III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 12 Y 13 DE FEBRERO DE 2026

ENFERMEDAD HER-2 LOW Y ULTRALOW

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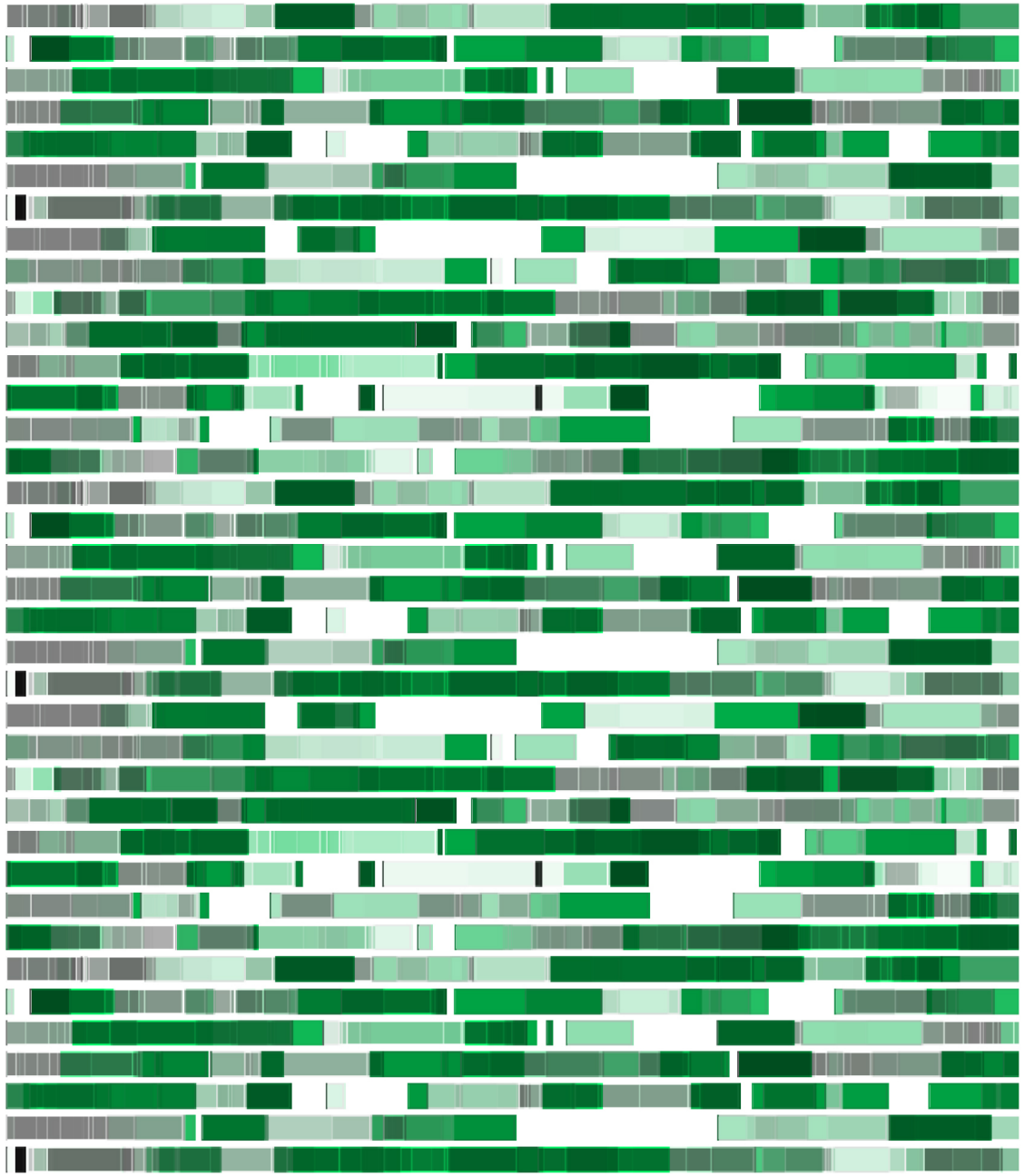
Organizador por:

HENDERE HEALTHCARE



CONFLICTOS DE INTERES

He colaborado con:

- Consultant or Advisory Role: Novartis, Pfizer, Gilead, Daiichi-AZ, Menarini
- Speaking: Pfizer, Novartis, Roche, Grunenthal, Eisai, Gilead, Daiichi-AZ, Lilly, MSD
- Travel-accommodation-inscription: Pfizer, Novartis, Roche, Gilead, Daiichi-AZ, Lilly

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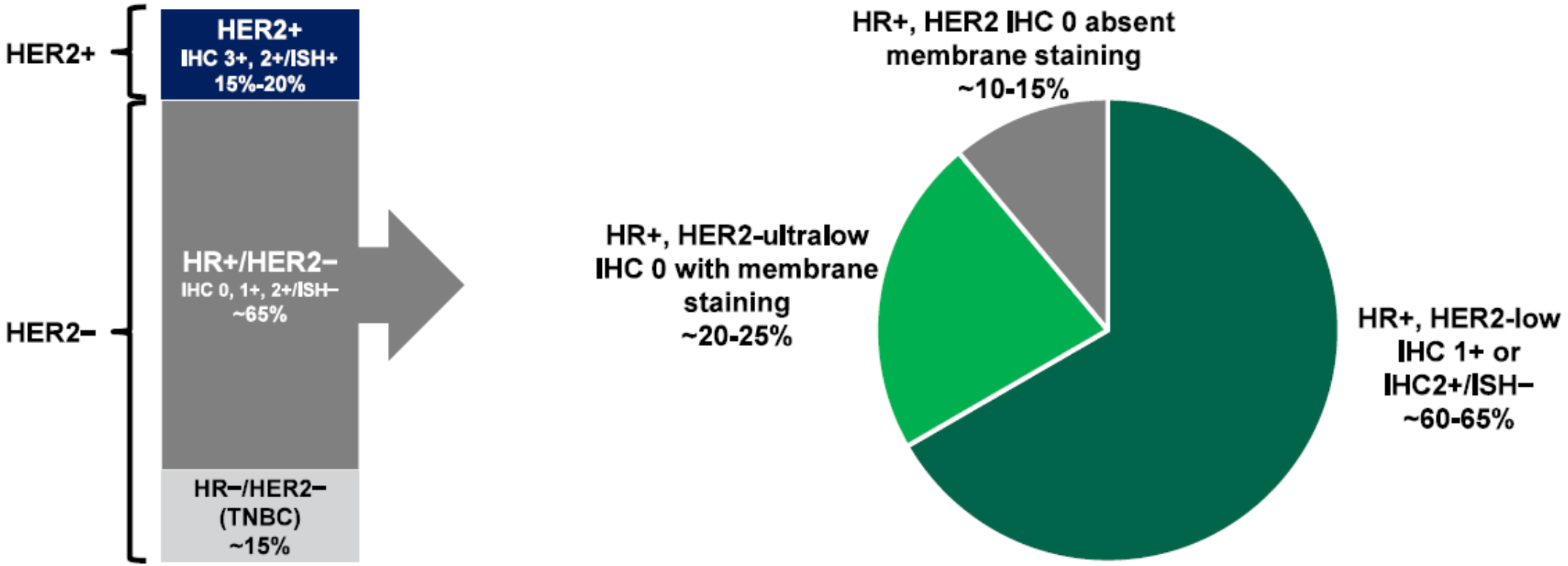
- COMO FUNCIONAN LOS FARMACOS ANTIHER2 EN HER2LOW Y ULTRALOW
- EVIDENCIA CLINÍCA ACTUAL
- ¿QUE NOS APORTARÁ EL FUTURO?

¿QUE ES HER2-LOW?
¿Y HER2-ULTRALOW?

The majority of HR+ HER2- mBC express clinically meaningful levels of HER2[1-5]

Guidelines recommend assessment of HER2 status in all newly diagnosed patients with BC and those patients who develop metastatic disease



1. Schettini F et al. *NPJ Breast Cancer*. 2021;7(1):1; 2. Tarantino P et al. *J Clin Oncol*. 2020;38(17):1951-1962; 3. Wolff A, et al. *J Clin Oncol*. 2023;41:3867–3872; 4. Denkert C, et al. *Lancet Oncol*. 2021;22:1151–1161; 5. Chen Z, et al. *Breast Cancer Res Treat*. 2023;202:313–323; 6.. Mehta S, et al. *J Clin Oncol*. 2024;42(Suppl. 16):Abstract e13156

HER2 IHC categories within HR+, HER2-negative mBC (per ASCO/CAP[2]):

IHC 2+/ISH−

Weak-to-moderate complete membrane staining in >10% of tumor cells

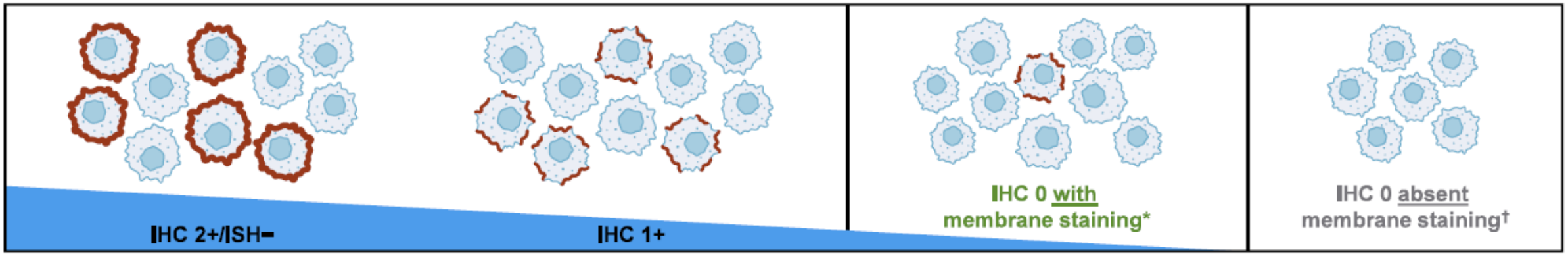
IHC 1+

Faint, incomplete membrane staining in >10% of tumor cells

IHC 0

Faint, incomplete membrane staining in ≤10% of tumor cells

Absent membrane staining



HER2-low ~60–65%[3,4]

HER2-ultralow* ~20–25%[3–5]

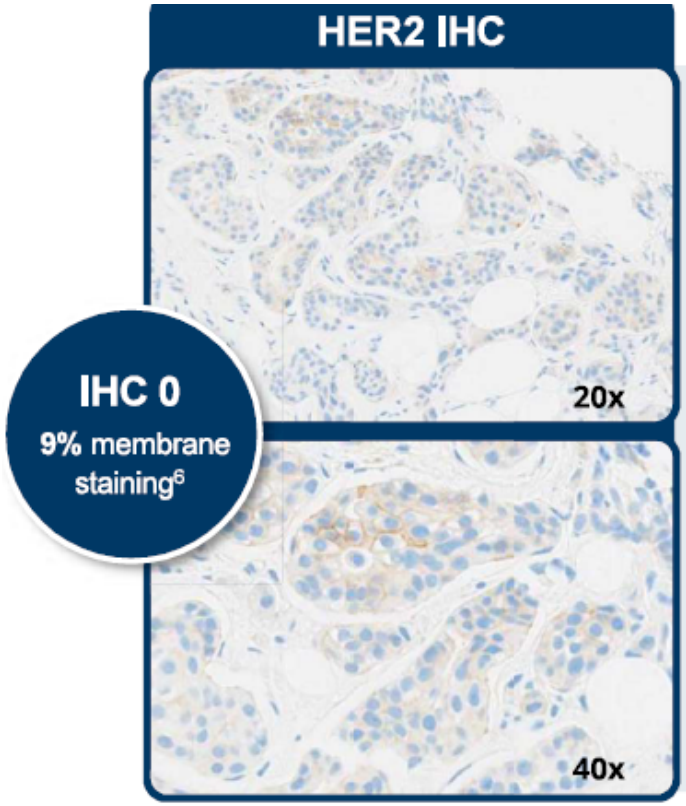
patient population: ~85% of HR+, HER2− mBC

Images adapted from Venetis K, et al. *Front Mol Biosci.* 2022;9:834651, CC BY 4,0 license available from: https://creativecommons,org/licenses/by/4,0/

*HER2-ultralow (HER2 IHC 0 with membrane staining of any intensity in ≤10% of tumor cells) was referred to as HER2 IHC >0 to <1+ in the DESTINY-Breast06 protocol; †no membrane staining is observed

1, Curigliano G et al. Presented at: ASCO Annual Meeting; May 31 – June 4, 2024; Chicago, IL, Presentation LBA1000; 2, Wolff AC, et al. *J Clin Oncol.* 2023;41:3867–3872; 3, Denkert C, et al. *Lancet Oncol.* 2021
4, Chen Z, et al. *Breast Cancer Res Treat.* 2023;202:313–323; 5, Mehta S, et al. *J Clin Oncol.* 2024;42(Suppl. 16):e13156 (Abstract)

Detectable levels of HER2 expression may be present in patients with HER2 IHC 0 mBC[1-4]



HER2-Ultralow Classification[6]

IHC 0 with membrane staining, defined as faint and incomplete membrane HER2 staining seen in 10% or fewer tumor cells

Patients previously identified as HER2-negative mBC may have actionable levels of HER2, categorized as HER2-ultralow (IHC 0 with membrane staining)[5,6]

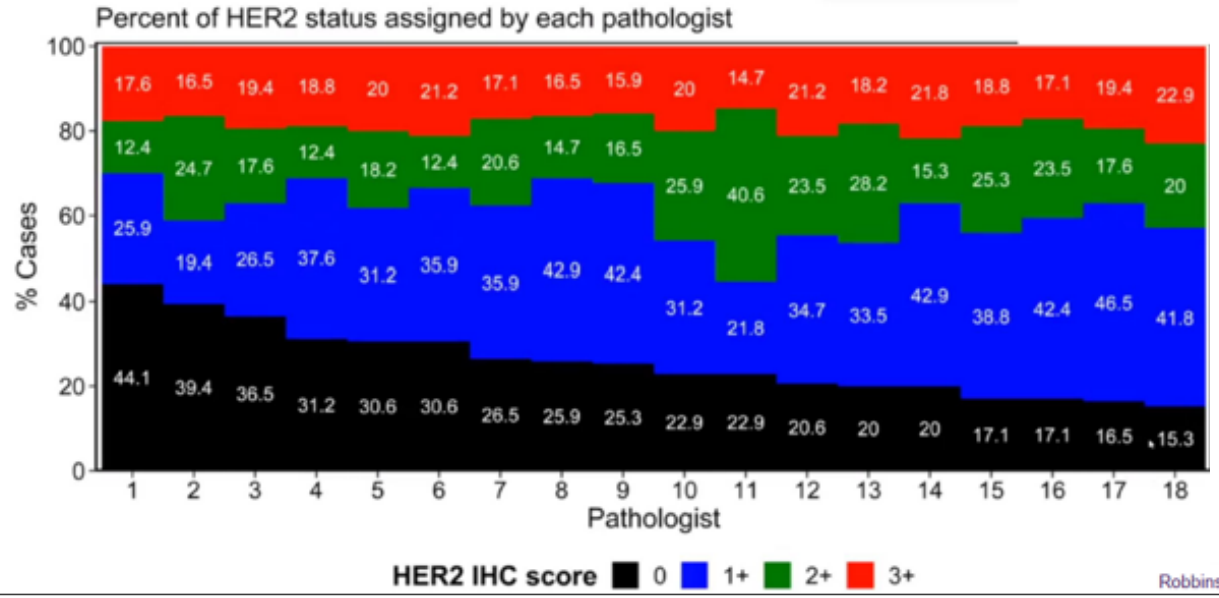
The ASCO-CAP guideline recommends[5]:

- Examine HER2 IHC cases at the lower end of the spectrum at high power (40x) to differentiate cells with and without staining
- Considering a second pathologist review for samples on the threshold of IHC 0 and IHC 1+

1. Venetis K, et al. *Front Mol Biosci*. 2022;9:834651; 2. Chen Z, et al. *Breast Cancer Res Treat*. 2023;202(2):313-323; 3. Boyraz B, Ly A. *Hum Pathol*. 2022;127:50-55; 4. Ardor GD, et al. *Breast J*. 2023;2023:9725647; 5. Wolff AC, et al. *J Clin Oncol*. 2023;41(22):3867-3872; 6. Bardia A et al. *N Engl J Med*. 2024. Supplement.

ALTA VARIABILIDAD INTEROBSERVADOR

Multi-institutional Assessment of Pathologist Scoring HER2 Immunohistochemistry

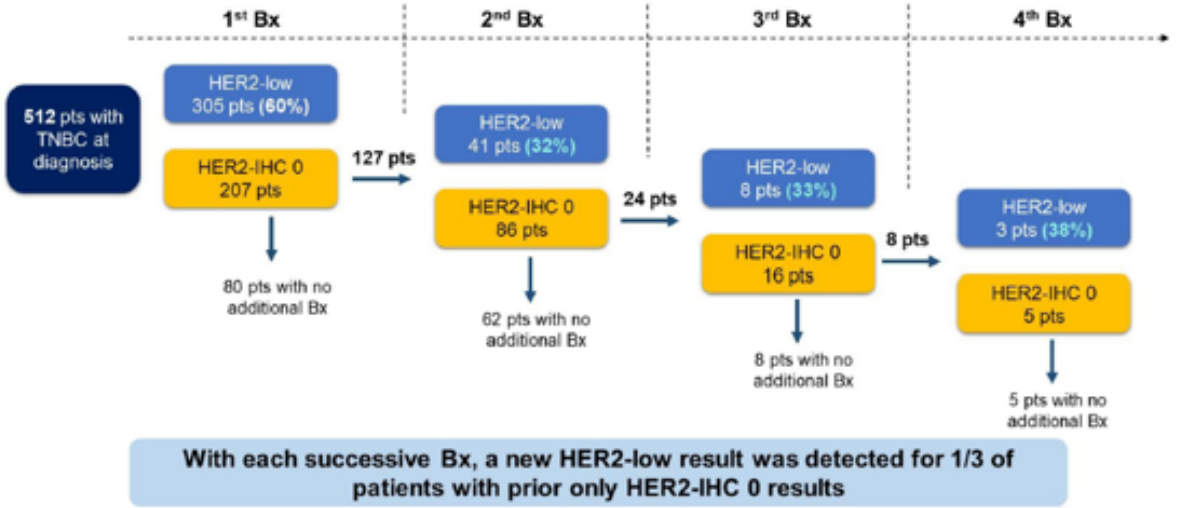


Robbins C et al. Mod Pathol 2023

EVOLUCION DE HER2 EN LAS SUCESIVAS BIOPSIAS

Results (Part 1) – Impact of Repeat Bxs:

Detection of HER-low in successive serial Bxs for pts without a prior HER2-low result



With each successive Bx, a new HER2-low result was detected for 1/3 of patients with prior only HER2-IHC 0 results

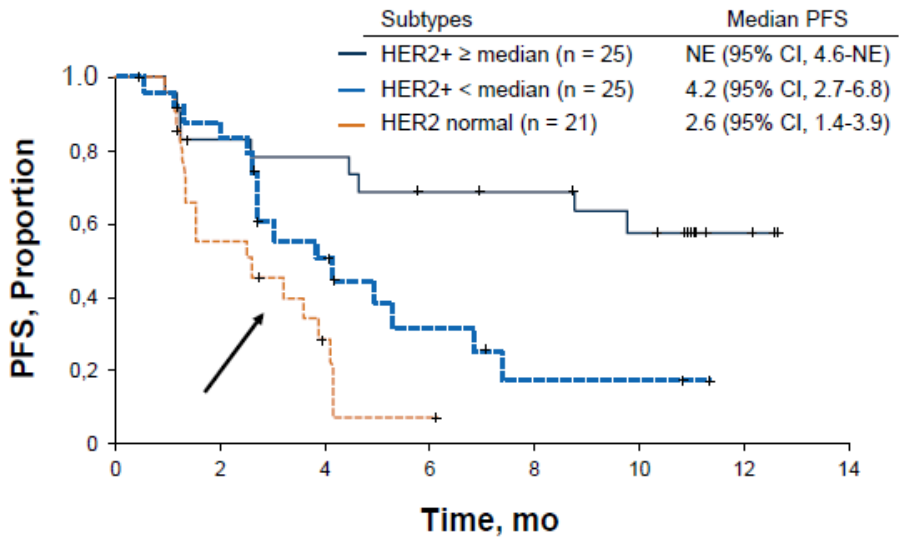
PRESENTED BY: Yael Bar, MD, PhD ybar@mgh.harvard.edu @BarYaelMD

COMO FUNCIONAN LOS FARMACOS ANTIHER2 EN HER2LOW Y ULTRALOW

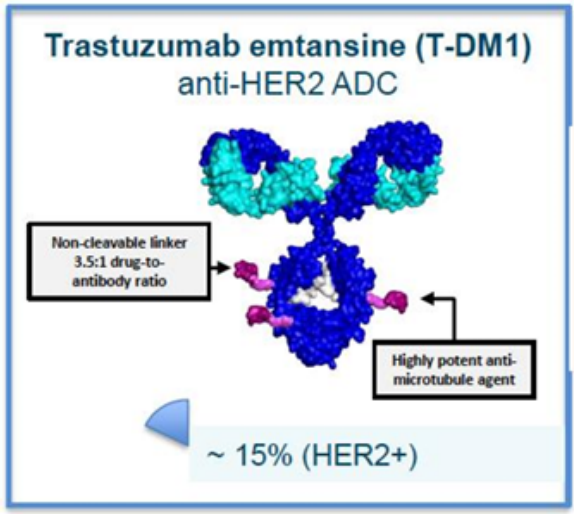
T-DM1 for HER2-Low BC

- Retrospective evaluation of T-DM1 in 21 cases of HER2-nonamplified MBC
- Only 1 response (ORR 4.8%) and mPFS 2.6 months

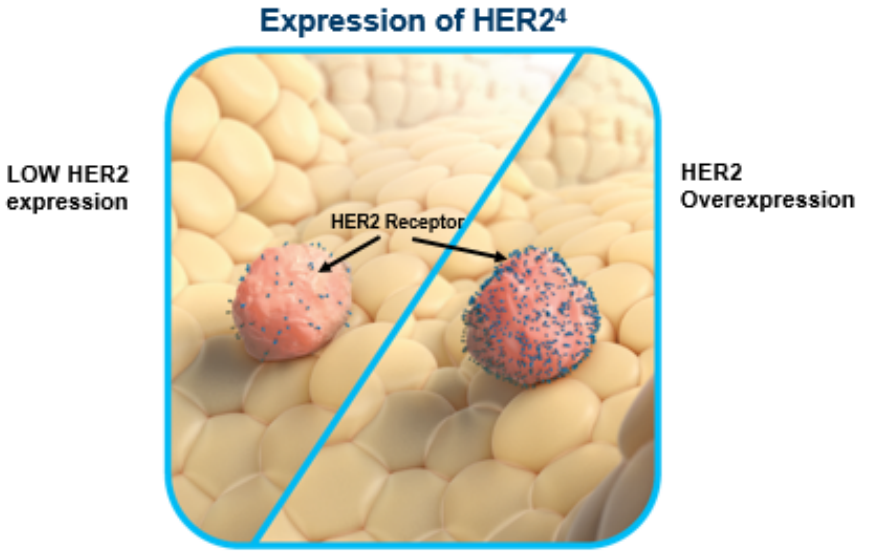
Little activity of T-DM1 in HER2-negative MBC



Burris HA et al. J Clin Oncol. 2011

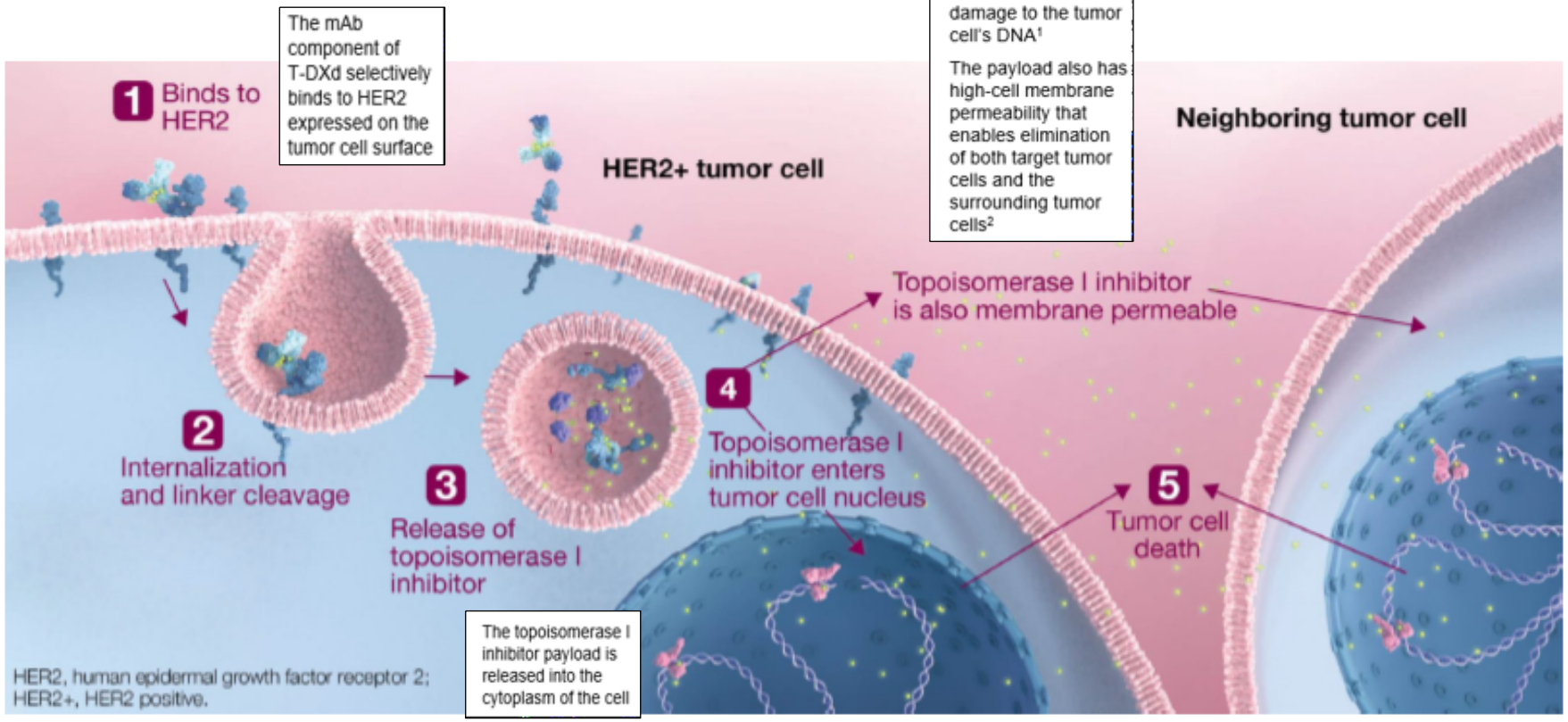


What occurs when there are less HER2 Receptors?



MECANISMO DE ACCION DE LOS ANTICUERPOS INMUNOCONJUGADOS NUEVA GENERACIÓN

T-DXd Allows for Efficient Delivery and Release of Topoisomerase I Inhibitor Payload at the Tumor Site[1,2]



1. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185; 2. Ogitani Y, et al. *Cancer Sci*. 2016;107:1039-1046.

Current Classification Strategies May Evolve to Reflect the Heterogeneity Patterns of HER2 Expression

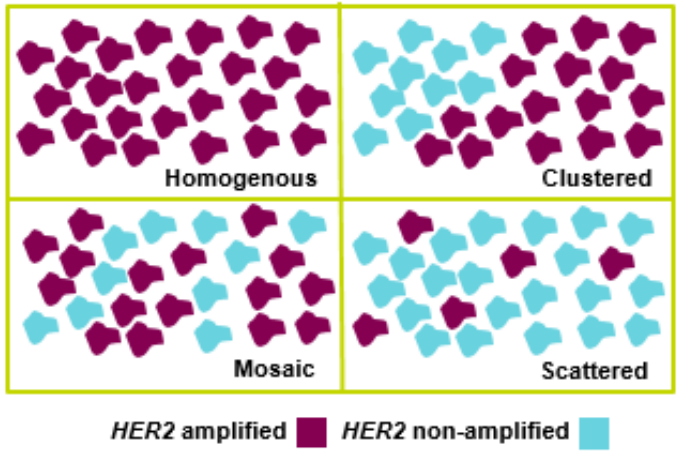
HER2 expression is non-binary and can be categorized in three ways by IHC 2+/3+ positivity[1,2]:

- ***Focal*** (<30% of cells stain positively)
- ***Heterogenous*** (30-79% of cells stain positively)
- ***Homogenous*** (≥ 80% of cells stain positively)

HER2 heterogeneity may occur in up to 34% of HER2 positive tumors, with 3 main patterns[2-5]

- ***Clustered Type:*** two distinct areas of the same tumor show differing HER2 expression
- ***Mosaic Type:*** diffuse intermingling of cells with variable HER2 expression
- ***Scattered Type:*** HER2 positive and/or amplified cells dispersed throughout a negative tumor area

Heterogeneity Types[4,8]

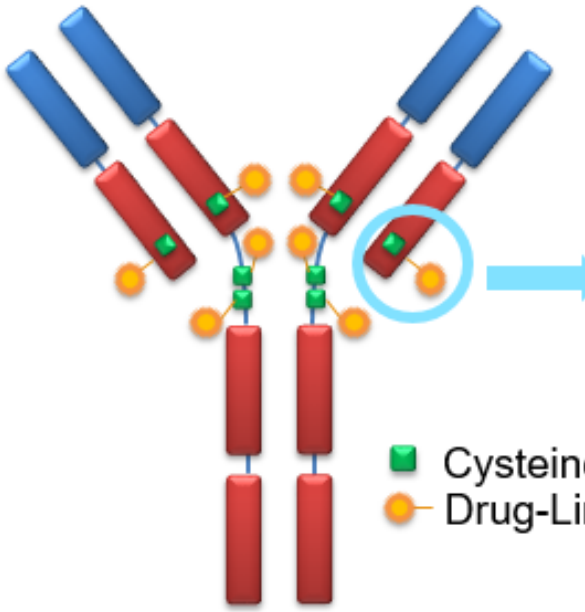


Conventional approaches to testing may not adequately classify patients with HER2 intratumoral heterogeneity [2,4-7]

- Intratumoral heterogeneity can be both genetic (related to gene amplification) and non-genetic (related to protein expression)[5,6]
- Assays in development such as GPA, are being investigated to better classify this patient population, particularly patients with non-genetic intratumoral heterogeneity[4-7]

1. Hurvitz SA, et al. *J Clin Oncol.* 2019;37(25):2206-2216 **2.** Pernas S and Tolaney SM. *Current Opin Oncol.* 2020; 32(6):545-554. **3.** Dieci MV, et al. *Cancer Treat Rev.* 2020;88:102064. **4.** Hou Y, et al. *Breast Cancer Res Treat.* 2017;166:447-457. **5.** Nitta H and Li Z. *Crit Rev Oncog.* 2020;25(3):233-240. **6.** Horii R, et al. *Virchows Arch.* 2021; Epub Ahead of Print. **7.** Tarantino T, et al. *J Clin Oncol* 2020;38(17):1951-1962. **8.** Hanna WM, et al. *Mod Pathol*. 2014;27(1):4-18.

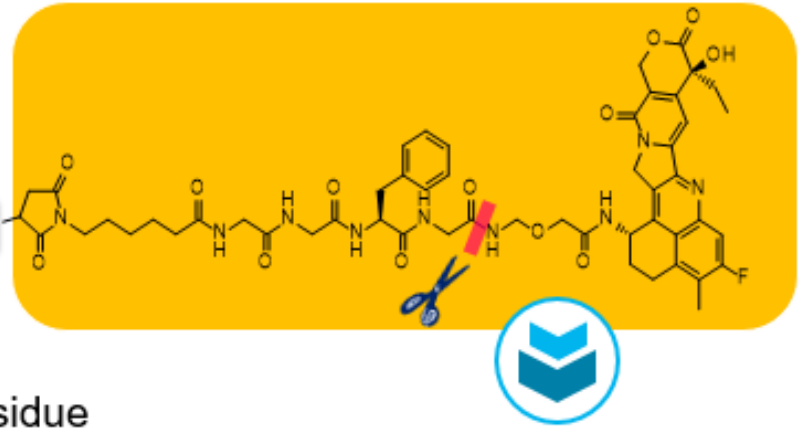
Trastuzumab Deruxtecan is a HER2 targeted ADC with 7 key attributes

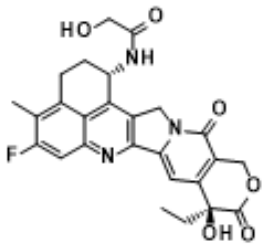


Conjugation chemistry

The tetrapeptide-based cleavable linker is connected to cysteine residues on the humanized anti-HER2 IgG1 monoclonal antibody with the same amino acid sequence as trastuzumab antibody

Proprietary Drug-Linker





Proprietary Payload (DXd)

Exatecan derivative

1. Topoisomerase I inhibitor payload
2. High potency of payload based on a cell-free assay topoisomerase I-mediated DNA relaxation assay
3. Payload with a short systemic half-life
4. Highly membrane permeable, which may enable a bystander effect
5. Stable in plasma
6. Designed to be cleaved by lysosomal enzymes overexpressed in tumor cells
7. Drug-to-antibody ratio of 7-8

Iwata H et al. Presented at: ASCO Annual Meeting; June 1–5, 2018; Chicago, IL.

ADC=antibody-drug conjugate; HER2=human epidermal growth factor receptor 2

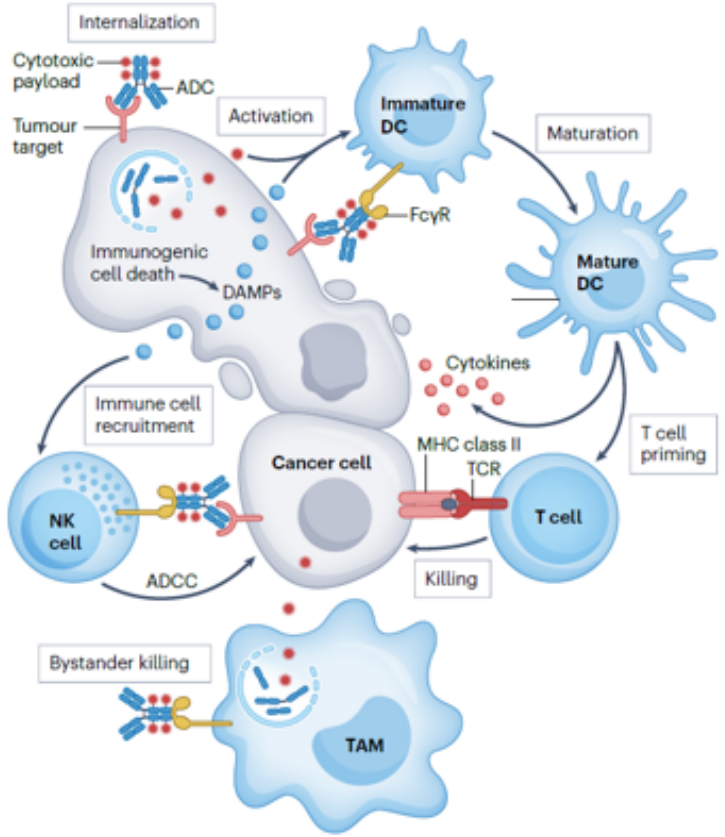
Aditional Mechanism of DXd release, Macrophagues

nature reviews cancer
https://doi.org/10.1038/s41568-025-00869-w

Review article
Check for updates

Unveiling the molecular and immunological drivers of antibody–drug conjugates in cancer treatment

Alfred Zippelius[1,2], Sara M. Tolaney[3], Paolo Tarantino[3,4], Joseph P. Balthasar[5] & Greg M. Thurber[6]



ADC internalization and cytotoxic payload release in tumour cells may lead to immunogenic cell death, signified by subsequential release of damage-associated molecular patterns (DAMPs) such as calreticulin, ATP and high-mobility group box 1 (HMGB1), which promote phagocytosis and dendritic cell (DC) activation, and act as chemoattractants for immune effectors. Some classes of cytotoxic payload also activate DCs directly. The Fc regions of ADCs can interact with Fcγ receptors (FcγRs) on DCs and other antigen-presenting cells to promote the uptake of tumour antigens via antibody-dependent cellular phagocytosis (ADCP), facilitating antigen presentation to T cells. Mature, antigen-loaded DCs migrate to lymph nodes, where they prime tumour-specific T cells and induce their migration to the tumour. Via Fc–FcγR interactions, tumour-associated macrophages (TAMs) internalize ADCs and release their payloads into the tumour microenvironment, resulting in bystander killing

Zippelius, A., Tolaney, S.M., Tarantino, P. *et al.* Unveiling the molecular and immunological drivers of antibody–drug conjugates in cancer treatment. *Nat Rev Cancer* **25**, 925–944 (2025)

nature communications

Article

https://doi.org/10.1038/s41467-025-58266-8

Effective extracellular payload release and immunomodulatory interactions govern the therapeutic effect of trastuzumab deruxtecan (T-DXd)

Received: 25 July 2024

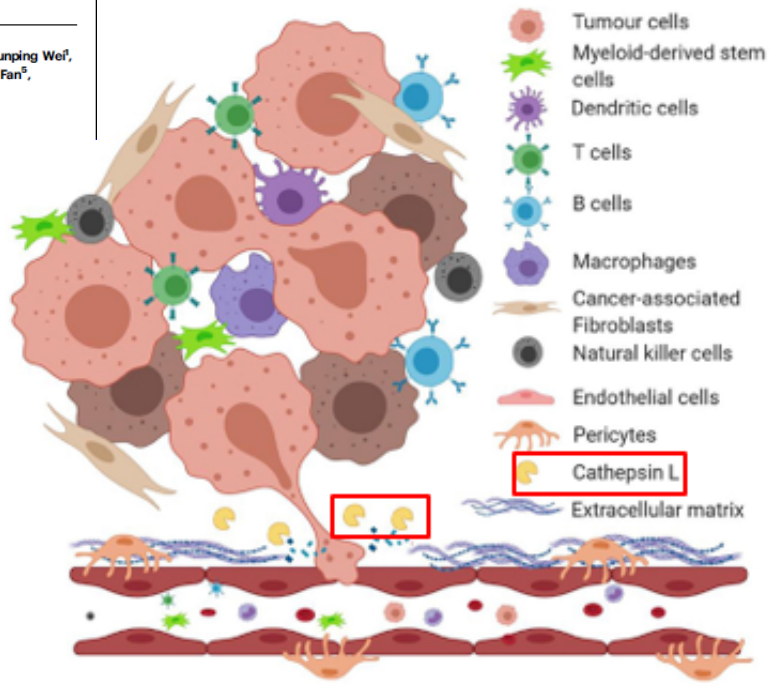
Accepted: 15 March 2025

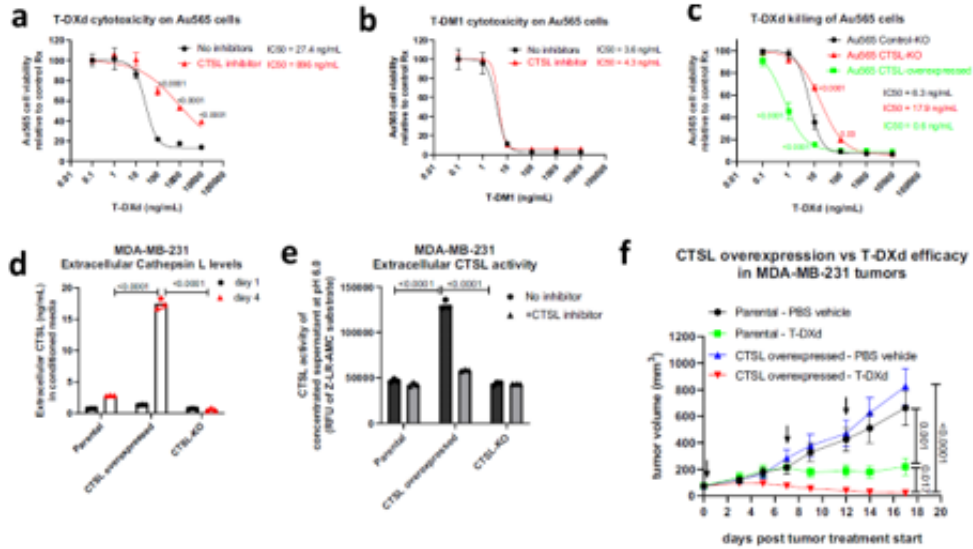
Published online: 02 April 2025

Check for updates

Li-Chung Tsao[1], John S. Wang[2], Xingru Ma[3], Sirajbir Sodhi[2], Joey V. Ragusa[3], Bushangqing Liu[4], Jason McBane[1], Tao Wang[1], Junping Wei[1], Cong-Xiao Liu[1], Xiao Yang[1], Gangjun Lei[1], Ivan Spasojevic[2,5], Ping Fan[5], Timothy N. Trotter[1], Michael Morse[1,2], Herbert Kim Lyerly[1,3,6] & Zachary C. Hartman[1,3,4,6]

Release DXd by catepsins



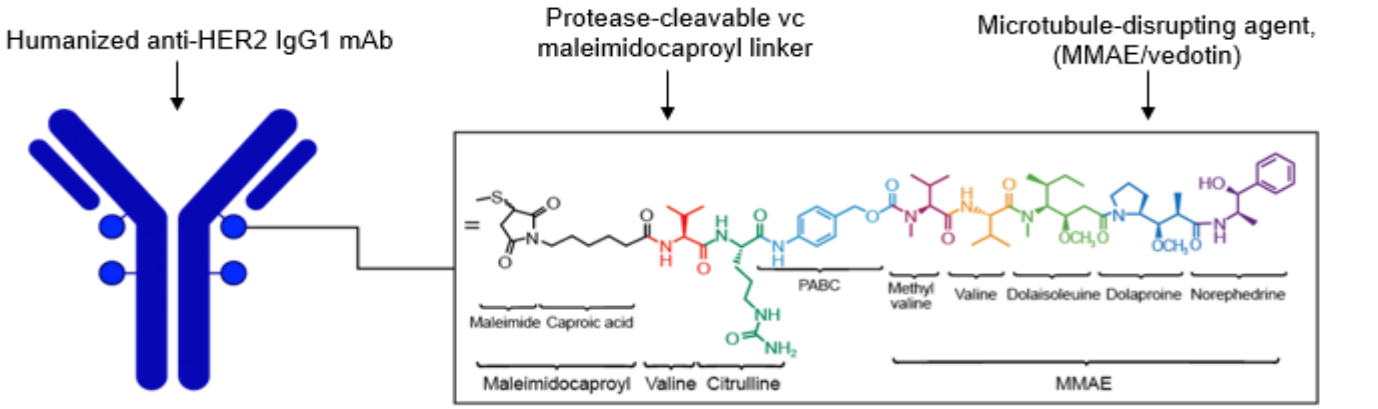


Tabish et al. Front. Nanotechnol., 06 May 2020 Sec. Biomedical Nanotechnology Volume 2 - 2020

Tsao, LC., Wang, J.S., Ma, X. *et al.* Effective extracellular payload release and immunomodulatory interactions govern the therapeutic effect of trastuzumab deruxtecan (T-DXd). *Nat Commun* **16**, 3167 (2025).

DV IS AN ADC COMPRISING OF 3 COMPONENTS WITH UNIQUE CONTRIBUTIONS TO ITS MULTIMODAL MOAS[1-6]

DV is an ADC Comprising of 3 Components With Unique Contributions to its Multimodal MoAs[1-6]



	DV	T-DM1	T-DXd	SG	EV
Antibody	**Disitamab** (HER2-directed)	**Trastuzumab** (HER2-directed)	**Trastuzumab** (HER2-directed)	**Sacituzumab** (Trop2-directed)	**Enfortumab** (Nectin-4 directed)
Payload	**MMAE** (microtubule disrupting agent)	**DM1** (microtubule inhibitor)	**Deruxtecan** (topoisomerase I inhibitor)	**SN-38** (topoisomerase I inhibitor)	**MMAE** (microtubule disrupting agent)
Cleavable linker	✓	✗	✓	✓	✓

- A fully humanized investigational IgG1 mAb (disitamab, which is distinct from trastuzumab) directed to the extracellular domain of HER2
- A protease-cleavable mc- vc linker that attaches MMAE to disitamab and enables preferential release of MMAE within target cells
- MMAE, a clinically validated microtubule disrupting agent

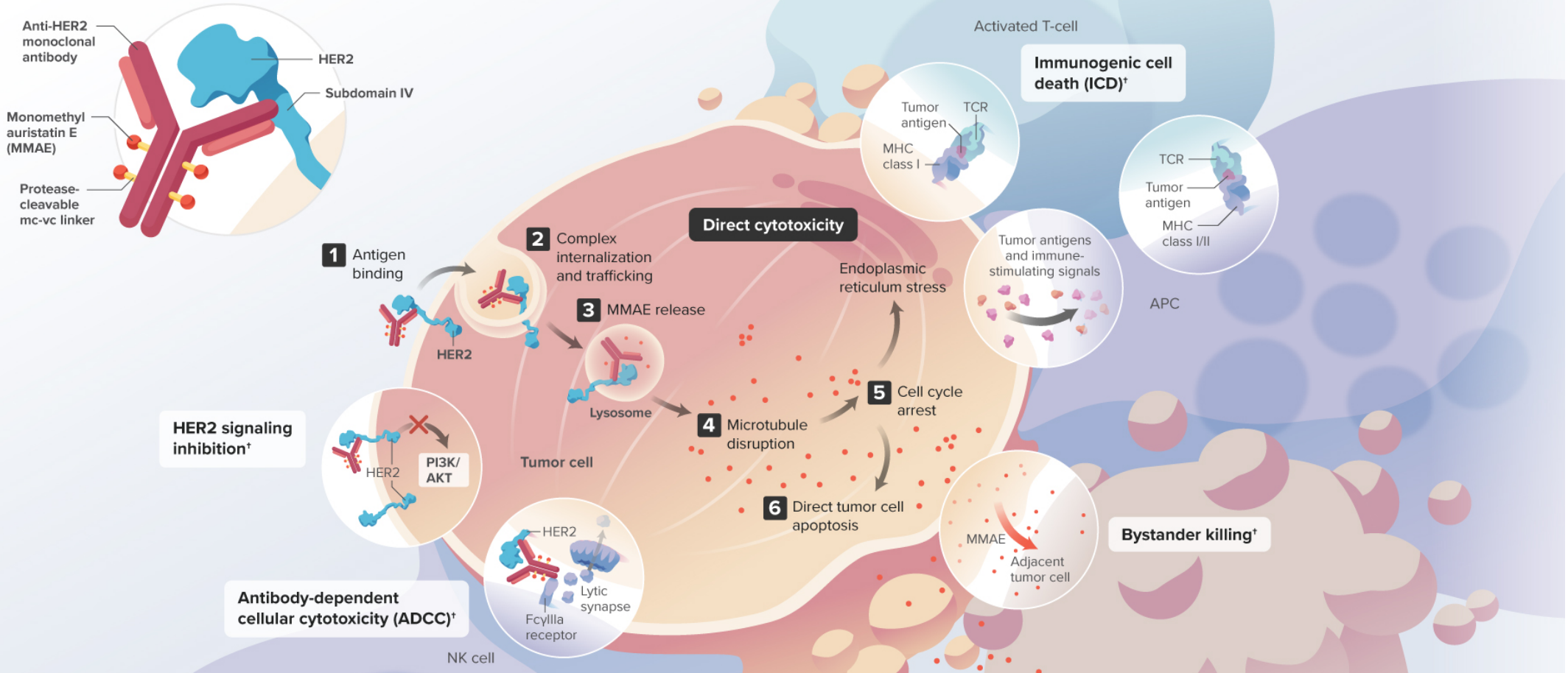
Disitamab Vedotin es una molécula en investigación y no está aprobado por la FDA ni por la EMA para el tratamiento de ninguna enfermedad. La seguridad y la eficacia de este compuesto no ha sido probada.

ADC: antibody-drug conjugate; **DM1:** derivative of maytansine; **DV:** disitamab vedotin; **EV:** enfortumab vedotin; **HER:** human epidermal growth factor receptor; **Ig:** immunoglobulin; **IHC:** immunohistochemistry; **ISH:** in situ hybridization; **mAb:** monoclonal antibody; **mc-vc:** maleimide caproic acid valine citrulline; **MMAE:** microtubule-disrupting agent monomethyl auristatin E; **MoA:** mechanism of action; **NGS:** next-generation sequencing; **SG:** sacituzumab govitecan; **T-DM1:** trastuzumab emtansine; **T-DXd:** trastuzumab deruxtecan; **UC:** urothelial carcinoma

1. Li H, et al. Cancer Biol Ther. 2016;17:346-354. **2.** Jiang J, et al. Toxicol Lett. 2020;324:30-37. **3.** Yao X, et al. Breast Cancer Res Treat. 2015;153:123-133. **4.** PADCEV® (enfortumab vedotin-ejfv) [prescribing information]. October 2022. **5.** ADCETRIS® (brentuximab vedotin) [prescribing information]. February 2022. **6.** TIVDAK® (tisotumab vedotin-tffv) [prescribing information]. January 2022.

DISITAMAB VEDOTIN

Proposed mechanism of action of an antibody-drug conjugate directed to HER2*



AKT: protein kinase B; **APC**: antigen-presenting cell; **HER2**: human epidermal growth factor receptor 2; **MHC**: major histocompatibility complex; **NK**: natural killer; **PI3K**: phosphoinositide 3-kinase; **TCR**: T-cell receptor

†Additional mechanisms of action and their potential to complement the direct cytotoxicity of some MMAE-based antibody-drug conjugates are currently under investigation

***Disitamab vedotin is an investigational agent, and its safety and efficacy have not been established.**

[Vic-]trastuzumab duocarmazine

The ADC [vic-]trastuzumab duocarmazine (SYD985) is comprised of the monoclonal antibody trastuzumab and a cleavable linker-drug called valine-citrulline-*seco*-DUocarmycin-hydroxyBenzamide-Azaindole (*vc-seco*-DUBA).

Table 2. Comparison of trastuzumab–emtansine (T-DM1) vs. trastuzumab–duocarmazine (SYD–986) vs. trastuzumab–deruxtecan (T-Dxd).

Antibody-Drug Conjugate	T-DM1	SYD-986	T-Dxd
HER2 targeting vehicle	Trastuzumab	Trastuzumab	Trastuzumab
Linker	Non-cleavable	Cleavable	Cleavable
Drug–antibody ratio	3.5:1	2.8:1	8:1
Cytotoxic moiety	Maytansine derivative	Seco-DUBA	Exatecan derivative
Cytotoxic moiety MoA	Antimicrotubule (mitotic poison)	Alkylating agent	Topoisomerase I inhibitor
Diffusible cytotoxic moiety?	✗	✗	✓
Bystander killing effect?	✗	✓	✓
Targets HER2-positive or homogenous tumors?	✓	✓	✓
Targets HER2-low or heterogeneous tumors?	✗	✓	✓

Legend: MoA = mechanism of action.

ARTICLES · Volume 20, Issue 8, P1124-1135, August 2019 Download Full Issue

Trastuzumab duocarmazine in locally advanced and metastatic solid tumours and HER2-expressing breast cancer: a phase 1 dose-escalation and dose-expansion study

Prof Udai Banerji, MD [a] · Prof Carla M L van Herpen, MD [b] · Cristina Saura, MD [c] · Fiona Thistlethwaite, MD [d] · Simon Lord, MD [e] · Victor Moreno, MD [f] · et al. Show more

Phase 1 dose-expansion study	Advanced BC, gastric, urothelial, or endometrial cancer with at least HER2 IHC 1+	146 (47 HER2-low BC)	Trastuzumab duocarmazine (SYD985)	ORR: 28% (95% CI, 13.8–46.8%) in HR+ HER2-low BC, 40% (95% CI, 16.3–67.6%) in HR- HER2-low BC

EVIDENCIA CLINÍCA ACTUAL

Reprinted from: nature.com/nm
DOI: https://doi.org/10.1038/s41591-025-03981-4
nature medicine

Trastuzumab deruxtecan in HER2-low metastatic breast cancer: long-term survival analysis of the randomized, phase 3 DESTINY-Breast04 trial

Shanu Modi, William Jacot, Hiroji Iwata, Yeon Hee Park, Maria Vidal Losada, Wei Li, Junji Tsurutani, Naoto T. Ueno, Khalil Zaman, Aleix Prat, Konstantinos Papazisis, Hope S. Rugo, Toshinari Yamashita, Nadia Harbeck, Seock-Ah Im, Michelino De Laurentiis, Jean-Yves Pierga, Xiaojia Wang, Andrea Gombos, Eriko Tokunaga, Cecilia Orbegoso Aguilar, Lotus Yung, Feng Xiao, Yingkai Cheng & David Cameron

DESTINY-Breast04

DESTINY-Breast04 Study Design:

An open-label, multicenter study (NCT03734029)[1-3]

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

N = 557

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Stratification factors
- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) vs HR−

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[d]
- PFS by BICR (all patients)
- **OS (HR+ and all patients)**

Secondary endpoints[d]
- **PFS by investigator**
- ORR by BICR and investigator
- DOR by BICR
- **Safety**
- Patient-reported outcomes (HR+)[e]

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI, 31.0-32.8 months)

ASCO, American Society of Clinical Oncology; BICR, blinded independent central review; CAP, College of American Pathologists; CDKi, cyclin-dependent kinase 4/6 inhibitors; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational-use-only [IUO] assay system, at the time of study. [c]TPC was administered according to the label. [d]Efficacy in the HR− cohort was an exploratory endpoint. [e]The patient-reported outcomes analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.

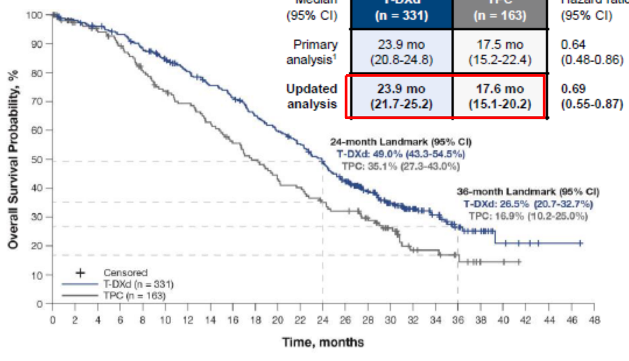
1. Modi S et al. *N Engl J Med*. 2022;387:9-20. 2. Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3. Prat A et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

DESTINY-Breast04

Overall Survival

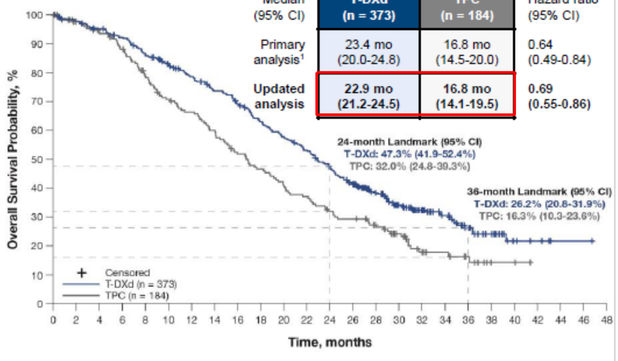
HR+ Cohort

	Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]		23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis		23.9 mo (21.7-25.2)	17.6 mo (15.1-20.2)	0.69 (0.55-0.87)



All Patients

	Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]		23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis		22.9 mo (21.2-24.5)	16.8 mo (14.1-19.5)	0.69 (0.55-0.86)



- In the HR+ cohort and all patients, median OS was consistent with results from the primary analysis,[1] showing a 31% reduction in risk of death for patients receiving T-DXd compared with those receiving TPC

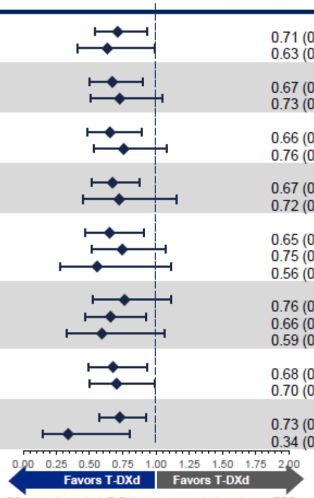
HR, hormone receptor; mo, month; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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

DESTINY-Breast04

Subgroup Analysis: OS in the HR+ Cohort

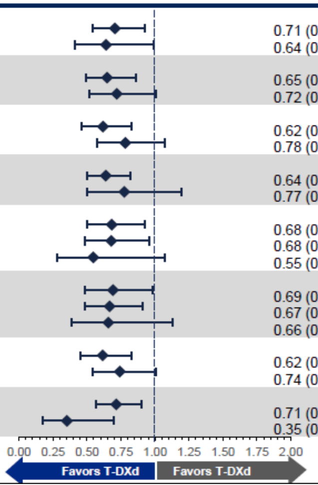
	No. of Events/No. of Patients T-DXd	No. of Events/No. of Patients TPC	OS, median (95% CI), mo T-DXd	OS, median (95% CI), mo TPC	Hazard Ratio for Death (95% CI)
Prior CDK4/6 inhibitors					
Yes	156/233	78/115	22.3 (19.8-24.3)	16.8 (13.6-19.5)	0.71 (0.54-0.94)
No	53/96	31/47	30.3 (23.0-35.1)	22.4 (15.6-27.2)	0.63 (0.41-0.99)
IHC status					
IHC 1+	121/192	67/96	22.9 (20.8-25.2)	16.9 (13.5-22.4)	0.67 (0.50-0.91)
IHC 2+/ISH−	90/139	43/67	24.2 (20.8-26.5)	19.1 (15.1-22.3)	0.73 (0.51-1.05)
Prior lines of chemotherapy					
1	118/203	63/93	25.5 (23.9-28.8)	19.4 (16.7-23.9)	0.66 (0.48-0.89)
≥2	93/127	47/69	19.0 (16.7-22.7)	14.0 (10.8-20.0)	0.76 (0.53-1.08)
Age					
<65 years	164/260	81/120	23.0 (20.8-24.8)	17.6 (14.8-20.0)	0.67 (0.52-0.88)
≥65 years	47/71	29/43	25.5 (21.0-28.8)	19.5 (9.2-30.6)	0.72 (0.45-1.15)
Race					
White	104/156	51/78	23.9 (19.8-24.8)	15.1 (12.3-19.9)	0.65 (0.47-0.91)
Asian	80/131	46/66	23.9 (21.7-28.7)	19.9 (16.7-27.2)	0.75 (0.52-1.07)
Other	25/37	12/16	21.5 (15.0-30.4)	15.2 (6.2-23.9)	0.56 (0.28-1.12)
Region					
Asia	80/128	42/60	23.4 (21.0-27.4)	19.9 (16.7-27.2)	0.76 (0.53-1.11)
Europe and Israel	102/149	49/73	23.9 (20.8-25.7)	17.6 (12.3-20.2)	0.66 (0.47-0.93)
North America	29/54	19/30	24.5 (15.8-28.9)	16.0 (8.8-22.3)	0.59 (0.33-1.06)
ECOG performance status					
0	109/187	59/95	26.0 (23.0-29.6)	20.2 (16.7-24.4)	0.68 (0.49-0.93)
1	102/44	51/68	21.4 (17.9-23.9)	14.9 (12.6-18.4)	0.70 (0.50-0.99)
Visceral disease at baseline					
Yes	201/298	99/146	22.9 (21.4-24.5)	17.5 (14.8-20.2)	0.73 (0.57-0.93)
No	10/33	11/17	NE (20.4-NE)	18.4 (13.5-NE)	0.34 (0.14-0.81)



DESTINY-Breast04

Subgroup Analysis: OS in All Patients

	No. of Events/No. of Patients T-DXd	No. of Events/No. of Patients TPC	OS, median (95% CI), mo T-DXd	OS, median (95% CI), mo TPC	Hazard Ratio for Death (95% CI)
Prior CDK4/6 inhibitors					
Yes	158/235	81/118	22.3 (19.7-24.2)	16.7 (14.0-19.4)	0.71 (0.54-0.92)
No	55/98	32/48	29.6 (22.9-35.1)	22.4 (15.6-27.2)	0.64 (0.41-0.98)
IHC status					
IHC 1+	137/214	77/107	22.7 (20.3-24.7)	15.7 (13.5-19.9)	0.65 (0.49-0.86)
IHC 2+/ISH−	105/159	51/77	23.6 (20.0-26.0)	17.1 (13.1-21.7)	0.72 (0.51-1.01)
Prior lines of chemotherapy					
1	129/221	69/100	25.5 (23.4-28.9)	18.2 (15.6-22.5)	0.62 (0.46-0.83)
≥2	113/151	59/83	18.1 (16.1-21.5)	14.0 (10.8-19.1)	0.78 (0.57-1.07)
Age					
<65 years	185/290	95/136	22.7 (20.3-24.4)	16.7 (14.0-19.1)	0.64 (0.50-0.82)
≥65 years	57/83	33/48	24.4 (18.4-28.0)	19.5 (11.1-30.2)	0.77 (0.50-1.19)
Race					
White	123/176	62/91	22.0 (18.2-24.2)	14.5 (10.7-19.4)	0.68 (0.50-0.93)
Asian	90/151	51/72	25.2 (21.7-29.6)	19.1 (15.7-24.3)	0.68 (0.48-0.96)
Other	26/38	13/17	21.2 (17.0-28.9)	15.2 (6.2-23.9)	0.55 (0.28-1.07)
Region					
Asia	90/147	47/66	24.0 (21.7-29.3)	19.1 (15.7-24.3)	0.69 (0.49-0.98)
Europe and Israel	118/166	59/85	22.3 (19.0-24.2)	14.8 (10.7-19.9)	0.67 (0.49-0.91)
North America	34/60	22/33	20.6 (13.6-25.9)	14.9 (10.5-19.5)	0.66 (0.38-1.13)
ECOG performance status					
0	117/200	68/105	25.9 (23.0-29.3)	19.4 (15.1-22.8)	0.62 (0.46-0.83)
1	125/173	60/79	20.6 (17.2-22.7)	14.5 (12.3-18.4)	0.74 (0.54-1.01)
Visceral disease at baseline					
Yes	227/332	109/157	22.4 (20.0-24.0)	16.9 (14.0-20.0)	0.71 (0.57-0.90)
No	15/41	19/27	NE (28.0-NE)	15.7 (12.9-20.6)	0.35 (0.18-0.70)

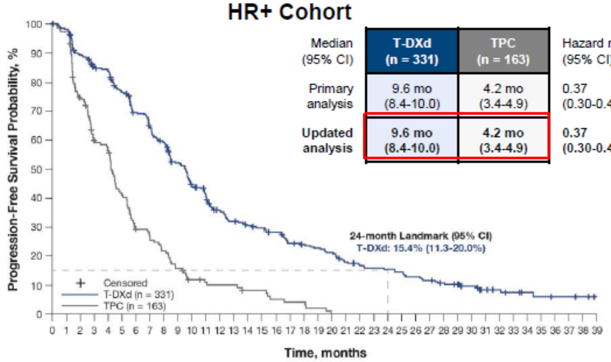


DESTINY-Breast04

Progression-Free Survival (by Investigator[a])

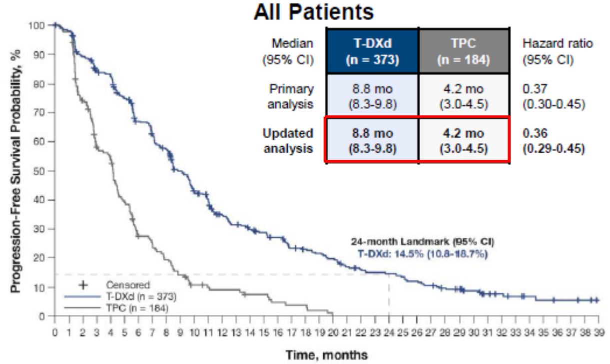
HR+ Cohort

	Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis		9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis		9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.46)



All Patients

	Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis		8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis		8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.36 (0.29-0.45)



- Median PFS was consistent with results from the primary analysis,[1] showing a reduction in risk of disease progression or death of 63% and 64% in the HR+ cohort and all patients, respectively, for the T-DXd arm compared with the TPC arm

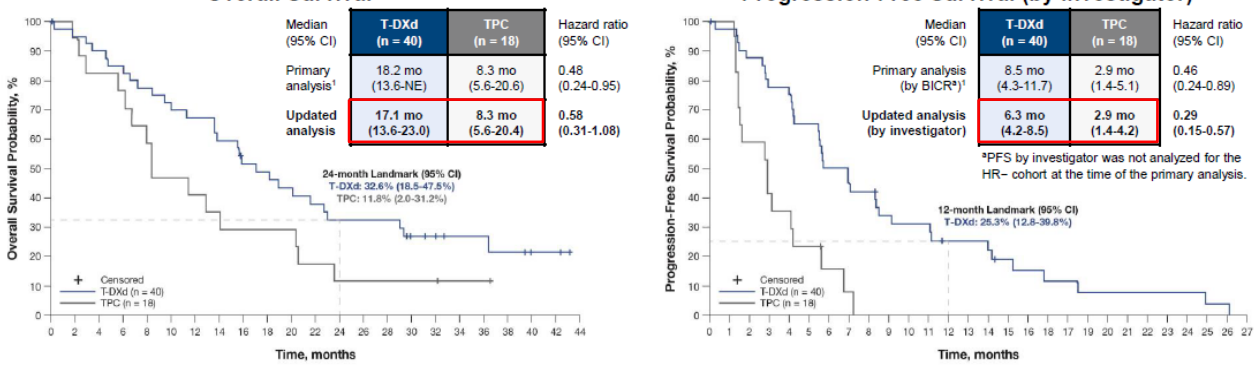
BICR, blinded independent central review; HR, hormone receptor; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved. At primary analysis, PFS by BICR for HR+ cohort was 10.1 mo and 5.4 mo for T-DXd and TPC, respectively (hazard ratio, 0.51). For all patients, the PFS by BICR was 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (hazard ratio, 0.50). The updated analysis is based on PFS by investigator.

DESTINY-Breast04

Efficacy in the HR− Cohort (Exploratory Analyses)

Overall Survival



Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	17.1 mo (13.6-23.0)	8.3 mo (5.6-20.4)	0.58 (0.31-1.08)

Patients still at risk:

T-DXd (n = 40)	40	38	36	34	31	28	26	23	19	18	16	14	12	12	12	8	7	5	5	4	2	2	0	
TPC (n = 18)	18	16	14	13	10	8	7	6	5	5	5	3	2	2	2	2	2	1	1	0	0	0	0	

Progression-Free Survival (by Investigator)

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	6.3 mo (4.2-8.5)	2.9 mo (1.4-4.2)	0.29 (0.15-0.57)

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.

Patients still at risk:

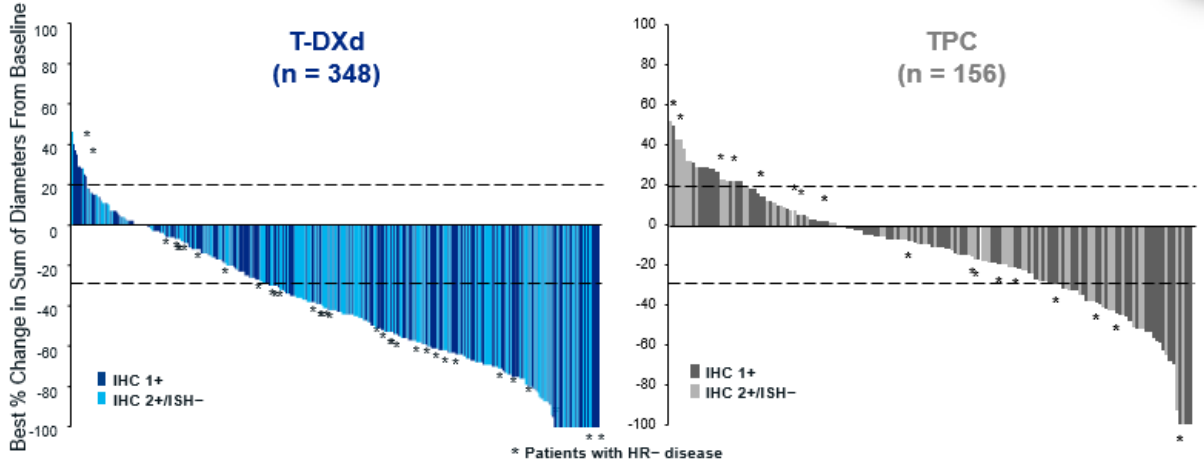
T-DXd (n = 40)	40	39	35	31	30	26	19	17	16	12	11	11	8	8	7	5	4	3	3	2	2	2	2	2	2	1	1	0
TPC (n = 18)	18	17	10	7	6	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- There was a 42% reduction in risk of death and 71% reduction in risk of disease progression or death for HR− patients receiving T-DXd compared with TPC

BICR, blinded independent central review; HR, hormone receptor; mo, month; NE, not evaluable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

DESTINY-Breast04: January 11, 2022, DCO

Best change in target lesions (all patients)



Shown are the best percentage changes from baseline in the sum of the largest diameters of measurable tumors in patients for whom data from both baseline and postbaseline assessments of target lesions by independent central review were available. The upper dashed horizontal line indicates a 20% increase in tumor size in the patients who had disease progression, and the lower dashed line indicates a 30% decrease in tumor size (partial response).
Modi S et al. *N Engl J Med*. 2022;387(1):9-20. Supplement.

DESTINY-Breast04: January 11, 2022, DCO

Confirmed ORR and best overall response

	Hormone receptor–positive[a,b]		All patients (HR+ and HR–)[b]		Hormone receptor–negative[a,b]	
	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 373)	TPC (n = 184)	T-DXd (n = 40)	TPC (n = 18)
Confirmed ORR, n (%) [95% CI]	175 (52.6) [47.0-58.0]	27 (16.3) [11.0-22.8]	195 (52.3) [47.1-57.4]	30 (16.3) [11.3-22.5]	20 (50.0) [33.8-66.2]	3 (16.7) [3.6-41.4]
CR, n (%)	12 (3.6)	1 (0.6)	13 (3.5)	2 (1.1)	1 (2.5)	1 (5.6)
PR, n (%)	164 (49.2)	26 (15.7)	183 (49.1)	28 (15.2)	19 (47.5)	2 (11.1)
SD, n (%)	117 (35.1)	83 (50.0)	129 (34.6)	91 (49.5)	12 (30.0)	8 (44.4)
PD, n (%)	26 (7.8)	35 (21.1)	31 (8.3)	41 (22.3)	5 (12.5)	6 (33.3)
Not evaluable, n (%)	14 (4.2)	21 (12.7)	17 (4.6)	22 (12.0)	3 (7.5)	1 (5.6)
DCR (CR + PR + SD), n (%)	293 (88.0)	110 (66.3)	325 (87.1)	121 (65.8)	32 (80.0)	11 (61.1)
Clinical benefit rate,[c] n (%)	237 (71.2)	57 (34.3)	262 (70.2)	62 (33.7)	25 (62.5)	5 (27.8)
Median DOR, months	10.7	6.8	10.7	6.8	8.6	4.9
Median time to response, months	2.76	2.73	2.73	2.22	1.51	1.41

[a]Hormone receptor status is based on data from the electronic data capture corrected for misstratification. [b]Analyses of the HR+ cohort and all patients were secondary endpoints; analyses of the HR− cohort were exploratory endpoints. [c]The clinical benefit rate is defined as the sum of complete response, partial response, and more than 6 months' stable disease, based on blinded independent central review.
Modi S et al. *N Engl J Med*. 2022;387(1):9-20. Click here to view cORR from Modi S et al. Presented at American Society of Clinical Oncology (ASCO) 2022, June 2022, LBA3

DESTINY-Breast04

Overall Safety Summary

- Median treatment duration was 8.2 months (range, 0.2-39.1 months) for T-DXd and 3.5 months (range, 0.3-19.7 months) for TPC
  - 16.4% of patients underwent treatment for ≥18 months in the T-DXd arm compared with 1.2% of patients in the TPC arm
- The most common TEAEs associated with treatment discontinuation for patients receiving T-DXd and TPC were investigator-assessed ILD/pneumonitis (10.2%) and peripheral sensory neuropathy (2.3%), respectively
- The most common TEAEs associated with dose reduction were nausea (4.6%) and decreased platelet count (3.0%) among patients receiving T-DXd vs decreased neutrophil count (10.5%) and palmar-plantar erythrodysesthesia syndrome (5.2%) among patients receiving TPC
- Exposure-adjusted incidence rates for any-grade TEAEs were 1.2 and 2.6 per patient-year for the T-DXd and TPC arms, respectively
  - This supports that longer T-DXd exposure does not increase toxicity
- Overall, the safety profile is consistent with results from the primary analysis (data cutoff, January 11, 2022)[1]

	Safety analysis set[a]	
n (%)	T-DXd (n = 371)	TPC (n = 172)
TEAEs	369 (99.5)	169 (98.3)
Grade ≥3	202 (54.4)	116 (67.4)
Serious TEAEs	108 (29.1)	44 (25.6)
TEAEs associated with dose discontinuation	62 (16.7)	14 (8.1)
TEAEs associated with dose interruptions	155 (41.8)	73 (42.4)
TEAEs associated with dose reductions	89 (24.0)	65 (37.8)
TEAEs associated with deaths	15 (4.0)	5 (2.9)
Total on-treatment deaths[b]	14 (3.8)	8 (4.7)

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]On-treatment death is defined as death that occurred any time from date of first dose through 47 days after the last dose of the study treatment.
1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

DESTINY-Breast06: Study Design

An open-label, randomized, multicenter, phase 3 study (NCT04494425)[1-4]

PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥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

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

866 patients

R 1:1

HER2-low = 713
HER2-ultralow = 153†

T-DXd
5.4 mg/kg Q3W
(n=436)

TPC
(n=430)

Capecitabine, 59.8%; nab-paclitaxel, 24.4%; paclitaxel, 15.8%

ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- PFS2 (INV) in ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes (HER2-low and ITT)

Exploratory endpoint

- Biomarkers

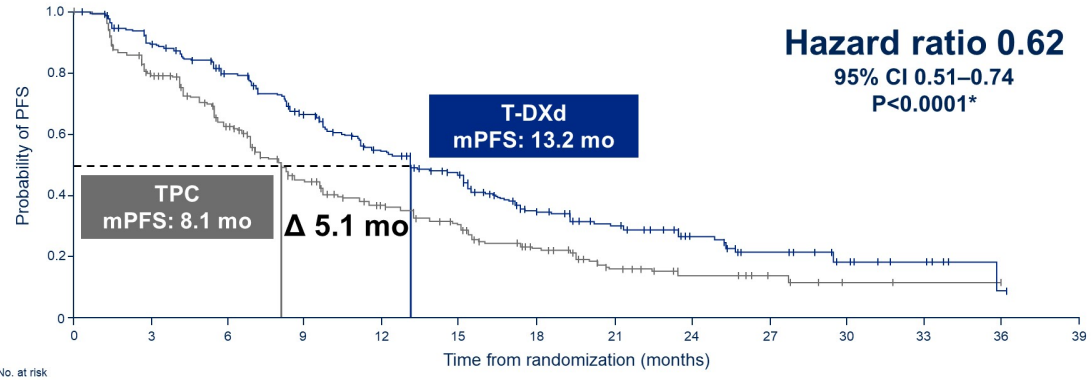
*Study enrollment was based on central HER2 testing. HER2 status was determined based on the most recent evaluable HER2 IHC sample prior to randomization. HER2-ultralow was defined as faint, partial membrane staining in ≤10% of tumor cells (also known as IHC >0<1+); †HER2-ultralow status as determined per IRT data (note: efficacy analyses in the HER2-ultralow subgroup were based on n=152 as determined per central laboratory testing data).

1. ClinicalTrials.gov. NCT04494425. https://www.clinicaltrials.gov/study/NCT04494425. Accessed May 31, 2024; 2. Curigliano G et al. Presented at: ASCO Annual Meeting; May 31 – June 4, 2024; Chicago, IL. Presentation LBA1000. 3. Bardia A et al. *N Engl J Med.* 2024; 4. Bardia A et al. Presented at: SABCS 2024 Meeting; December 10–13, San Antonio, TX. Presentation LB1-04

DESTINY-Breast06

PFS (BICR) in HER2-low: primary endpoint

10



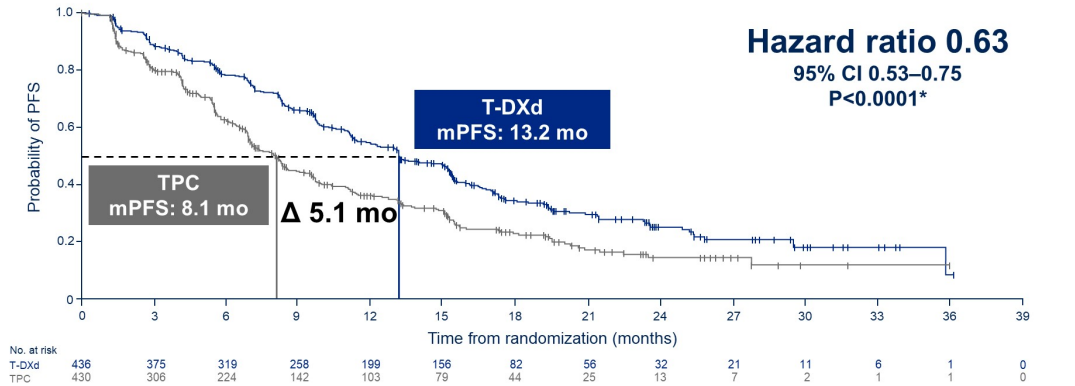
T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*P-value of <0.05 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

DESTINY-Breast06

PFS (BICR) in ITT: key secondary endpoint

11



T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in ITT

*P-value of <0.015 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; ITT, intent-to-treat; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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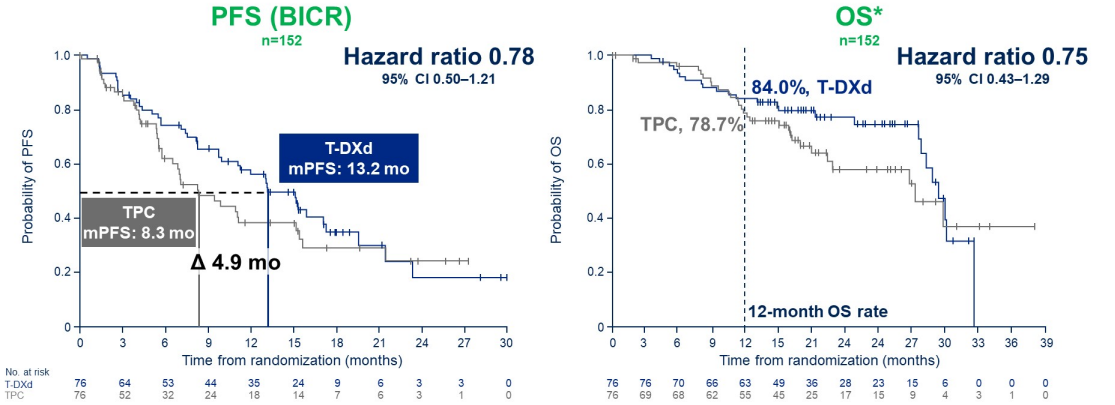
DESTINY-Breast06

PFS and OS in HER2-ultralow: prespecified exploratory analyses

13



PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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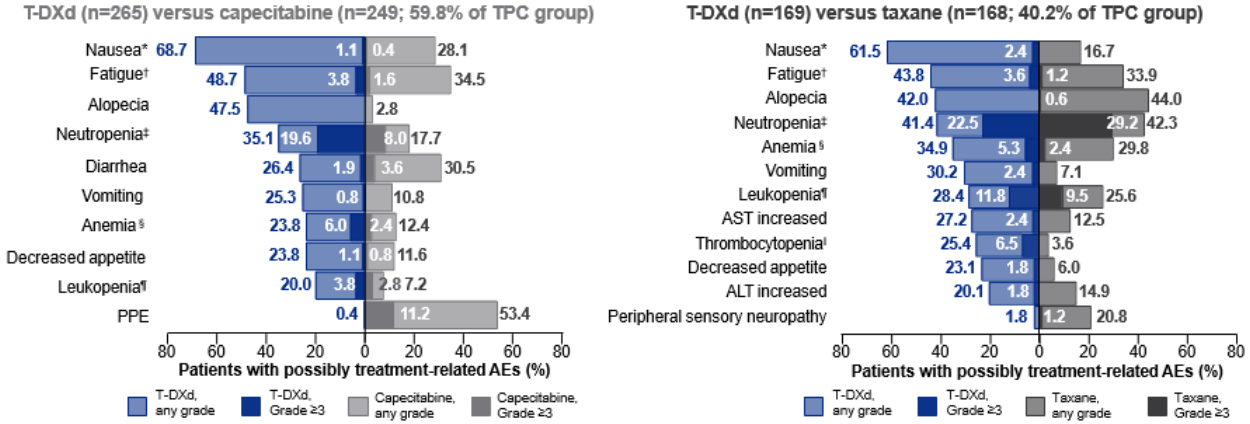
Treatment-related AEs in ≥20% of patients

ESMO 2025 BREAST CANCER Annual Congress



Neutropenia was the most common Grade ≥3 treatment-related AE with T-DXd and taxane, with similar rates; in capecitabine, the most common Grade ≥3 treatment-related AE was PPE, with rates exceeding 10%

*Use of antiemetic agents was recommended, but not mandated, prior to each dose of T-DXd for prevention of chemotherapy-induced nausea and vomiting; †includes the preferred terms fatigue, asthenia, malaise, and lethargy; ‡includes the preferred terms neutropenia and neutrophil count decreased; §includes the preferred terms anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased; ¶includes the preferred terms leukopenia and white blood cell count decreased; ‖includes the preferred terms platelet count decreased and thrombocytopenia
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

DESTINY-Breast06

Patient demographics and key baseline characteristics

	HER2-low*		ITT (HER2-low and HER2-ultralow)		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Age, median (range), years	58.0 (28–87)	57.0 (32–83)	58.0 (28–87)	57.0 (32–83)	58.0 (33–85)	57.5 (34–82)
Female, n (%)	359 (100)	353 (99.7)	436 (100)	429 (99.8)	76 (100)	76 (100)
ECOG PS at screening, n (%)†						
0	207 (57.7)	218 (61.6)	252 (57.8)	257 (59.8)	44 (57.9)	39 (51.3)
1	148 (41.2)	128 (36.2)	178 (40.8)	163 (37.9)	30 (39.5)	35 (46.1)
HER2 status, n (%)‡						
IHC 0 with membrane staining (HER2-ultralow)	–	–	76 (17.4)	76 (17.7)	76 (100)	76 (100)
IHC 1+ (HER2-low)	238 (66.3)	234 (66.1)	239 (54.8)	234 (54.4)	–	–
IHC 2+/ISH− (HER2-low)	117 (32.6)	118 (33.3)	117 (26.8)	118 (27.4)	–	–
ER/PR status, n (%)§						
ER+/PR+	206 (57.4)	193 (54.5)	253 (58.0)	237 (55.1)	46 (60.5)	44 (57.9)
ER+/PR−	141 (39.3)	152 (42.9)	167 (38.3)	181 (42.1)	26 (34.2)	29 (38.2)
ER−/PR+	3 (0.8)	2 (0.6)	3 (0.7)	2 (0.5)	–	–
Primary endocrine resistance¶	105 (29.2)	116 (32.8)	128 (29.4)	140 (32.6)	23 (30.3)	24 (31.6)
De-novo disease at diagnosis, n (%)	111 (30.9)	104 (29.4)	133 (30.5)	132 (30.7)	22 (28.9)	28 (36.8)
Bone-only disease at baseline, n (%)	11 (3.1)	10 (2.8)	13 (3.0)	13 (3.0)	2 (2.6)	3 (3.9)
Visceral disease at baseline, n (%)	309 (86.1)	299 (84.5)	376 (86.2)	364 (84.7)	66 (86.8)	65 (85.5)
Liver metastases at baseline, n (%)	243 (67.7)	232 (65.5)	296 (67.9)	283 (65.8)	52 (68.4)	51 (67.1)

*HER2-low status defined at randomization per IRT data, and HER2-ultralow status defined per central laboratory testing data. With mis-stratification, the combined sample size of these two populations may not match the ITT total; †n=14 patients had missing ECOG PS status at baseline; ‡n=2 patients in the ITT (1 per treatment group) were found to have HER2 IHC 0 with absent membrane staining per central laboratory testing; §patients with ER−/PR− status were excluded from the study; however, n=1 patient with ER−/PR− status was randomized in error; ¶defined as relapse while on the first 2 years of adjuvant endocrine therapy, or progressive disease within the first 6 months of first-line endocrine therapy for metastatic breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; PR, progesterone receptor; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

DESTINY-Breast06

Prior therapies

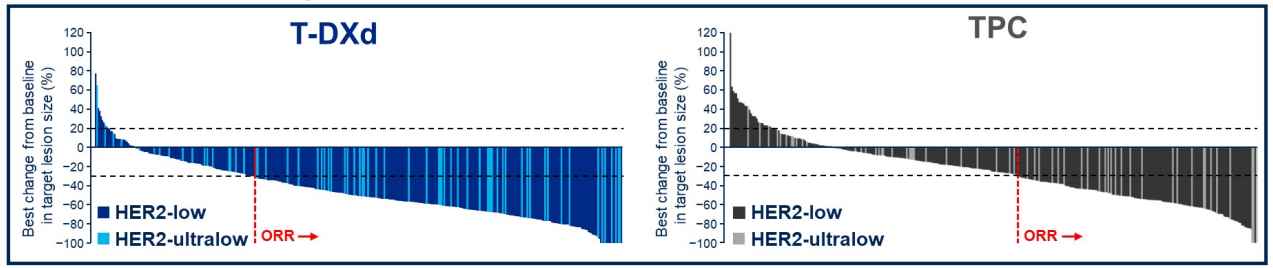
	HER2-low*		ITT (HER2-low and HER2-ultralow)		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
ET in the metastatic setting						
Lines of ET						
Number of lines, median (range)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)
Number of lines, n (%)						
1	54 (15.1)	67 (19.0)	65 (14.9)	82 (19.2)	11 (14.5)	15 (19.7)
≤6 months on first-line ET + CDK4/6i	33 (9.2)	33 (9.4)	37 (8.5)	40 (9.3)	4 (5.3)	7 (9.2)
2	242 (67.6)	236 (67.0)	295 (67.8)	288 (67.3)	52 (68.4)	52 (68.4)
≥3	62 (17.3)	49 (13.9)	75 (17.2)	58 (13.6)	13 (17.1)	9 (11.8)
Prior therapies, n (%)						
ET monotherapy	189 (52.6)	183 (51.7)	230 (52.8)	223 (51.9)	41 (53.9)	40 (52.6)
ET with CDK4/6i	318 (88.6)	316 (89.3)	388 (89.0)	385 (89.5)	69 (90.8)	69 (90.8)
ET with other targeted therapy†	120 (33.4)	105 (29.7)	143 (32.8)	127 (29.5)	22 (28.9)	22 (28.9)
Adjuvant/neoadjuvant setting‡						
Prior therapies, n (%)						
ET	227 (63.2)	218 (61.6)	275 (63.1)	256 (59.5)	48 (63.2)	38 (50.0)
Cytotoxic chemotherapy	192 (53.5)	196 (55.4)	228 (52.3)	234 (54.4)	36 (47.4)	38 (50.0)
Taxane	151 (42.1)	151 (42.7)	179 (41.1)	177 (41.2)	28 (36.8)	26 (34.2)
Anthracycline	167 (46.5)	173 (48.9)	197 (45.2)	206 (47.9)	30 (39.5)	33 (43.4)

*HER2-low status defined at randomization per IRT data, and HER2-ultralow status defined per central laboratory testing data; †other targeted therapies were mTORi (23.8%), PI3Ki (4.2%), or PARPi (0.9%) in the ITT; ‡approximately 30% of the patient population had de-novo metastatic disease and were not included in this category
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mTORi, mammalian target of rapamycin inhibitor; PARPi, poly-adenosine diphosphate ribose polymerase inhibitor; PI3Ki, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha inhibitor; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

DESTINY-Breast06

15

Antitumor activity



	HER2-low*		ITT		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Confirmed ORR, n (%)	**203 (56.5)**	**114 (32.2)**	**250 (57.3)**	**134 (31.2)**	**47 (61.8)**	**20 (26.3)**
Best overall response, n (%)						
Complete response	9 (2.5)	0	13 (3.0)	0	4 (5.3)	0
Partial response	194 (54.0)	114 (32.2)	237 (54.4)	134 (31.2)	43 (56.6)	20 (26.3)
Stable disease	125 (34.8)	170 (48.0)	148 (33.9)	212 (49.3)	22 (28.9)	42 (55.3)
Clinical benefit rate, n (%)†	275 (76.6)	190 (53.7)	334 (76.6)	223 (51.9)	58 (76.3)	33 (43.4)
Median duration of response, mo	14.1	8.6	14.3	8.6	14.3	14.1

ORR based on RECIST v1.1; response required confirmation after 4 weeks
*HER2-low status defined at randomization per IRT data, and HER2-ultralow status defined by central laboratory testing data; †defined as complete response + partial response + stable disease at Week 24, by blinded independent central review
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRT, interactive response technology; ITT, intent-to-treat; mo, months; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

2024 ASCO ANNUAL MEETING #ASCO24

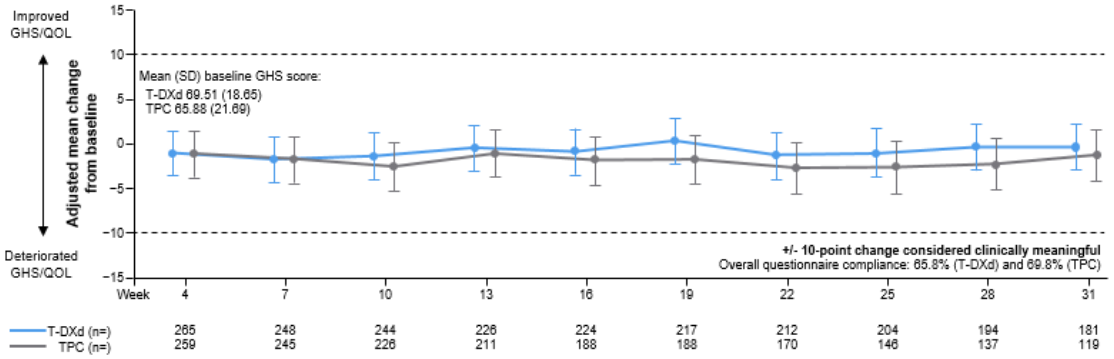
PRESENTED BY: Giuseppe Curigliano, MD, PhD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

DESTINY-Breast06: March 18, 2024 DCO

Overall GHS/QOL was maintained over 31 weeks with T-DXd and TPC in the ITT population; data were consistent in HER2-low

Mean change from baseline in QLQ-C30 GHS/QOL over 31 weeks or until PD (whichever earlier): ITT (HER2-low and HER2-ultralow)

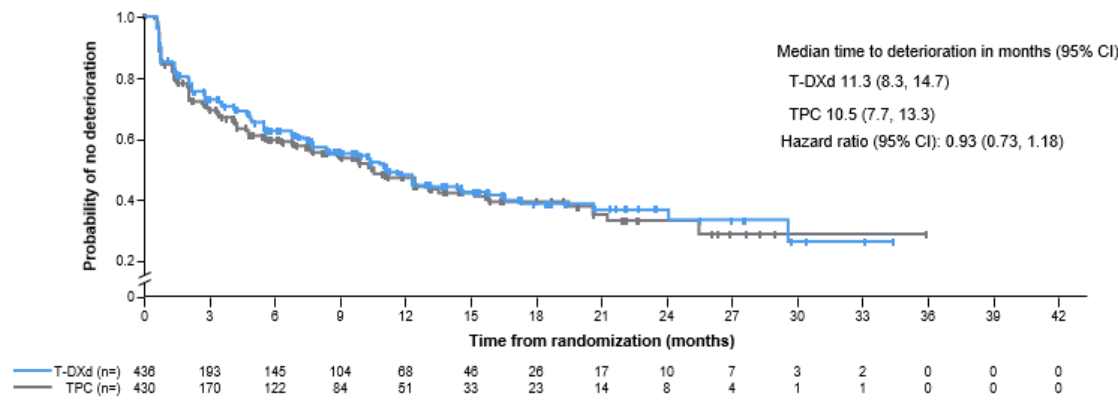


Bars represent 95% confidence intervals. Baseline is defined as the last assessment on or prior to randomization, or before the first dose if assessment only available after randomization. CFB analysis was performed by using an MMRM with treatment, visit, treatment-by-visit interaction, prior CDK4/6i use (yes vs no), HER2 IHC expression ((IHC 0 with membrane staining vs IHC 1+ vs IHC 2+/ISH−), and prior taxane use in the non-metastatic setting (yes vs no) as fixed effects, baseline score as a covariate, and the baseline-by-visit interaction. An unstructured covariance matrix was assumed, and the Kenward-Roger approximation was used to estimate the degrees of freedom
Hu X et al. Presented at: ESMO Annual Meeting, September 13-17, 2024; Barcelona, Spain. Presentation LBA22

DESTINY-Breast06: March 18, 2024 DCO

Time to deterioration in QLQ-C30 GHS/QOL was similar with T-DXd and TPC

Time to deterioration in QLQ-C30 GHS/QOL: ITT population



Vertical tick mark indicates a censored observation
Hu X et al. Presented at: ESMO Annual Meeting, September 13-17, 2024; Barcelona, Spain. Presentation LBA22

DISITAMAB VEDOTIN, A HER2-DIRECTED ANTIBODY-DRUG CONJUGATE, IN PATIENTS WITH ER2-OVEREXPRESSION AND HER2-LOW ADVANCED BREAST CANCER: A PHASE I/IB STUDY

Jiayu Wang[1], Yunjiang Liu[2], Qingyuan Zhang[3], Wei Li[4], Jifeng Feng[5], Xiaojia Wang[6], Jianmin Fang[7], Yiqun Han[1], Binghe Xu[1]

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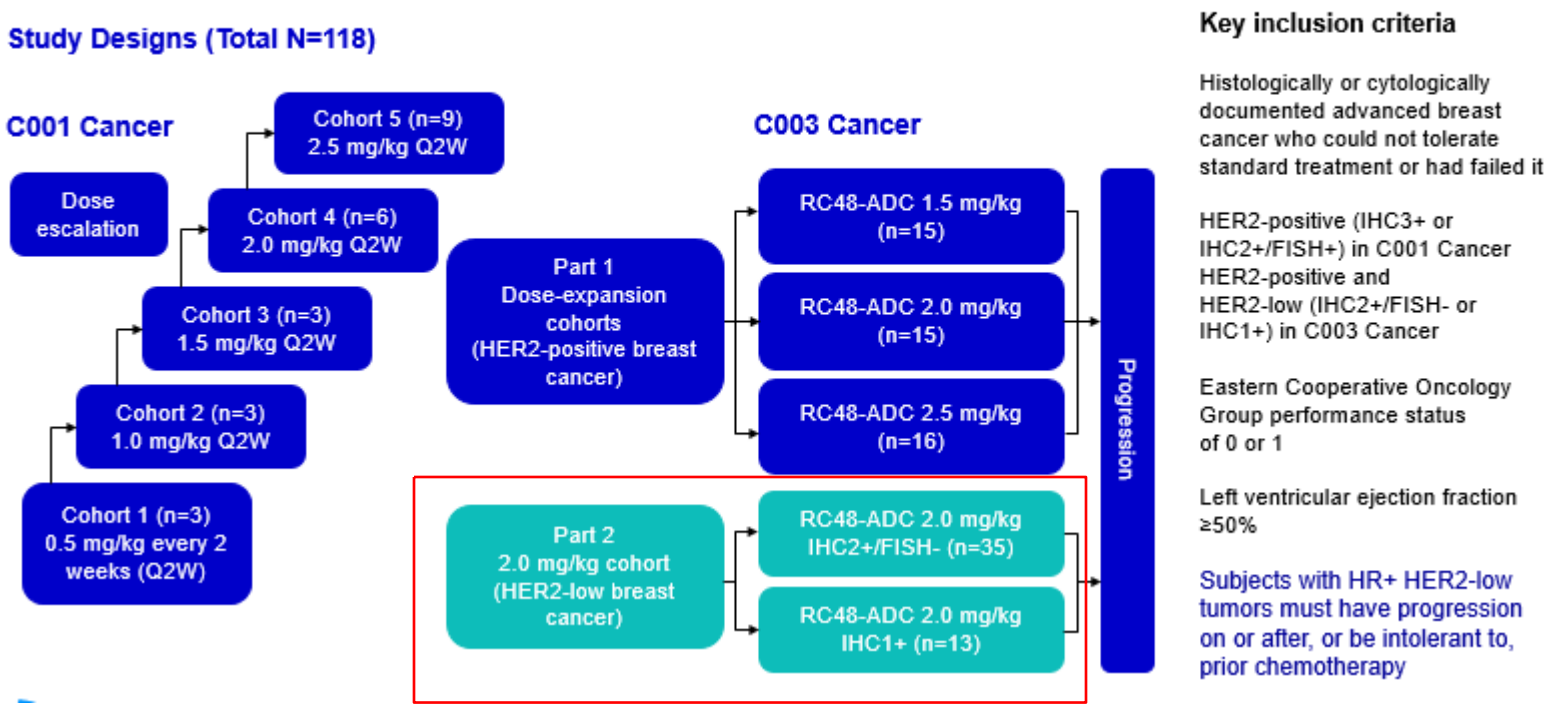
Cancer Commun (Lond). 2024;44:833–851.

DV (RC48) for Breast Cancer: C001 and C003 Cancer Trials



Key inclusion criteria

Histologically or cytologically documented advanced breast cancer who could not tolerate standard treatment or had failed it

HER2-positive (IHC3+ or IHC2+/FISH+) in C001 Cancer
HER2-positive and HER2-low (IHC2+/FISH- or IHC1+) in C003 Cancer

Eastern Cooperative Oncology Group performance status of 0 or 1

Left ventricular ejection fraction ≥50%

Subjects with HR+ HER2-low tumors must have progression on or after, or be intolerant to, prior chemotherapy

Data cutoff: December 31, 2020.
ADC, antibody-drug conjugate; DV, disitamab vedotin; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; Q2W, every 2 weeks.
Wang J, et al. Presented at: American Society of Clinical Oncology; June 4-8, 2021; Virtual. Abstract 1022.

Baseline Characteristics in Patients With HER2-Low Advanced Breast Cancer (IHC2+/FISH–, IHC1+)

	2.0 mg/kg* (n=35)	2.0 mg/kg* (n=31)	Total (n=66)
Median age (range), years	55.0 (29–69)	53.0 (27–69)	54.5 (27–69)
Sex, n (%) Female	35 (100)	31 (100)	66 (100)
Median time from initial diagnosis (range), years	4.00 (0.5–16.0)	6.00 (0.7–25.0)	4.90 (0.5–25.0)
ECOG PS score, n (%)			
0	27 (77.1)	18 (58.1)	45 (68.2)
1	8 (22.9)	13 (41.9)	21 (31.8)
Most common metastasis sites of disease†, n (%)			
Visceral	32 (91.4)	24 (77.4)	56 (84.8)
Liver	25 (71.4)	12 (38.7)	37 (56.1)
Lung	19 (54.3)	11 (35.5)	30 (45.5)
HR status, n (%)			
HR+	33 (94.3)	27 (87.1)	60 (90.9)
HR–	2 (5.7)	4 (12.9)	6 (9.1)
Missing	0	0	0

	2.0 mg/kg* (n=35)	2.0 mg/kg* (n=31)	Total (n=66)
HER2 expression, n (%)			
IHC 1+	0	31 (100)	31 (47.0)
IHC 2+/FISH–	35 (100)	0	35 (53.0)
IHC 2+/FISH+ or IHC 3+	0	0	0
Median number of prior anticancer regimens (range)	2 (0–12)	4 (0–8)	3 (0–12)
Prior systemic anticancer therapy,‡ n (%)			
≥3 systemic chemotherapy	6 (17.1)	8 (25.8)	14 (21.2)
Trastuzumab	2 (5.7)	1 (3.2)	3 (4.5)§
Pertuzumab	0	0	0
HER2-targeted TKI	0	0	0
Endocrine therapy	26 (74.3)	23 (74.2)	49 (74.2)
CDK 4/6 inhibitor	5 (14.3)	9 (29.0)	14 (21.2)
Other systemic therapy	6 (17.1)	12 (38.7)	18 (27.3)

Data cutoff date: October 30, 2021.

*Patients were separated based on IHC status. †Patients with advanced breast cancer may combine multiple site metastases. ‡These patients with advanced breast cancer who had received prior multiple lines therapy; §These patients were diagnosed with HER2-overexpression breast cancer at the time of surgery, received trastuzumab in the adjuvant stage, and had HER2-low breast cancer after recurrence and metastasis.

CDK=cyclin-dependent kinase; FISH=fluorescence in-situ hybridization; HER2=human epidermal growth factor receptor 2; HER2-low=HER2-low expressing; IHC=immunohistochemistry; TKI=tyrosine kinase inhibitor.

Wang J, et al. *Cancer Commun (Lond)*. 2024;44:833–851.

Summary of Response and Anti-Tumor Activity Data in Patients With HER2-Low Advanced Breast Cancer (IHC2+/FISH–, IHC1+)*

Outcomes	IHC 2+/FISH- 2.0 mg/kg (*n* = 35)	IHC1+ 2.0 mg/kg (*n* = 31)	Total (*n* = 66)
Confirmed best overall response, *n* (%)			
CR	0	1 (3.2)	1 (1.5)
PR	15 (42.9)	6 (19.4)	21 (31.8)
SD	17 (48.6)	16 (51.6)	33 (50.0)
PD	3 (8.6)	7 (22.6)	10 (15.2)
NE	0	1 (3.2)	1 (1.5)
Confirmed ORR, *n* (%)	15 (42.9)	7 (22.6)	22 (33.3)
95% CI	26.3%-60.6%	9.6%-41.1%	22.2%-46.0%
Confirmed DCR, *n* (%)	31 (88.6)	23 (74.2)	54 (81.8)
95% CI	73.3%-96.8%	55.4%-88.1%	70.4%-90.2%
Median DOR, months	5.6	7.3	5.6
95% CI, months	4.1-8.6	2.8-9.5	4.3-8.3
Median PFS, months	6.6	4.1	5.1
95% CI, months	4.1-8.3	2.7-5.5	4.1-6.6

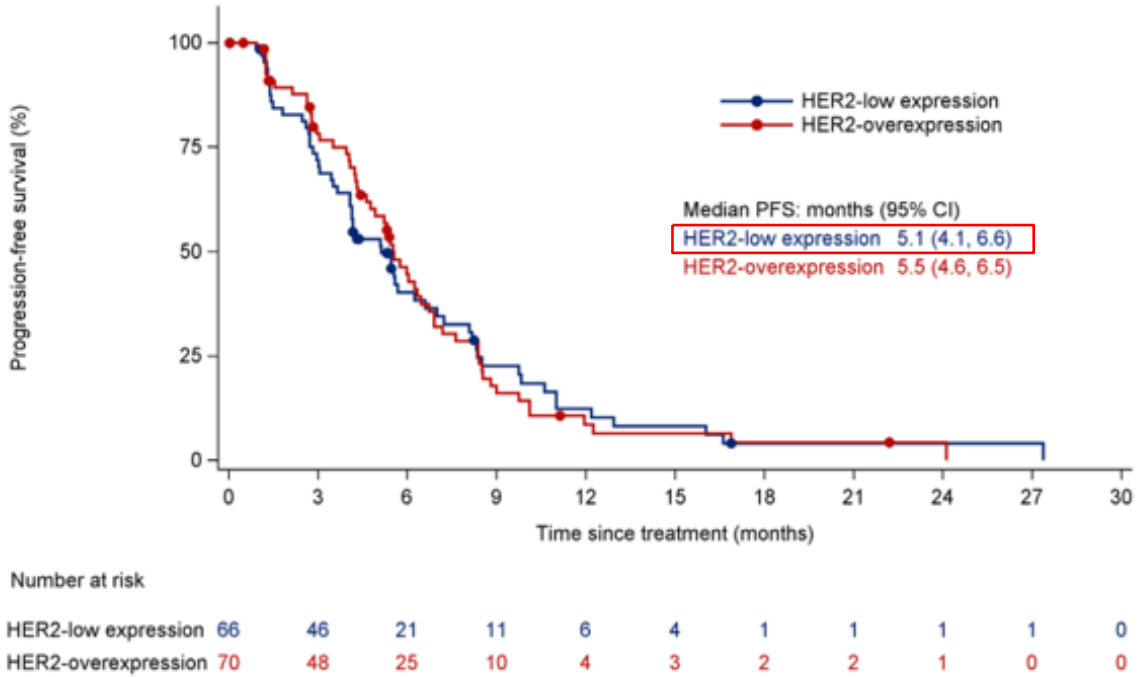
Data cutoff date: October 30, 2021.

*Analysis was performed on the enrolled analysis population that included patients with HER2-low breast cancer who provided informed consent and were enrolled in the dose expansion. All patients received ≥ 1 dose of disitamab vedotin.

CR=complete response; DCR=disease control rate; DOR=duration of response; FISH=fluorescence in-situ hybridization; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; NE=not evaluable; ORR=response rate; PD=progressive disease; PFS=progression-free survival; PR=partial response; SD=stable disease.

Wang J, et al. *Cancer Commun (Lond)*. 2024;44:833–851.

PFS for Patients With HER2+ and HER2-Low Advanced Breast Cancer



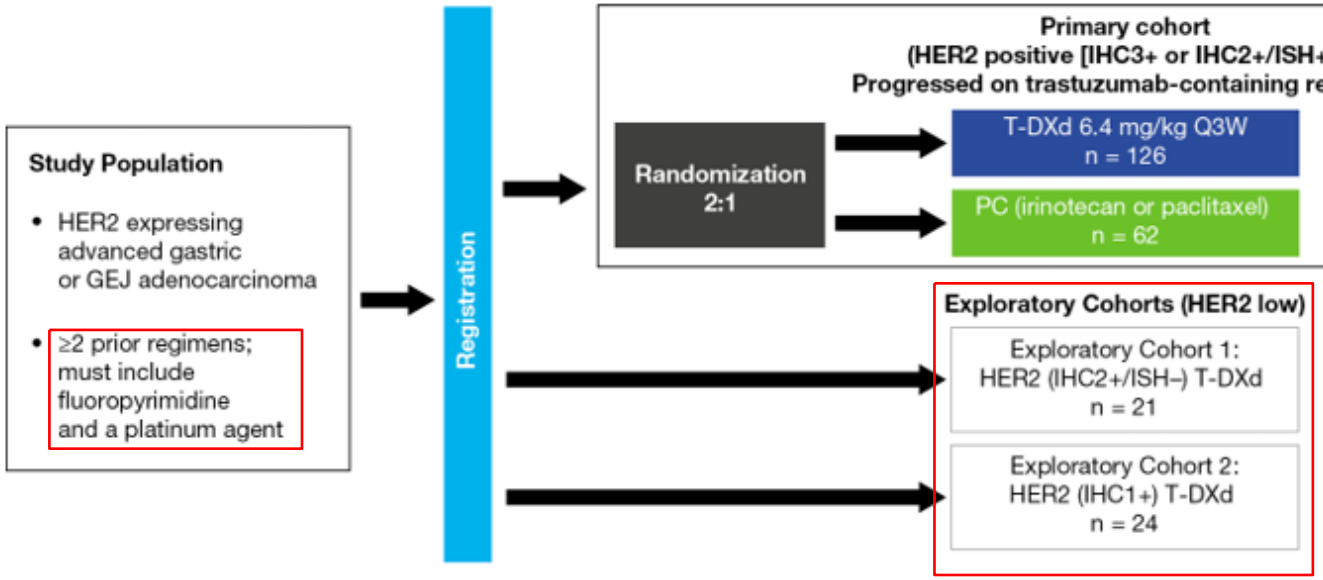
Data cutoff date: October 30, 2021.

CI=confidence interval; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; PFS=progression-free survival.

Wang J, et al. *Cancer Commun (Lond)*. 2024;44:833–851.

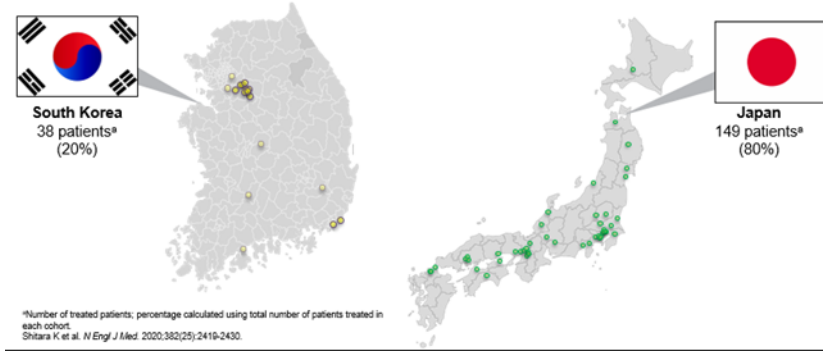
DESTINY-Gastric01: June 3, 2020, DCO

A Phase 2, Open-Label, Randomized, Multicenter Study



Yamaguchi K et al. Presented at: ASCO Virtual Congress 2021; June 4-8, 2021.

Patients were enrolled at 48 different study sites in Japan and 18 in South Korea



DESTINY-Gastric01

Study Objectives

Primary Objective

- Determine the efficacy and safety of T-DXd treatment compared to physician's choice of chemotherapy in patients with HER2 positive (IHC 3+, IHC 2+/ISH+), locally advanced or metastatic gastric or GEJ adenocarcinoma who progressed on ≥2 prior regimens

Exploratory Objectives

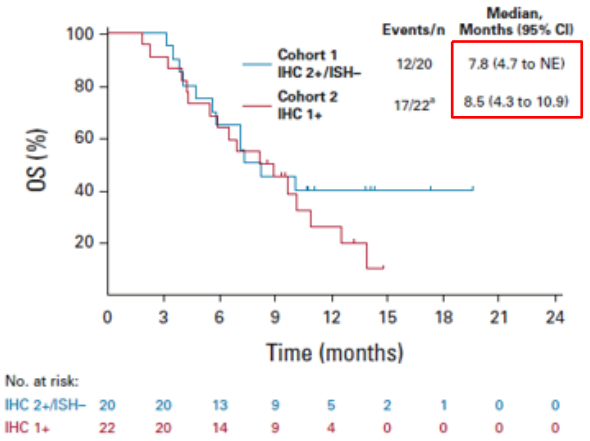
- Determine the efficacy and safety of T-DXd treatment in patients with HER2 IHC 2+/ISH- advanced gastric or GEJ adenocarcinoma
- Determine the efficacy and safety of T-DXd treatment in patients with HER2 IHC 1+ advanced gastric or GEJ adenocarcinoma

Shitara K et al. *N Engl J Med.* 2020;382(25):2419-2430.

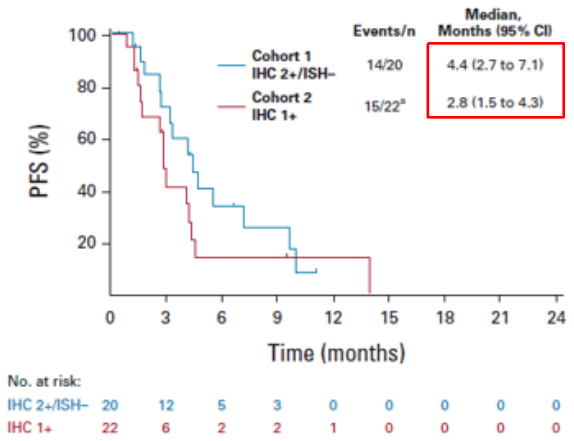
DESTINY-Gastric01 Exploratory Cohorts: November 8, 2019, DCO

Overall Survival and Progression-Free Survival

Overall Survival[b]



Progression-Free Survival[c]



Vertical lines show censored data.
[a]2 patients excluded from analysis due to a missing central laboratory HER2 status.
[b]8 patients (40%) in cohort 1 and 5 patients (23%) in cohort 2 had their data censored.
[c]6 patients (30%) in cohort 1 and 7 patients (32%) in cohort 2 had their data censored
Yamaguchi K et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.00575.

DESTINY-Gastric01 Exploratory Cohorts: November 8, 2019, DCO

Summary of Efficacy

Endpoint	Cohort 1 IHC 2+/ISH− (n = 19)	Cohort 2 IHC 1+ (n = 21)
Confirmed[a] ORR by ICR, n (%) [95% CI][b]	5 (26.3) [9.1-51.2]	2 (9.5) [1.2-30.4]
Confirmed[a] BOR by ICR, n (%) [95% CI][b]		
CR, n (%)	0	0
PR, n (%)	5 (26.3)	2 (9.5)
SD, n (%)	12 (63.2)	13 (61.9)
PD, n (%)	2 (10.5)	6 (28.6)
Confirmed disease control rate by ICR, n (%) [95% CI][b,c]	17 (89.5) [66.9-98.7]	15 (71.4) [47.8-88.7]
Individual DoR per patient, months[d]	9.7	8.1
	6.8	12.5
	8.3	
	2.4	
	4.1	

[a]Confirmed ORR was defined as CR or PR that was confirmed on a follow-up scan performed at least 4 weeks after the initial CR or PR. [b]Assessed in the response evaluable set (cohort 1, n = 19; cohort 2, n = 21 [1 patient in each cohort was excluded because they had no baseline measurable tumors and 2 patients were excluded from cohort 2 because they did not have a HER2 status central laboratory result for efficacy analyses]). 95% CIs are the exact binomial confidence interval. [c]DCR was defined as proportion of patients who had confirmed CR, PR, or SD as confirmed BOR. [d]Assessed individually in patients who had confirmed CR or PR (cohort 1, n = 5; cohort 2, n = 2).
Yamaguchi K et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.00575.

DESTINY-Gastric01 Exploratory Cohorts: November 8, 2019, DCO

Conclusions of T-DXd Treatment in Advanced HER2-Low Expressing Gastric/GEJ Cancer

- **T-DXd demonstrated antitumor activity in patients with HER2-low gastric or GEJ adenocarcinoma[1,2]**
  - Exploratory cohort 1 (IHC 2+/ISH−): confirmed ORR, 26.3%; median OS, 7.8 months; median PFS, 4.4 months
  - Exploratory cohort 2 (IHC 1+): confirmed ORR, 9.5%; median OS, 8.5 months; median PFS, 2.8 months
- **These findings provide preliminary evidence that T-DXd has clinical activity in patients with heavily pretreated, HER2-low (IHC 2+/ISH−, IHC 1+), gastric or GEJ adenocarcinoma**

¿QUÉ NOS APORTARÁ EL FUTURO?

DESTINY-Breast15 (DS8201-0001-CIS-MA)

Study of Trastuzumab Deruxtecan in Patients Who Have Hormone Receptor-negative or Hormone Receptor-positive HER2-low or HER2 IHC 0 Unresectable/Metastatic Breast Cancer

A Phase 3b, Multicenter, Global, Interventional, Open-label Study of Trastuzumab Deruxtecan in Patients Who Have Unresectable and/or Metastatic HER2-low or HER2 IHC 0 Breast Cancer (North America, Asia, Europe, South America, Australia)

Study Design

- Unresectable or metastatic BC
- HR+ or HR-
- HER2 IHC 0 or HER2-low (IHC 1+ or IHC 2+/ISH-)
- Never previously HER2+ (IHC 3+ or IHC 2+/ISH+)
- Up to 2 prior lines in metastatic setting (N ≈ 250)

Allocation

- **Cohort 1**
  - HR-/HER2-low mBC (n ≈ 100)
- **Cohort 2**
  - HR-/HER2 IHC 0 mBC (n ≈ 50)
- **Cohort 3**
  - HR+/HER2-low mBC (n ≈ 50)
- **Cohort 4**
  - HR+/HER2 IHC 0 mBC (n ≈ 50)

T-DXd 5.4 mg/kg q3w

Primary Endpoint

- Time to next treatment (TTNT)

Key Secondary Endpoints

- Real-world progression-free survival (rwPFS)

Secondary Endpoints

- Time to treatment discontinuation (TTD)
- Objective response rate (ORR)
- QoL/PROs
- Safety/Tolerability

1. Modi S, et al. Presented at: SABCS 2023 Meeting. December 5-9. Poster PO2-19-06

ClinicalTrials.gov Identifier: NCT05950945

Key Inclusion Criteria

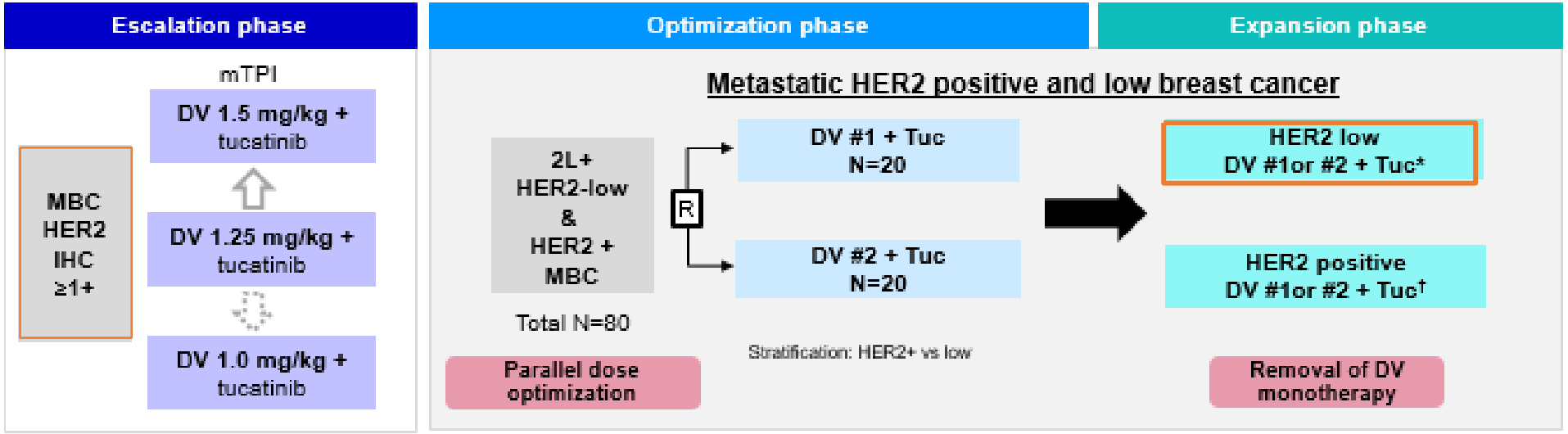
- Patients with HR+ HER2-low mBC (Cohort 3) must have either had recurrent disease within 2 years of initiation of adjuvant ET, disease progression on CDK4/6i-based regimen within 12 months of completion of CDK4/6i therapy, or disease progression within 12 months of CDK4/6i therapy in the metastatic setting
- Participants with brain metastases are allowed in the study. The brain lesion(s) should be small (<2 cm), untreated, asymptomatic, not requiring urgent medical intervention, and are asymptomatic and clinically stable

Key Exclusion Criteria

- Prior treatment with an ADC

SGNDV-004 Study Design (Breast Cancer Cohort; November 2024)

The study is for signal seeking to generate preliminary safety and efficacy data for the combination of DV and tucatinib



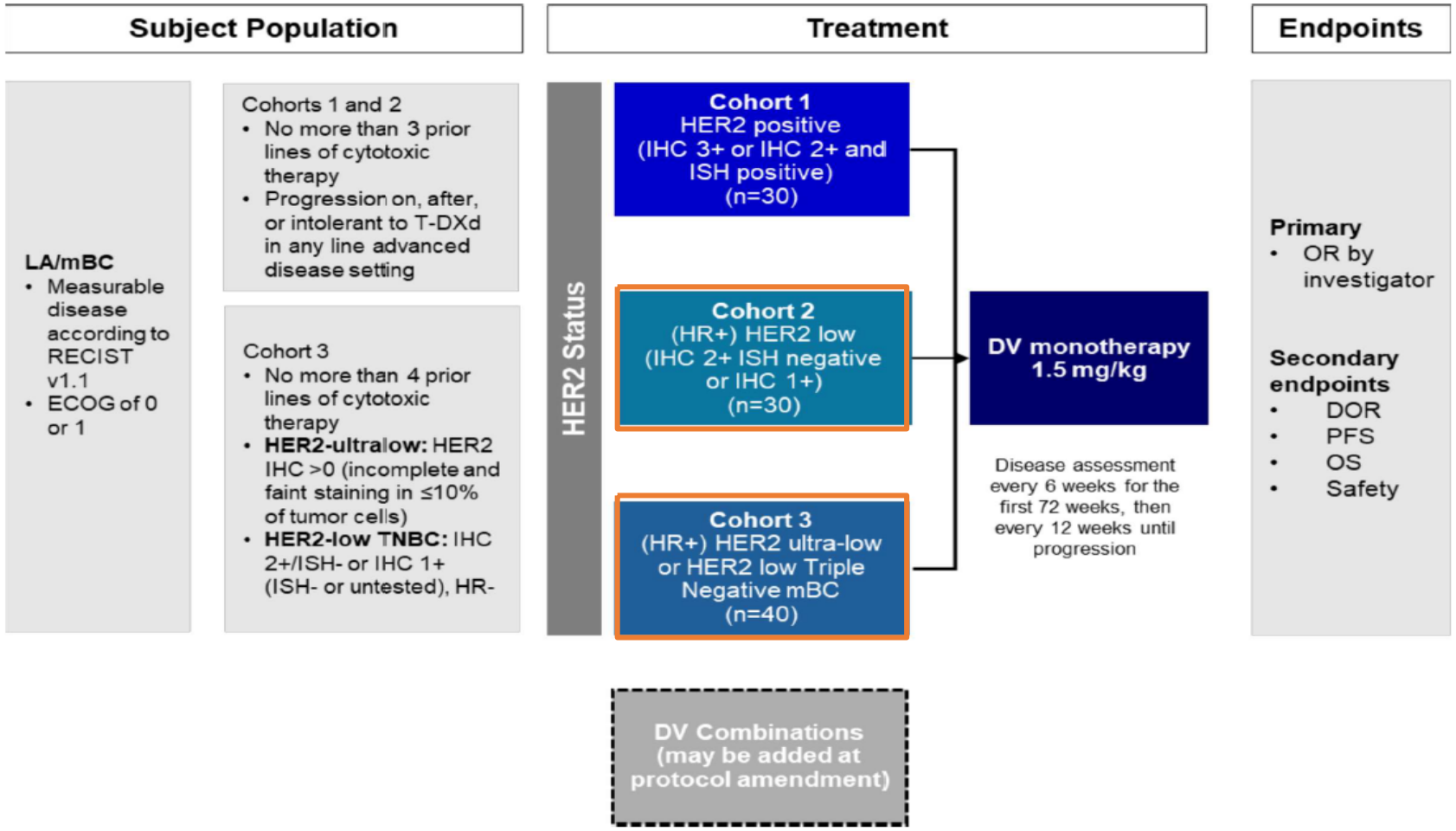
NCT06157892 https://clinicaltrials.gov/study/NCT06157892 ultimo acceso enero 2026

*HER2 low enrollment stops when 30 pts in each arm Opti+ Exp; †HER2 + enrollment stops when 30 pts in each arm Opti+ Exp.

2L=second-line; DV=disitamab vedotin; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; MBC=metastatic breast cancer; mTPI=modified toxicity probability internal; Opti+ Exp=optimization + expansion; Tuc=tucatinib.

A PHASE 1B/2, OPEN-LABEL, MULTICOHORT STUDY OF DISITAMAB VEDOTIN IN ADULTS WITH HER2 EXPRESSING ADVANCED BREAST CANCER

NCT06966453 último acceso enero 2026



Not yet recruiting

ERADICATE: A Phase Ib/II Study of Elacestrant Plus Trastuzumab Deruxtecan in Patients With CDK4/6 Inhibitor and Endocrine-resistant HR+/HER2-low or HER2-ultralow Metastatic Breast Cancer (ERADICATE)

ClinicalTrials.gov ID NCT07198724

Sponsor Sarah Sammons, MD

Information provided by Sarah Sammons, MD, Dana-Farber Cancer Institute (Responsible Party)

Last Update Posted 2025-11-05

Recruiting

PROVIDENCE - Prospective Non-interventional Study (NIS) to Examine Patient-reported Outcomes and Real-world Clinical Data in Patients With HER2-positive, HER2-low or HER2-ultralow Unresectable or Metastatic Breast Cancer Treated With Trastuzumab Deruxtecan (PROVIDENCE)

ClinicalTrials.gov ID NCT05573893

Sponsor AstraZeneca

Information provided by AstraZeneca (Responsible Party)

Last Update Posted 2025-12-26

Recruiting

Safety and Efficacy of T-DXd vs. CDK4/6i-based ET as First-line Therapy of HR-positive and HER2-low/Ultralow Advanced Breast Cancer Patients Classified as Non-luminal Subtype (PONTIAC)

ClinicalTrials.gov ID NCT06486883

Sponsor MedSIR

Information provided by MedSIR (Responsible Party)

Last Update Posted 2025-11-28

Recruiting

A Study of DB-1303/BNT323 vs Investigator's Choice Chemotherapy in HER2-Low, Hormone Receptor Positive Metastatic Breast Cancer (DYNASTY-Breast02)

ClinicalTrials.gov ID NCT06018337

Sponsor DualityBio Inc.

Information provided by DualityBio Inc. (Responsible Party)

Last Update Posted 2025-07-18

DESTINY-Gastric03 Fase 1

Ph1b/2 Study of the Safety and Efficacy of T-DXd Combinations in Advanced HER2+ Gastric Cancer

D967LC00001 | DESTINY-Gastric03 | NCT04379596 | 2023-504888-16-00

CONCLUSIONES

- La aparición del concepto HER2-low y mas recientemente de HER2-ultralow nos abre nuevos horizontes de tratamiento siendo aun más imprescindible un diagnóstico certero.
- Los ADC poseen la precisión del antígeno y la potencia de la QT en una sola molécula.
- TDM1 es un ADC de 1ª generación, con grandes resultados pero también con ciertas limitaciones, que nos han impulsado a trabajar para mejorarlas.
- T-DXd forma parte de los ADC de nueva generación con sólidos resultados gracias a su mecanismo de acción optimizado.
- Hay nuevas moléculas prometedoras en estudio (disitamab vedotin, trastuzumab duocarmacina…) no solo en cáncer de mama sino también en otros tumores.
- Se abre un futuro prometedor con nuevas dianas terapéuticas y resultados esperanzadores.

GRACIAS!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025