NOVELTIES IN BREAST CANCER TREATMENT & SAFETY INITIATIVES

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CONFLICT OF INTEREST/ FINANCIAL DISCLOSURE

- None to disclose

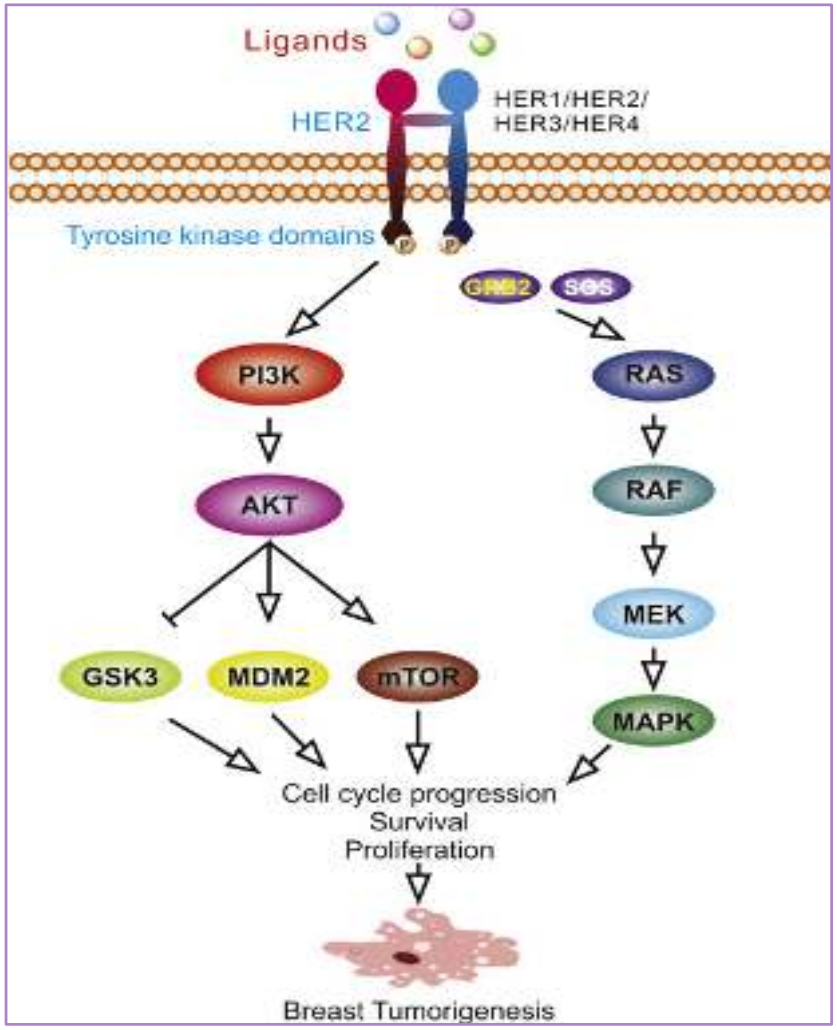
OBJECTIVES

Define	Define HER2-low breast cancer
Understand	Understand the clinical opportunities of identifying HER2-low as a targetable subset of breast cancer
Discuss	Discuss the practice-changing results of the DESITNY-breast04 trial and the role of fam-trastuzumab deruxtecan-nxki (ENHERTU) in HER2-low breast cancer
Identify	Identify three medication-safety challenges with HER2-directed chemotherapy and a strategy to prevent each one

WHAT IS HER2?

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2)

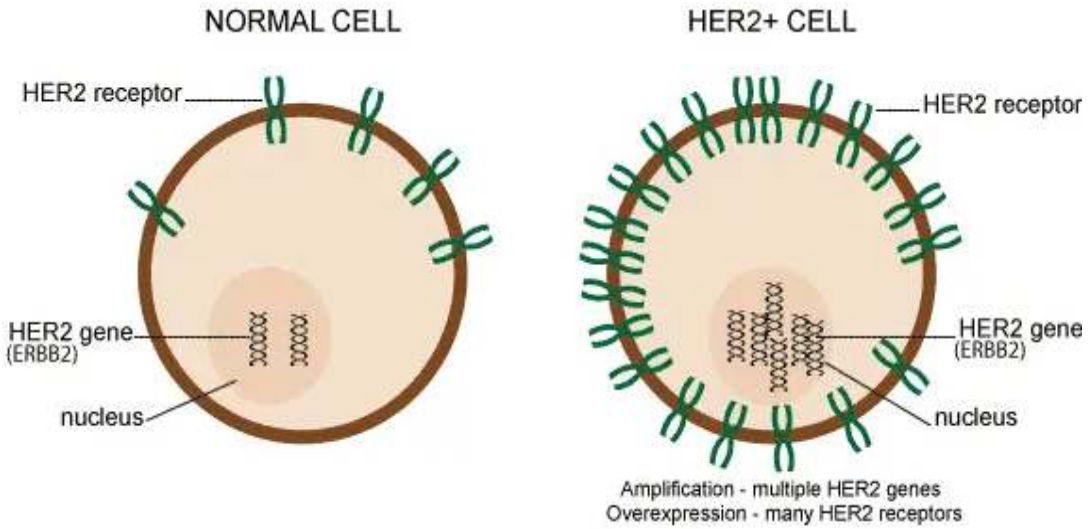
- Tyrosine kinase receptor
- Initiates a variety of signaling pathways leading to cell proliferation, survival, differentiation, angiogenesis, and invasion
- HER2 is overexpressed in 15-20% of invasive breast cancer

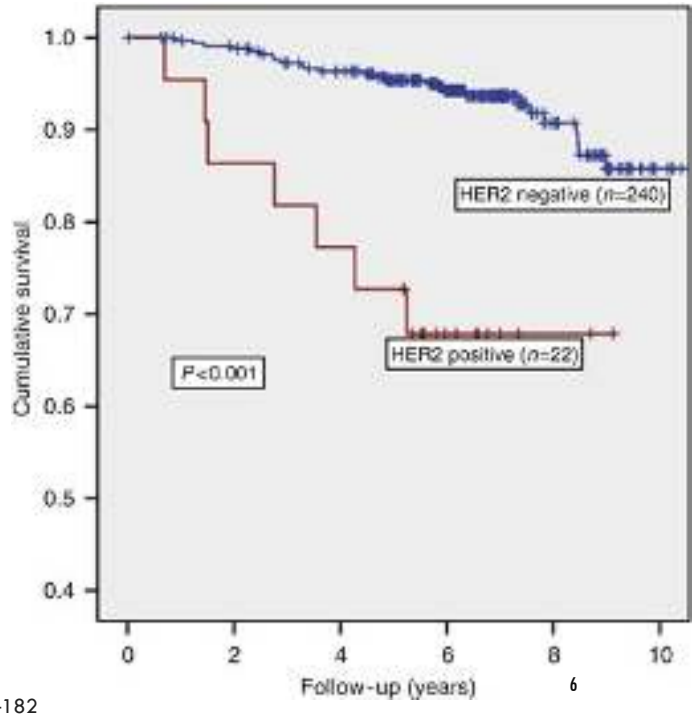


Burstein HJ, et al. The distinctive nature of HER2-positive cancers. N Engl J Med. 2005;353(16):1652-1654
Marchiò C, et al. *Semin Cancer Biol.*2021;72:123-135
Yixiao Feng, et al, Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis, Genes & Diseases, Volume 5, Issue 2, 2018, Pages 77-106

PROGNOSIS OF HER2-POSITIVE BREAST CANCER

- In the 1980's, Slamon and colleagues reported the **prognostic impact of ERBB2 amplification** in breast cancer and correlation with overexpression of HER2 receptors
- HER2-positive breast cancer associated with shorter survival compared to HER2-negative breast cancer

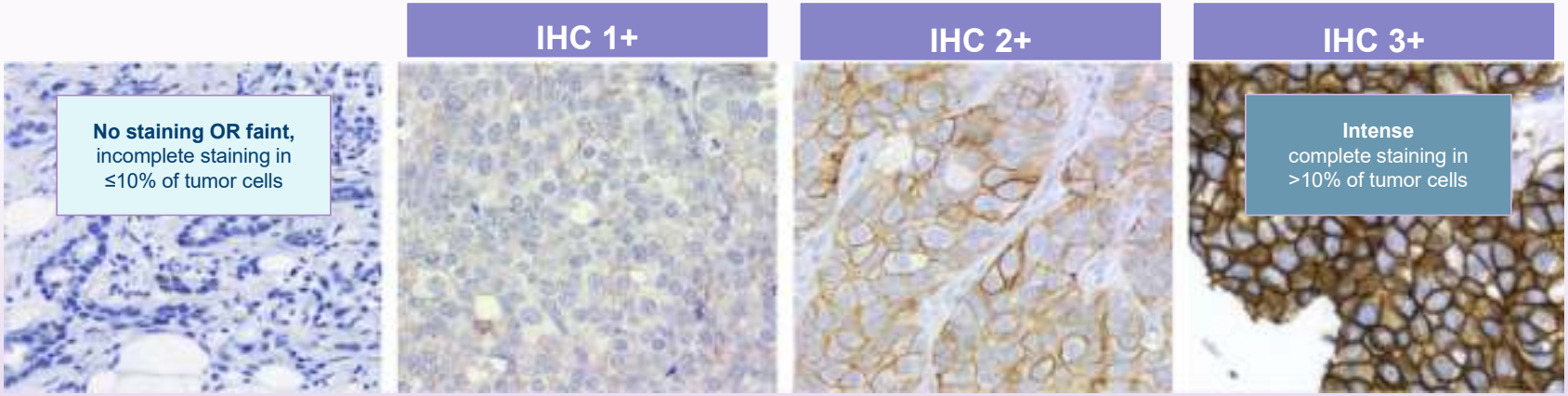




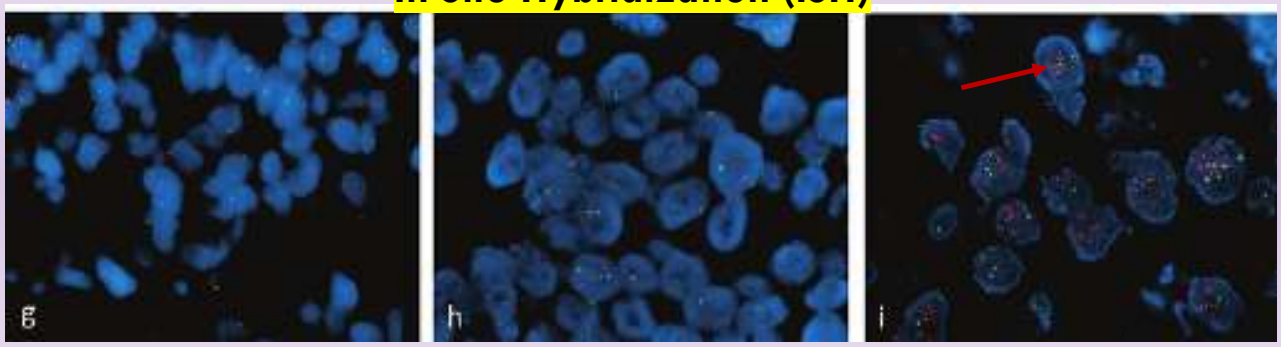
Slamon DJ, et al. (1987) Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 235: 177–182

TESTING FOR HER2

Immunohistochemistry (IHC)

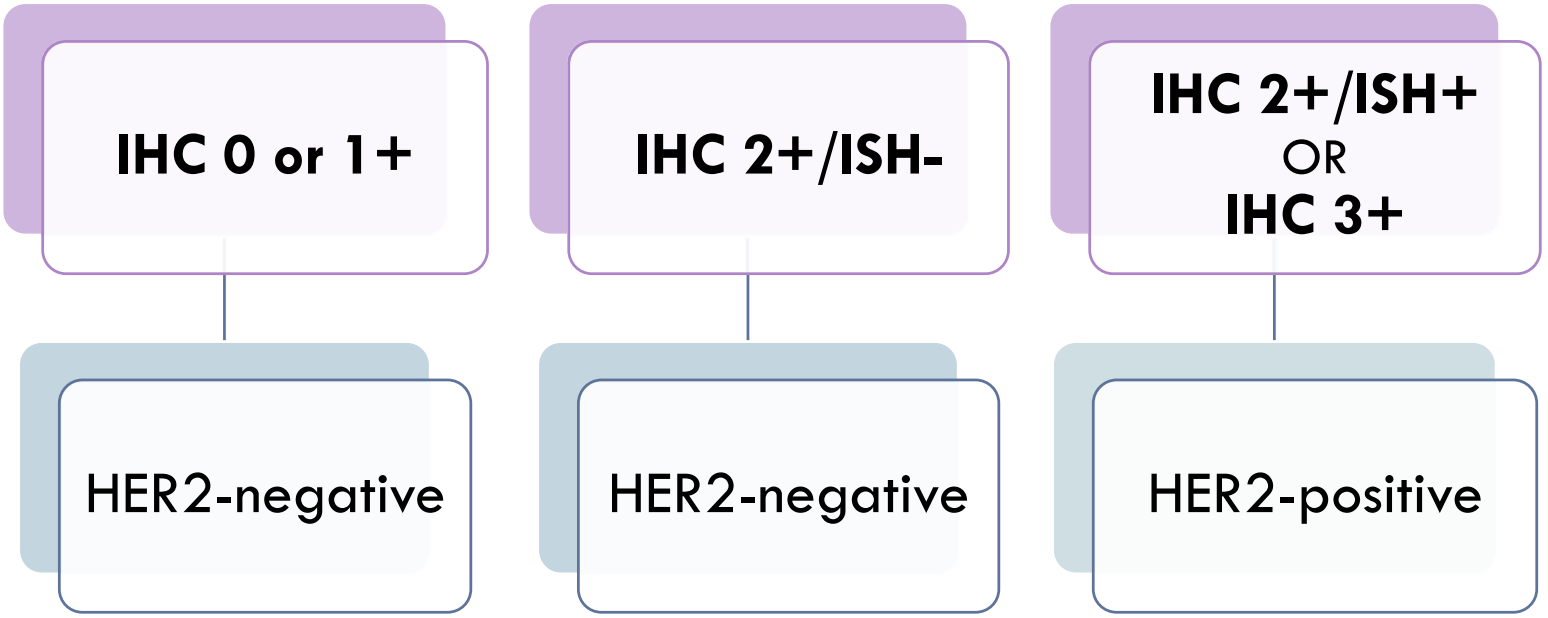


In Situ Hybridization (ISH)



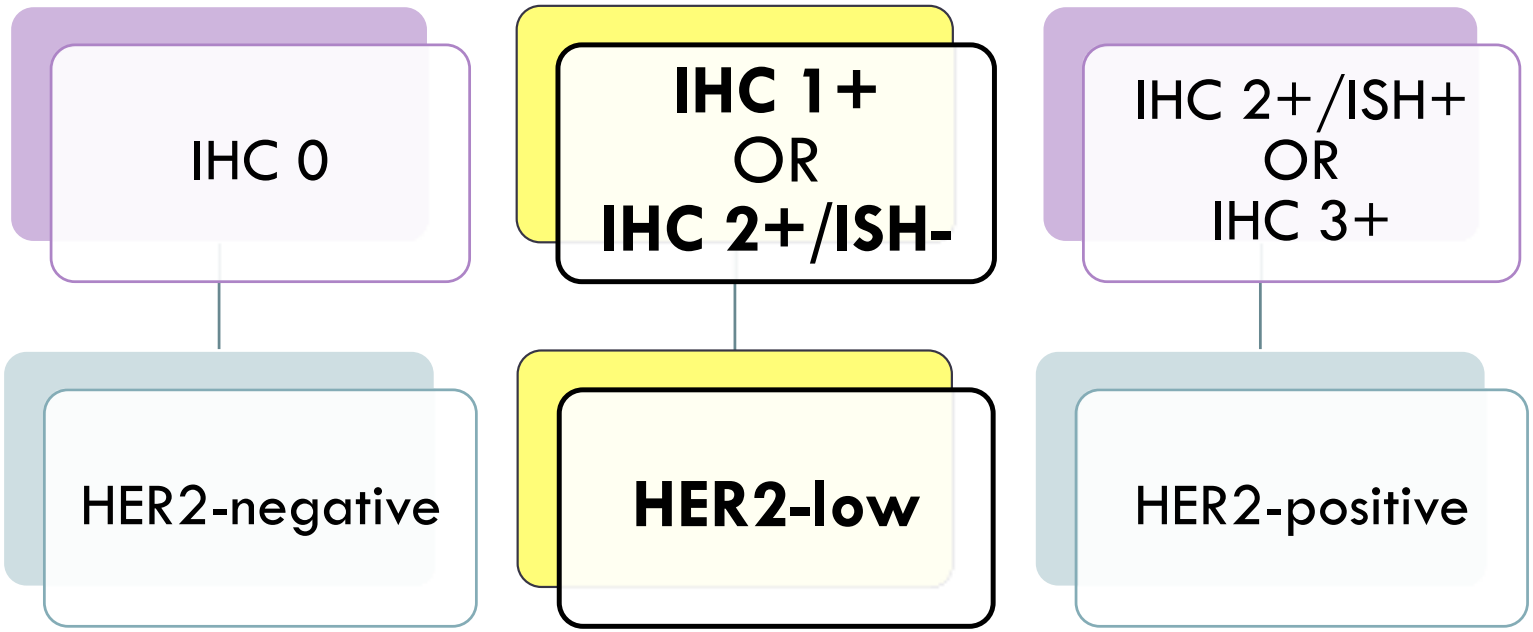
Marchiò C, et al. *Semin Cancer Biol.*2021;72:123-135

TRADITIONAL HER2 CLASSIFICATIONS



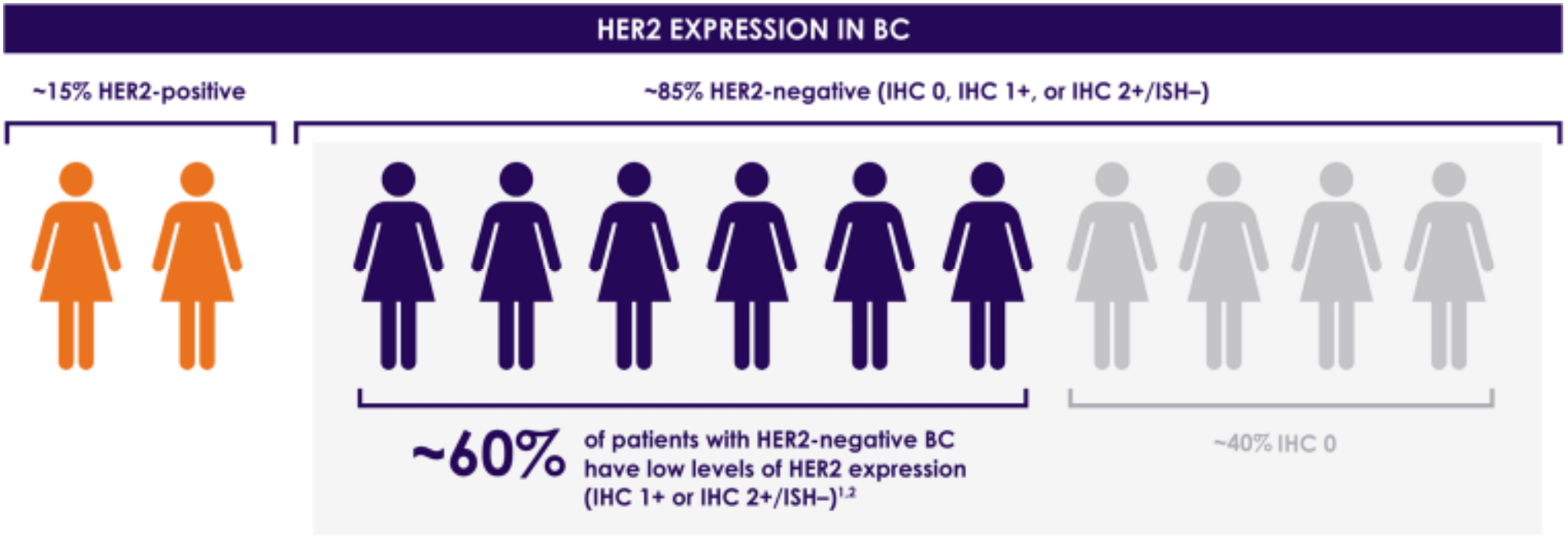
Wolff AC, Hammond EH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice guideline focused update. *J Clin Oncol*. 2018;36(20):2105-2122

UPDATED* HER2 CLASSIFICATIONS



Burstein HJ. *N Engl J Med*. 2005;353(16):1652-1654
Marchiò C, et al. *Semin Cancer Biol*. 2021;72:123-135
Tarantino P, et al. HER2-low breast cancer: pathological and clinical landscape. J Clin Oncol. 2020;38(17):1951-1962.

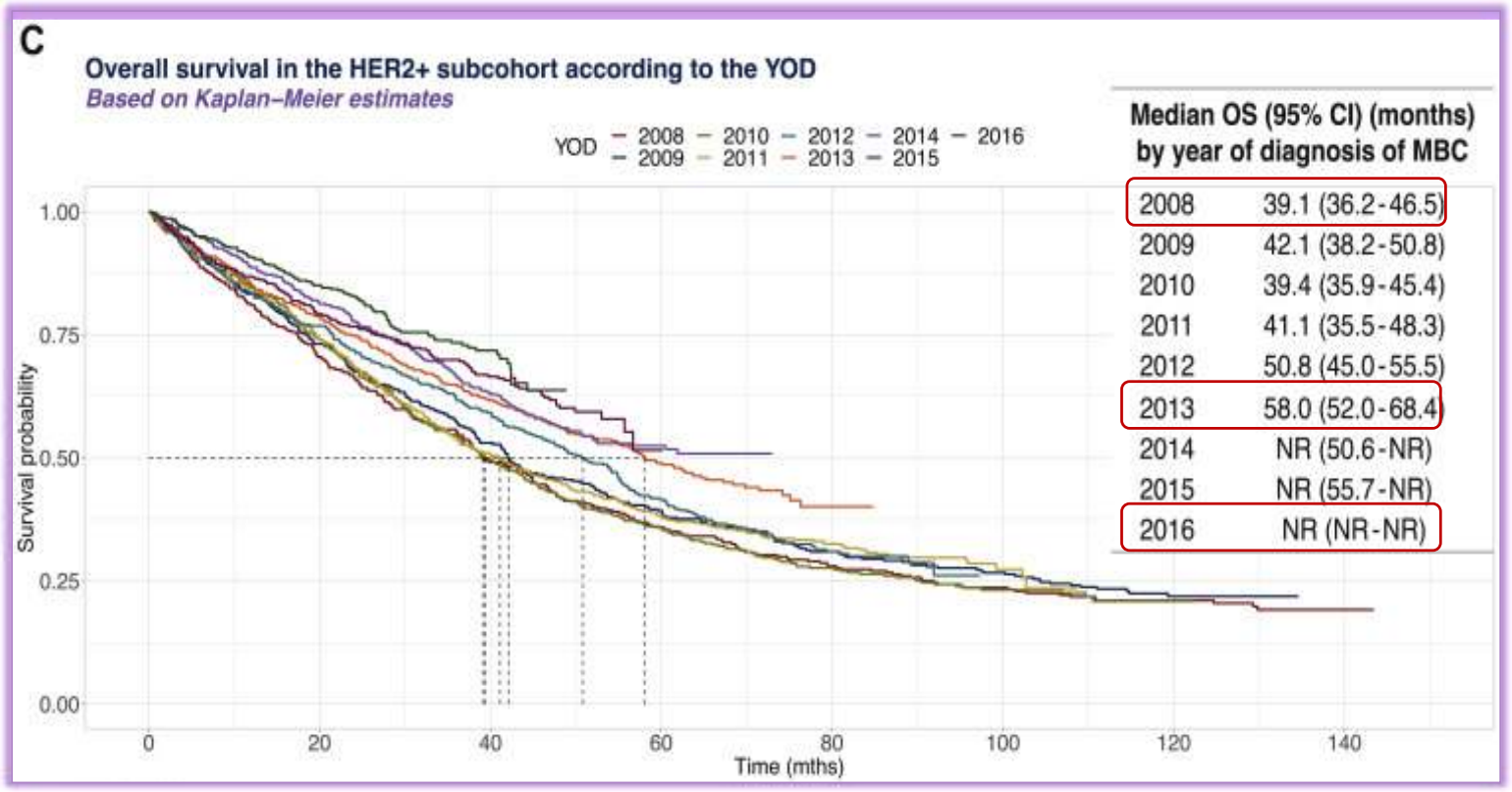
HER2-LOW CLINICAL SIGNIFICANCE



Enhertu. 2022 Daiichi Sankyo, Inc. and AstraZeneca. https://www.enhertuhcp.com/en/her2-low-breast/about-her2-low-mbc. Accessed May 23, 2023.
Schettini F, et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. NPJ Breast Cancer. 2021;7(1):1.
Tarantino P, et al. HER2-low breast cancer: pathological and clinical landscape. J Clin Oncol. 2020;38(17):1951-1962.

WHY IS IT A CRITICAL OPPORTUNITY TO IDENTIFY HER2-LOW AS A TARGETABLE SUBSET?

PROGNOSIS OF HER2-POSITIVE BREAST CANCER



Grinda T, et al. Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008-2017 ESME cohort. *ESMO Open*. 2021;6(3):100114.

NSABP B-31 TRIAL

HER2 STATUS AND BENEFIT FROM ADJUVANT TRASTUZUMAB

- 10% of samples were **nonamplified (HER2-negative)**
- HER2-negative patients appeared to benefit from trastuzumab

Table 1. Relative Risks of Disease Progression and Death among Patients in the ACTH Group as Compared with the ACT Group.*

End Point and Central HER2 Assay†	ACT	ACTH	Relative Risk (95% CI)	P Value	P Value for the Interaction
	no. of events/total no. of events				
Disease progression					
HER2-positive	163/875	85/804	0.47 (0.37–0.62)	<0.001	0.47
HER2-negative	20/92	7/82	0.34 (0.14–0.80)	0.014	
Death					
HER2-positive	55/875	38/804	0.66 (0.43–0.99)	0.047	0.08
HER2-negative	10/92	1/82	0.08 (0.01–0.64)	0.017	

ACT = doxorubicin, cyclophosphamide, and paclitaxel, and **ACTH = ACT plus trastuzumab.**

Paik S, et al. HER2 status and benefit from adjuvant trastuzumab in breast cancer. *N Engl J Med.* 2008;358(13):1409-1411.

NSABP B-47 TRIAL

PHASE-3 TRIAL CONDUCTED TO TEST BENEFIT OF TRASTUZUMAB IN HER2-LOW

Included:

- Node-positive or high-risk node-negative breast cancer
- IHC 1+, 2+ and ISH negative

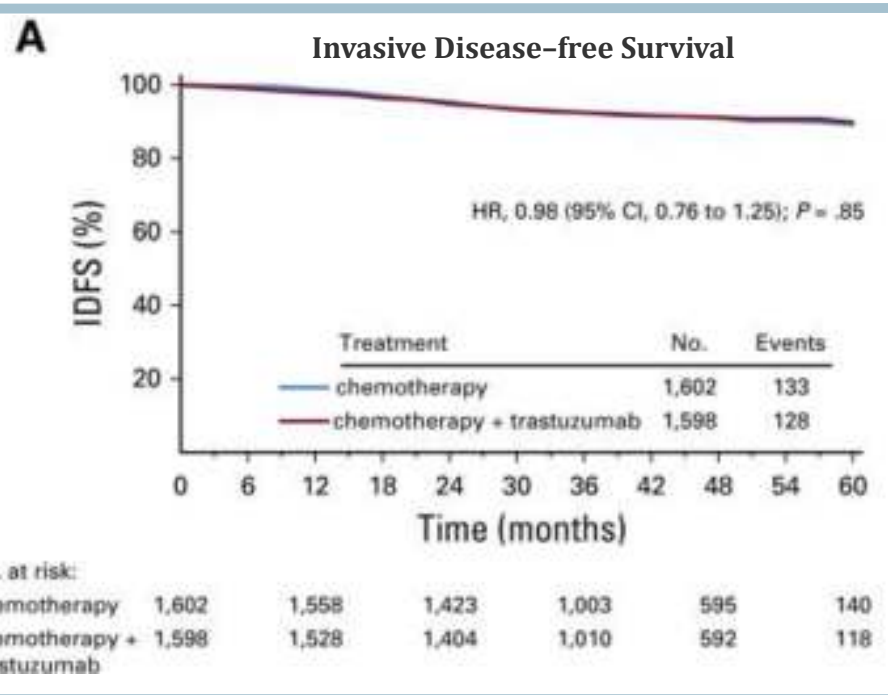
Docetaxel + Cyclophosphamide (TC)
OR
Doxorubicin + Cyclophosphamide (AC) → weekly paclitaxel (WP)

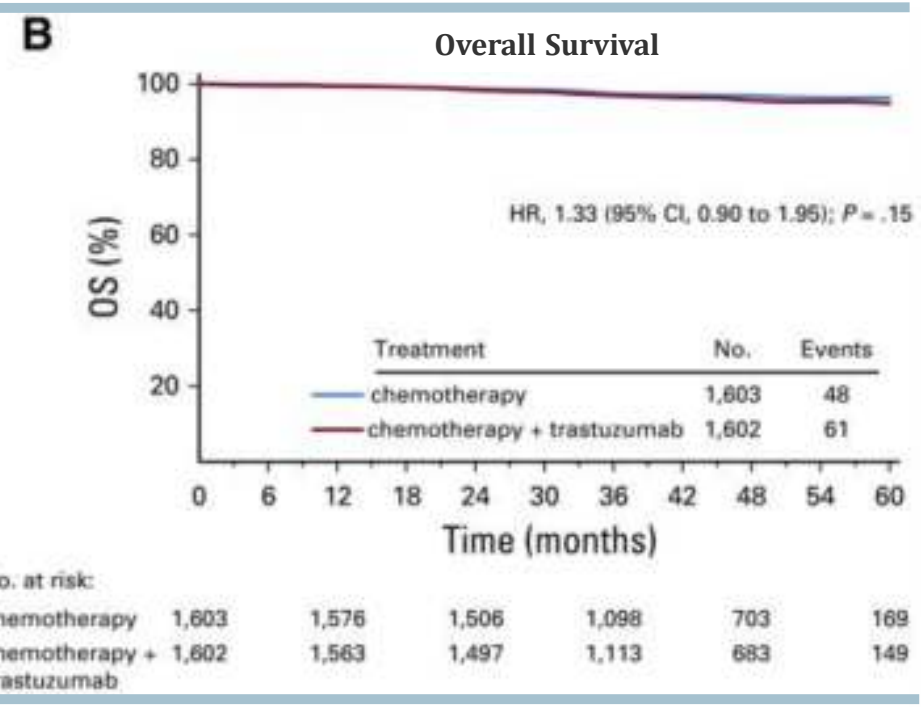
VS

TC + Trastuzumab → trastuzumab x 1 year
OR
AC → WP + trastuzumab → trastuzumab x 1 year

Fehrenbacher L, et al. NSABP B-47/NRG Oncology Phase III Randomized Trial Comparing Adjuvant Chemotherapy With or Without Trastuzumab in High-Risk Invasive Breast Cancer Negative for HER2 by FISH and With IHC 1+ or 2. *J Clin Oncol.* 2020;38(5):444-453.

NSABP B-47 TRIAL





No benefit of adjuvant trastuzumab for HER2-low patients

Fehrenbacher L, et al. NSABP B-47/NRG Oncology Phase III Randomized Trial Comparing Adjuvant Chemotherapy With or Without Trastuzumab in High-Risk Invasive Breast Cancer Negative for HER2 by FISH and With IHC 1+ or 2. *J Clin Oncol*. 2020;38(5):444-453.

CHALLENGES

- HER2-low expression is **highly variable** in time
- **Accuracy of assays** to differentiate HER2 0 from HER2 1+
- **Pathologist reader discordance**
  - Fernandez AI, et al. suggests 26% concordance between diagnosis of HER2 0 and HER2 1+

Fernandez AI, et al. Examination of Low ERBB2 Protein Expression in Breast Cancer Tissue. JAMA Oncol. 2022;8(4):607-610

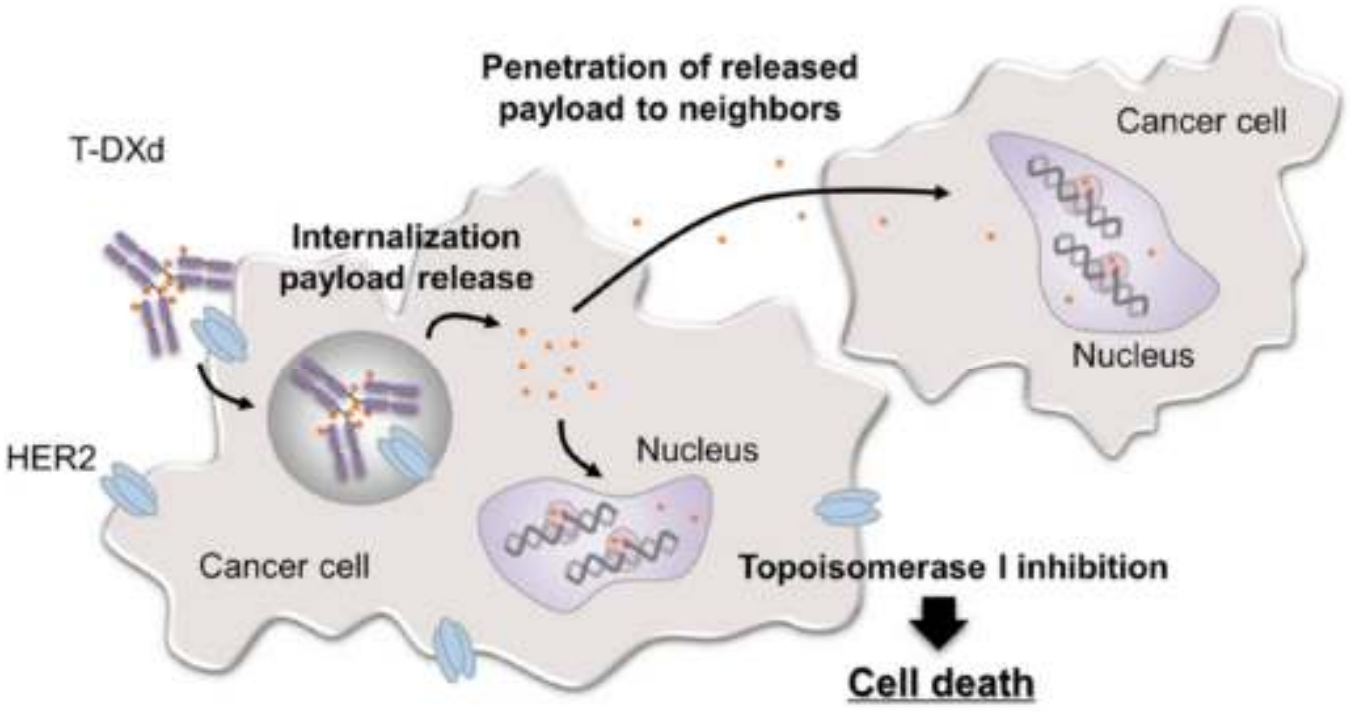
FAM-TRASTUZUMAB DERUXTECAN-NXKI (ENHERTU)

ENHERTU: NEXT GENERATION HER2 ANTIBODY-DRUG CONJUGATE

Enhertu	ADC Attributes	Kadcyla
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

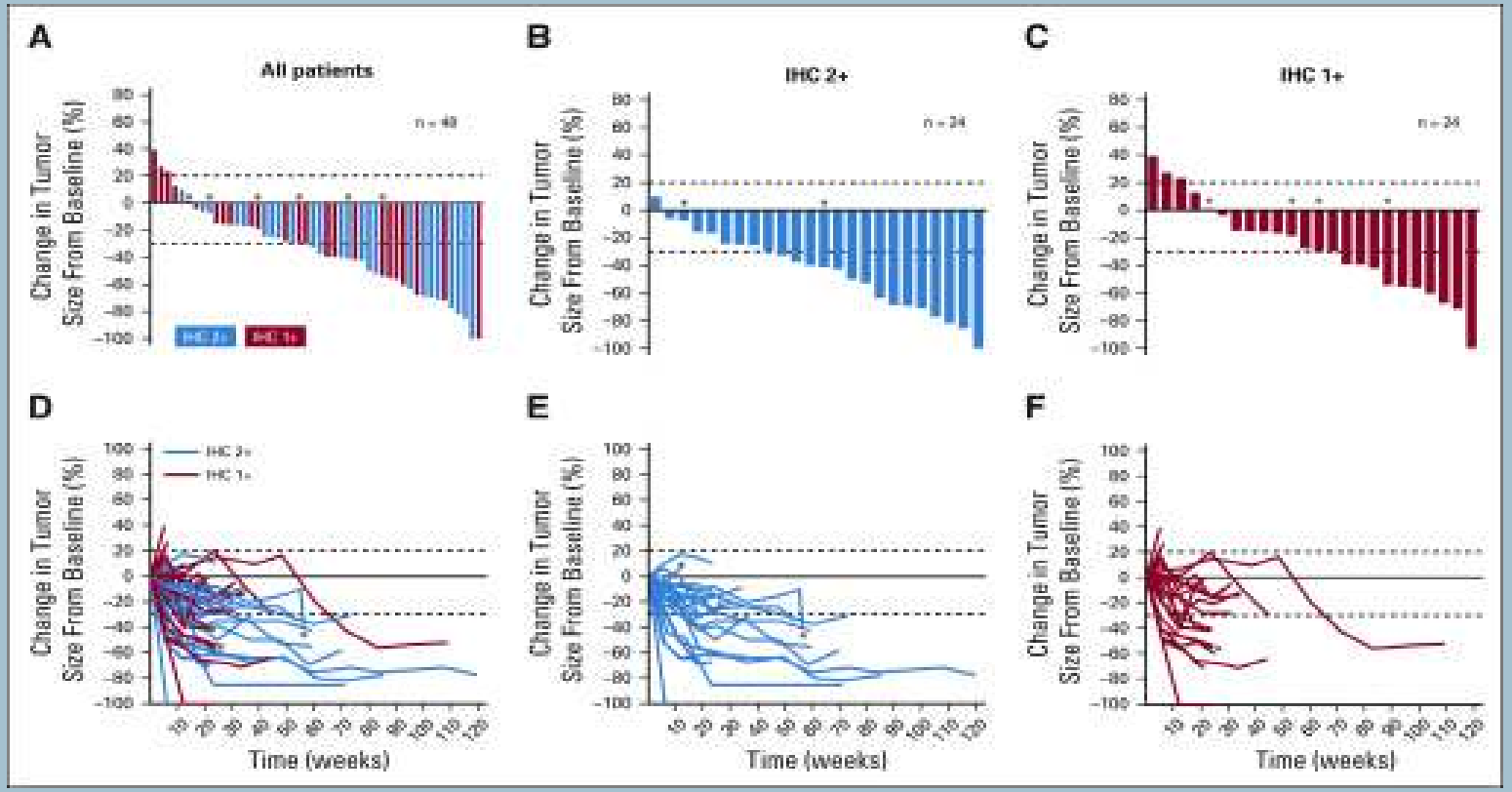
Nakada T et al. Chem Pharm Bull (Tokyo). 2019;67:173-85.
Ogitani Y et al. Cancer Sci. 2016;107:1039-46.
Ogitani Y et al. Clin Cancer Res. 2016;22:5097-108.
Trail PA et al. Pharmacol Ther. 2018;181:126-42
LoRusso PM et al. Clin Cancer Res. 2011;17:6437-47

ENHERTU MOA: BYSTANDER EFFECT



Shitara K, *et al*. Discovery and development of trastuzumab deruxtecan and safety management for patients with HER2-positive gastric cancer. *Gastric Cancer* 24, 780–789 (2021).

PHASE 1 TRIAL OF ENHERTU IN HER2-LOW



***ORR 37% with activity both in IHC 1+ and 2+**

***mPFS 11 months**

Modi S, et al. Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low-Expressing Advanced Breast Cancer: Results From a Phase Ib Study. *J Clin Oncol*. 2020;38(17):1887-1896.

DESTINY-BREAST04 TRIAL

- **HER2-low** (IHC 1+, IHC 2+/ISH-), **unresectable, and/or MBC treated with 1-2 prior lines of chemotherapy in the metastatic setting**
- **HR+ with endocrine refractory disease**

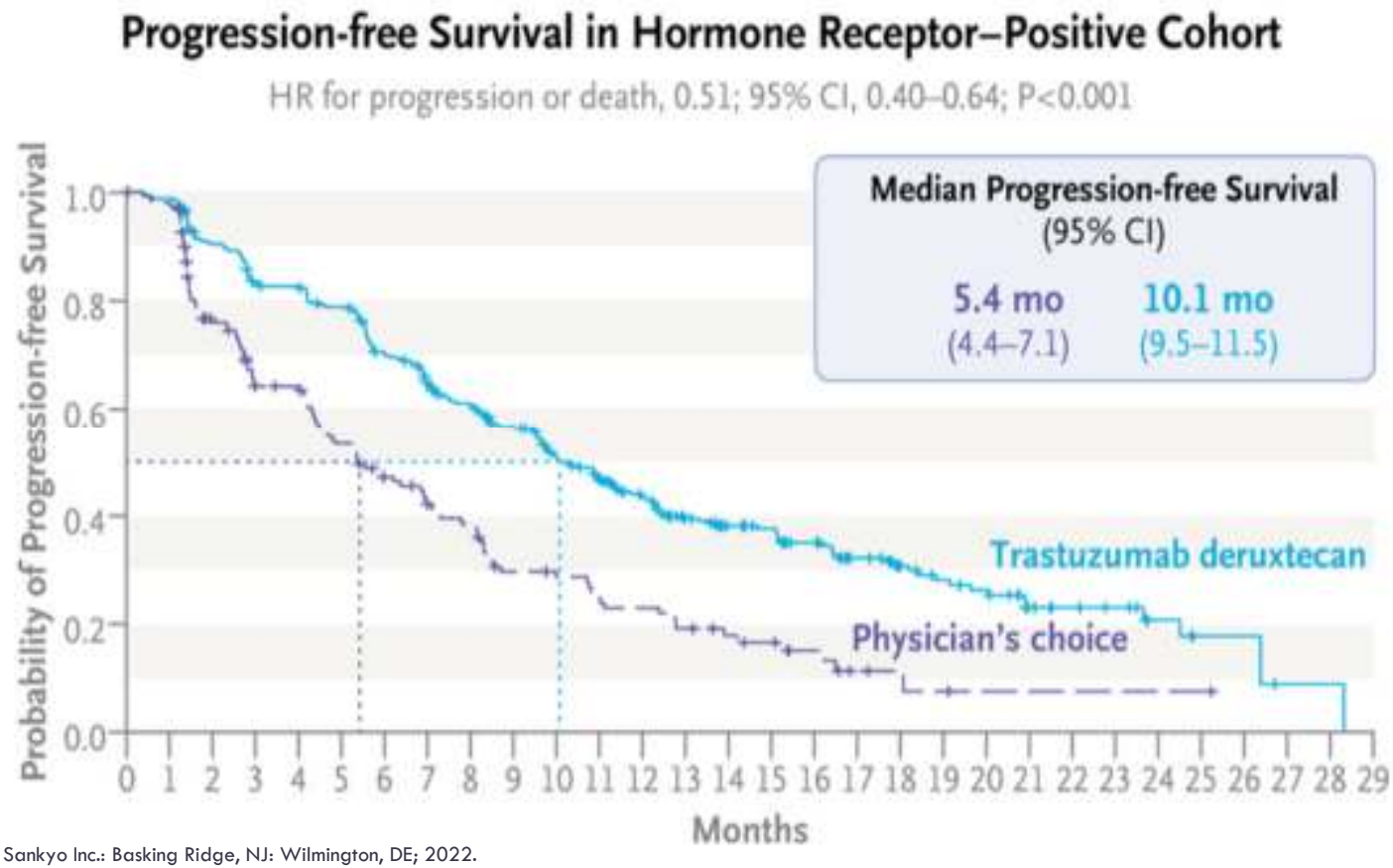
R
n =557

Enhertu
5.4 mg/kg Q3 weeks
(n = 373)

Physician's Choice
Eribulin, capecitabine, nab-paclitaxel, gemcitabine, paclitaxel
(n = 184)

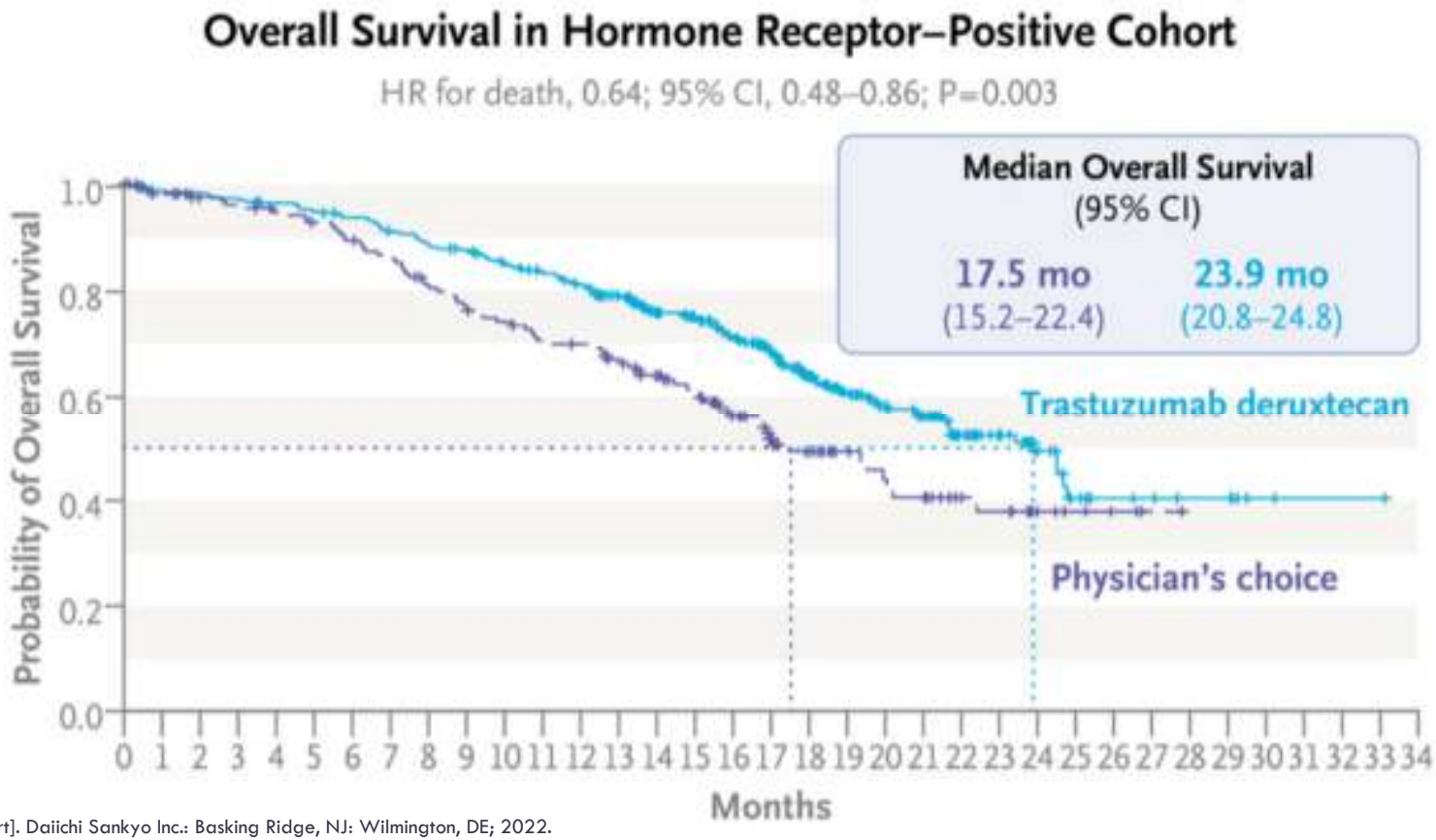
ClinicalTrials.gov. Trastuzumab deruxtecan (DS-8201a) versus investigator's choice for HER2-low breast cancer that has spread or cannot be surgically removed [DESTINY-Breast04]. https://clinicaltrials.gov/ct2/show/NCT03734029. Accessed May 11, 2023
Modi S, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med.* 2022;387(1):9-20.

PROGRESSION FREE SURVIVAL (PFS) IN HR+



ENHERTU [package insert]. Daiichi Sankyo Inc.: Basking Ridge, NJ: Wilmington, DE; 2022.
Modi, S. et al. for the DESTINY-Breast04 Trial. N Engl J Med 2022; 387:9-20

OVERALL SURVIVAL (OS) IN HR+



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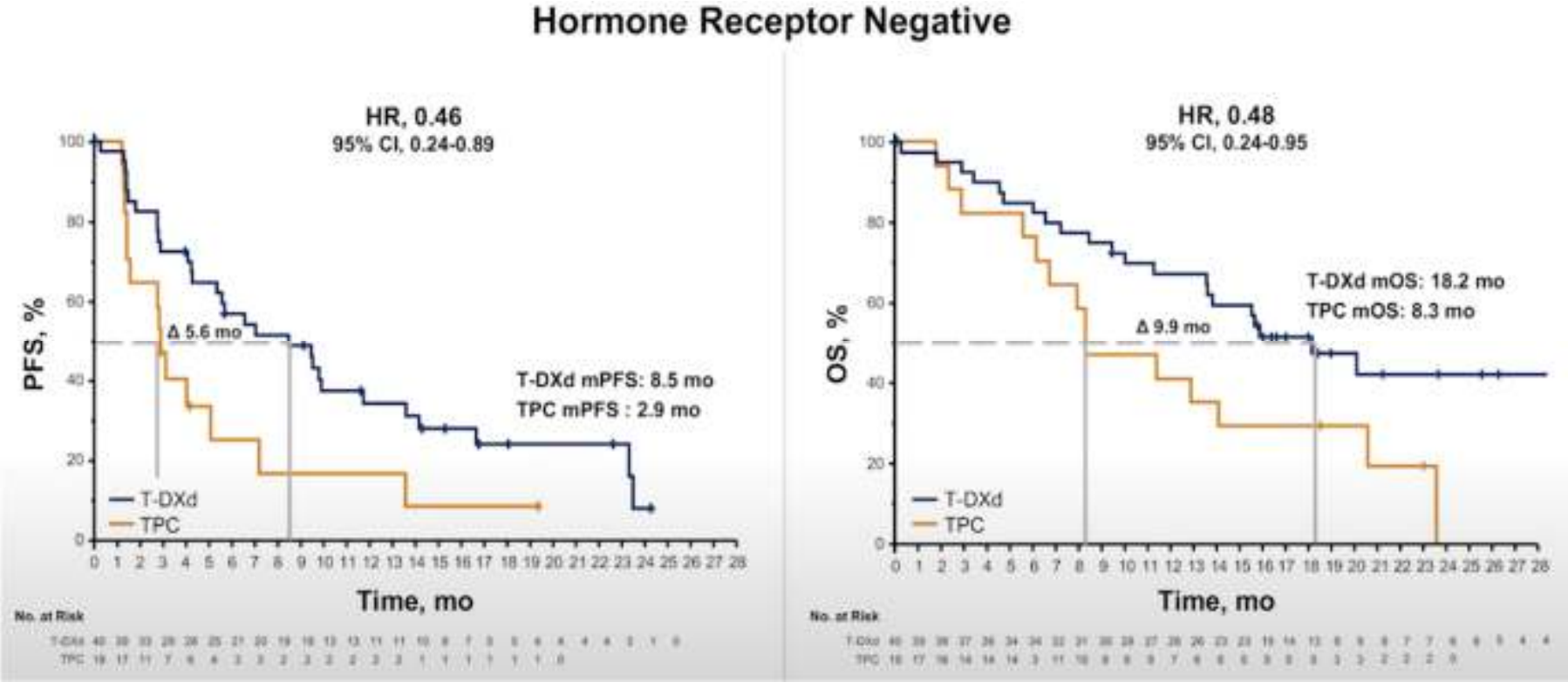
Modi, S. et al. for the DESTINY-Breast04 Trial. N Engl J Med 2022; 387:9-20

PFS AND OS IN HR- (EXPLORATORY ENDPOINTS)



Modi, S. et al. for the DESTINY-Breast04 Trial. N Engl J Med 2022; 387:9-20

DRUG-RELATED ADVERSE EVENTS

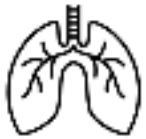
Median duration of treatment
- Enhertu: 8 mo (range, 0-33)
- Physician's Choice: 3.5 mo (range, 0-18)

T-DXd is moderately emetogenic, which includes delayed nausea and/or vomiting. Administer prophylactic antiemetic medications per local institutional guidelines for prevention of CINV

Table 3. Most Common Drug-Related Adverse Events (in ≥20% of Patients) in the Safety Analysis Set.[A]

Event	Trastuzumab Deruxtecan (N=371)		Physician's Choice of Chemotherapy (N=172)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Blood and lymphatic system disorders				
Neutropenia†	123 (33.2)	51 (13.7)	88 (51.2)	70 (40.7)
Anemia‡	123 (33.2)	30 (8.1)	39 (22.7)	8 (4.7)
Thrombocytopenia§	88 (23.7)	19 (5.1)	16 (9.3)	1 (0.6)
Leukopenia¶	86 (23.2)	24 (6.5)	54 (31.4)	33 (19.2)
Gastrointestinal disorders				
Nausea	271 (73.0)	17 (4.6)	41 (23.8)	0
Vomiting	126 (34.0)	5 (1.3)	17 (9.9)	0
Diarrhea	83 (22.4)	4 (1.1)	31 (18.0)	3 (1.7)
Constipation	79 (21.3)	0	22 (12.8)	0
Investigations: increased aminotransferase levels‖	87 (23.5)	12 (3.2)	39 (22.7)	14 (8.1)
General disorders: fatigue**	177 (47.7)	28 (7.5)	73 (42.4)	8 (4.7)
Metabolism and nutrition disorders: decreased appetite	106 (28.6)	9 (2.4)	28 (16.3)	2 (1.2)
Skin and subcutaneous tissue disorders: alopecia	140 (37.7)	0	56 (32.6)	0

ENHERTU [package insert]. Daiichi Sankyo Inc.: Basking Ridge, NJ: Wilmington, DE; 2022.
Modi, S. et al. for the DESTINY-Breast04 Trial. N Engl J Med 2022; 387:9-20



DRUG-RELATED ADVERSE EVENTS

ILD/Pneumonitis

Drug-Related ILD/Pneumonitis, n (%)	Enhertu n = 371
Grade 1	13 (3.5)
Grade 2	24 (6.5)
Grade 3	5 (1.3)
Grade 4	0
Grade 5	3 (0.8)
Any grade/total	45 (12.1)

Median time to first onset from the pooled population: 5 mo (range 0.9 to 23)

LVEF Decrease

LVEF Decrease, n (%)	Enhertu n = 371
Grade 1	1 (0.3)
Grade 2	14 (3.8)
Grade 3	1 (0.3)
Grade 4	0
Grade 5	0
Any grade/total	16 (4.3)

Cardiac Failure

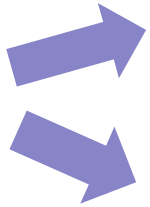
Cardiac failure, n (%)	Enhertu n = 371
Grade 1	0
Grade 2	1 (0.3)
Grade 3	1 (0.3)
Grade 4	0
Grade 5	0
Any grade/total	2 (0.5)

ENHERTU [package insert]. Daiichi Sankyo Inc.: Basking Ridge, NJ: Wilmington, DE; 2022.
Modi, S. et al. for the DESTINY-Breast04 Trial. N Engl J Med 2022; 387:9-20

ILD AND PNEUMONITIS:
MONITORING AND MANAGEMENT

Monitoring

Signs and symptoms that may indicate ILD/pneumonitis	Promptly investigate evidence of ILD
• Cough • Dyspnea • Fever • New or worsening respiratory symptoms	• Evaluate patients with suspected ILD by radiographic imaging • Consider consultation with a pulmonologist



Management Strategies

Asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg/day prednisolone or equivalent)
- Withhold Enhertu until recovery to grade 0
  - If resolved in ≤ 28 days from date of onset, maintain dose
  - If resolved in > 28 days from date of onset, reduce dose one level

Symptomatic ILD (grade ≥ 2)

- Promptly initiate systemic corticosteroid treatment (eg, ≥ 1 mg/kg/day prednisolone or equivalent)
  - Continue for at least 14 days followed by gradual taper for at least 4 weeks
- Permanently discontinue Enhertu

ENHERTU [package insert]. Daiichi Sankyo Inc.: Basking Ridge, NJ: Wilmington, DE; 2022.

DOSAGE AND ADMINISTRATION

5.4 mg/kg once every 3 weeks

Given as a 5.4 mg/kg IV infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity

First Infusion	Administer over **90 minutes**
Subsequent Infusions	Administer over **30 minutes** if prior infusions were well tolerated

Use **5% Dextrose Injection USP** to dilute.
DO NOT use Sodium Chloride Injection, USP.

Dose Modifications

Starting Dose: 5.4 mg/kg

First Dose Reduction: 4.4 mg/kg

Second Dose Reduction: 3.2 mg/kg

Requirement for Further Dose Reduction: Discontinue Treatment

Do not re-escalate after a dose reduction is made

Permanently discontinue Enhertu in case of severe infusion reactions

ENHERTU [package insert]. Daiichi Sankyo Inc.: Basking Ridge, NJ: Wilmington, DE; 2022.

SUMMARY OF TRIAL AND IMPACT

Enhertu is the first HER2-targeted therapy to demonstrate improved efficacy in HER2-low

DESTINY-Breast04 establishes Enhertu as the new standard of care for HER2-low

Potential improvement for ~50% of all metastatic breast cancer patients in this setting

MEDICATION-SAFETY CHALLENGES WITH HER2-DIRECTED CHEMOTHERAPY & STRATEGIES TOWARDS PREVENTION

MEDICATION SAFETY 1999

- Medical errors are estimated to account for
  - Approx. **98,000 deaths/year**
  - About 7,000 deaths due to medications alone

- Total national cost of **preventable** adverse events: **$17-28 billion/year**

"More people die in a given year as a result of medical errors than from motor vehicle accidents and breast cancer."

Kohn, L. et al. To err is human: Building a safer health system. Washington, D.C.: National Academy Press. 2000

PREVALENCE OF MEDICATION ERRORS

An estimate of 1 to 4 errors per 1000 orders are from chemotherapy medication errors

Approximately 3% of errors involving chemotherapy are reported

Northfelt DW, et al. *Proc Am Soc Clin Oncol*. 2003;22:542. Abstract 2181.
Schulmeister L. *Oncol Nurs Forum*. 1999;23:1033–42.
Weingart, S. et al. Chemotherapy medication errors. *Lancet Oncol* 2018; 19: e191-99

1. ORDERING/PRESCRIBING

LOOK-ALIKE SOUND-ALIKE

Prevention strategies

- **List by generic name, using a "dash"**
- **Include brand and generic name**
- **Physically separate when storing**

trastuzuamb (HERCEPTIN) intrathecal injection
trastuzumab-anns (KANJINTI) chemo IVPB 250 mL NS
trastuzumab-dkst (OGIVRI) chemo IVPB 250 mL NS
trastuzumab 600 mg-hyaluronidase-oysk 10,000 units (HERCEPTIN HYLECTA) subcutaneous injection
trastuzumab-qyyp (TRAZIMERA) chemo IVPB 250 mL NS
ado-trastuzumab emtansine (KADCYLA) chemo IVPB 250 mL NS
fam-trastuzumab deruxtecan-nxki (ENHERTU) IVPB in dextrose 5 % 100 mL

[Image] Trastuzumab orders. NewYork-Presbyterian Columbia. Captured on May 1, 2023. Screenshot by author.

Weingart, S. et al. Chemotherapy medication errors. *Lancet Oncol* 2018; 19: e191-99

2. DISPENSING

BARCODING/SCANNING

PharmacyKeeper

Camera system in the IV cleanroom

1. Component check
- Tech scans items pulled

2. Photo documentation
- Pictures of vials/ IV bags
- Quantities of each diluent and medication

3. Pharmacist approval
- Compares patient label to scanned components
- Approves products and quantities

MedKeeper. (2020). Retrieved 29 December 2020, from https://www.medkeeper.com/
Weingart, S. et al. Chemotherapy medication errors. *Lancet Oncol* 2018; 19: e191-99

3. ADMINISTRATION

DRUG MONITORING

Computerized order-entry systems (CPOE)

Patient communication

Nursing check-list

Weingart, S. et al. Chemotherapy medication errors. *Lancet Oncol* 2018; 19: e191-99

PATIENT COMMUNICATION:
CHEMOTHERAPY COUNSELING CARD

FAM-TRASTUZUMAB DERUXTECAN-NXKI (ENHERTU)

Administration: every 3 weeks

Side effects: nausea, vomiting, diarrhea

Monitor: lungs (cough, shortness of breath), heart, liver function, CBC panel, BMP panel

FAM-TRASTUZUMAB DERUXTECAN-NXKI (ENHERTU)

Name: DOB:
Physician:
Office #:
Cancer/diagnosis:

Start date:

Comments:

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PUTTING IT ALL TOGETHER

The diagnosis of “HER2-low” remains challenging

Enhertu, a novel antibody-drug conjugate have not only improved outcomes in HER2+ breast cancer, but also allowed us to move beyond new populations

Understanding the medication-use process and safety techniques helps to prevent medication errors

NOVELTIES IN BREAST CANCER TREATMENT & SAFETY INITIATIVES

Jessica El-Miniawi, PharmD

CITATIONS

- Burstein HJ, et al. The distinctive nature of HER2-positive cancers. N Engl J Med. 2005;353(16):1652-1654
- ClinicalTrials.gov. Trastuzumab deruxtecan (DS-8201a) versus investigator's choice for HER2-low breast cancer that has spread or cannot be surgically removed [DESTINY-Breast04]. https://clinicaltrials.gov/ct2/show/NCT03734029. Accessed May 11, 2023
- Enhertu. 2022 Daiichi Sankyo, Inc. and AstraZeneca. https://www.enhertuhcp.com/en/her2-low-breast/about-her2-low-mbc. Accessed May 23, 2023.
- Fehrenbacher L, et al. NSABP B-47/NRG Oncology Phase III Randomized Trial Comparing Adjuvant Chemotherapy With or Without Trastuzumab in High-Risk Invasive Breast Cancer Negative for HER2 by FISH and With IHC 1+ or 2. *J Clin Oncol.* 2020;38(5):444-453.
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