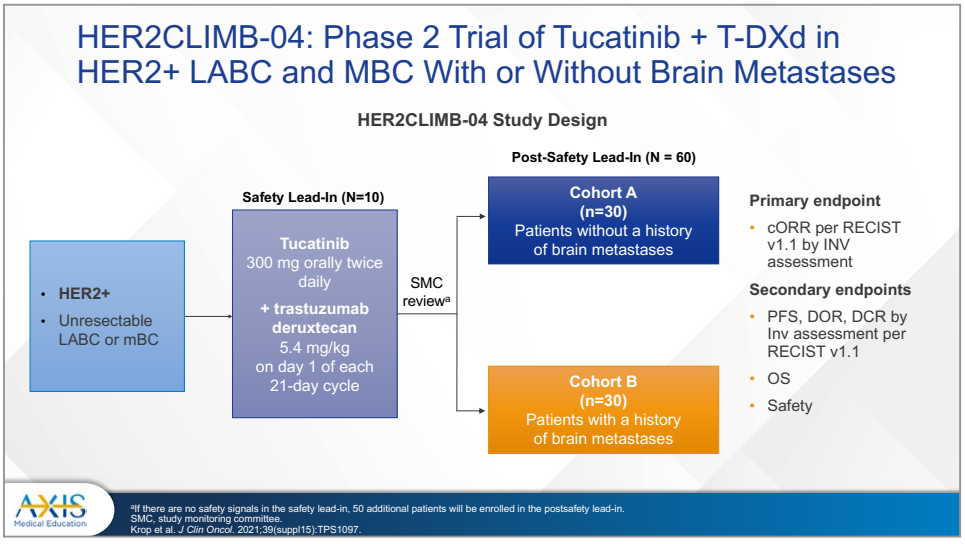
- MTD not reached, RP2D (2.5 mg/kg Q3wk, weekly TBD)
- 2 DLTs for G2 keratitis
- 43% keratitis (mainly G1 to 2), with prophylaxis
- No ILD reported
- ~ 20% required dose reductions
- cORR in 29 pts at 25 mg/kg Q3wk
  - 1 in 8 (13%) in HER2+ MBC
  - 9 in 29 (31%) in all HER2+

Ab, antibody; cORR, confirmed overall response rate; DE+DX, dose escalation/expansion; DLT, dose-limiting toxicity; FIH, first in human; GEA, gastroesophageal adenocarcinoma; MTD, maximum tolerated dose; P, pertuzumab; RD, recommended dose; RP2D, dose level chosen by sponsor; T, trastuzumab.
Jhaveri et al. *Ann Oncol*. 2022:33(suppl 7:S197-S224.

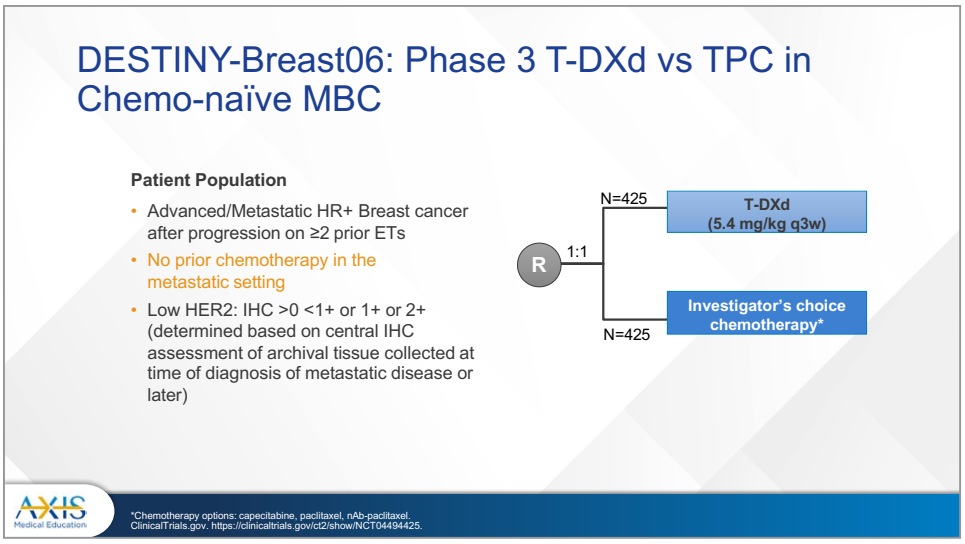
- Another agent to watch would be the bispecific HER2 ADC ZW49. This is an agent that has a proprietary or a statin toxin covalently linked to this protease cleavable valine citrulline linker; the DAR is 2, and this agent has been studied in ongoing phase 1 trials, including dose escalation and expansion, with some issues with keratitis being noted. And as we talk about toxicities in a bit, we'll recognize that this is something that we may need to be watchful of for some of these ADCs: ocular toxicity.



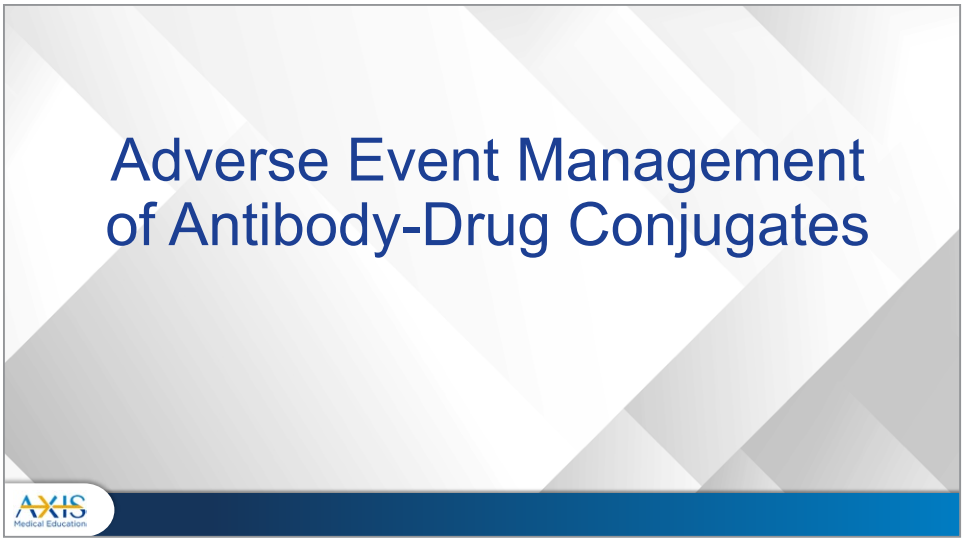
- Other trials that may inform what we do in the future for HER2+ breast cancer patients… The DESTINY-Breast09 trial is looking to move T-DXd +/- pertuzumab up to even an earlier-line setting. These are patients that have metastatic disease with a disease-free interval of >6 months from the last chemo or HER2-targeted therapy in the early-stage setting and are being treated in the first-line setting, except endocrine therapy is permitted upfront. And randomization is 1 to 1 to 1 to T-DXd plus pertuzumab or the placebo for pertuzumab vs the standard of the CLEOPATRA regimen of taxane, trastuzumab, pertuzumab. The primary and secondary endpoints are shown here. So this is an ongoing trial.



- Another ongoing study that is one to watch would be the HER2CLIMB-04 trial in which the ADC T-DXd, which we've been talking about in detail today, is being combined with the tyrosine kinase inhibitor tucatinib in patients with or without brain mets, and the study schema is shown here.



- Finally, DESTINY-Breast06 is another study that is an important one to watch because this potentially could move T-DXd even earlier in advanced or metastatic HR-positive breast cancer patients after progression on endocrine therapy. This would be a first-line chemotherapy study in the metastatic setting. Of note, the low HER2 is defined as >0 but <1+, so this ultra-low HER2 randomization is T-DXd vs investigator's choice chemotherapy, with the chemo options being capecitabine or a taxane.



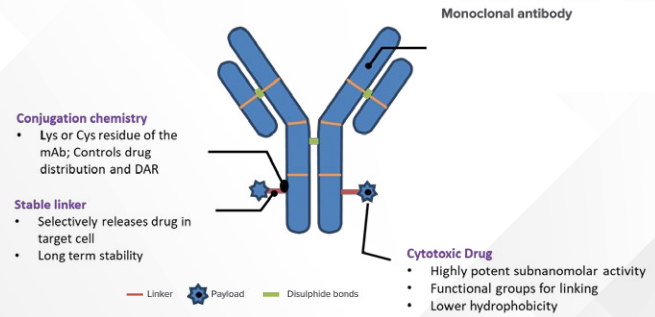
- So now let's switch gears a bit and talk about adverse event management of HER2 ADCs. First, we'll review some toxicities from established therapies, the monoclonal antibodies trastuzumab and pertuzumab.

Toxicities from Established Therapy

- Trastuzumab and pertuzumab
  - Cardiac dysfunction
    - > Generally predictable, risk factors understood, preventive strategies
    - > Can occur with any HER2-targeted agent
  - Rare infusion-related reactions
  - Diarrhea: generally exacerbated by chemotherapy
    - > Antidiarrheal therapy
  - Rash: uncommon
    - > Topical immunosuppression, ultraviolet protection

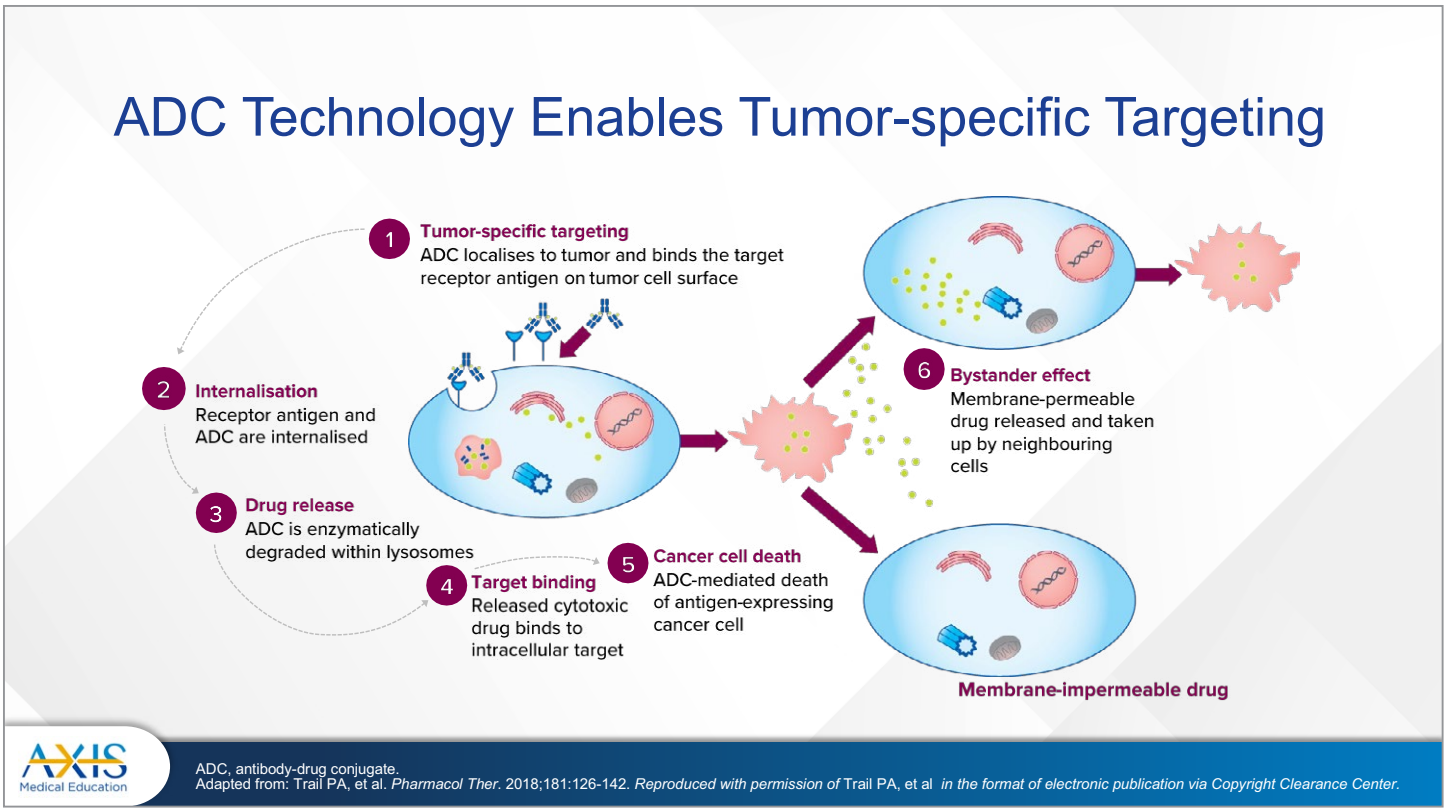
We're all well aware at this point of the potential for cardiac dysfunction, although it is generally predictable, and we've identified risk factors and some preventative strategies. This is a toxicity that can occur with any HER2-targeted therapy, in addition to some infusion-related reactions. With pertuzumab particularly, we do see some diarrhea at times. This is generally exacerbated by the concomitant use of chemotherapy but can be largely well handled with antidiarrheal medication. Uncommonly, we see rash and topical immunosuppression and UV protection is recommended.

ADCs Consist of Numerous Elements, Including the Monoclonal Antibody, Conjugated Drug, and Stable Linker



ADC, antibody drug conjugate; Cys, cysteine; DAR, drug-to-antibody ratio: Lys, lysine; mAb, monoclonal antibody.
Nakada T, et al. *Chem Pharm Bull.* 2019;67(3):173-185. *Permission requested from Chem Pharm Bull.*

This slide illustrates the various components of ADCs. These are novel agents that are quite effective in bringing chemotherapy payloads directly to tumor cells. They consist of numerous elements, including the monoclonal antibody, a cytotoxic drug, and a stable linker. These are thought to be of somewhat modular design, where that monoclonal antibody is selective for an antigen with a high copy number on the target tumor cell. And the cytotoxic drug is attached to the antibody via a linker, and that linker has to be selectively releasing the drug into the target cell but long-term stable in the circulation to hopefully prevent off-target toxicities. The chemotherapy payload itself has to be highly potent, and this is the ability of these agents to put chemotherapy payloads onto these antibodies that would not be safe to administer. And free circulation is thought to be linked to the remarkable activity of these agents.



- As we look at the cartoon that shows us how these agents work, you'll start with the top of the slide with the number 1, where it says tumor-specific targeting. So the ADC localizes to the tumor, and it binds the target receptor antigen on the tumor cell surface and then is internalized. And the receptor antigen and the ADC are both internalized as a complex, where then that drug is released. The agent is enzymatically degraded within the lysosomes, and the chemotherapy drug is released. It binds to the intracellular target, and you have cancer cell death that's ADC-mediated of the antigen-expressing cell.

  What's really unique is there are certain agents, of which trastuzumab deruxtecan is one, where we see this very important bystander effect that is linked to the membrane permeability of the drug being released and taken up by neighboring cancer cells that have some of the target. And this is the purported mechanism for the efficacy of trastuzumab deruxtecan in patients with HER2-low tumors. So, some of that target being available.

On-Target and Off-Target Toxicities of ADCs

On-Target

- Cytotoxic effect on (noncancer) cells that **express the target antigen**
- Mechanism of action is likely **related to/may be the same** as effect on cancer cells

Off-Target

- Cytotoxic effect on (noncancer) cells that **do NOT express the target antigen** (or have minimal expression)
- A few potential mechanisms of off-target toxicity have been described

ADC, antibody-drug conjugate.

With the availability of ADCs, we now recognize that there are on-target toxicities as well as off-target toxicities. So on target would be considered the cytotoxic effect on noncancer cells that express the target antigen and the mechanism of action is likely related to or may be the same as the effect on the cancer cells. Whereas that off-target toxicity is when you have toxicity that is related to cytotoxic effects on noncancer cells that don't express the antigen or have very minimal expression of the antigen. And a few potential mechanisms have been described in terms of the off-target toxicities.

Established ADCs for HER2+ Breast Cancer

ADC Attributes	T-DM1	T-DXd
Approval	2013: second-line MBC 2019: post-neoadjuvant	2019: third-line and later MBC 2022: second-line MBC
Payload MoA	Anti-microtubule	Topoisomerase 1 inhibitor
Drug-to-antibody ratio	~ 3.5:1	~8:1
Tumor-selective cleavable linker?	No	Yes
Bystander antitumor effect	No	Yes

ADC, antibody-drug conjugate; MBC, metastatic breast cancer; MoA, mechanism of action; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Nakada T et al. *Chem Pharm Bull* (Tokyo). 2019;67:173-85; Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097-108; Trial PA et al. *Pharmacol Ther*. 2018;181:126-42; Ogitani Y. et al. *Cancer Sci*. 2016;107:1039-46; LoRusso PM, et al. *Clin Cancer Res*. 2011;17:6437-47.

As we've discussed, our 2 main ADCs in breast cancer, especially in HER2+ breast cancer, specifically, are T-DM1 and T-DXd. And as a reminder, you see the approval time periods and the shift of T-DXd to the second-line setting as recently as 2022. The chemotherapy payloads being different with these 2 agents, and again, that bystander antitumor effect being really very much linked to T-DXd and not seen with T-DM1.

EMILIA: Adverse Events with T-DM1 vs Lapatinib + Capecitabine

Adverse Event, %	Lapatinib + Capecitabine (n = 488)		T-DM1 (n = 490)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any	98	57	96	41
Diarrhea	80	21	23	2
Hand-foot syndrome	58	16	1	0
Vomiting	29	5	19	1
Neutropenia	9	4	6	2
Hypokalemia	9	4	9	2
Fatigue	28	4	35	2
Nausea	45	3	39	1
Mucosal inflammation	19	2	7	<1
Anemia	8	2	10	3
Increased AST	9	1	22	4
Increased ALT	9	1	17	3
Thrombocytopenia	3	<1	28	13

Adverse events of grade ≥3 with an incidence of ≥ 2% in either group.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Verma et al. *N Engl J Med*. 2012;367:1783-1791.

- As we look at the toxicities with T-DM1, we again review the pivotal EMILIA trial, in which this agent was compared against what had been our standard, lapatinib and capecitabine, focusing on Grade 3 toxicities: 41% were noted, Grade 3 or higher in the T-DM1 arm. The majority of these were related to thrombocytopenia, some liver function abnormality… largely very well-tolerated agent.

Toxicities from T-DM1 Therapy

- Mild nausea
  - Symptomatic
- Thrombocytopenia, transaminitis
  - Dose reduction, delay
- Peripheral neuropathy
  - Dose reduction
- Most common (≥25%) in MBC:
  - Fatigue
  - Nausea
  - Musculoskeletal pain
  - Hemorrhage
  - Thrombocytopenia
  - Headache
  - Increased transaminases
  - Constipation
  - Epistaxis

Warning/Precaution	Monitoring	Management
Hepatoxicity	Monitor hepatic function (serum transaminases and bilirubin) prior to initiation and prior to each dose	Dose modifications or permanently discontinue
Cardiac toxicity	Assess LVEF prior to initiation and at regular intervals (eg, every 3 months) during treatment	Withhold dose or discontinue
Pulmonary toxicity	Monitor for sign and symptoms (dyspnea, cough, fatigue, and pulmonary infiltrates)	Permanently discontinue for ILD/pneumonitis
Infusion-related reactions	Monitor for signs and symptoms during and after infusion	Slow or interrupt infusion Administer appropriate medical therapy Permanently discontinue for life threating IRR
Hemorrhage	Use with caution, additional monitoring when concomitant use of anticoagulation and antiplatelet therapy	
Thrombocytopenia	Monitor platelet counts prior initiation and prior to each dose	Dose modifications
Neurotoxicity	Monitor for sign and symptoms on an ongoing basis	Withhold dose temporarily for Grade 3/4 peripheral neuropathy until resolution to Grade ≤2
Embryo-fetal toxicity	Advise patients of risk and need for contraception	

ILD, interstitial lung disease; LVEF, left ventricular ejection fraction.
KADCYLA Prescribing Information, 2022.

- Here we see that it can also cause mild nausea but, mainly, as I mentioned a moment ago, thrombocytopenia, transaminitis. Peripheral neuropathy can be seen but it's generally quite mild. And you see more of the common toxicities highlighted on the left on the last bullet point. And you see some of the management suggestions in terms of dose modifications, slowing or interrupting the infusion for infusion-related reactions, dose modifications for thrombocytopenia, and for neurotoxicity. And of course, for patients that could become pregnant, we have to advise them that it's not safe to do so. There is a risk and a need for contraception due to embryo-fetal toxicity.

Special Considerations: T-DM1 and Hepatotoxicity

- Permanently discontinue treatment in patients with serum transaminases >3 × ULN and concomitant total bilirubin >2 × ULN
- In clinical trials, cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies (5 cases out of 1,624, 1 of which was fatal). Two of these five cases of NRH were observed in EMILIA and 2 were observed in KATHERINE.
  - Diagnosis can be confirmed only by histopathology
  - *NRH should be considered in all patients with clinical symptoms of portal hypertension and/or cirrhosis-like pattern seen on the computed tomography scan of the liver but with normal transaminases and no manifestations of cirrhosis. Upon NRH diagnosis, treatment must be permanently discontinued*

ULN, upper limit of normal.
KADCYLA Prescribing Information, 2022.

There are some special considerations with T-DM1 in terms of hepatic toxicity. It's recommended to permanently discontinue treatment in patients with serum transaminases 3 times the upper limit of normal and a concomitant total bilirubin of 2 times or higher than the upper limit of normal. There have also been some rare cases of nodular regenerative hyperplasia, and 2 of these cases have been, 2 of these 5 cases of NRH were observed in the EMILIA trial, and 2 were observed in the KATHERINE trial. There was a fatality reported in the past so this is something that we have to be very mindful of and diagnosis can only be confirmed by histopathology. So this should be kept on your radar and, of course, patients should permanently discontinue.

Similar Rates of All Grade and Grade ≥3 Drug-related TEAEs Between Arms, with no Grade 4/5 ILD/Pneumonitis

Drug-related TEAEs in ≥20% of Patients

System Organ Class Preferred term, n (%)	T-DXd (n=257)		T-DM1 (n=261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system disorders				
Neutropenia*	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anaemia†	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia‡	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia§	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhoea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue¶	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
AST increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
ALT increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia**	93 (36.2)	1 (0.4)	6 (2.3)	0

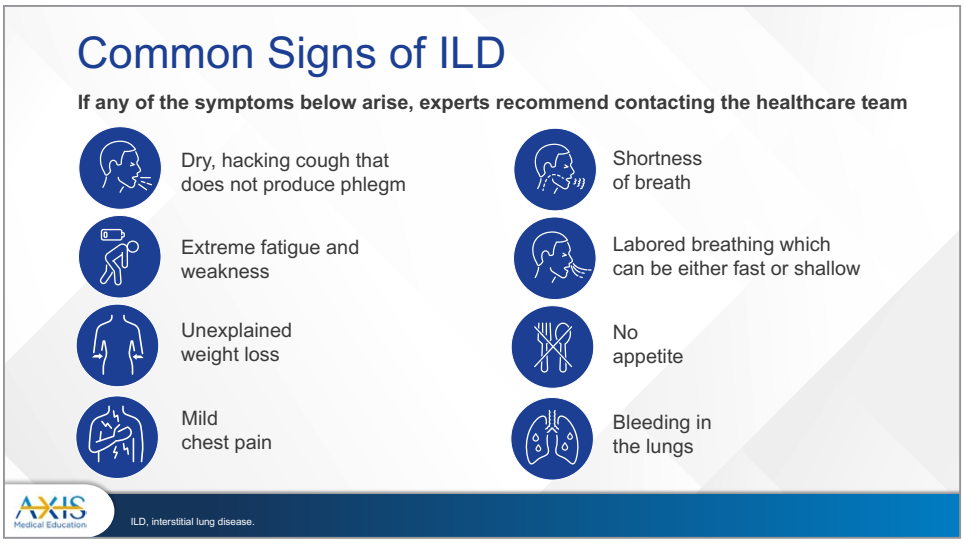
Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis,†† n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n=257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n=261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

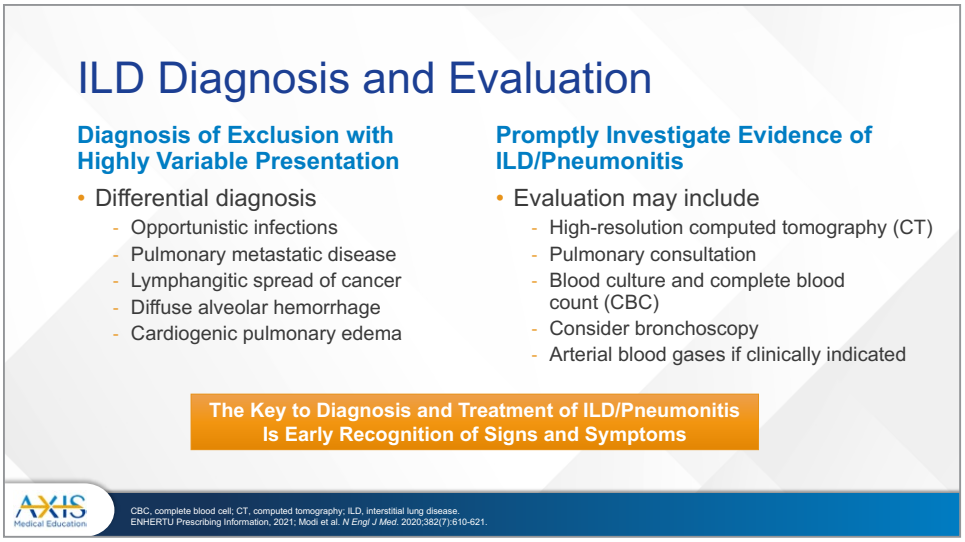
- Most drug-related TEAEs were gastrointestinal or hematologic in nature
- There were no Grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

Adverse events were managed according to the protocol. *This category includes the preferred terms neutrophil count decreased and neutropenia. †This category includes the preferred terms haemoglobin decreased, red blood cell count decreased, anaemia, and haematocrit decreased. ‡This category includes the preferred terms white blood cell count decreased and leukopenia. §This category includes platelet count decreased and thrombocytopenia. ¶This category includes the preferred terms fatigue, asthenia, and malaise. **Grade 1 alopecia: T-DXd=26.5%, T-DM1=2.3%. Grade 2: T-DXd=9.3%. ††Patients with prior history of ILD/pneumonitis requiring steroids were excluded.
ALT, alanine transaminase; AST, aspartate aminotransferase; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
Cortes et al. *Ann Oncol*. 2021;32(suppl 5):S1283-S1346.

As a reminder, the DB03 trial, which did put these 2 highly active ADCs head to head, T-DM1 vs T-DXd, we've previously reviewed the PFS and OS data and the response rate information. But in terms of toxicity, there is an adverse interest of special interest with T-DXd, that's, namely, ILD pneumonitis. And in earlier studies there were some fatalities. Thankfully, in this trial there were no Grade 5 ILD events, whether that's related to this patient population that's being treated earlier in the treatment course... Remember, about 50% of these patients were receiving therapy in the second line. It's unclear. But, in any case, that's good news in this trial. Mainly, other issues that are much more common include nausea, some vomiting, GI toxicities, mainly, and some blood count issues that can largely be well managed with the use of supportive treatments.



As I mentioned, due to the fatalities that have been seen in the past with this agent, we do have to be very mindful of common signs of ILD and if any of the symptoms below arise, experts recommend contacting a healthcare team. So a dry or hacking cough that does not produce phlegm, shortness of breath, weakness. A lot of these, as you'll notice, are very common side effects that we see with our anticancer therapies. So having this on your radar is really important and asking pointed questions about changes in pulmonary symptoms is really very important.

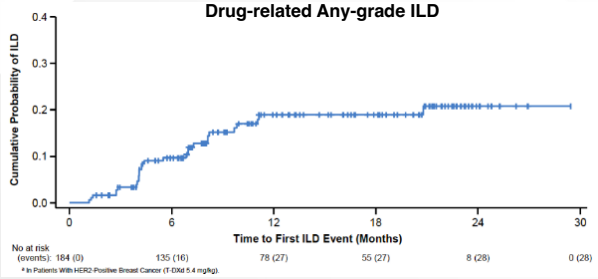


It is a diagnosis of exclusion with a variable presentation. And so, of course, we need to engage with our other colleagues, such as our pulmonary colleagues, to rule out other causes like infection and to make sure that we're putting patients through appropriate diagnostic workup, including high-resolution imaging, blood culturing, and bronchoscopy when indicated.

Warnings and Precautions: ILD/Pneumonitis Monitoring and Management

ILD, n (%)	T-DXd 5.4 mg/kg (N=184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade/ Total
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	25 (13.6)
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	28 (15.2)

Cumulative Probability of Adjudicated Drug-related Any-grade ILD



Interrupt trastuzumab deruxtecan and initiate corticosteroid treatment if ILD/pneumonitis is suspected

Promptly investigate Evidence of ILD

- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

For Asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (eg, ≥0.5 mg/kg prednisone or equivalent)
- Withhold T-DXd until recovery to Grade 0
  - If resolved in ≤28 days from date of onset, maintain dose
  - If resolved in >28 days since onset, reduce dose 1 level

For Symptomatic ILD (Grade ≥2)

- Promptly initiate corticosteroid treatment (eg, ≥1 mg/kg prednisone or equivalent)
- Permanently discontinue T-DXd

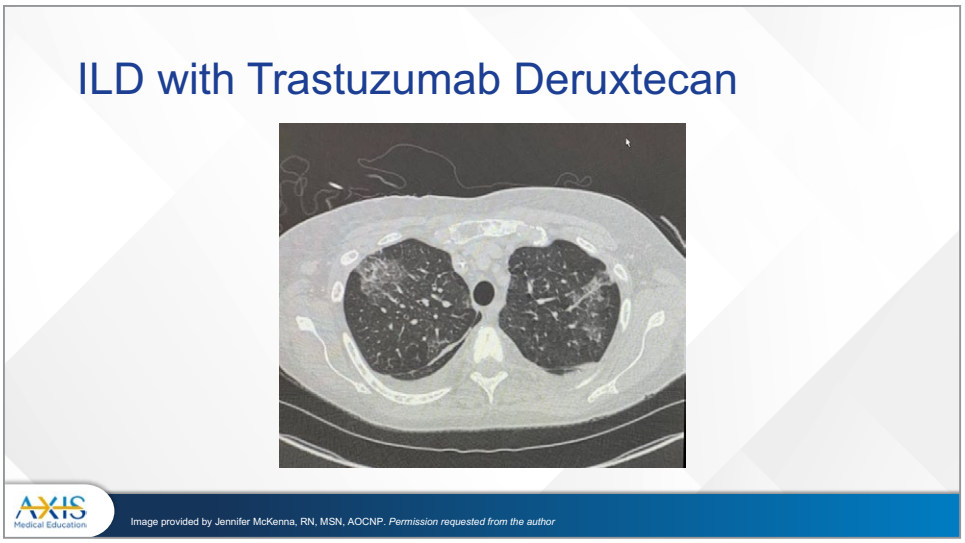
AXIS Medical Education

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.
ENHERTU Prescribing Information, 2021; Modi et al. *N Engl J Med*. 2020;382(7):610-621.

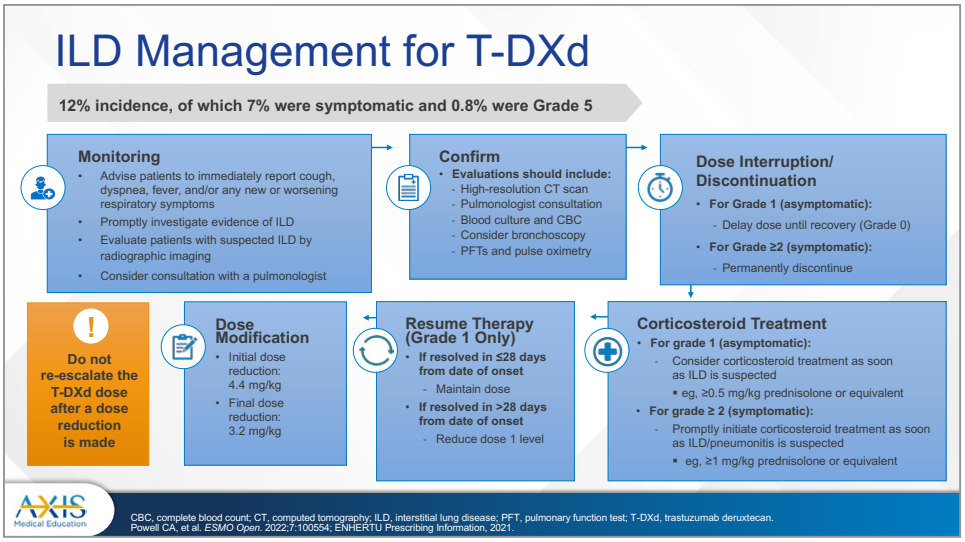
In the earlier studies with this agent, I mentioned there were some Grade 5 events. This is shown here from the DESTINY-Breast01 trial. And again, there was a hint that perhaps some of this kind of leveled off at the 12-month mark. But certainly, I think it's too early to make any decisions about when to feel comforted that this could not happen. And again, we really need to make sure that this is a side effect that's on our radar because of the variable clinical course.

We do need to remember that all patients who have any signs or symptoms should be thoroughly investigated. And even for asymptomatic Grade 1, consider steroids and withhold until the patients recover to Grade 0 toxicities. If it takes <28 days, you can resume the same dose, but if it takes longer than 28 days, a dose reduction is required.

What's really unique about this agent is with the presence of symptomatic ILD Grade 2, we're actually supposed to discontinue the drug and that's unlike any other therapy that we're used to using in breast cancer. I think it just speaks to the fact that with the fatalities that were noted, we should err on the side of caution and certainly discontinue when patients are symptomatic.



- So this is just a CT scan that shows us that typical ILD pattern that can be seen with trastuzumab deruxtecan. And you see that lacy, ground-glass opacity pattern.



- I've already gone through some of this but it's a nice algorithm here to take you through the monitoring, the confirmation stage, and the dose interruption and discontinuation. This algorithm should be closely followed, especially when it comes to real challenging patients and consideration of dose reductions and resumption of therapy at appropriate doses or perhaps not at all.

T-DXd Package Insert Black Box Warning

- ILD and pneumonitis, including fatal cases, have been reported
- Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms
- Permanently discontinue in all patients with Grade 2 or higher ILD/pneumonitis
- Advise patients of the risk and the need to immediately report symptoms

Severity	Treatment Modification
Asymptomatic ILD/pneumonitis (Grade 1)	Interrupt T-DXd until resolved to Grade 0, then: • If resolved in 28 days of less from date of onset, maintain dose • If resolved in greater than 28 days from date of onset, reduce dose on level • Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected
Symptomatic ILD/pneumonitis (Grade 2 or greater)	• Permanently discontinue T-DXd • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected

ENHERTU Prescribing Information, 2021.

- Again, there is a black box warning: Permanently discontinue trastuzumab deruxtecan in all patients with Grade 2 or higher ILD pneumonitis. And we need to advise our patients of the risk and the need to report immediately any symptoms.

Toxicities from T-DXd Therapy

- Most common (≥20%) in MBC:
  - Nausea
  - Decreased white blood cell count
  - Decreased hemoglobin
  - Decreased neutrophil count
  - Decreased lymphocyte count
  - Fatigue
  - Decreased platelet count
  - Increased AST
  - Vomiting
  - Increased ALT
  - Alopecia
  - Increased blood alkaline phosphatase
  - Constipation
  - Musculoskeletal pain
  - Decreased appetite
  - Hypokalemia
  - Diarrhea
  - Respiratory infection

Warning/Precaution	Monitoring	Management
ILD	Monitor for and promptly investigate signs and symptoms (cough, dyspnea, fever, and other new or worsening respiratory symptoms) Advise patients of the risk and to immediately report symptoms	Evaluate patients with suspected ILD by radiographic imaging Consider consultation with a pulmonologist For asymptomatic (Grade 1) ILD, consider corticosteroid treatment (eg, ≥0.5 mg/kg/day prednisolone or equivalent). Withhold until recovery For symptomatic (Grade ≥2) ILD, promptly initiate systemic corticosteroid treatment (eg, ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks Permanently discontinue in all patients with Grade 2 or higher ILD/pneumonitis
Neutropenia	Monitor CBCs prior to initiation and prior to each dose, and as clinically indicated	Dose interruption or reduction
Left ventricular dysfunction	Assess LVEF prior to initiation and at regular intervals during treatment as clinically indicated	Treatment interruption or discontinuation Permanently discontinue if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed Permanently discontinue in patients with symptomatic congestive heart failure
Embryo-fetal toxicity	Advise patients of risk and need for contraception	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan.
ENHERTU Prescribing Information, 2021.

- As I mentioned earlier, this is a therapy that's mainly associated with GI toxicities that are pretty well managed. And the ILD, fortunately, does not occur that frequently.

FDA-approved ADCs with Reported Ocular Toxicity

ADC	Tumor Type	Antibody Target	Chemotherapy Payload	Findings
Belantamab mafodotin*	Multiple myeloma	BCMA	Auristatin F/MMAF	72%-77% of patients reported microcyst-like epithelial changes
Tisotumab vedotin	Cervical cancer	Tissue factor (TF)	Auristatin E/MMAE	Ocular events: 60%, including conjunctival AEs, dry eye, corneal AEs, blepharitis
Enfortumab vedotin	Urothelial cancer	Nectin-4	Auristatin E/MMAE	Ocular events: 40%, including dry eye, keratitis, blurred vision
Trastuzumab deruxtecan	HER2+/HER2-low breast cancer	HER2	Topoisomerase I inhibitor	11% of patients reported dry eye
Trastuzumab emtansine	HER2+ breast cancer	HER2	Maytansine/DM1	Conjunctivitis, photophobia, dry eye, increased lacrimation, blurred or impaired vision reported in <10% of patients
Gemtuzumab ozogamicin	CD33+ AML	CD33	Calicheamicin	1 reported case of ocular bleeding in elderly patient with AML
Polatuzumab vedotin	DLBCL	CD79b	Auristatin E/MMAE	1.2% of patients reported blurred vision

*Being withdrawn from the market as of Nov 2022.
AEs, adverse events; AML, acute myeloid leukemia; BCMA, B-cell maturation antigen; DLBCL, diffuse large B-cell lymphoma; MMAE, monomethylauristatin E; MMAF, monomethylauristatin F.
Piccaluga et al, 2004; BLENREP Prescribing Information, 2020; TIVDAK Prescribing Information, 2021; PADCEV Prescribing Information, 2022;
ENHERTU Prescribing Information, 2021; KADCYLA Prescribing Information, 2022; POLIVY Prescribing Information, 2020.

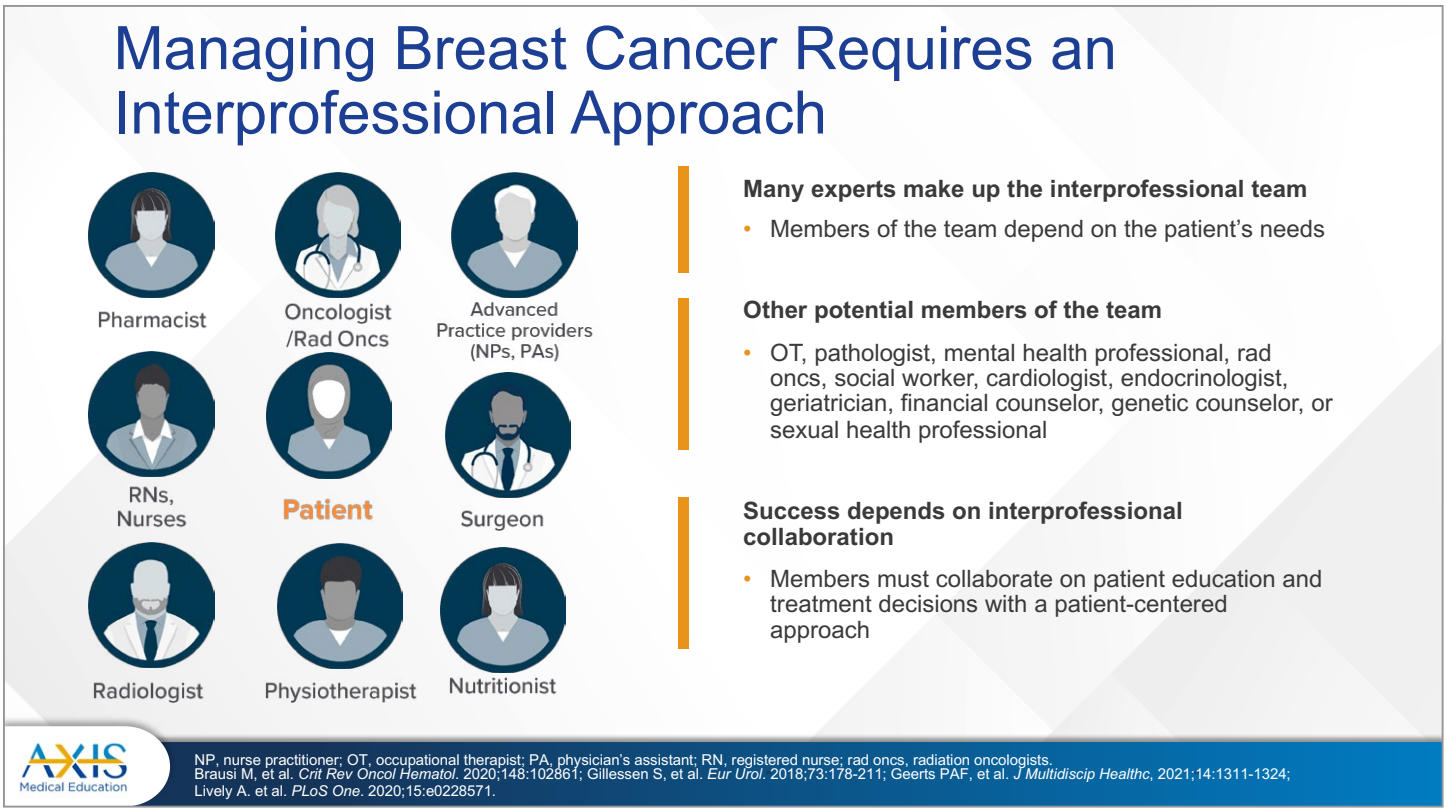
So moving on to ocular toxicities. This is a new toxicity that, as medical oncologists, we'll have to learn to handle and hopefully have the help of our colleagues, ophthalmologists and optometrists. Because, as you see in this table, this is a toxicity that's been reported with quite a few different ADCs, for other tumor types. Focusing on the agents that we're discussing today, trastuzumab deruxtecan and trastuzumab emtansine, there have been some cases of ocular toxicity as well.

HER2-directed Therapies: AE Concerns

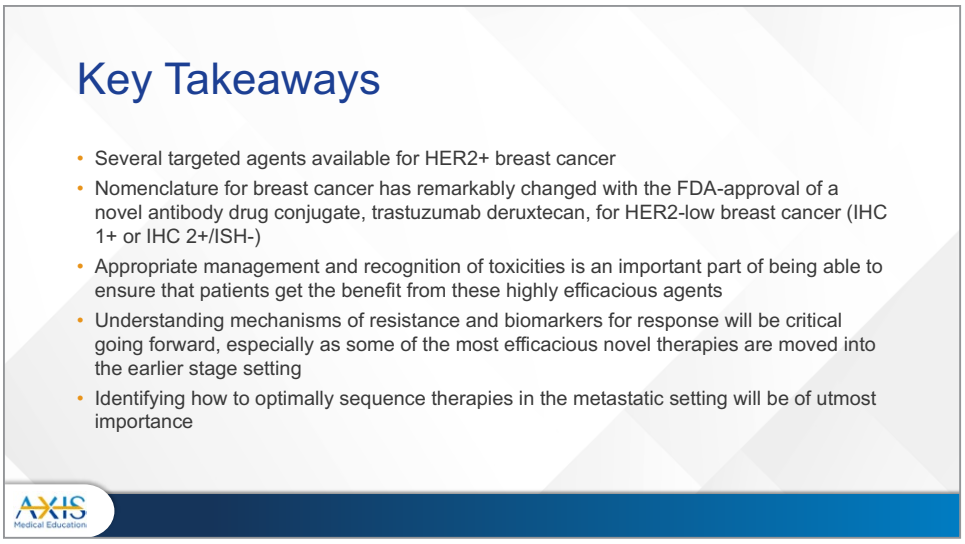
- HER2-directed antibodies
  - Cardiac toxicity and monitoring
  - Infusion reactions
- Small molecule TKIs
  - Gastrointestinal toxicity: diarrhea
  - Skin toxicity
- ADCs
  - T-DM1: thrombocytopenia, neuropathy, elevated LFTs
  - T-DXd: nausea/vomiting, fatigue, ILD

ADC, antibody drug conjugate; AE, adverse events; GI, gastrointestinal; ILD, interstitial lung disease; LFTs, liver function tests; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKIs, tyrosine kinase inhibitors.

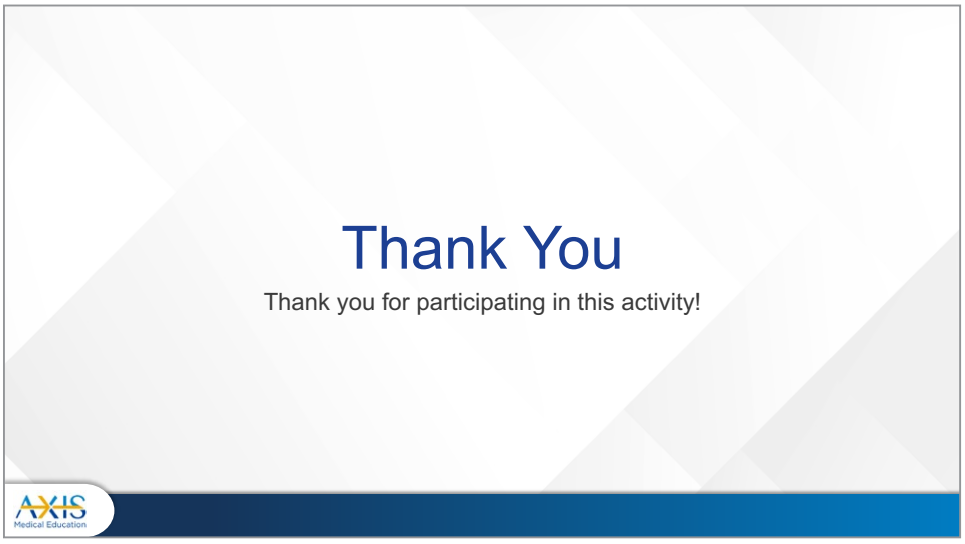
So a summary in terms of some of the other therapies we've talked about, the HER2-directed antibodies and the cardiac monitoring, infusion reactions. We haven't talked much—this program is more focused on ADCs. But the toxicities with regards to small molecule tyrosine kinase inhibitors include diarrhea and some skin toxicity. And we've discussed the ADC toxicities.



I would just like to really point out the importance of the team approach when it comes to allowing our patients to safely continue on these highly efficacious therapies. Many experts make up the interprofessional team and members of the team depend on the patient's needs. You see, of course, our medical oncologists, our advanced practice providers, of course, our other colleagues such as surgeons and radiologists, our nutrition colleagues, our physiotherapists—it's really certainly a team approach to make sure that our patients are getting the benefit of these highly directed or highly efficacious therapies. Members must collaborate on patient education and treatment decisions. And of course, at the center of all this is the patient, who we need to keep in mind.



- And so finally, I'll end with a few key takeaways. With the availability of several targeted agents, we've made considerable progress in treating what was once considered one of the most aggressive subtypes of breast cancer, namely, HER2+ breast cancer. The nomenclature for breast cancer has remarkably changed based on the approval of a novel ADC, namely, trastuzumab deruxtecan for HER2-low breast cancer. Appropriate management and recognition of toxicities is an important part of being able to ensure that our patients get the benefit from these highly efficacious agents. And finally, understanding mechanisms of resistance and biomarkers for response will be critical going forward. Especially as some of our most efficacious novel therapies are moved into the earlier stage setting, identifying how to optimally sequence the therapies that we have in the metastatic setting will be of utmost importance.



- So thank you for your attention.

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