

REENGINEERING THE APPROACH TO METASTATIC BREAST CANCER

A Stepwise Guide to HER2 Testing and Management for HER2-Low and -Ultralow Disease

PART 1: Unveiling HER2-low and -ultralow Expression in Metastatic BC: Implications for the Multidisciplinary Care Team

Supported by educational grants from AstraZeneca Pharmaceuticals and Daiichi Sankyo, Inc.

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Project Overview

- HER2-directed therapies transformed the treatment of breast cancer (BC). Initially, this benefit was limited to ~15% of patients with clear HER2 amplification or overexpression; however, it is now recognized that patients previously classified as “HER2-negative” may still derive meaningful benefit from antibody–drug conjugates (ADCs).

- This emerging understanding challenges traditional binary HER2 classification and underscores new diagnostic and therapeutic complexities. With the recognition of HER2-low and now HER2-ultralow disease categories, oncologists, pathologists, and multidisciplinary care teams face evolving questions about testing accuracy, interpretation, and therapeutic decision-making.

PURPOSE: Provide practical guidance on the identification and interpretation of HER2-low/-ultralow metastatic BC (mBC) using real world examples of how select institutions have optimized their testing and reporting algorithms

3-PART ACTIVITY SERIES

ACTIVITY 1 – Unveiling HER2-low and -ultralow Expression in mBC: Implications for the Multidisciplinary Care Team

ACTIVITY 2 – What’s Your Protocol? Streamlining Oncology/Pathology Collaboration Throughout the BC Journey

ACTIVITY 3 – Mastering HER2-low and -ultralow mBC: Precise Testing for Targeted Therapeutic Selection

HER2: Human epidermal growth factor receptor 2

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Faculty



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Department of Hematology and Medical Oncology

Professor
Department of Gynecology & Obstetrics

Co-Director
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Disclosures

DR MEISEL DISCLOSES THE FOLLOWING:

- **ADVISORY BOARD:** AstraZeneca, Olema Oncology, Pfizer Inc., and Sermonix Pharmaceuticals
- **RESEARCH:** AstraZeneca, Olema Oncology, Sermonix Pharmaceuticals
- **CONSULTING FEES:** AstraZeneca, Genetech, Inc., GSK, Novartis Pharmaceuticals Corporation, Olema Oncology, Pfizer Inc., Sermonix Pharmaceuticals

DR SOLIMAN DISCLOSES THE FOLLOWING:

- **ADVISORY BOARD:** AstraZeneca, Lilly, Novartis Pharmaceuticals Corporation, and Pfizer Inc./Arivinas

DR LI DISCLOSES THE FOLLOWING:

- **ADVISORY BOARD:** Lilly and Roche
- **RESEARCH SUPPORT:** Champions Oncology, Inc.
- **CONSULTING FEES:** Cancer Expert Now, LLC

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Learning Objectives

1. Identify the clinical implications of HER2-low and ultra-low expression in patients with mBC to apply appropriate clinical strategies for patients based on tumor molecular subtype

2. Evaluate the clinical efficacy and application of ADCs in HER2-low and ultra-low expressing mBC to inform evidence-based treatment decisions in clinical practice

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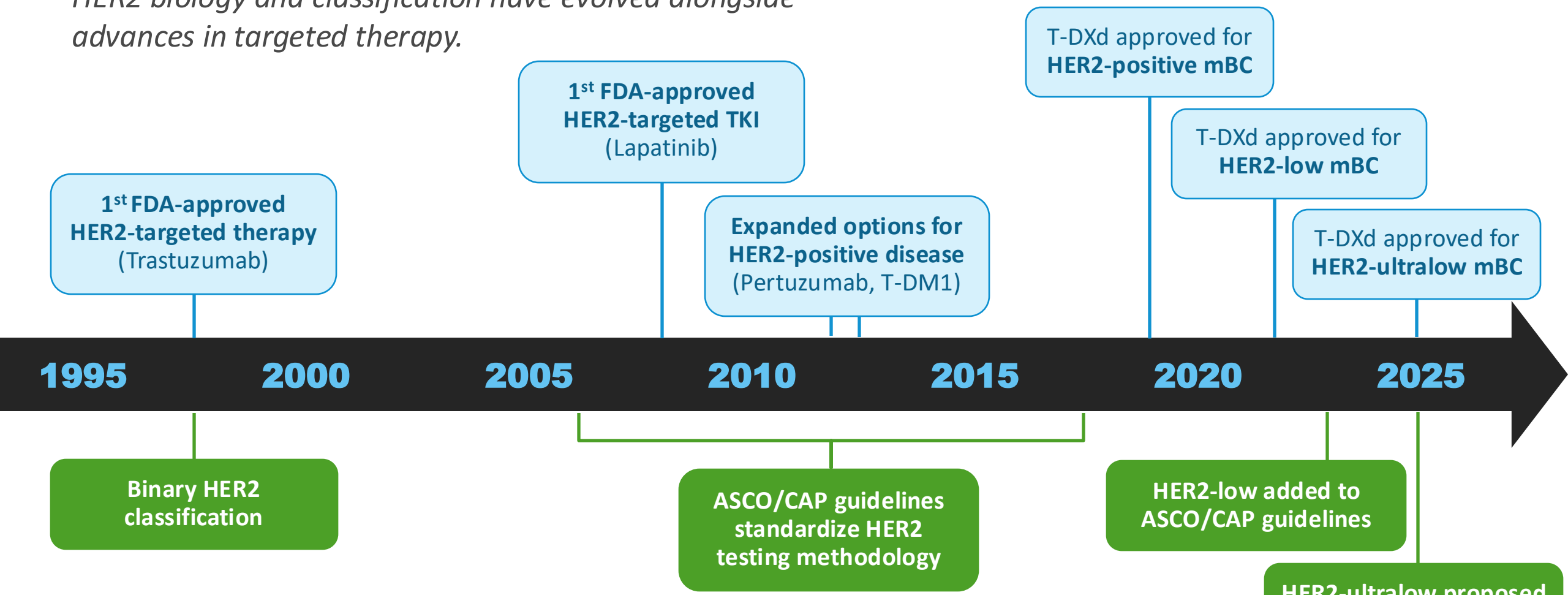
EVOLUTION OF HER2 IN MBC

HER2 biology and classification have evolved alongside advances in targeted therapy.



ASCO/CAP: American Society of Clinical Oncology/College of American Pathologists;
T-DM1: trastuzumab emtansine; **T-DXd:** Trastuzumab deruxtecan; **TKI:** tyrosine kinase inhibitor

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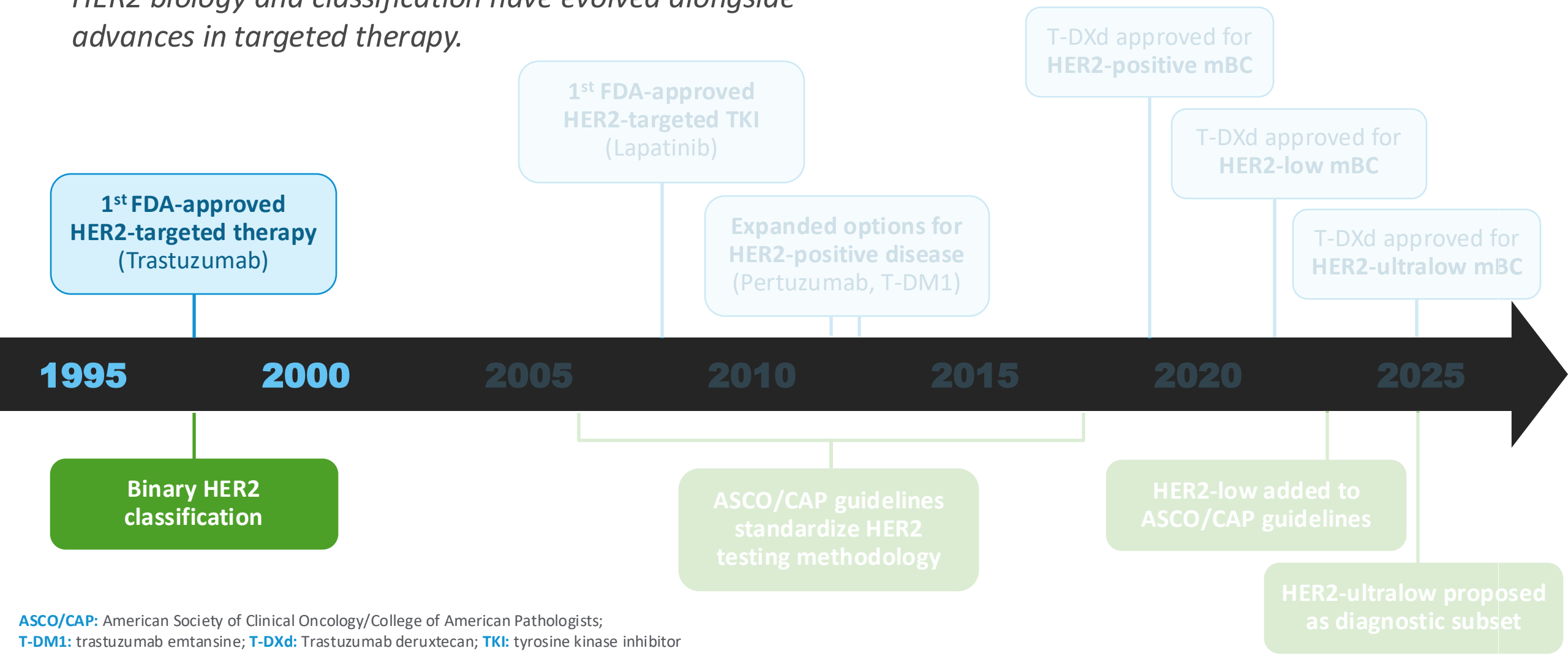

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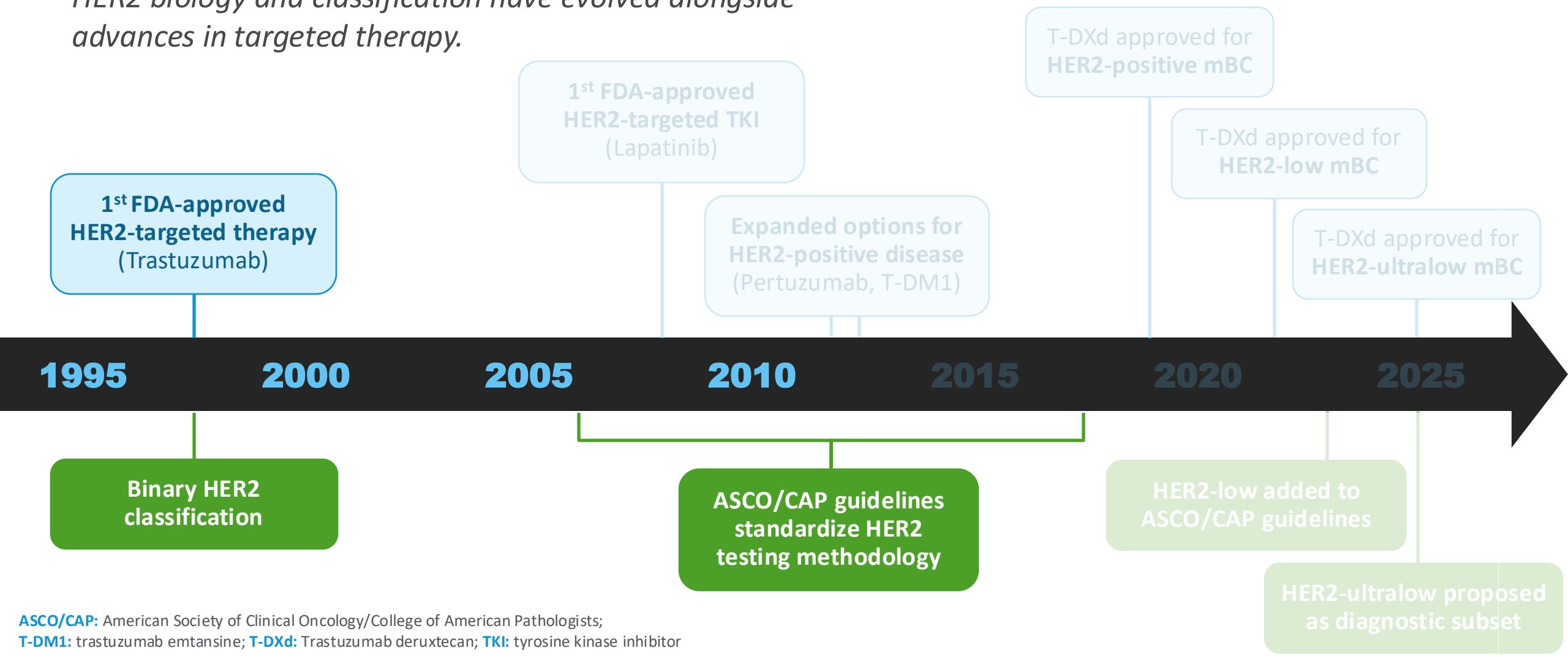

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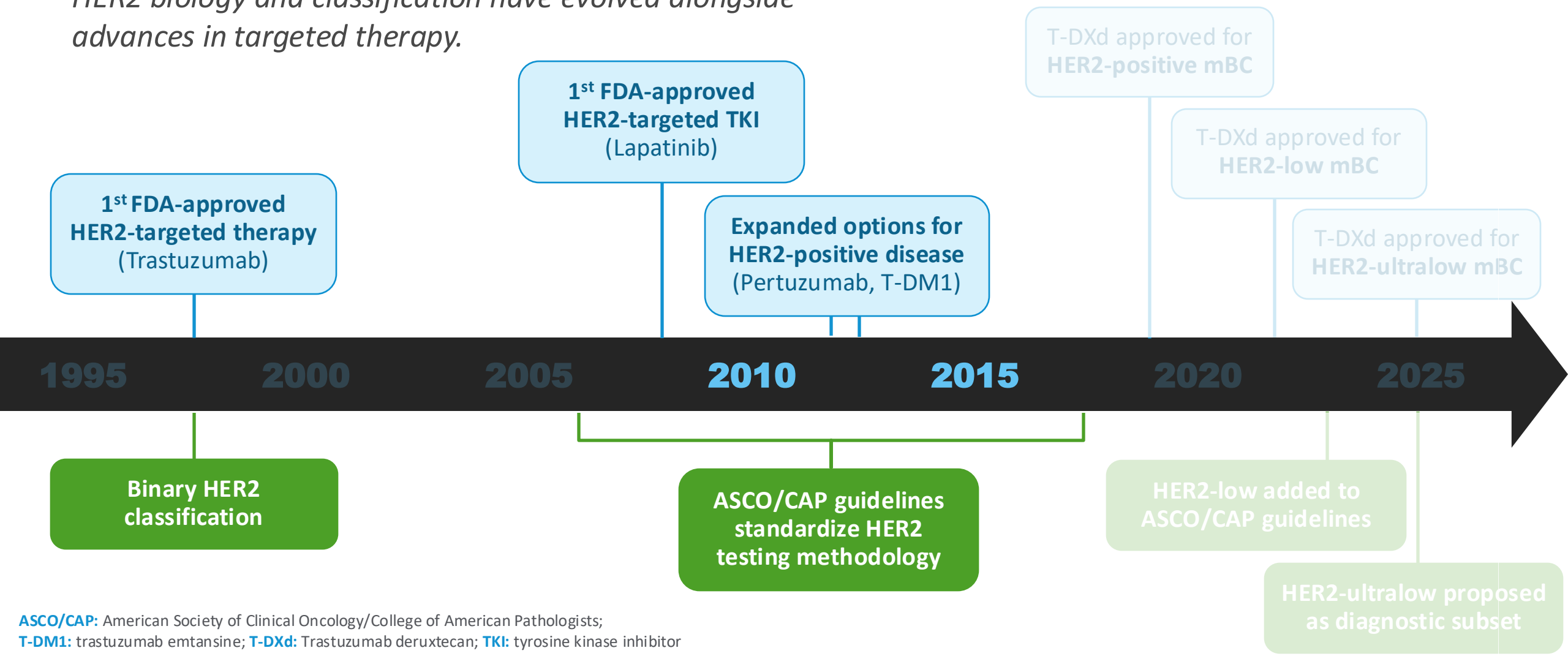

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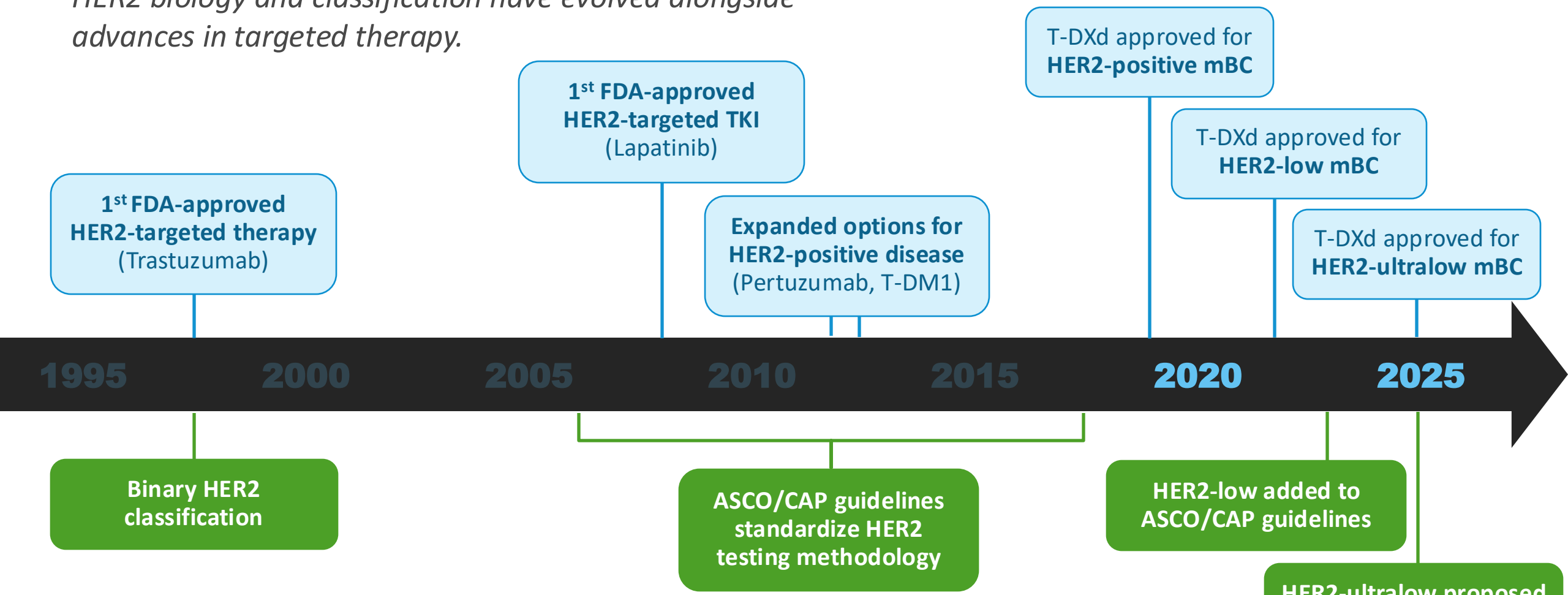

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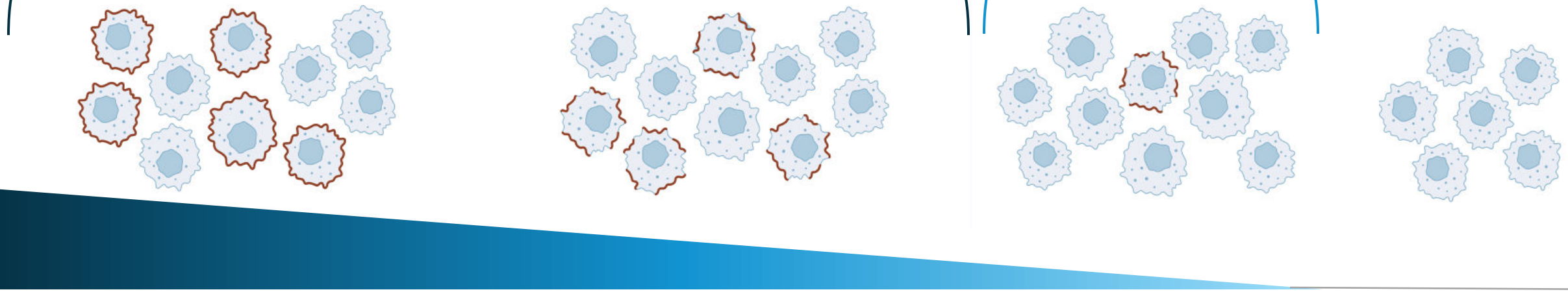
DEFINING HER2-LOW AND -ULTRALOW IN mBC

MULTICENTER RESCORED COHORT

HER2-LOW
(~55% of tumors)

HER2-ULTRALOW
(~11% of tumors)



ICH 2+/ISH–
Weak-to-moderate complete membrane staining, >10% tumor cells

ICH 1+
Faint, incomplete membrane staining, >10% tumor cells

Faint, incomplete membrane staining, ***≤10% tumor cells***

ICH 0
Absent/ no observable staining

*IHC **2+ requires reflex ISH** (2+/ISH+ = HER2-positive)*

1. Bardia A, et al. *N Engl J Med.* 2024;391(22):2110–2122. **2.** Lv H, et al. *Breast Cancer Res.* 2025;27(1):45.
3. Tarantino P, et al. *Ann Oncol.* 2023;34(8):645-659. **4.** Wolff AC, et al. *Arch Pathol Lab Med.* 2023;147(9):993–1000.

IHC: Immunohistochemistry; **ISH:** in situ hybridization
Prevalence varies by assay and rescoring; figures reflect cited cohort.

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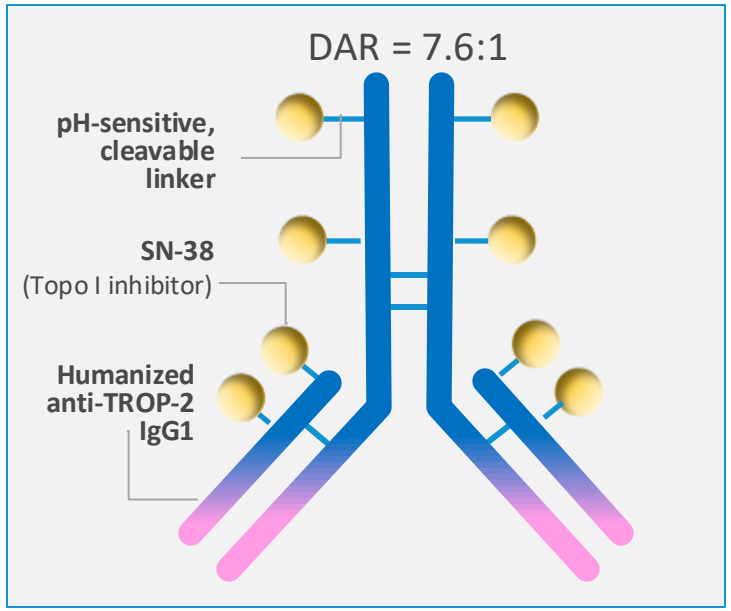
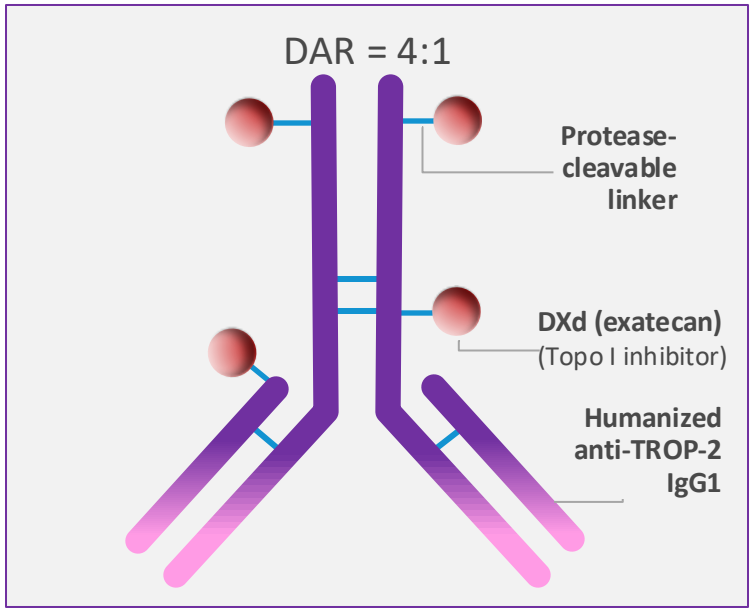
ANTIBODY-DRUG CONJUGATES IN MBC

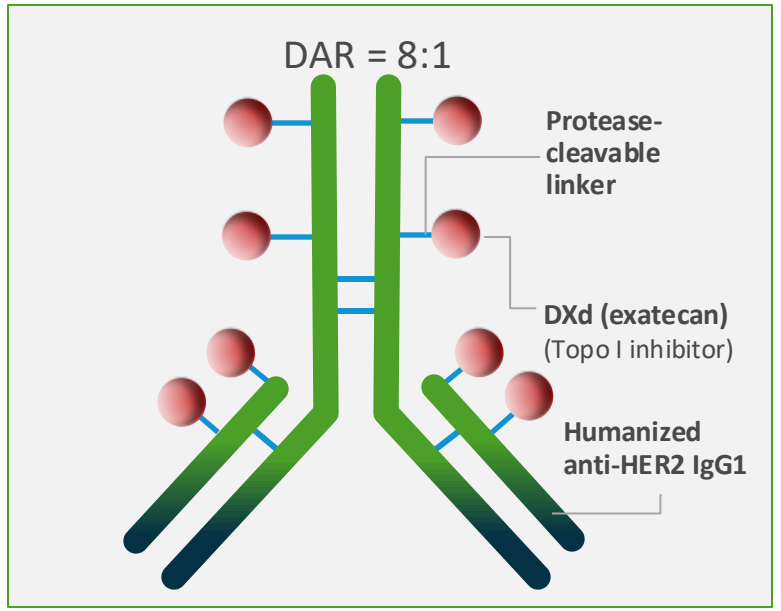
SACITUZUMAB GOVITECAN

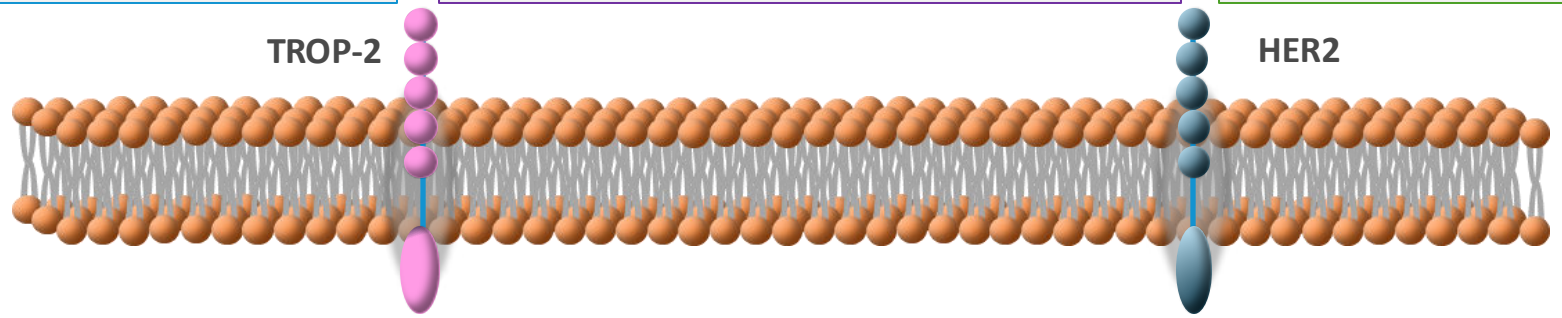


DATOPOTAMAB DERUXTECAN



TRASTUZUMAB DERUXTECAN





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4. Starodub AN, et al. *Clin Cancer Res.* 2015;21(17):3870-3878. **5.** Tamura K, et al. *Lancet Oncol.* 2019;20(6):816-826.

DAR: drug to antibody ratio;
IgG1: immunoglobulin 1;
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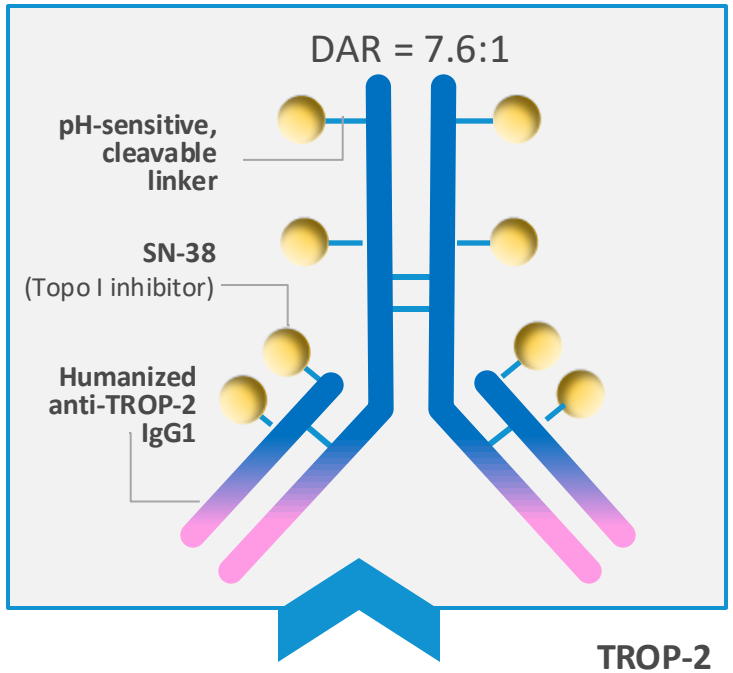

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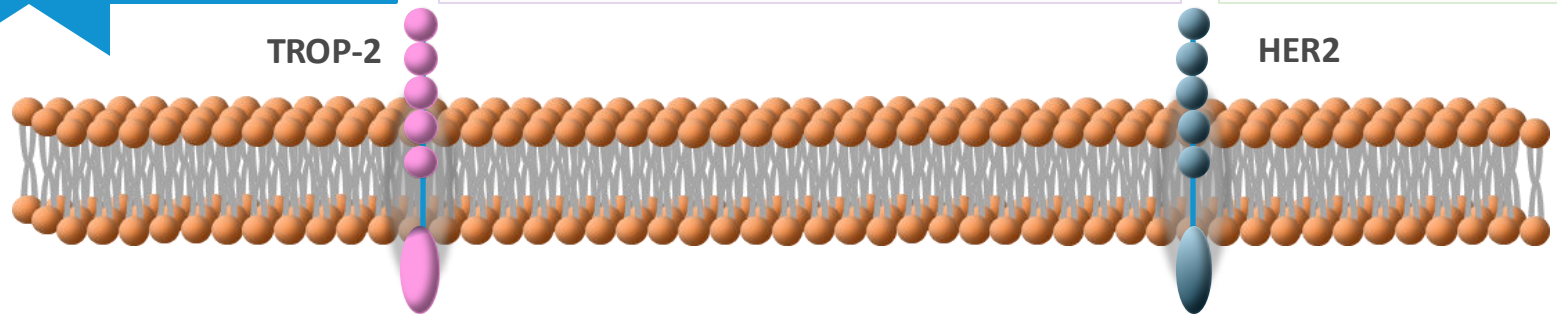

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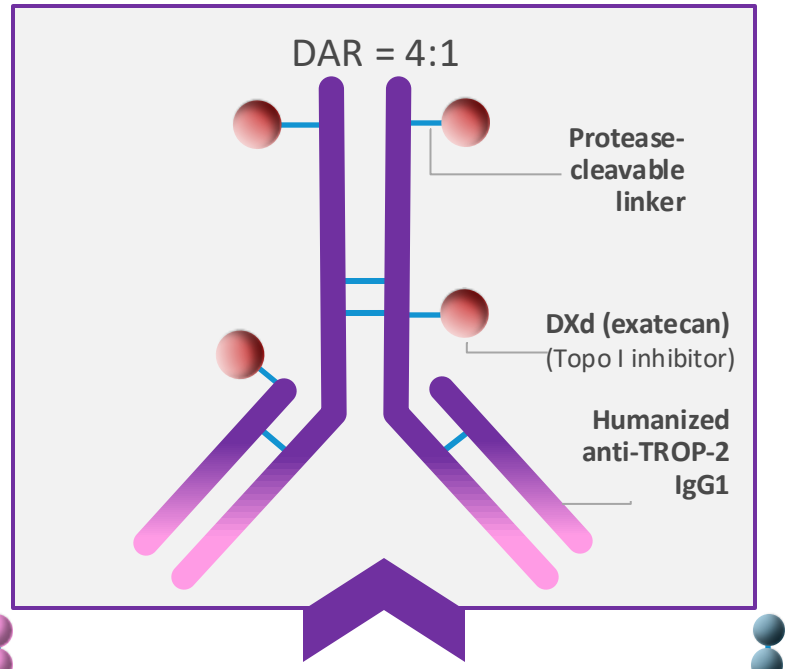

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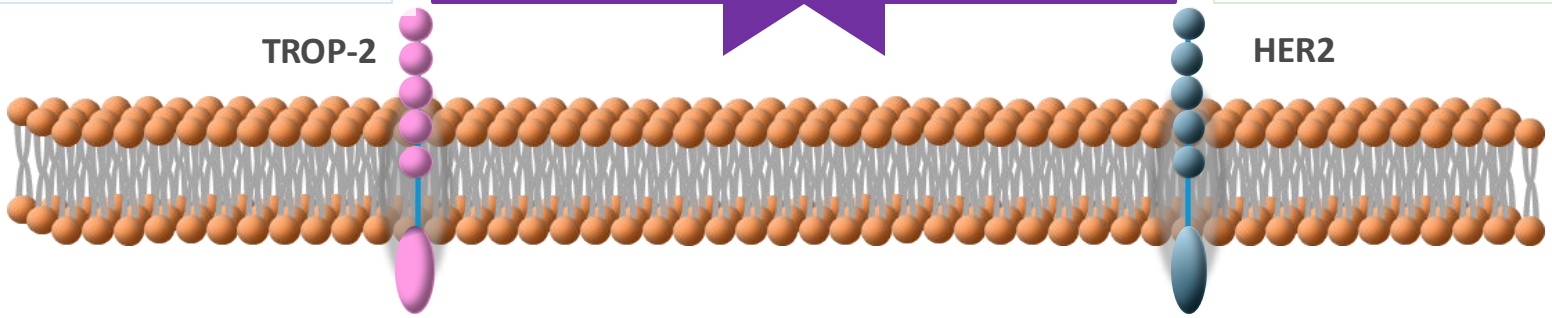

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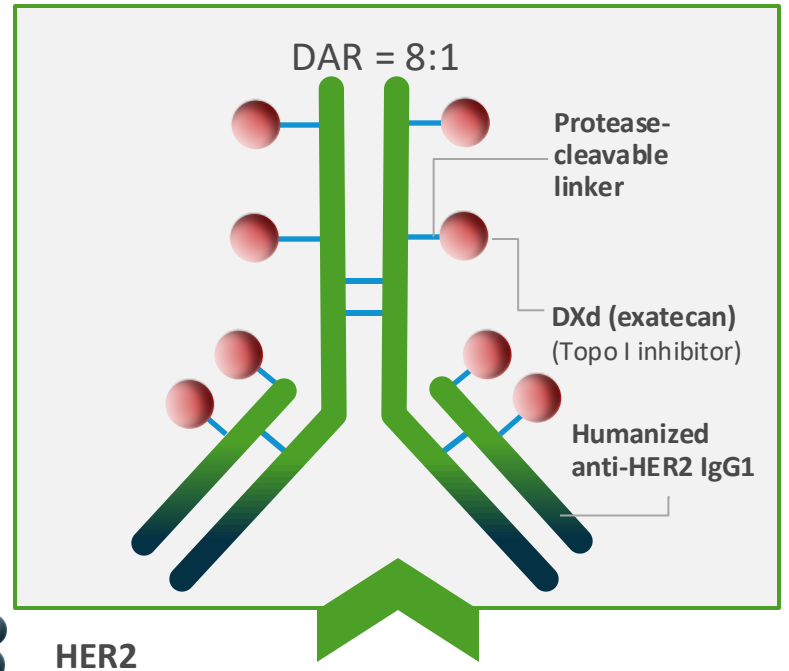

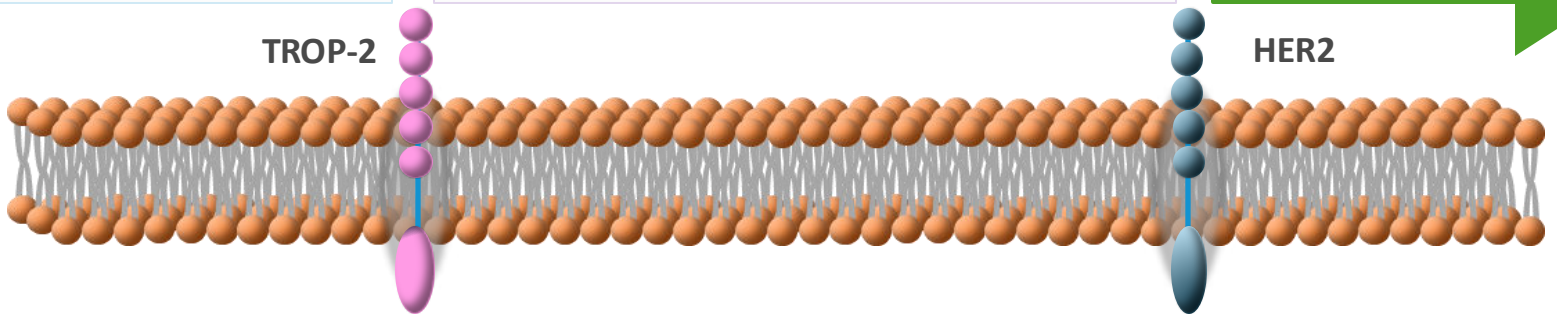

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REDEFINING TREATMENT FOR HER2-LOW BC

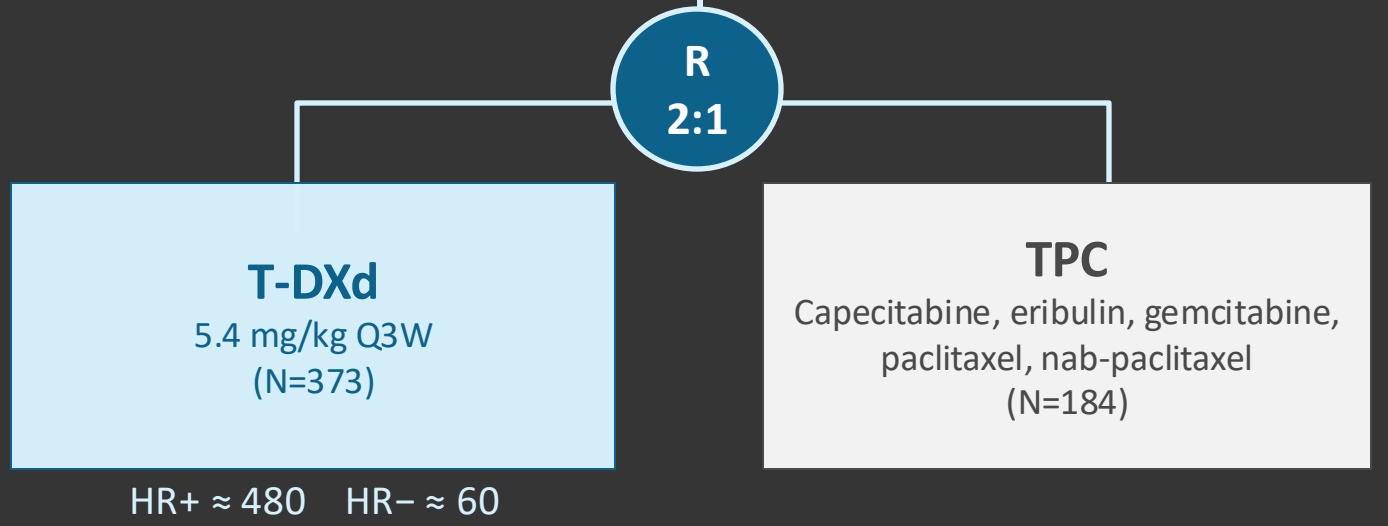
DESTINY BREAST-04

STRATIFICATION FACTORS

- *Centrally assessed HER2 status (IHC 1+ vs IHC 2+/ISH−)*
- *1 vs 2 prior lines of chemotherapy*
- *HR+ (with vs without prior treatment with CDK4/6 inhibitor) vs HR-*

KEY ELIGIBILITY CRITERIA

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



PRIMARY ENDPOINT

PFS by BICR (HR+)

KEY SECONDARY ENDPOINTS

PFS by BICR (all patients) , OS (HR+ and all patients)

BICR: blinded independent review committee; **OS:** overall survival; **PFS:** progression-free survival; **TPC:** treatment of physician's choice; **Q3W:** once every three weeks

Modi S, et al. *N Engl J Med.* 2022;387(1):9-20.

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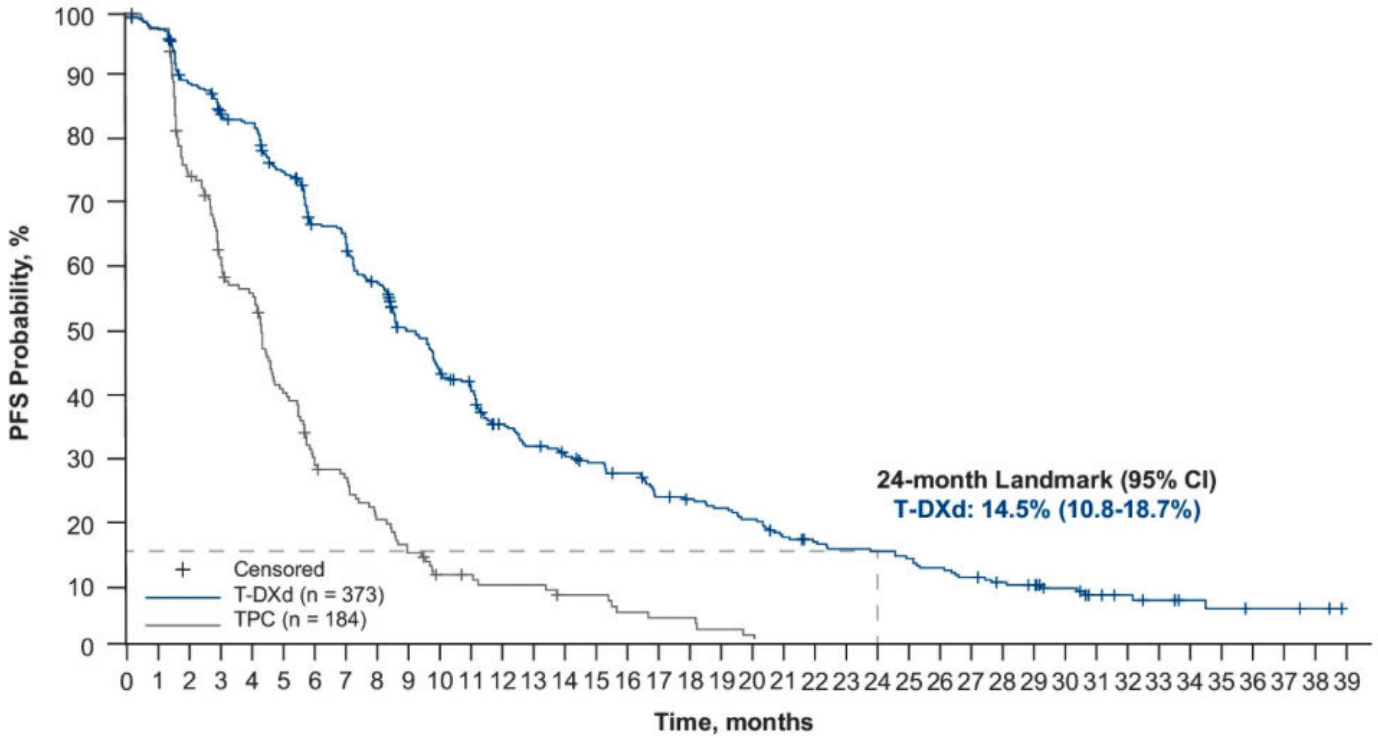
DESTINY BREAST-04

PROGRESSION-FREE SURVIVAL

	T-DXd (n = 373)	TPC (n = 184)
	Overall	
Median PFS, mo	**8.8**	4.2
HR (95% CI)	0.36 (0.29-0.45)	
	HR+	
Median PFS, mo	**9.6**	4.2
HR (95% CI)	0.37 (0.30–0.46)	
	HR-	
Median PFS, mo	**6.3**	2.9
HR (95% CI)	0.29 (0.15–0.57)	

PFS OVER TIME



CI: confidence interval; **HR:** hazard ratio; **HR+:** hormone receptor-positive; **HR-:** hormone receptor-negative

Modi S, et al. *Nat Med.* 2025.

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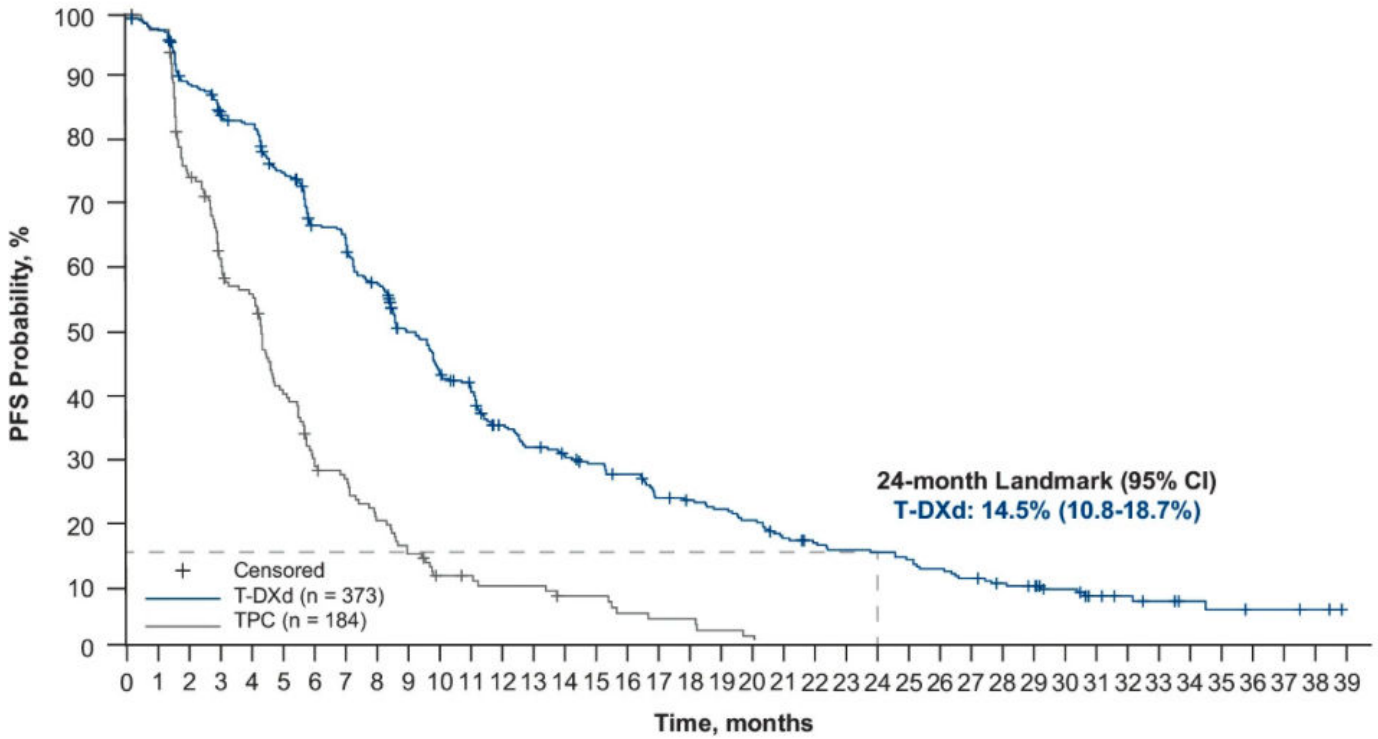

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Modi S, et al. *Nat Med.* 2025.

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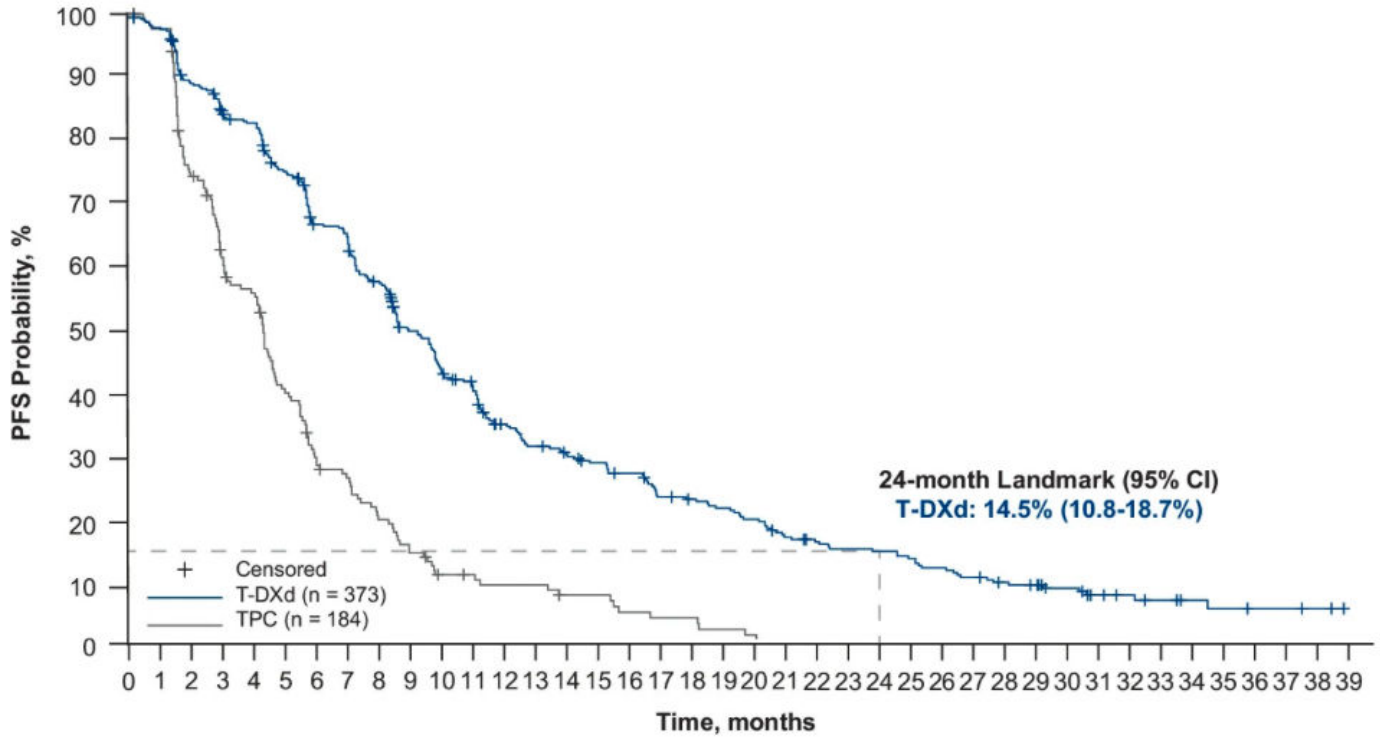
DESTINY BREAST-04

PROGRESSION-FREE SURVIVAL

	T-DXd (n = 373)	TPC (n = 184)
	Overall	
Median PFS, mo	**8.8**	4.2
HR (95% CI)	0.36 (0.29-0.45)	
	HR+	
Median PFS, mo	**9.6**	4.2
HR (95% CI)	0.37 (0.30–0.46)	
	HR-	
Median PFS, mo	**6.3**	2.9
HR (95% CI)	0.29 (0.15–0.57)	

PFS OVER TIME



CI: confidence interval; **HR:** hazard ratio; **HR+:** hormone receptor-positive; **HR-:** hormone receptor-negative

Modi S, et al. *Nat Med.* 2025.

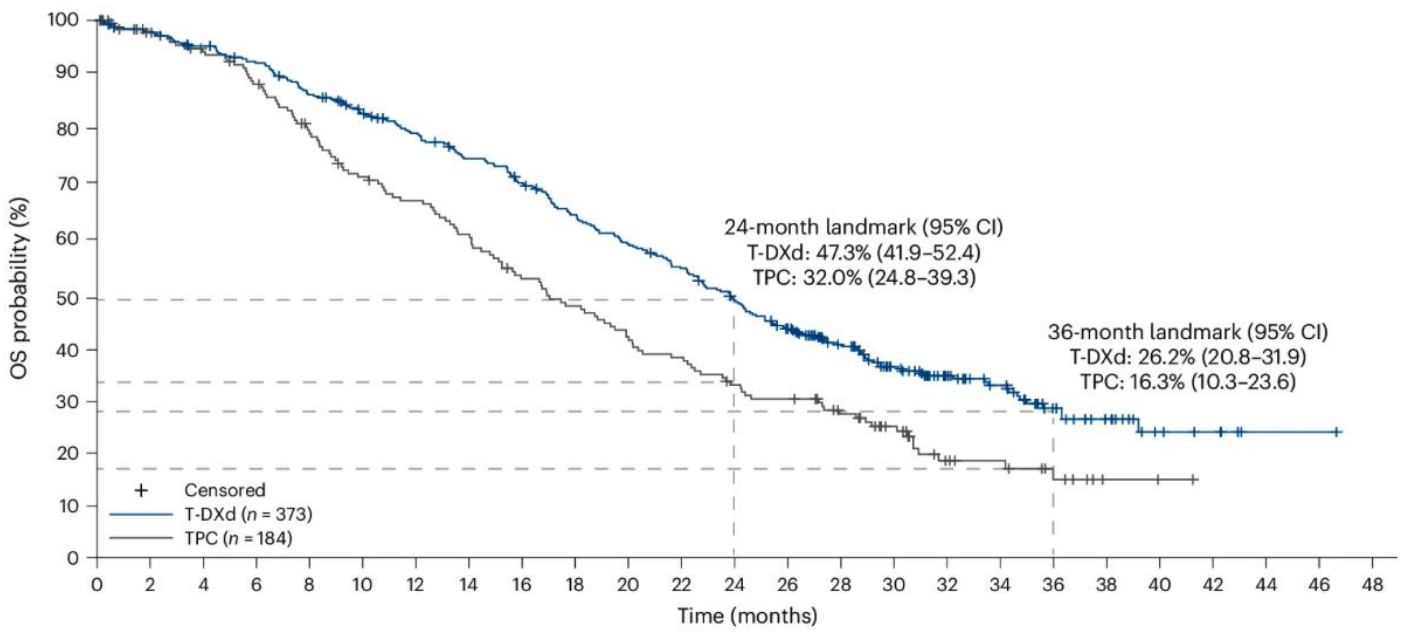
EFFICIENT

DESTINY BREAST-04

OVERALL SURVIVAL

	T-DXd (n = 373)	TPC (n = 184)
	Overall	
Median OS, mo	**22.9**	16.8
HR (95% CI)	0.69 (0.55–0.86)	
	HR+	
Median OS, mo	**23.9**	17.6
HR (95% CI)	0.69 (0.55–0.87)	
	HR-	
Median OS, mo	**17.1**	8.3
HR (95% CI)	0.58 (0.31–1.08)	

OS OVER TIME



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Modi S, et al. *Nat Med.* 2025.

EFFICIENT

DESTINY BREAST-04

OVERALL SURVIVAL

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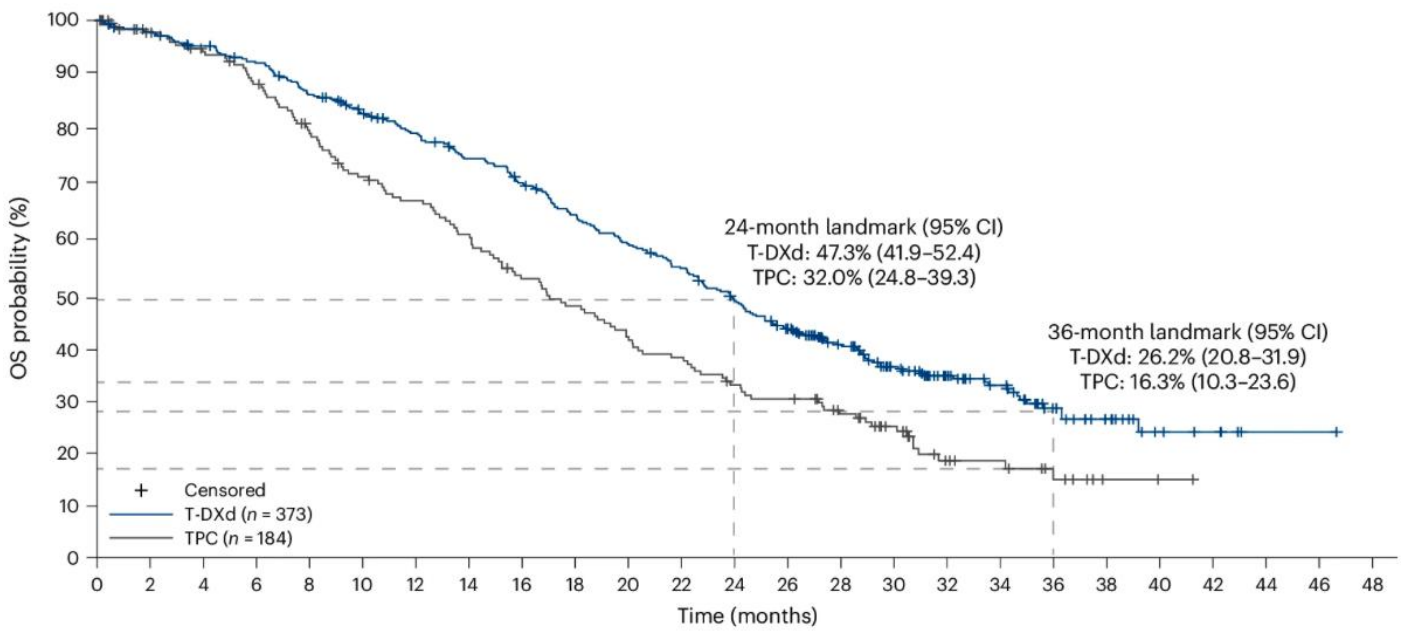
OS OVER TIME



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Modi S, et al. *Nat Med.* 2025.

EFFICIENT

DESTINY BREAST-04

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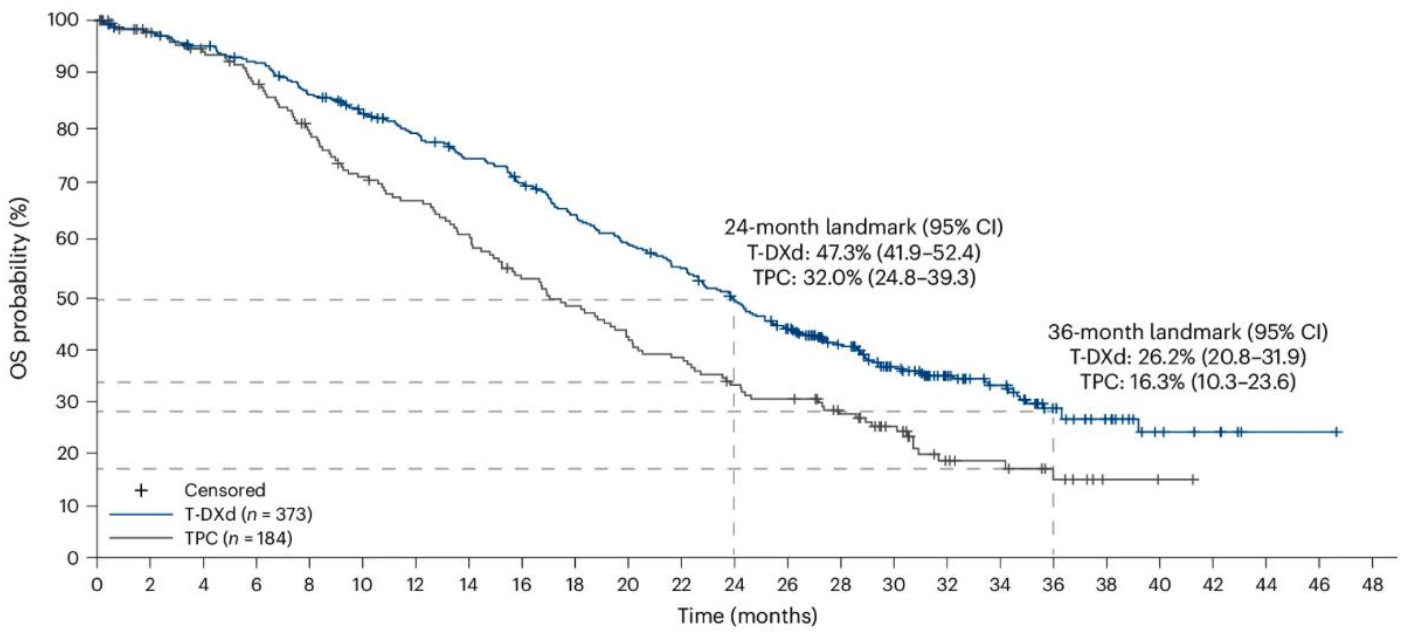
OS OVER TIME



CI: confidence interval; **HR:** hazard ratio; **HR+:** hormone receptor-positive; **HR-:** hormone receptor-negative

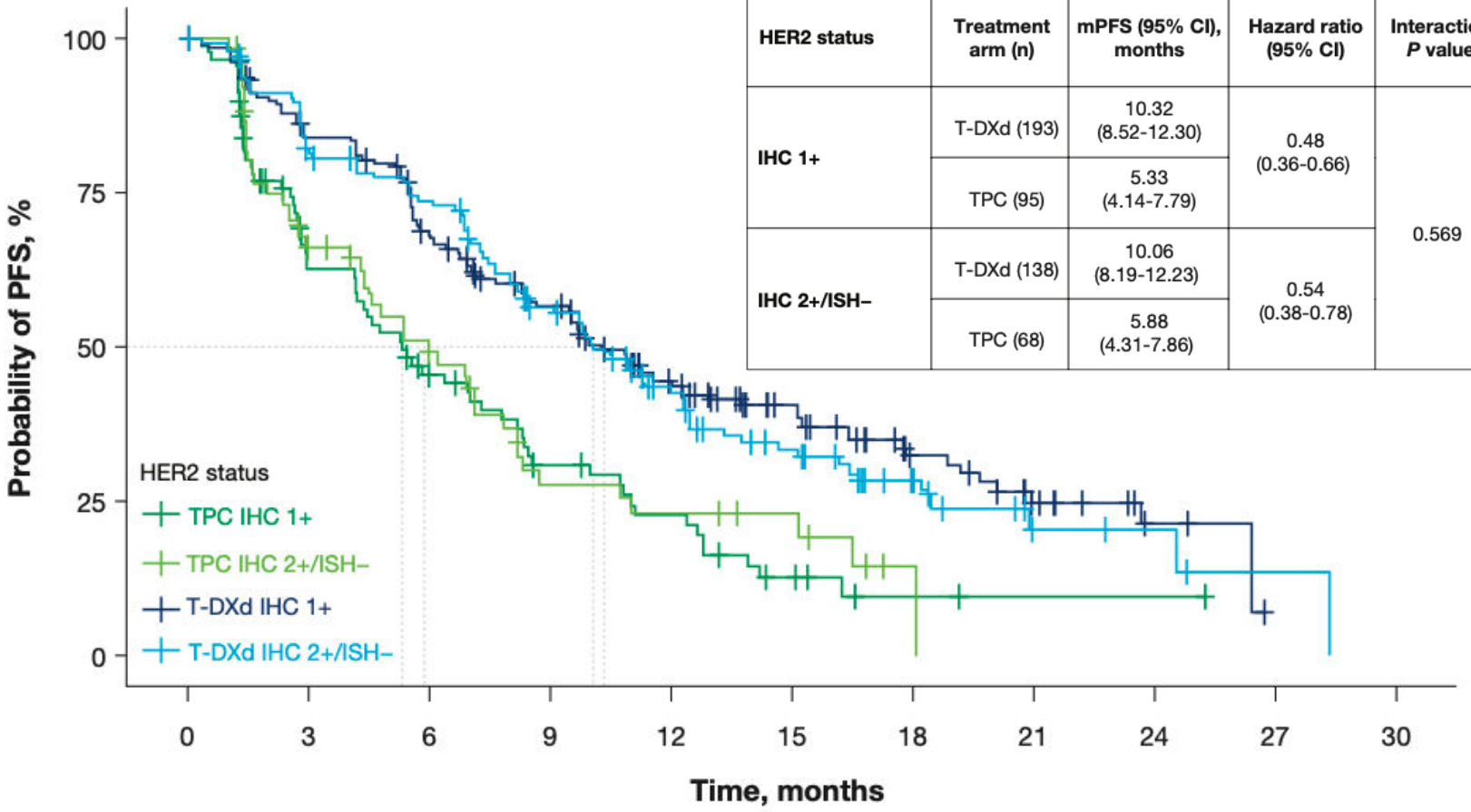
Modi S, et al. *Nat Med.* 2025.

EFFICIENT

DESTINY BREAST-04

PFS BY HER2 IHC STATUS

HER2 status	Treatment arm (n)	mPFS (95% CI), months	Hazard ratio (95% CI)	Interaction *P* value
IHC 1+	T-DXd (193)	10.32 (8.52-12.30)	0.48 (0.36-0.66)	0.569
	TPC (95)	5.33 (4.14-7.79)		
IHC 2+/ISH−	T-DXd (138)	10.06 (8.19-12.23)	0.54 (0.38-0.78)	
	TPC (68)	5.88 (4.31-7.86)		



In addition to IHC status, T-DXd demonstrated clinically meaningful improvements in PFS and cORR vs TPC across biomarker-defined subgroups.

Ueno N, et al. *Ann Oncol.* 2024;35(Suppl 4):S401–S402.

cORR: confirmed objective response rate

EFFICIENT



FACULTY DISCUSSION

How did the results of DESTINY-Breast04 change your approach to patients previously labeled as “HER2-negative”?

EFFICIENT

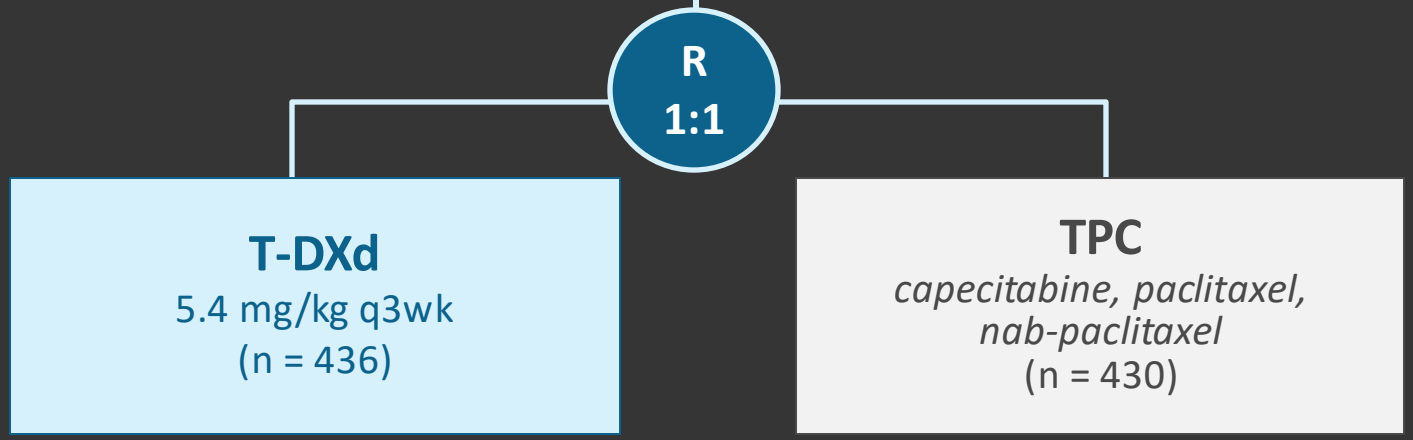
REDEFINING TREATMENT FOR HER2-LOW BC

DESTINY BREAST-06

Designed to see if benefits of T-DXd extend to HER2-low and ultralow disease treated earlier in the metastatic setting

KEY ELIGIBILITY CRITERIA

- HR-positive BC, **HER2-low or HER2-ultralow**
- ≥ 2 lines of ET ± targeted therapy for mBC ***OR*** 1 line for mBC ***AND*** progression ≤6 months of starting first-line ET + CDK4/6i ***OR*** recurrence ≤24 months of starting adjuvant ET
- **Chemo-naïve**



PRIMARY ENDPOINT

PFS by BICR in HER2-low group

KEY SECONDARY ENDPOINTS

PFS by BICR in the ITT, OS in HER2-low group, OS in the ITT (HER2-low/ultralow)

ET: endocrine therapy; **ITT:** intention-to-treat

Bardia A, et al. *N Engl J Med.* 2024;391(22):2110-2122.

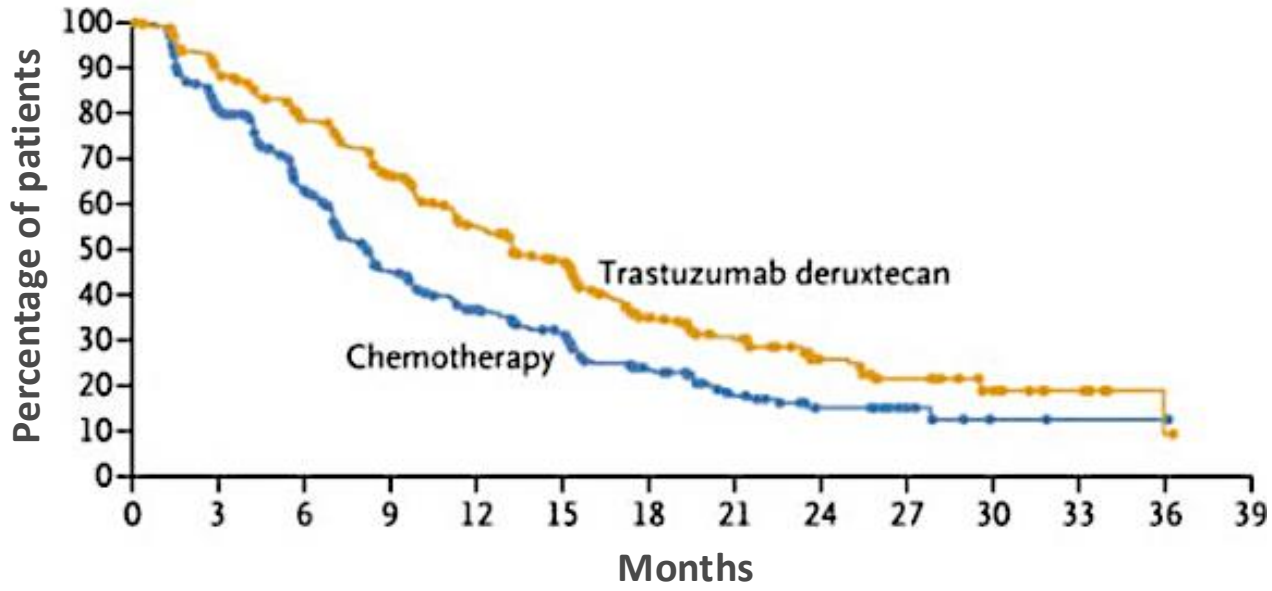
EFFICIENT

DESTINY BREAST-06

PROGRESSION-FREE SURVIVAL

	T-DXd (n = 436)	TPC (n = 430)
	ITT	
Median PFS, mo	**13.2**	8.1
HR (95% CI)	0.63 (0.53–0.75) *P<0.001*	
	HER2-low	
Median PFS, mo	**13.2**	8.1
HR (95% CI)	0.62 (0.51–0.74)	
	HER2-ultralow	
Median PFS, mo	**13.2**	8.3
HR (95% CI)	0.78 (0.50–121)	

PFS OVER TIME



DATA FOR OVERALL SURVIVAL WERE IMMATURE.

Bardia A, et al. *N Engl J Med* 2024;391:2110-2122.

EFFICIENT

LANDMARK FDA-APPROVAL

T-DXD IN HER2-ULTRALOW BC

Based on DESTINY-Breast 06, on January 27, 2025, the FDA approved T-DXd for:

Unresectable or metastatic HR-positive, HER2-low or HER2-ultralow BC that has progressed on one or more ET in the metastatic setting



FINDINGS FROM DESTINY-BREAST06 PROMPTED A LANDMARK FDA APPROVAL

FDA: U.S. Food and Drug Administration

Fam-trastuzumab deruxtecan-nxki [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761139s000lbl.pdf.

EFFICIENT

LANDMARK FDA-APPROVAL

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Based on DESTINY-Breast 06, on January 27, 2025, the FDA approved T-DXd for:

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FDA: U.S. Food and Drug Administration

Fam-trastuzumab deruxtecan-nxki [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761139s000lbl.pdf.

EFFICIENT



FACULTY DISCUSSION

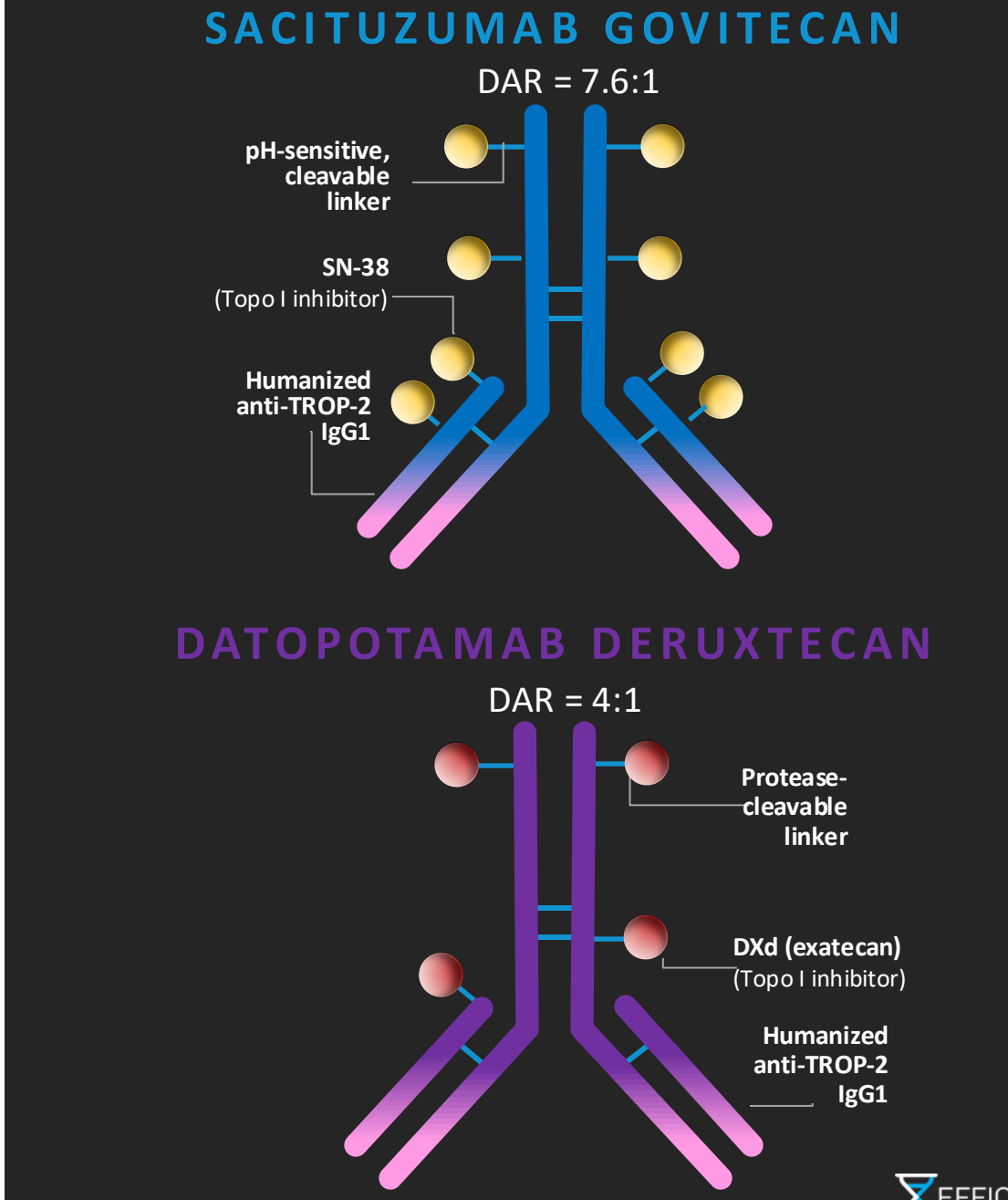
Does true HER2-0 breast cancer really exist, or do current assays fail to detect ultra-low expression that may still respond to T-DXd?

EFFICIENT

TROP2-TARGETED ADCS

ROLE IN HER2-LOW AND ULTRALOW MBC

- Pivotal trials designed in traditional HER2-negative populations (before the recognition of HER2-low)
- Commonly used in patients with HER2-low and HER2-ultralow mBC, especially after progression on ET, chemotherapy, or HER2-targeted ADCs such as T-DXd
- *Understanding where TROP2-directed ADCs fit helps inform real-world sequencing decisions for patients with HER2-low disease.*

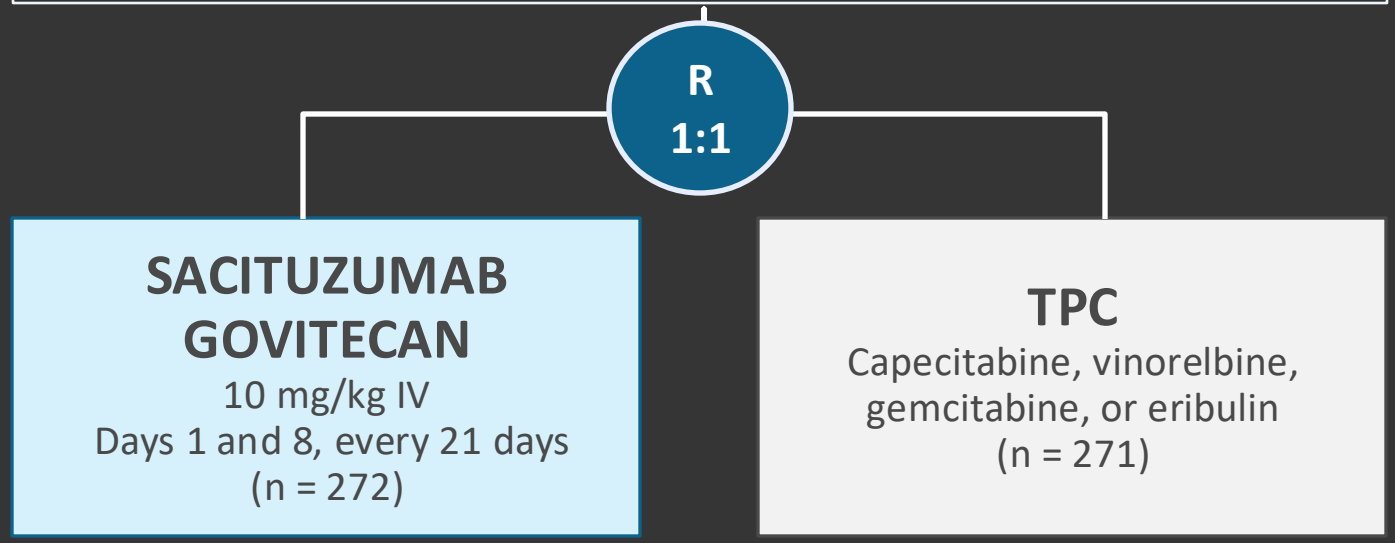


1. Rugo HS, et al. *Future Oncol.* 2020;16(12):705-715. **2.** Bardia A, et al. *Future Oncol.* 2024;20(8):423-436.
3. Dent RA, et al. *Future Oncol.* 2023;19(35):2349-2359. **4.** Modi S, et al. *N Engl J Med.* 2022;387(1):9-20.
5. Bardia A, et al. *N Engl J Med*. 2024;391(22):2110-2122.

TROPICS-02
SACITUZUMAB GOVITECAN

KEY ELIGIBILITY CRITERIA

- Metastatic or locally recurrent inoperable HR+/HER2-neg BC that progressed after:
  - ≥ 1 ET, taxane, and CDK4/6 inhibitor in any setting
  - ≥ 2, but < 4, lines of chemotherapy for metastatic disease
- IHC 0, IHC 1+, IHC 2+/ISH Negative
- Measurable disease by RECIST 1.1



PRIMARY ENDPOINT

PFS by BICR

KEY SECONDARY ENDPOINTS

OS, ORR, DoR, CBR by LIR and BICR, PRO, safety

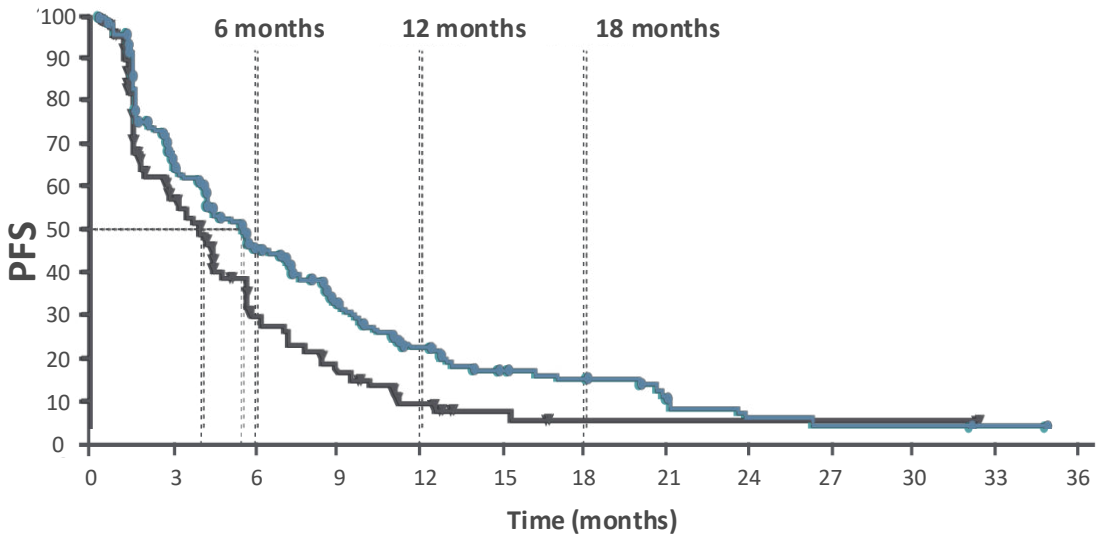
CBR: clinical benefit rate; **DoR:** duration of response; **IV:** intravenous; **LIR:** local investigator review; **PRO:** patient-reported outcomes; **SoC:** standard of care

Adapted from Rugo HS, et al. *Ann Oncol.* 2022; 33(Suppl 7):S1386. Rugo HS, et al. *J Clin Oncol.* 2022;40(29):3365–3376. Study of Sacituzumab Govitecan-hziy Versus Treatment of Physician's Choice in Participants With HR+/HER2- Metastatic Breast Cancer (TROPiCS-02). ClinicalTrials.gov Identifier: NCT03901339.

EFFICIENT

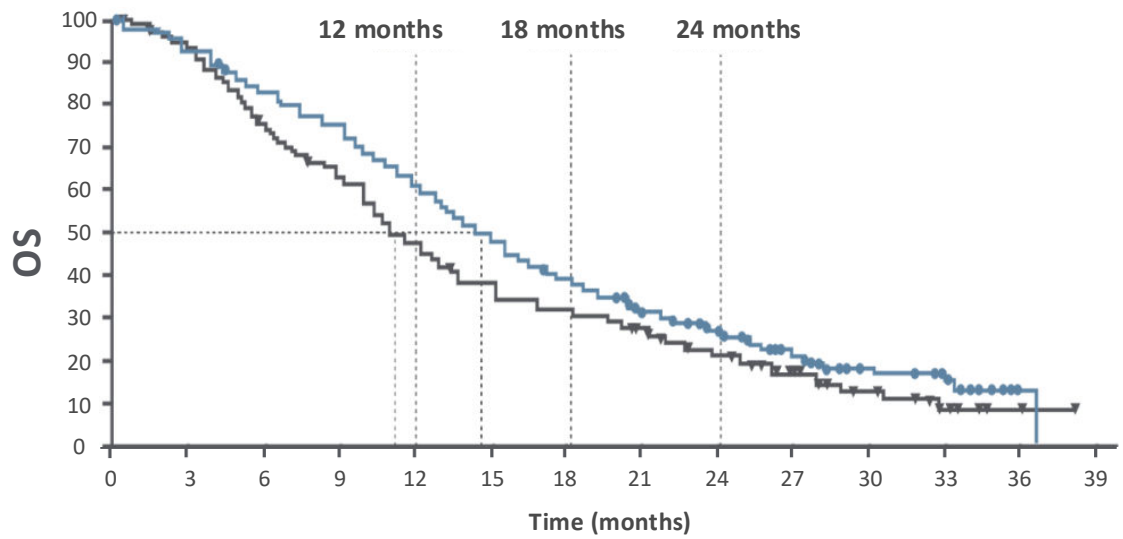
TROPICS-02
SURVIVAL OUTCOMES

PFS



	SG (n = 272)	TPC (n = 271)
Median PFS, months (95% CI)	5.5 (4.2–6.9)	4.0 (3.0–4.4)
Stratified HR (95% CI)	0.65 (0.53-0.81)	
Nominal *P*-value*	0.0001	

OS



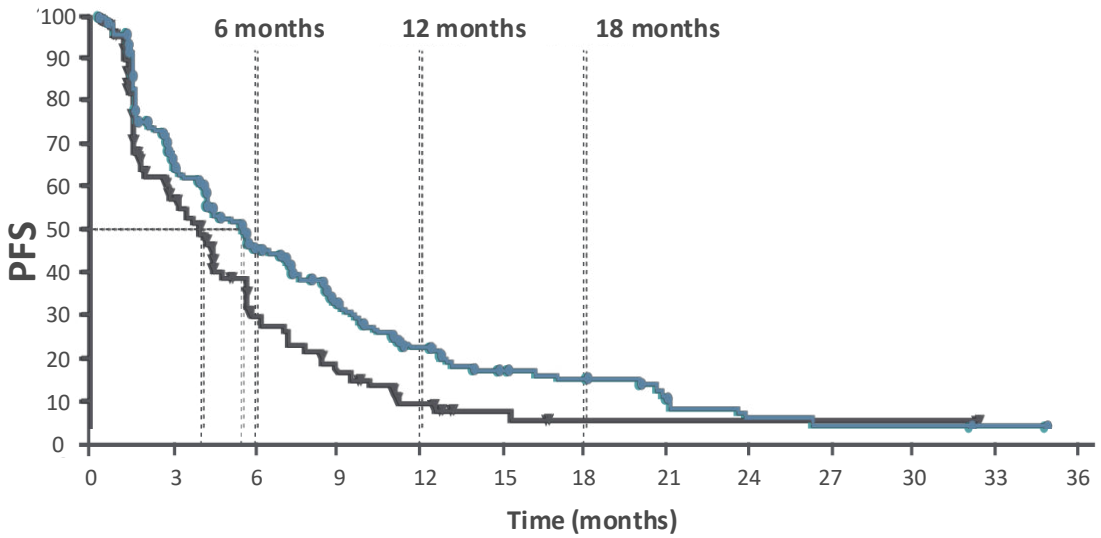
	SG (n = 272)	TPC (n = 271)
Median OS, months (95% CI)	14.5 (13.0–16.0)	11.2 (10.2–12.6)
Stratified HR (95% CI)	0.79 (0.65–0.95)	
Nominal *P*-value*	0.0133	

1. Adapted from: Rugo HS, et al. *J Clin Oncol*. 2022;40(29):3365–3376. **2.** Rugo HS, et al. *Ann Oncol.* 2022; 33(Suppl 7):S1386.
3. Rugo HS, et al. *Lancet* 2023;402(10411):1423-1433. **4.** Tolaney SM, et al. *J Clin Oncol.* 2023;41(16 Suppl):1003.

SG: sacituzumab govitecan

TROPICS-02
SURVIVAL OUTCOMES

PFS



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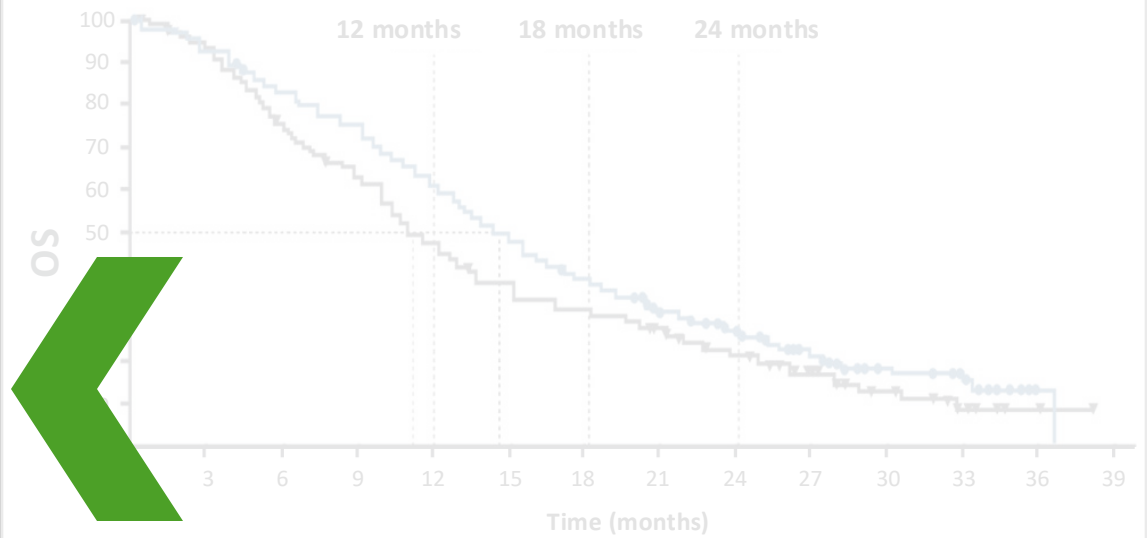
OS



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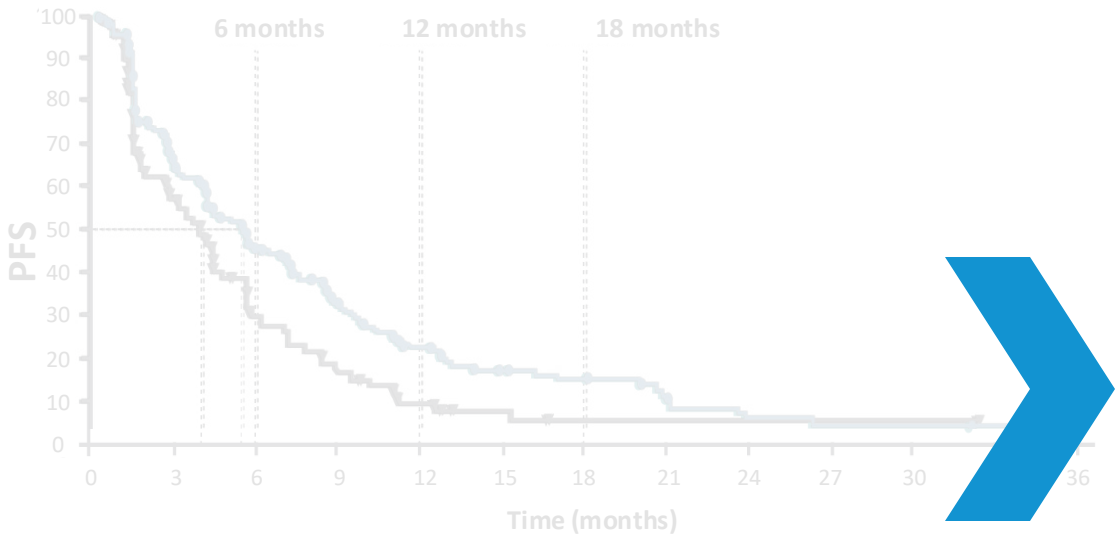
SG: sacituzumab govitecan

TROPICS-02
SURVIVAL OUTCOMES

PFS



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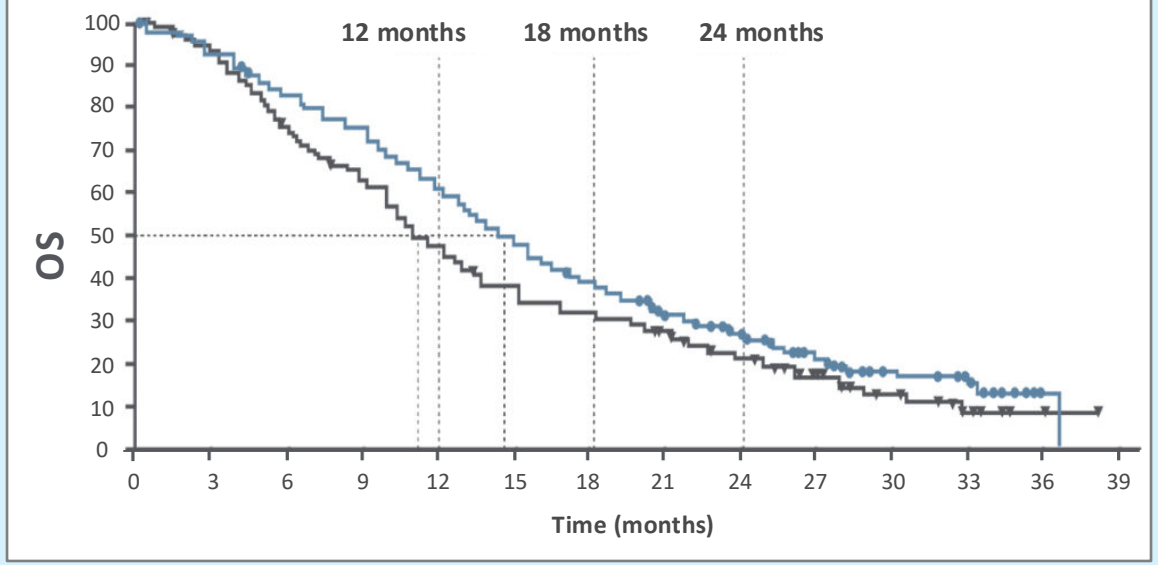

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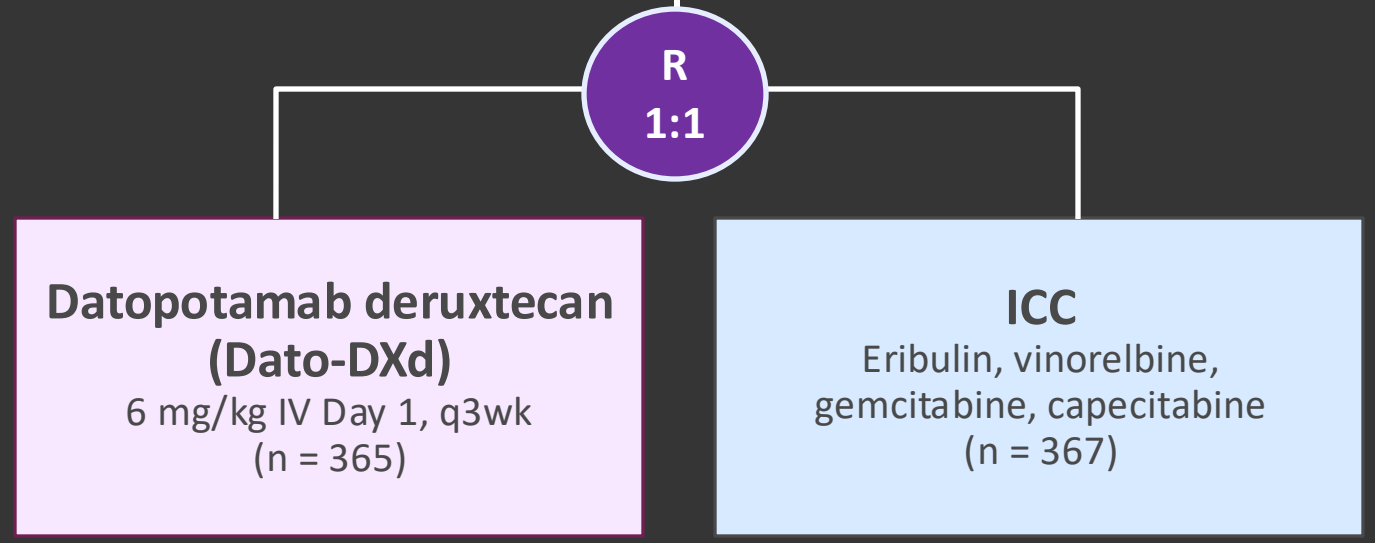
SG: sacituzumab govitecan

TROPION-BREAST01
DATO-DXD

KEY ELIGIBILITY CRITERIA

- Unresectable or metastatic HR+/HER2-neg BC
- Prior endocrine therapy (ET)
- 1–2 prior lines of CT in inoperable/metastatic setting



DUAL PRIMARY ENDPOINTS

PFS by BICR per RECIST v1.1, OS

SECONDARY ENDPOINTS

ORR, PFS by investigator, safety

ICC: investigator's choice of chemotherapy

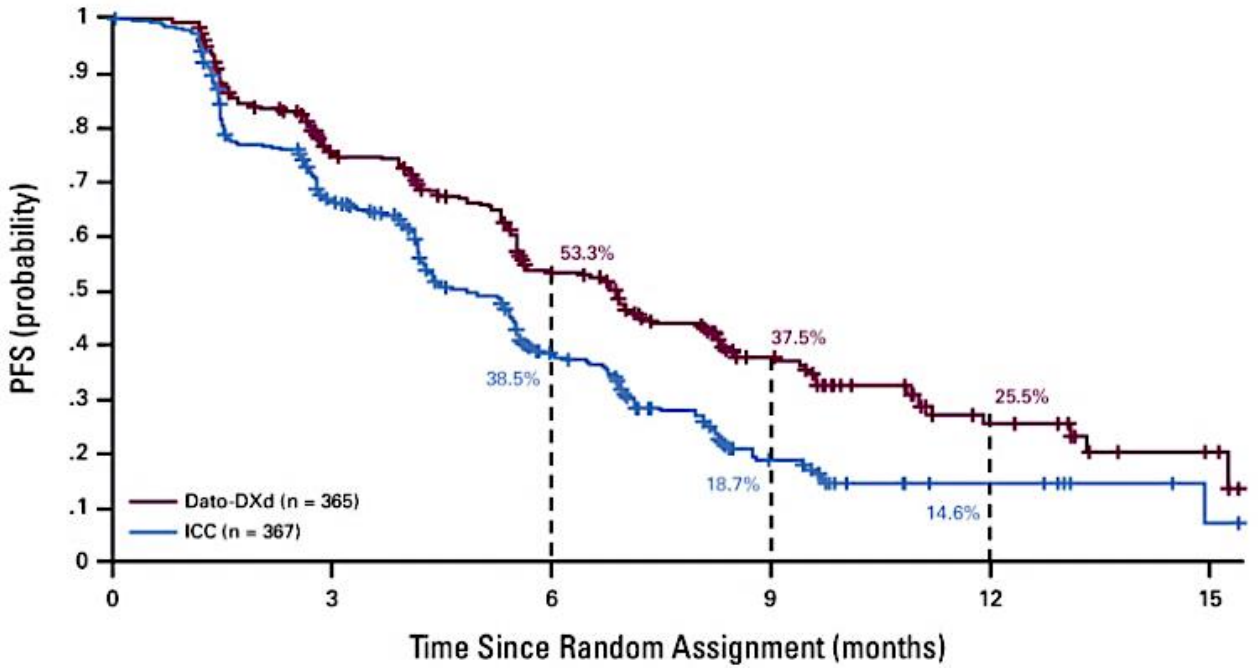
Bardia A, et al. *Ann Oncol.* 2023;34(suppl 2): LBA11.

TROPION-BREAST01

SURVIVAL OUTCOMES

PFS

	Dato-DXd (n = 365)	ICC (n = 367)
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	0.63 (0.52–0.76)	
P-value	<0.0001	



TREND TOWARD IMPROVED OS WITH Dato-DXd VS ICC (HR 0.84; 95% CI 0.62–1.14); HOWEVER, DATA WERE IMMATURE AT ANALYSIS

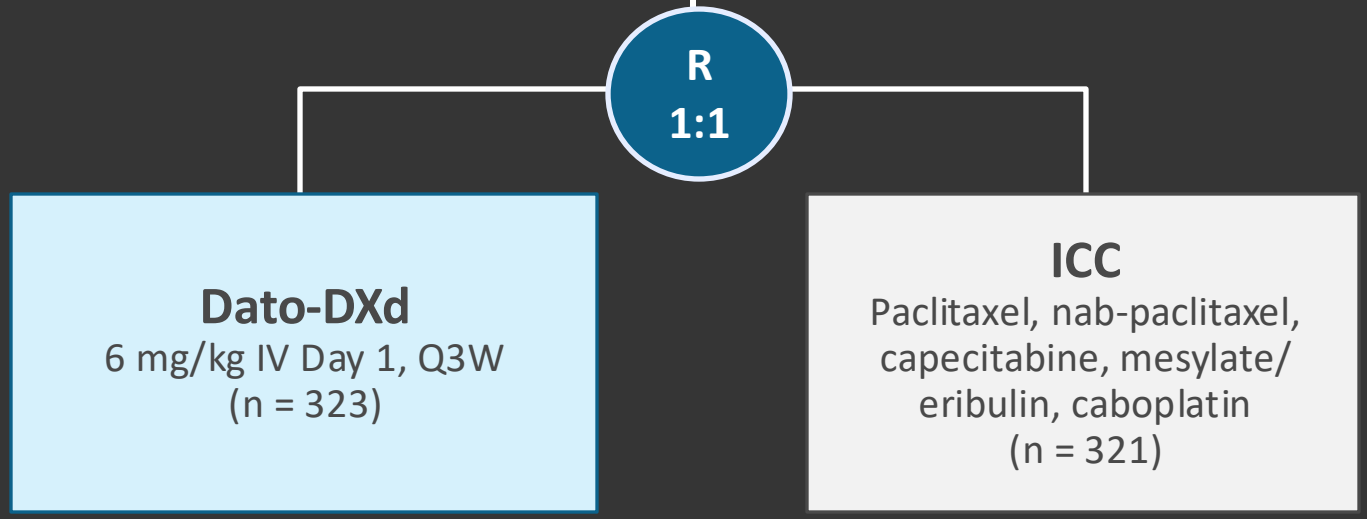
Bardia A, et al. *J Clin Oncol.* 2025;43(3):285-296.

REDEFINING TREATMENT FOR HER2-LOW BC

TROPION-BREAST02

KEY ELIGIBILITY CRITERIA

- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy in the locally recurrent inoperable or metastatic setting
- Immunotherapy not an option
- ECOG PS 0 or 1



DUAL PRIMARY ENDPOINTS

PFS by BICR per RECIST v1.1, OS

SECONDARY ENDPOINTS

ORR, DoR, PFS by investigator, safety

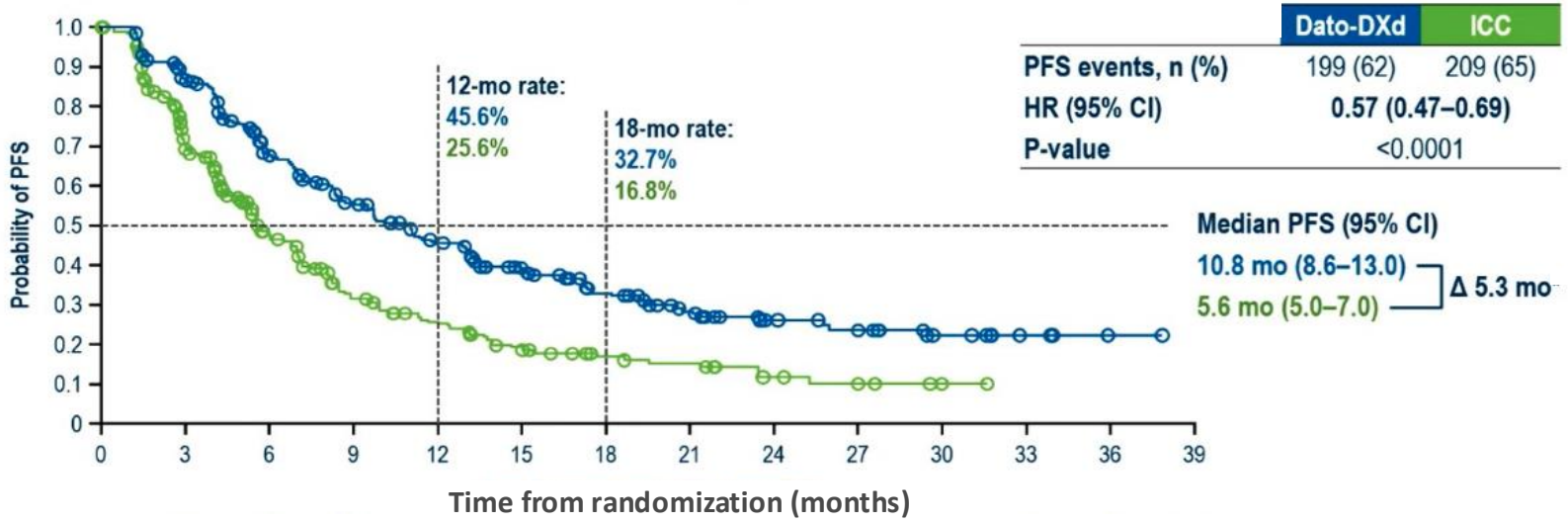
TNBC: triple-negative breast cancer

Rugo HS, et al. *Oncologist.* 2024;29(9):768-779.

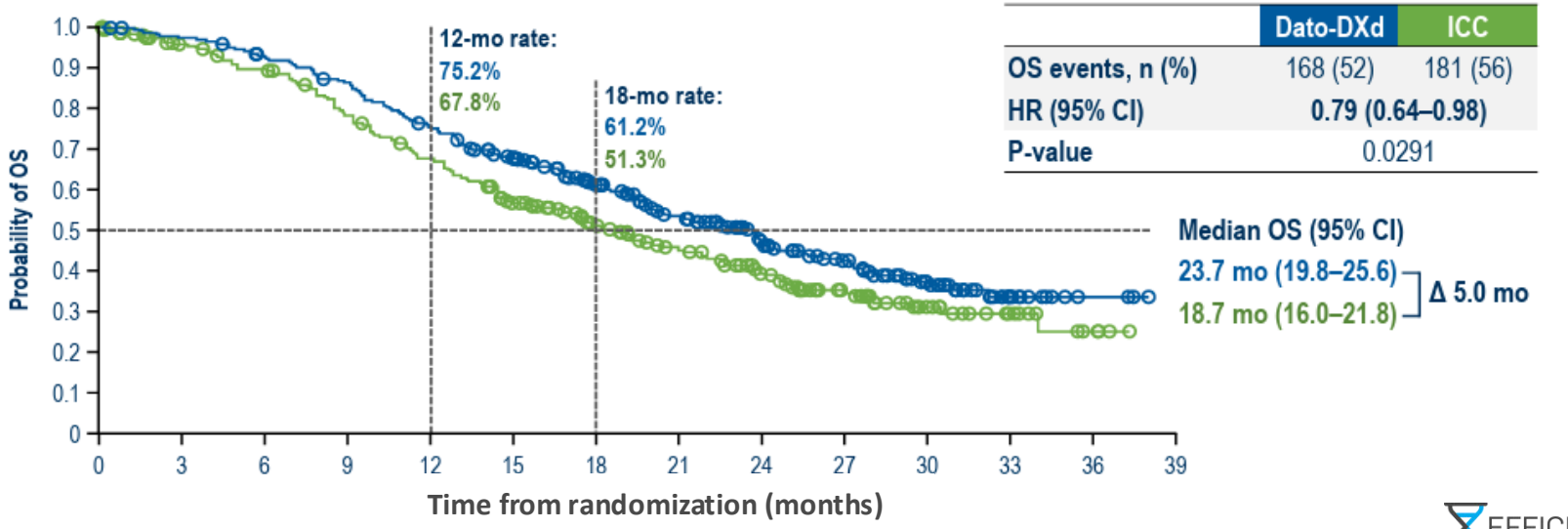
EFFICIENT

TROPION-BREAST02: SURVIVAL OUTCOMES

Dato-DXd significantly improved PFS vs chemotherapy as first-line treatment in patients advanced TNBC



Trend toward improved OS (HR 0.79; 95% CI 0.64–0.98), though data remain immature



Dent RA, et al. *Ann Oncol.* 2025;36:S1681-S1682.

EFFICIENT

TROPION-BREAST02: SURVIVAL OUTCOMES

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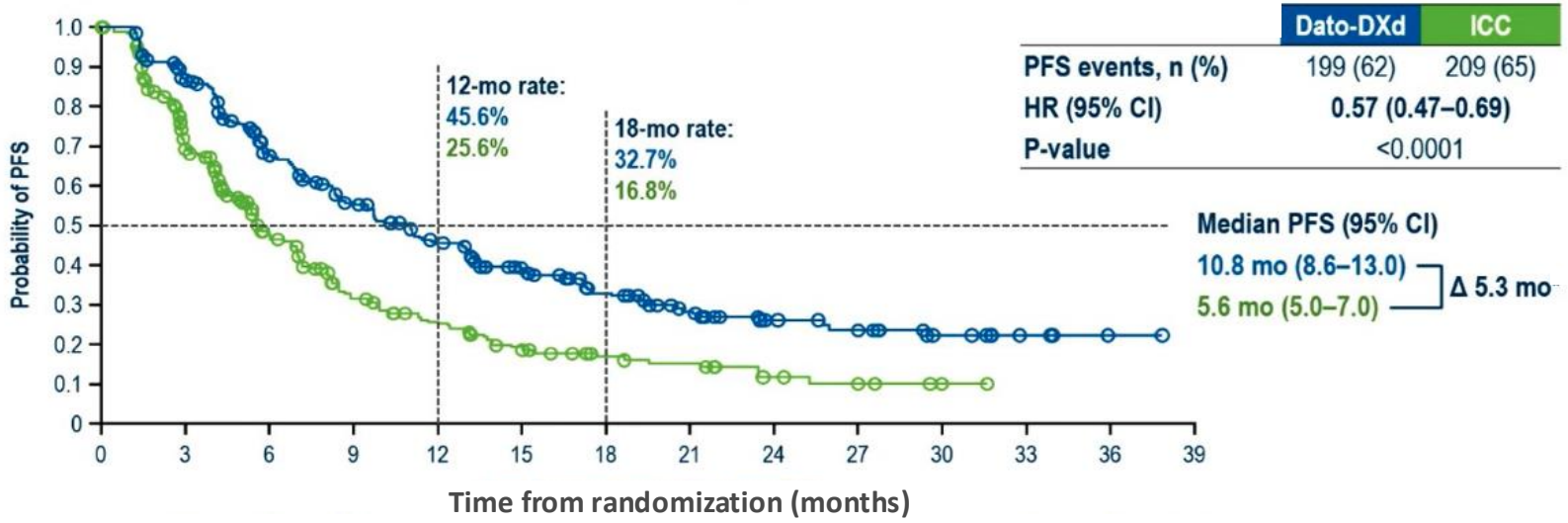

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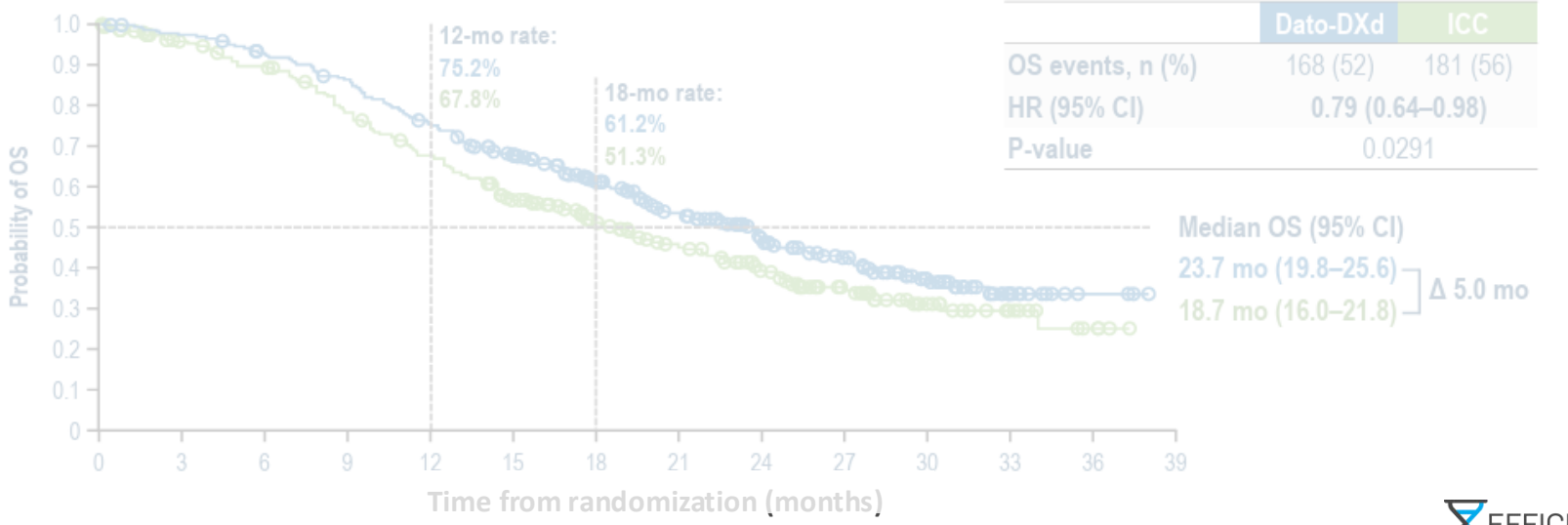

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EFFICIENT

TROPION-BREAST02: SURVIVAL OUTCOMES

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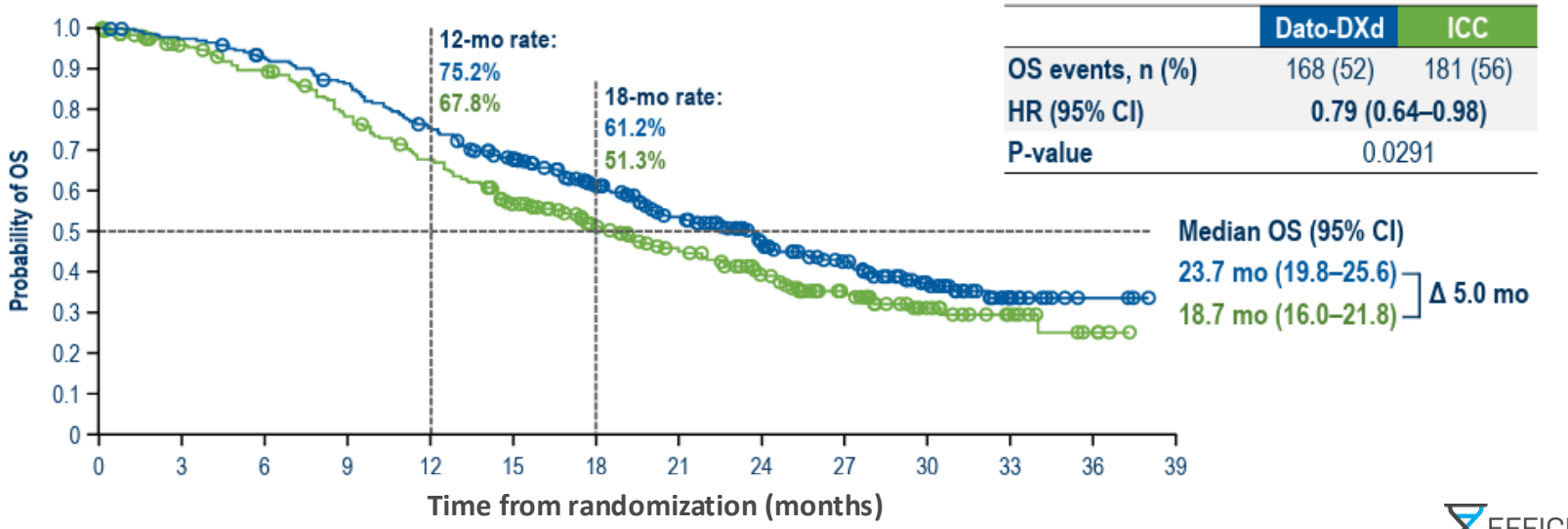

Dent RA, et al. *Ann Oncol.* 2025;36:S1681-S1682.

EFFICIENT



FACULTY DISCUSSION

How are you currently sequencing available ADCs (T-DXd, SG, Dato-DXd) for patients with HER2-low and HER2-ultralow mBC?

EFFICIENT

TOXICITY MANAGEMENT ACROSS ADCs

	KEY TOXICITIES	ESSENTIAL MANAGEMENT PRINCIPLES
TRASTUZUMAB DERUXTECAN	**Interstitial lung disease (ILD)**	• Monitoring for respiratory symptoms • Prompt interruption and corticosteroids if ILD suspected
	Nausea/vomiting	• Aggressive antiemetic prophylaxis (triple/quadruple regimen for high-risk)
SACITUZUMAB GOVITECAN	**Neutropenia**	• CBC monitoring • Early use of G-CSF if indicated
	Diarrhea	• Prompt antidiarrheal therapy (loperamide) • Maintain hydration
DATOPOTAMAB DERUXTECAN	**Oral mucositis/stomatitis**	• Daily oral hygiene • Steroid-containing mouthwash • Cryotherapy during infusion
	ILD	• ILD vigilance as with T-DXd

1. Modi S, et al. *N Engl J Med.* 2022;387(1):9-20. **2.** Bardia A, et al. *N Engl J Med.* 2024;391(22):2110-2122. **3.** Rugo HS, et al. *J Clin Oncol.* 2022;40(29):3365–3376.
4. Meric-Bernstam F, et al. *Oncologist.* 2025;30(3):oyaf031. **5.** Heist RS, et al. *Cancer Treat Rev.* 2024;125:102720.

CBC: complete blood count;
G-CSF: granulocyte colony-stimulating factor

EFFICIENT

TOXICITY MANAGEMENT ACROSS ADCs

	KEY TOXICITIES	ESSENTIAL MANAGEMENT PRINCIPLES
TRASTUZUMAB DERUXTECAN	**Interstitial lung disease (ILD)**	• Monitoring for respiratory symptoms • Prompt interruption and corticosteroids if ILD suspected
	Nausea/vomiting	• Aggressive antiemetic prophylaxis (triple/quadruple regimen for high-risk)
SACITUZUMAB GOVITECAN	Neutropenia	• CBC monitoring • Early use of G-CSF if indicated
	Diarrhea	• Prompt antidiarrheal therapy (loperamide) • Maintain hydration
DATOPOTAMAB DERUXTECAN	Oral mucositis/stomatitis	• Daily oral hygiene • Steroid-containing mouthwash • Cryotherapy during infusion
	ILD	• ILD vigilance as with T-DXd

1. Modi S, et al. *N Engl J Med.* 2022;387(1):9-20. **2.** Bardia A, et al. *N Engl J Med.* 2024;391(22):2110-2122. **3.** Rugo HS, et al. *J Clin Oncol.* 2022;40(29):3365–3376.
4. Meric-Bernstam F, et al. *Oncologist.* 2025;30(3):oyaf031. **5.** Heist RS, et al. *Cancer Treat Rev.* 2024;125:102720.

CBC: complete blood count;
G-CSF: granulocyte colony-stimulating factor

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TOXICITY MANAGEMENT ACROSS ADCs

	KEY TOXICITIES	ESSENTIAL MANAGEMENT PRINCIPLES
TRASTUZUMAB DERUXTECAN	Interstitial lung disease (ILD)	• Monitoring for respiratory symptoms • Prompt interruption and corticosteroids if ILD suspected
	Nausea/vomiting	• Aggressive antiemetic prophylaxis (triple/quadruple regimen for high-risk)
SACITUZUMAB GOVITECAN	**Neutropenia**	• CBC monitoring • Early use of G-CSF if indicated
	Diarrhea	• Prompt antidiarrheal therapy (loperamide) • Maintain hydration
DATOPOTAMAB DERUXTECAN	Oral mucositis/stomatitis	• Daily oral hygiene • Steroid-containing mouthwash • Cryotherapy during infusion
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TRASTUZUMAB DERUXTECAN	Interstitial lung disease (ILD)	• Monitoring for respiratory symptoms • Prompt interruption and corticosteroids if ILD suspected
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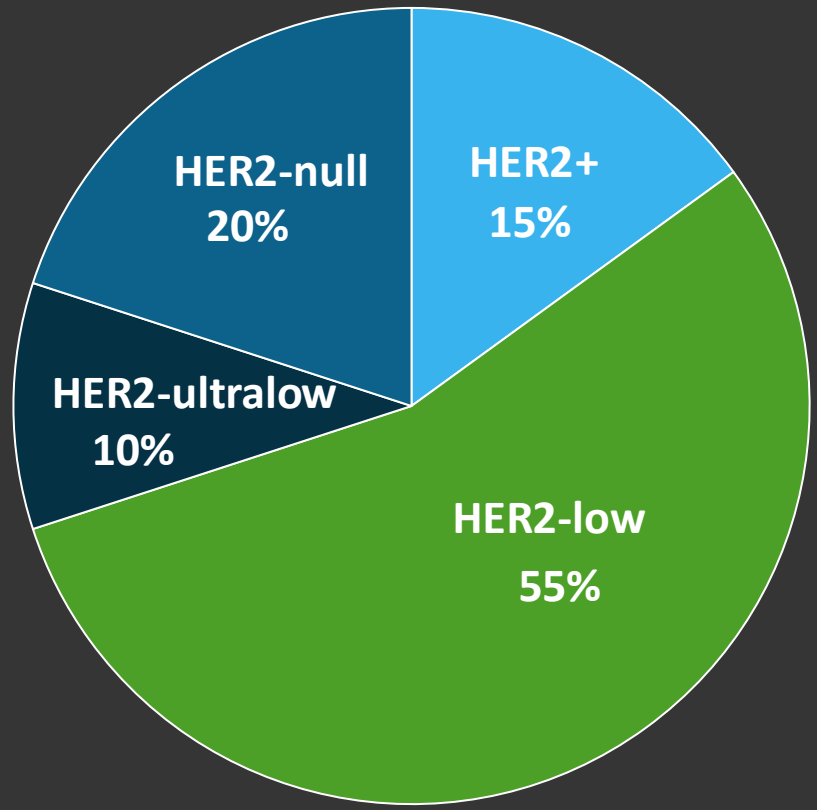
HER2(ULTRA)-LOW BC
EPIDEMIOLOGY & CLINICOPATHOLOGY

- Most traditionally “HER2-negative” BCs now fall within the HER2-low or HER2-ultralow spectrum
  - *Most of these patients may be eligible for HER2-targeted therapy*
- Most HER2-low tumors occur in HR^{+} disease

While the prognostic significance of HER2-low is unclear, the therapeutic implications emphasize the importance of accurate testing and classification.

APPROXIMATE DISTRIBUTION OF HER2 EXPRESSION IN BC



1. Zhang H, et al. *Mod Pathol.* 2022;35(8):1075-1082. **2.** Lv H, et al. *Breast Cancer Res.* 2025;27(1):45.
3. National Cancer Institute (NCI). NCI Website. 2023. https://seer.cancer.gov/statfacts/html/breast-subtypes.html.
4. Viale G, et al. *ESMO Open.* 2023;8(4):101615. **5.** Cha CD, et al. *NPJ Breast Cancer.* 2025;11(1):31.
6. Park WK, et al. *Cancers.* 2024;16(14):2566.

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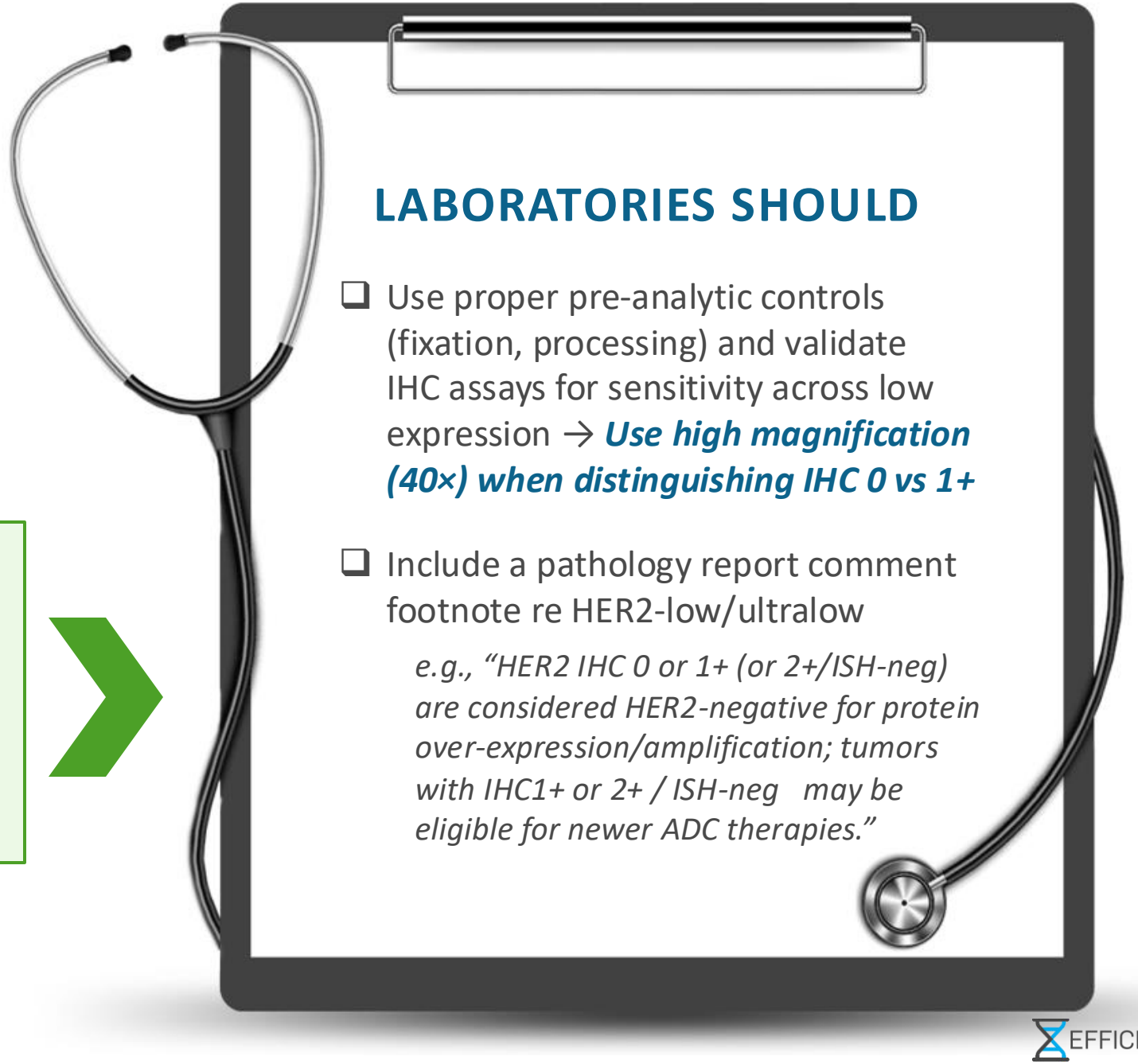
HER2 TESTING AND REPORTING IN BC

The 2023 ASCO-CAP has ***not changed scoring thresholds for HER2 positivity***

CURRENT APPROACH

Differentiate IHC 0 vs 1+ and accurately report IHC 1+ / IHC 2+ with ISH-negative, given the clinical relevance of newer ADC therapies in “HER2-low” tumors



LABORATORIES SHOULD

- ❑ Use proper pre-analytic controls (fixation, processing) and validate IHC assays for sensitivity across low expression → ***Use high magnification (40×) when distinguishing IHC 0 vs 1+***
- ❑ Include a pathology report comment footnote re HER2-low/ultralow

  e.g., “HER2 IHC 0 or 1+ (or 2+/ISH-neg) are considered HER2-negative for protein over-expression/amplification; tumors with IHC1+ or 2+ / ISH-neg may be eligible for newer ADC therapies.”

Wolff AC, et al. *Arch Pathol Lab Med.* 2023;147(9):993–1000.

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FUTURE DIRECTIONS

- **EXPANDING THERAPEUTIC HORIZONS:**
  Emerging ADCs (e.g., MRG002, disitamab vedotin, patritumab deruxtecan) across the HER2-low and ultralow spectrum
- **ADCS MOVING EARLIER:**
  Ongoing trials evaluating T-DXd, SG, and Dato-DXd in earlier treatment lines and novel combinations
- **REFINING HER2 TESTING:**
  Advances in assay sensitivity, digital pathology, and AI-based quantitation

FUTURE OUTLOOK

The convergence of precise testing, earlier ADC integration, and next-generation agents will continue to redefine the HER2-negative landscape and personalize therapy.

1. Zhang S, et al. *Eur J Cancer*. 2025;230:115794 2. Wang J, et al. *Cancer Commun (Lond)*. 2024;44(7):833-851 3. Pistilli B, et al. *Nat Med*. 2025;31(10):3492-3503. 4. Patel P, et al. *NPJ Breast Cancer*. 2025;11(1):81. 5. Albuquerque DAN, et al. *NPJ Digit Med*. 2025;8(1):144.

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