

foro debate oncología

Zaragoza 26-29 septiembre 2023



Desarrollo diferentes fármacos disponibles: *Trastuzumab – Deruxtecan*

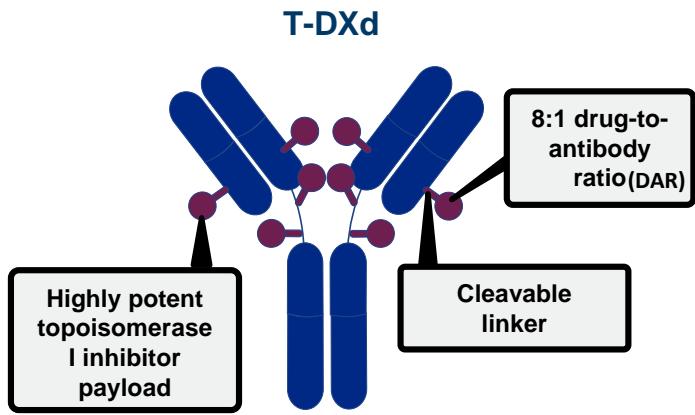
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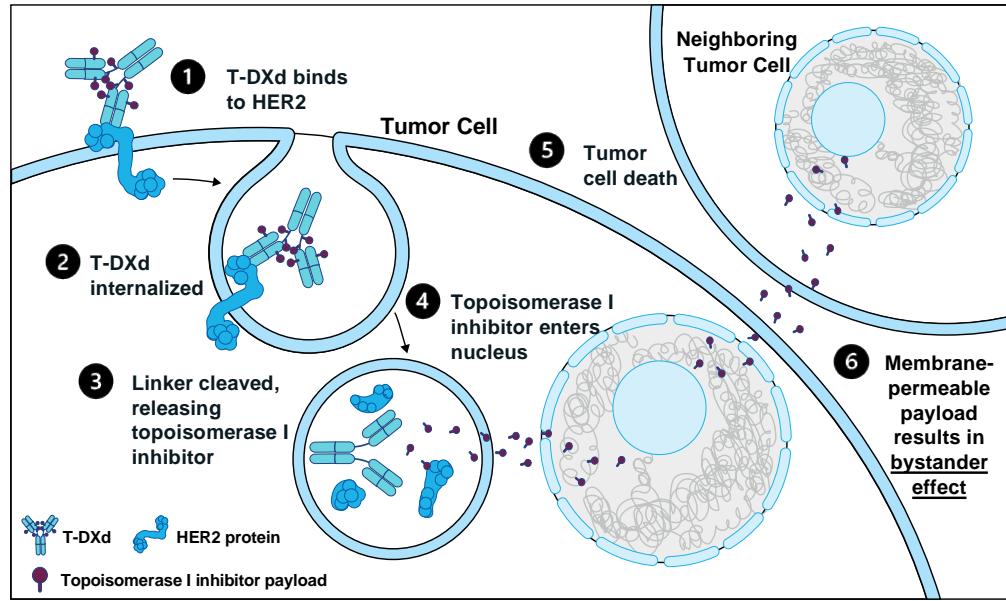
Disclosures

- Honoraria for educational materials by Novartis, Gilead and Daiichi-Sankyo
- Travel expenses by Novartis and Gilead
- Recipient of a 2022 Rio Hortega contract by the Instituto de Salud Carlos III

Trastuzumab-deruxtecan (T-DXd): structure and mechanism of action



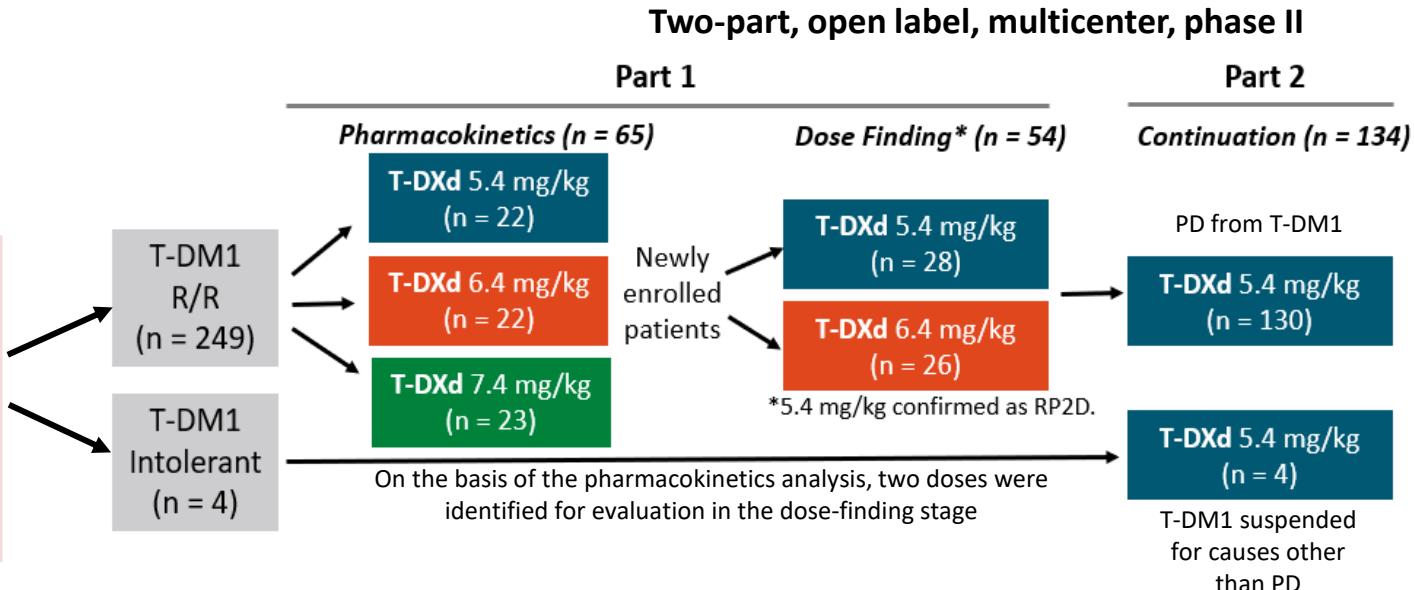
Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect



Adapted with permission from Modi S et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

T-DXd after T-DM1: DESTINY-Breast01 and the start of a revolution

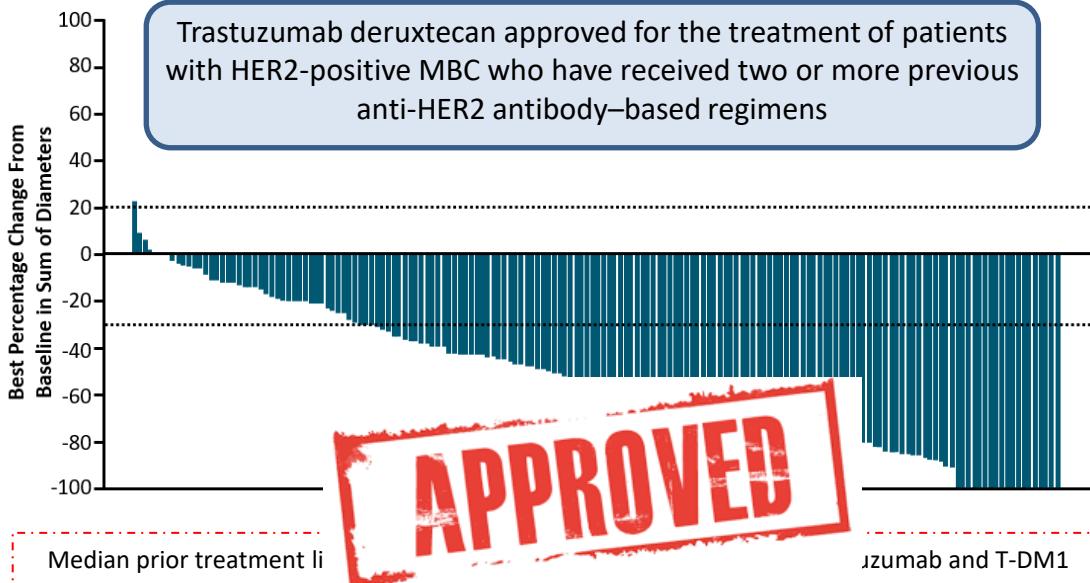
HER2+ ABC
Prior T-DM1
ECOG PS 0-1
Brain metastases allowed (MRI)
Significant ILD excluded



- Primary endpoint: **ORR**
- Secondary endpoints: investigator-assessed ORR, DCR, DoR, CBR, PFS, OS, PK, safety

Total enrolled at 5.4 mg/kg: n = 184

T-DXd showed impressive outcomes in pretreated HER2+ MBC

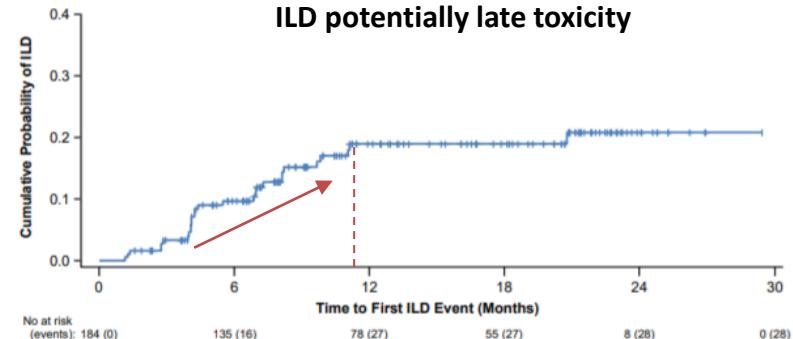
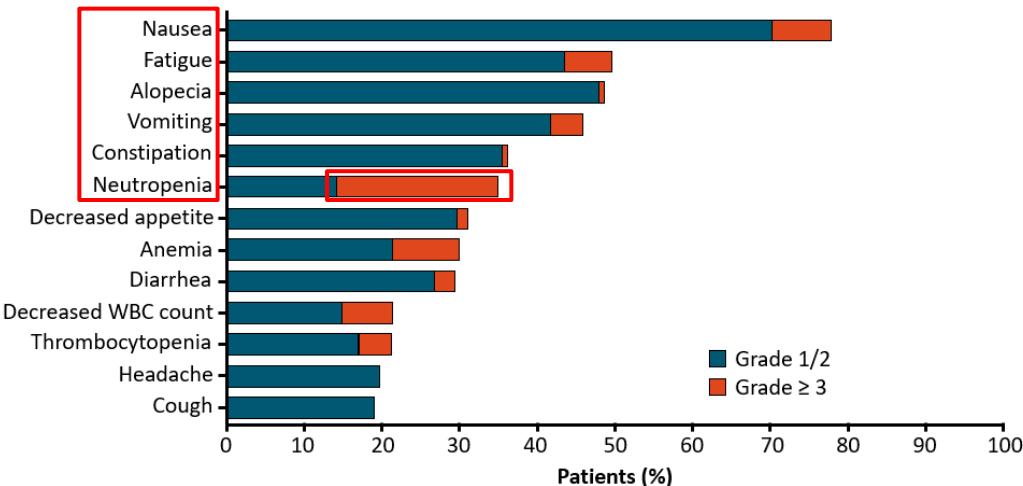


Confirmed in the BESTINY-Breast02 phase III RCT of T-DXd vs. TPC after T-DM1:

- mPFS: 17.8 months vs. 6.9 months
- mOS: 39.2 months vs 26.5 months

Response (ITT)	T-DXd 5.4 mg/kg (N = 184)
ORR (by ICR; n = 112), % (95% CI)	61.4 (54.0-68.5)
▪ CR (n = 11)	6.5
▪ PR (n = 101)	54.9
▪ SD (n = 67)	35.9
▪ PD (n = 3)	1.6
▪ NE (n = 2)	1.1
DCR, % (95% CI)	97.3 (93.8-99.1)
6-mo CBR, % (95% CI)	76.1 (69.3-82.1)
Median DoR, mos (95% CI)	20.8 (15.0 - NR)
Median time to response, mos (95% CI)	1.6 (1.4-2.6)
mPFS: 19.4m (95%CI: 14.1 - NE)	
mOS: 24.6m (95%CI: 23.1 - NE)	

Safety profile of T-DXd



ILD: interstitial lung disease

- Nausea/vomiting well manageable with standard premedication for **high hematogenic regimens**

AE, n (%)	T-DXd 5.4 mg/kg (N = 184)					Any Grade
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
ILD	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	28 (15.2)

ILD rates reduced to ~10% or less (any G) thanks to better detection (TAC)/management (corticosteroids) of asymptomatic cases

T-DXd in second line: Destiny-Breast03

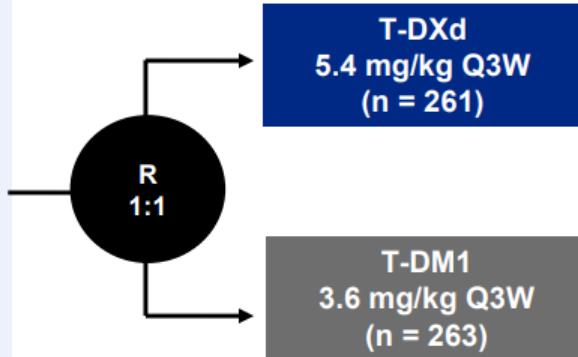
An open-label, multicenter study (NCT03529110)

Patients

- Unresectable or metastatic HER2-positive^a breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting^b
- Could have clinically stable, treated brain metastases

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Interim analysis for PFS (data cutoff: May 21, 2021)

- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

Primary endpoint

- PFS (BICR)

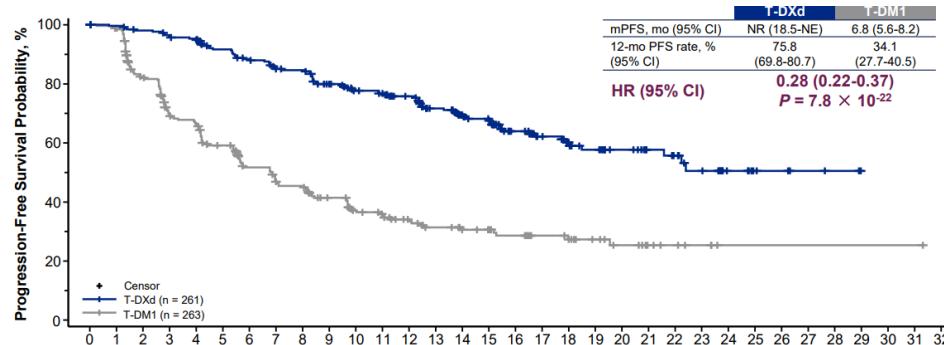
Key secondary endpoint

- OS

Secondary endpoints

- ORR (BICR and investigator)
- DOOR (BICR)
- PFS (investigator)
- Safety

DESTINY-Breast03: primary objective PFS by BICR

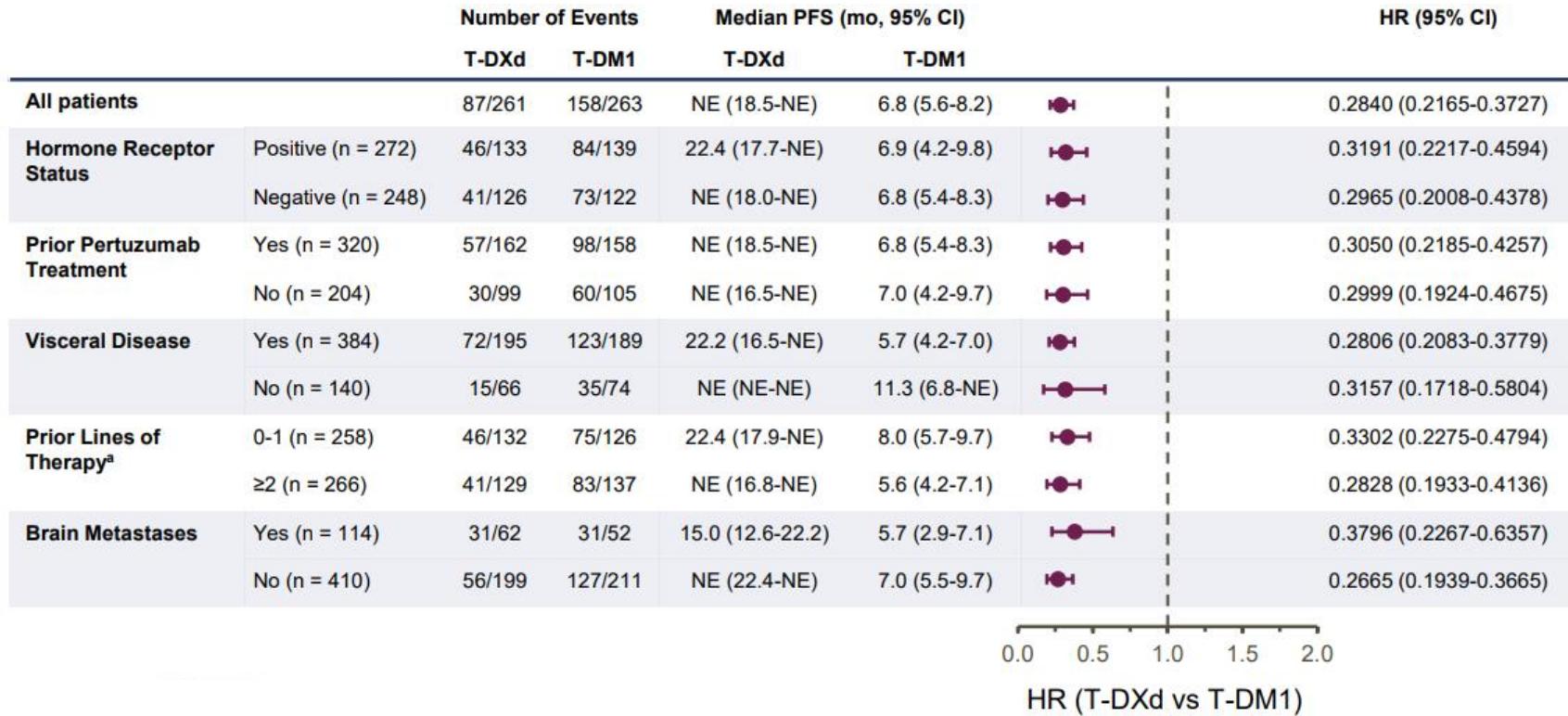


New standard
2nd line in
HER2+ MBC

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

^aP = .007172, but does not cross pre-specified boundary of P < .000265

Results in key subgroups



^aRapid progressors on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.

Targeting HER2-negative breast cancer with anti-HER2 agents: the beginnings

Drug	NCT	Ref	Phase	Overall BC pts (HER2-low pts)	Setting	Treatments	Main results
mAbs Trastuzumab	NCT01275677	Fehrenbacher L. et al. [22] III		3,270 (3,270)	Early, adjuvant	Adjuvant CT with or without trastuzumab	5y DFS: 89.8% versus 89.2% HR 0.98; $p = 0.85$
Pertuzumab	NCT02491892	Gianni L. et al. [23]	II	78 (74)	Advanced	Pertuzumab monotherapy	ORR: PR 2.5% (2 pts)



Standard anti-HER2 agents
not effective in EBC and MBC



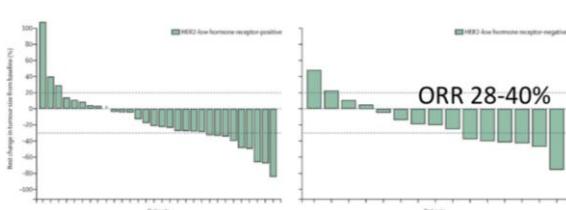
ASCO 2018, the congress that changed it all

BREAST CANCER—METASTATIC

A phase I expansion cohorts study of SYD985 in heavily pretreated patients with HER2-positive or HER2-low metastatic breast cancer.

Check for updates

Cristina Saura, Fiona Thistlethwaite, Udal Banerji, Simon Lord, Victor Moreno, Jain MacPherson ...

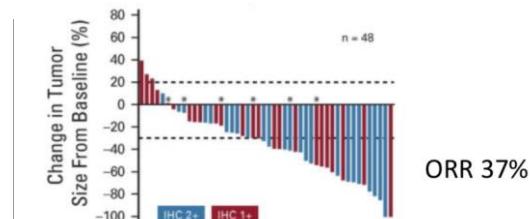


DEVELOPMENTAL THERAPEUTICS—CLINICAL PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

Trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing solid tumors: Long-term results of a large phase 1 study with multiple expansion cohorts.

Check for updates

Hiroji Iwata, Kenji Tamura, Toshihiko Doi, Junji Tsurutani, Sharu Modi, Haeseong Park, ...

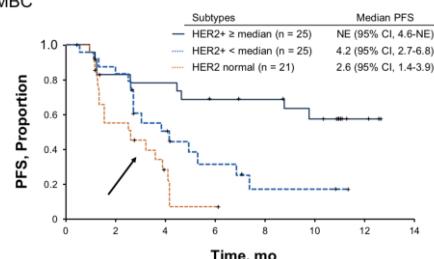


Trastuzumab-Duocarmazine

Trastuzumab-Deruxtecan

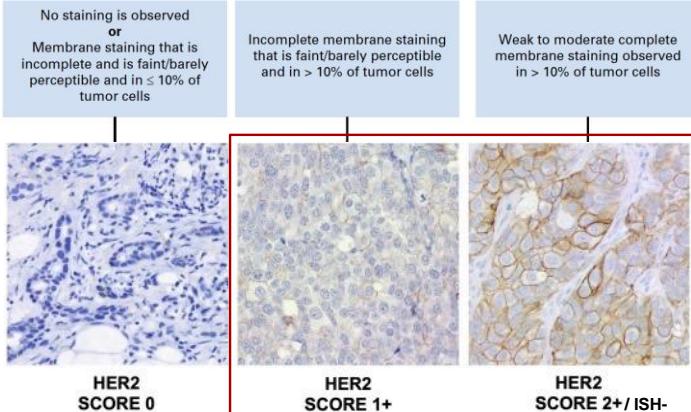
- Retrospective evaluation of T-DM1 in 21 cases of HER2-nonamplified MBC
- Only 1 response (ORR 4.8%) and mPFS 2.6 months

Little activity of T-DM1
in HER2-negative MBC

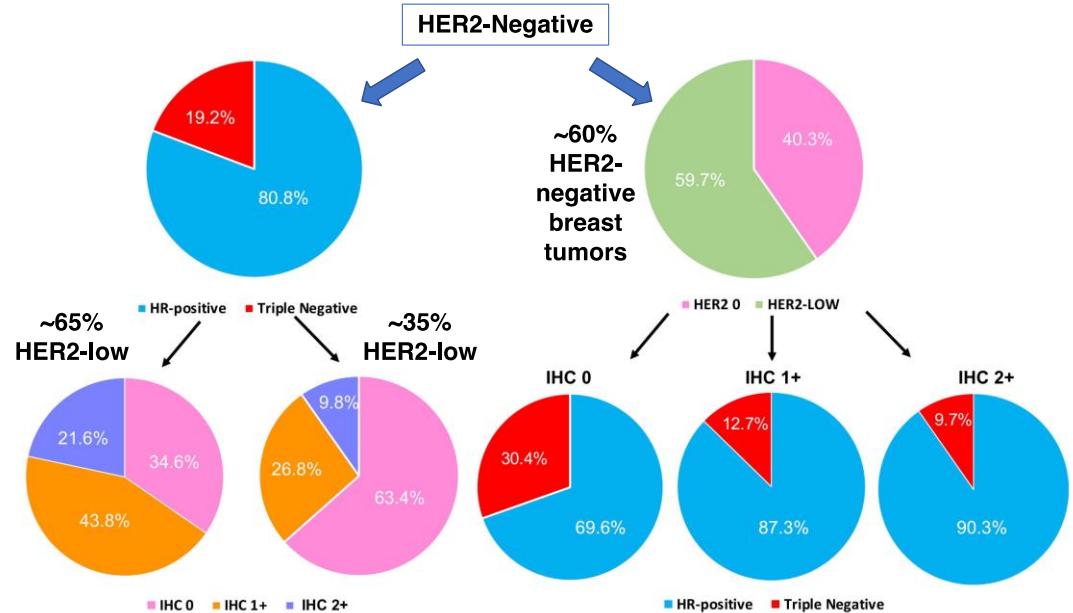


Novel potent anti-HER2 ADCs showed activity!

HER2-low: a novel therapeutic target for ADCs



About 50% of breast cancers are HER2-low according to the current definition



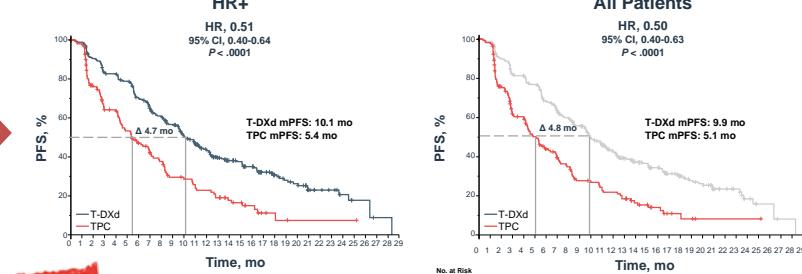
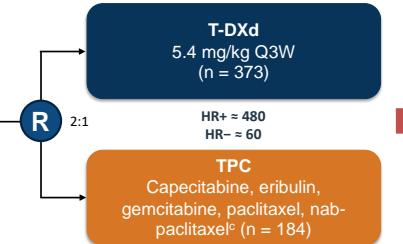
Adapted from Schettini F et al. Npj Breast Cancer 2021

DESTINY-Breast04: a paradigm shift

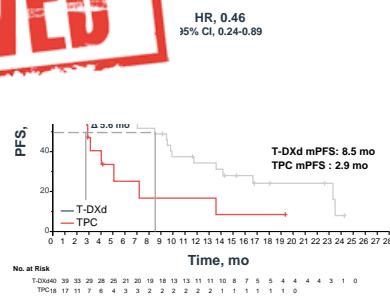
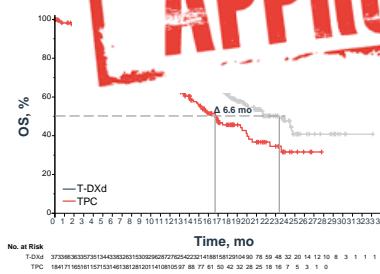
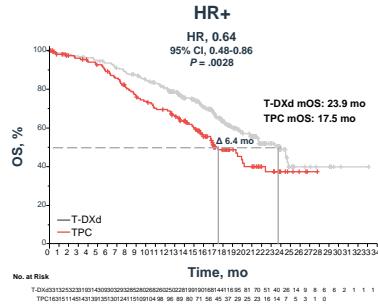
An open-label, multicenter phase III study (NCT03734029)

- 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^a

- Stratification**
- 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 CDK4/6 inhibitor) vs HR-

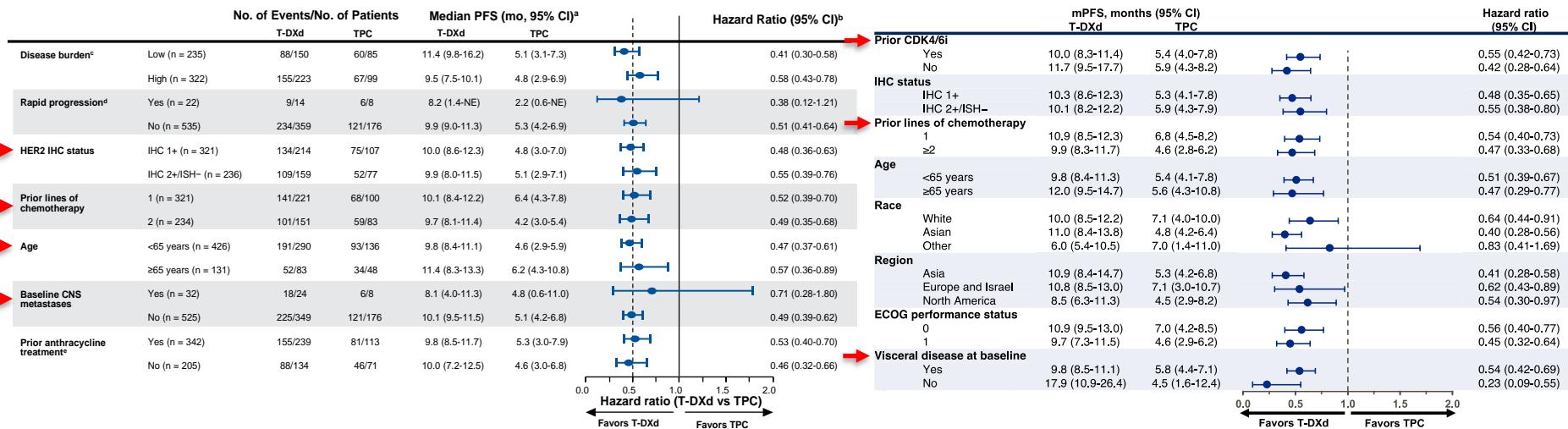


Key secondary endpoints



At least 1 prior line of CT in stage IV or as I line if PD<6 months or during (neo)adjuvant CT

Consistent benefit according to main subgroups

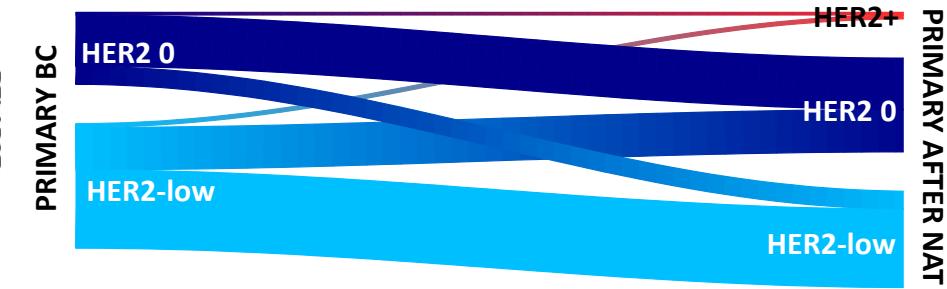
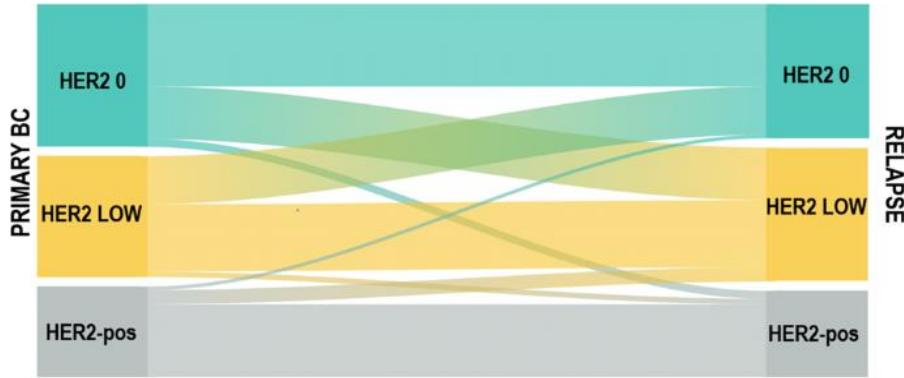


Overall

HR+

HER2-low status heterogeneity

- HER2 status can be **heterogeneous** within lesions and between lesions
- Multiple studies have confirmed the **instability of HER2-low expression** during the natural course of the disease



Adapted from Schettini F et al. ESMO Breast 2023

- Analytical factors (pathology method, inter-pathologist disagreement)

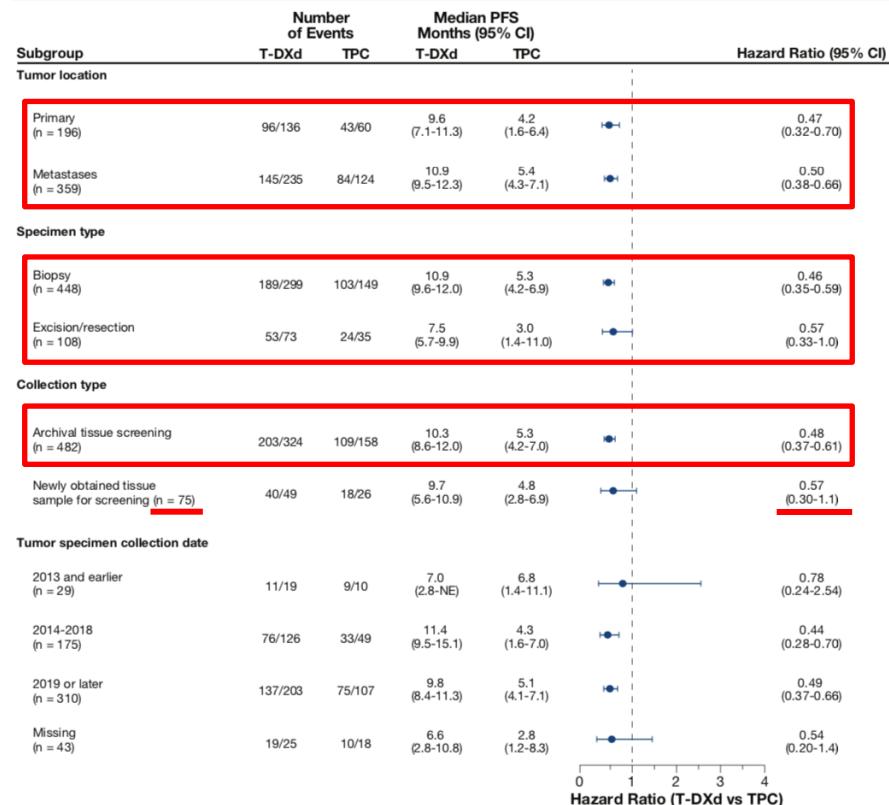
HER2-low status heterogeneity over time and T-DXd efficacy

Table 1. Tumor Sample Characteristics

Characteristics, n (%)	Not Enrolled Patients (n = 783)	Enrolled Patients (n = 557)	Total Screened Patients (N = 1340)
Region			
North America	232 (29.6)	93 (16.7)	325 (24.3)
Europe	323 (41.3)	231 (41.5)	554 (41.3)
Asia, excluding China	169 (21.6)	171 (30.7)	340 (25.4)
China	59 (7.5)	62 (11.1)	121 (9.0)
Tumor location			
Primary	349 (44.6)	196 (35.2)	545 (40.7)
Metastases	432 (55.2)	359 (64.5)	791 (59.0)
Missing	2 (0.3)	2 (0.4)	4 (0.3)
Specimen type			
Biopsy	547 (69.9)	448 (80.4)	995 (74.3)
Excision/resection	236 (30.1)	108 (19.4)	344 (25.7)
Other	0	1 (0.2)	1 (0.1)
Collection type			
Archival tissue	701 (89.5)	482 (86.5)	1183 (88.3)
Newly obtained tissue	82 (10.5)	75 (13.5)	157 (11.7)
Tumor specimen collection date			
2013 or earlier	82 (10.5)	29 (5.2)	111 (8.3)
2014-2018	308 (39.3)	175 (31.4)	483 (36.0)
2019 or later	369 (47.1)	310 (55.7)	679 (50.7)
Missing	24 (3.1)	43 (7.7)	67 (5.0)
Historical HER2 test type^a			
VENTANA PATHWAY 4B5	154 (19.7)	106 (19.0)	260 (19.4)
HERCEPTEST	72 (9.2)	59 (10.6)	131 (9.8)
Others (pooled, including CB11 and SP3)	13 (1.7)	6 (1.1)	19 (1.4)
Not available	544 (69.5)	386 (69.3)	930 (69.4)

^aThe local test type was extracted from pathology reports when available; however, this information was missing for a significant proportion of the reports (n = 930).

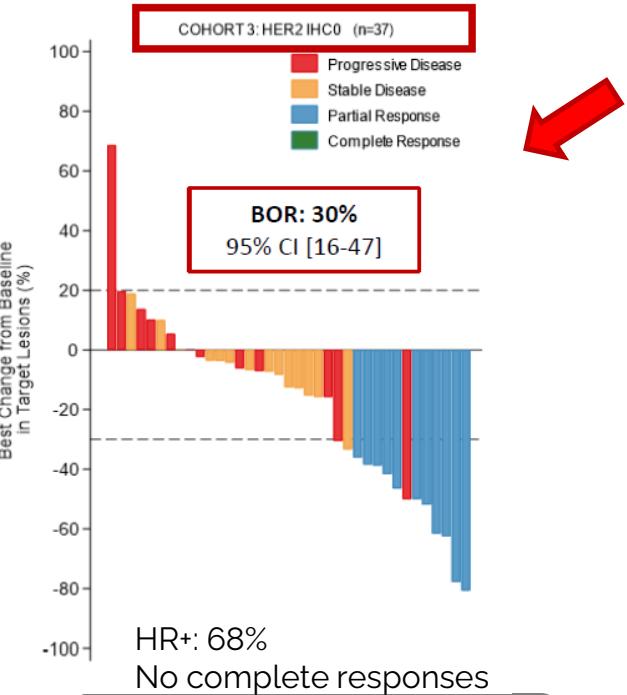
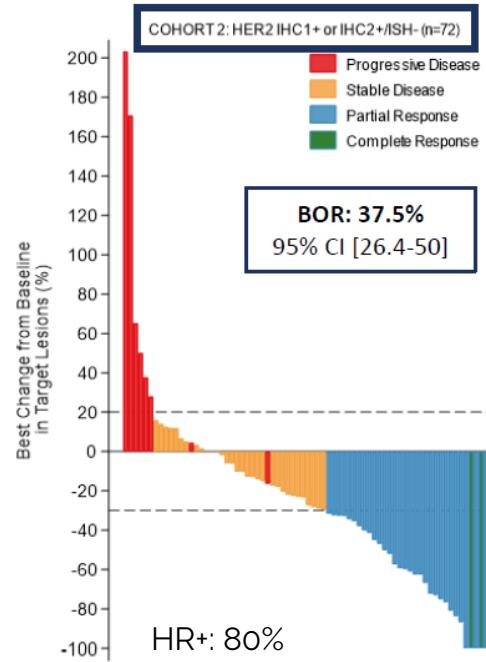
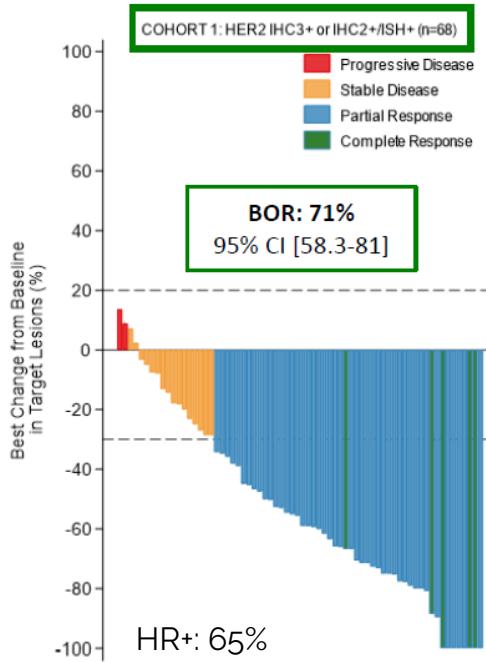
Figure 2. Median PFS by Tumor Sample Characteristics Among Patients Enrolled in DESTINY-Breast04



Effective irrespective of biopsy timing, specimen type and tumor location

T-DXd activity from HER2+ to HER2 0: the DAISY phase II trial

T-DXd for advanced breast cancer patients (ABC), regardless HER2 status

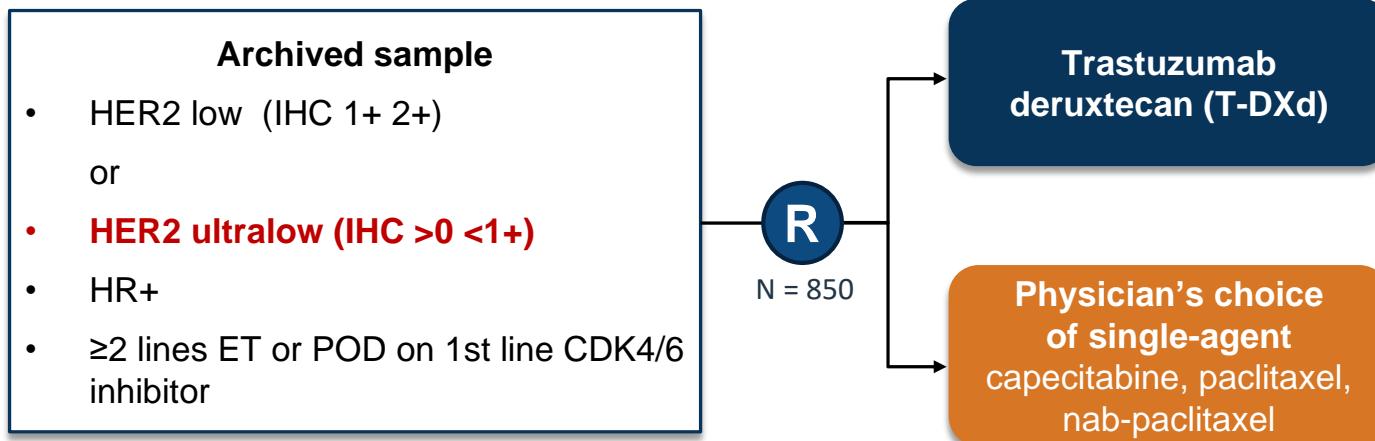


HER2 0 category also includes tumors with membrane staining that is faint/barely perceptible and in ≤10% of tumor cells → “Ultralow” tumors?

mDOR: 6.8 mo (95% CI, 2.8-NR)
mPFS: 4.2 mo (95% CI, 2.0-5.7)

From DAISY to DESTINY-Breast06: targeting HER2-ultralow MBC

DESTINY-Breast06

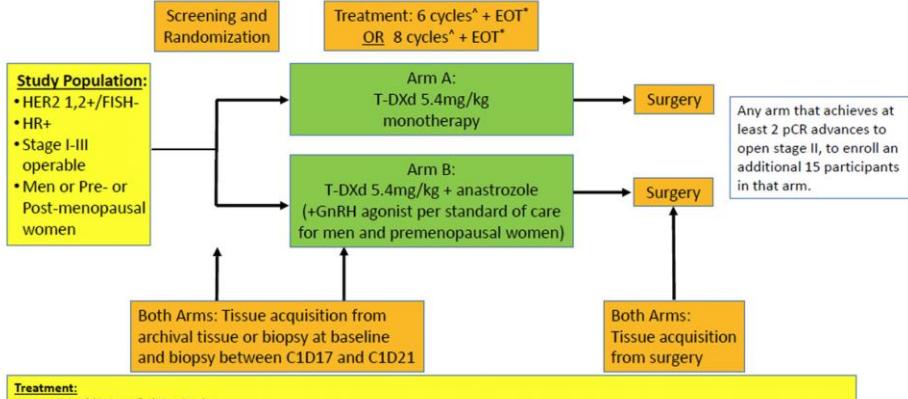


Main differences with DB04:

- Includes ultralow tumors
- CT-naïve patients
- Restricted to HR+ MBC

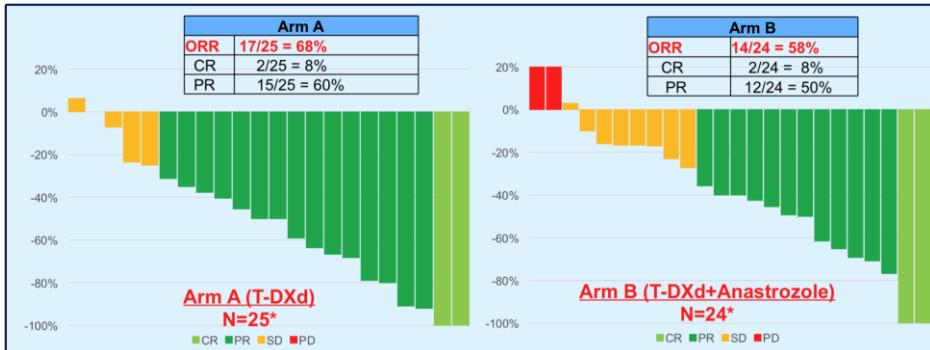
Neoadjuvant T-DXd in HR+/HER2-low: first evidence

TRIO-US B-12 TALENT



Treatment:
 Arm A: T-DXd (5.4 mg/kg) IV q21 days
 Arm B: T-DXd (5.4 mg/kg) IV q21 days + anastrozole 1 mg po QD q21 days (+ GnRH agonist (goserelin, leuprolide, or triptorelin) per standard of care for men and premenopausal women.)
^a Participants enrolled prior to protocol version 4.2 will receive six cycles of one of the following regimens prior to surgery. Those participants who have not yet had surgery at the time of protocol version 4.2 release will have the option to receive eight cycles, instead of six cycles, of the regimen to which they were randomized. Participants enrolling into protocol version 4.2 will receive eight cycles of one of the following regimens prior to surgery.
^{*}EOT 21-28 days after last dose of T-DXd

Activity outcomes



- RCB 0/I rate: 15% both arms
- Surgical outcomes still pending for 24% and 31% in arm A and B
- Addition of ET seems not beneficial

T-DXd development pipeline in breast cancer

Disease	Study	2017-2019	2020	2021	2022	2023	2024	2025
Early Breast Cancer	DS8201-A-U305 NCT04622319	Adjuvant post-neoadjuvant	Phase 3 DESTINY-Breast05 <i>HER2 positive primary breast cancer following neoadjuvant therapy (vs. T-DM1)</i>					Recruiting North America, South America, Europe, Asia, Australia 2030
	D967RC00001 NCT05113251		Neoadjuvant	Phase 3 DESTINY-Breast11 <i>HER2 positive early-stage breast cancer with neoadjuvant monotherapy or following THP vs. ddAC-THP</i>				Recruiting North America, South America, Europe, Asia 2026

Disease	Study	2017 - 2019	2020	2021	2022	2023	2024	2025
Metastatic Breast Cancer	D9670C00001 NCT04494425		Phase 3 DESTINY-Breast06 <i>HER2-low MBC, hormone receptor positive (vs. physician's choice)</i>					Active, not recruiting North America, South America, Europe, Asia, Australia 2026
	D967JC00001 NCT04538742		Phase 1b/2 DESTINY-Breast07 <i>HER2 positive MBC in combination with other anti-cancer agents</i>					Active, not recruiting North America, South America, Europe, Asia, Australia ¹
	D967JC00002 NCT04556773		Phase 1b DESTINY-Breast08 <i>HER2-low, HR+ or HR-, MBC in combination with other anti-cancer agents</i>			Active, not recruiting North America, South America, Asia, Europe, Australia ²		
	D967UC00001 NCT04784715		Phase 3 DESTINY-Breast09 <i>HER2 positive, first-line MBC ± pertuzumab (vs. taxane, trastuzumab and pertuzumab)</i>					Recruiting North America, South America, Europe, Asia, Africa 2029
	D9673C00007 NCT04739761		Phase 3b/4 DESTINY-Breast12 <i>HER2 positive MBC ± Brain Metastasis, disease progression on previous anti-HER2 based regimen</i>					

Courtesy of Daiichi Sankyo

A good drug for many tumors

DESTINY-PanTumor02: A Phase 2 Study of T-DXd for HER2-Expressing Solid Tumors

An open-label, multicenter study (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
 - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines^{1)a}
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



n=40 per cohort planned
(Cohorts with no objective responses in the first 15 patients were to be closed)

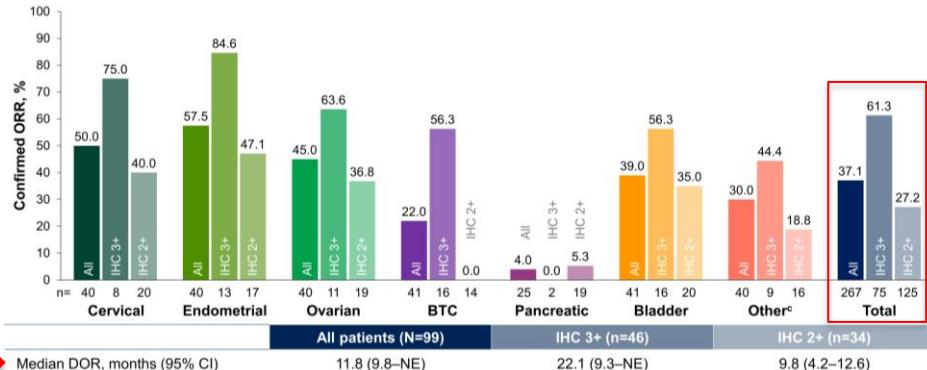


Primary endpoint

- Confirmed ORR (investigator)^c
- Secondary endpoints
- DOR^c
- DCR^c
- PFS^c
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022



Median DOR, months (95% CI)

All patients (N=99)

IHC 3+ (n=46)

IHC 2+ (n=34)

11.8 (9.8–NE)

22.1 (9.3–NE)

9.8 (4.2–12.6)

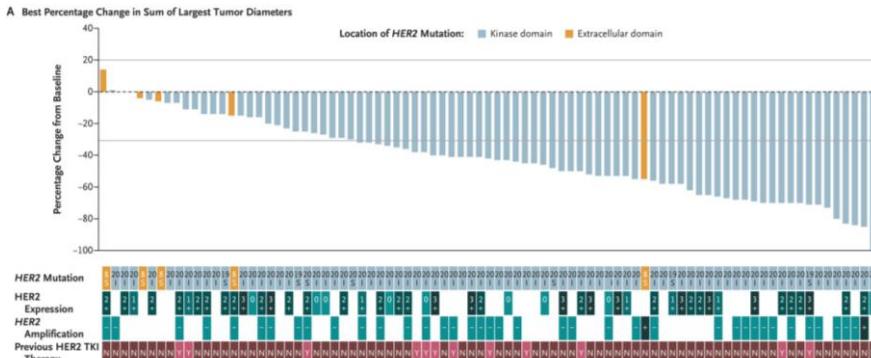
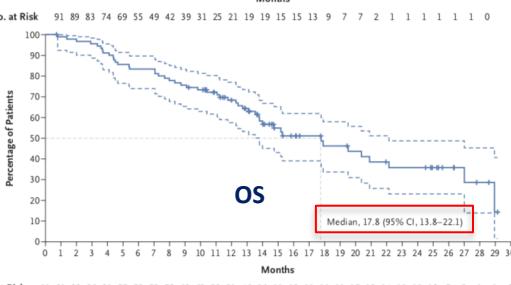
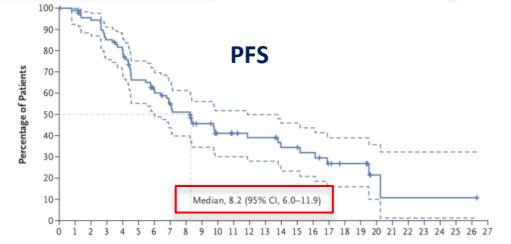
DESTINY-Lung01

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in HER2-Mutant Non-Small-Cell Lung Cancer

Bob T. Li, M.D., Ph.D., M.P.H., Egbert F. Smit, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Hibiki Udagawa, M.D., Julian Mazheres, M.D., Misako Nagasaka, M.D., Ph.D., Lyudmila Bazhenova, M.D., Andreas N. Salatos, M.D., Enriqueta Peral, M.D., Ph.D., Jose M. Pacheco, M.D., Maurice Peral, M.D., Luis Paz-Ares, M.D., Kapil Saxena, M.D., Ryota Shiga, B.Sc., Yingkai Cheng, M.D., Ph.D., Sudhasatta Achanya, Ph.D., Patrik Vitazka, M.D., Ph.D., Javad Shahidi, M.D., David Planchard, M.D., Ph.D., and Pasi A. Janne, M.D., Ph.D., for the DESTINY-Lung01 Trial Investigators^a



➤ ORR 55% (95%CI: 44–65%)

➤ Responses were observed across different HER2 mutation subtypes and in cases with no detectable HER2 expression or amplification

T-DXd development program in solid tumors other than breast

Multiple Tumor Types and Combinations

DS8201-A-J101

DESTINY-PanTumor01

DS8201-A-U105

PETRA

DS8201-A-U106

BEGONIA

HUDSON

Metastatic Gastric/GEJ Cancer

DESTINY-Gastric01

DESTINY-Gastric02

DESTINY-Gastric03

DESTINY-Gastric04

DESTINY-Gastric06

Metastatic Colorectal Cancer

DESTINY-CRC01

DESTINY-CRC02

Metastatic Lung Cancer

DESTINY-Lung02

DESTINY-Lung03

DESTINY-Lung04

DESTINY-Lung05

Where do we go as a research community?

We still don't know who are the patients truly benefiting from T-DXd

- How low can we go?
- Is transcriptomic better than IHC, giving HER2 assessment reproducibility issues?
- Is a biomarker truly needed for initial prescription?
- Which are the mechanisms of resistance?
- Are they related to the Ab, to the payload or both?



Externally Sponsored Research/Investigator Initiated Study

Study Name	Sponsor	Other Identifiers	Population	Design
DAISY	Unicancer	UC-0105/1815	Advanced breast cancer	Phase 2, multicenter, open-label, 3-cohort biomarker study (Mosele F <i>Nat Med</i> 2023: first showing activity in HER2 0)
DEBBRAH	Medica Scientia Innovation Research (MedSIR)	MEDOPP243	HER2+ advanced breast cancer with untreated/treated brain metastases or leptomeningeal carcinomatosis	Phase 2, multicenter, open-label, single arm, 5-cohort
HER2-PREDICT	SOLTI Breast Cancer Group	SOLTI-1804	Patients who will participate, are participating, or have participated in DESTINY-Breast02, DESTINY-Breast03, and DESTINY-Breast04 trials	Translational , multicenter, observational study
Jonsson Comprehensive Cancer Center-NCT04553770	Jonsson Comprehensive Cancer Center	NCI-2020-06086 (CTRP Registry Identifier)	Early stage, HER2-low, hormone receptor positive breast cancer	Phase 2, multicenter, open-label, randomized, 2-arm study w/wo anastrozole
National Cancer Institute-NCT04294628	National Cancer Institute (NCI)	NCI-2020-01206 (CTRP Registry Identifier)	HER2 expressing advanced solid tumors	Phase 1, open-label, single-arm
TUXEDO-1	Medical University of Vienna	Eudra Clinical Trial Identifier: 2020-000981-41	HER2+ metastatic breast cancer with brain metastases	Phase 2, open-label, single-arm (Bartsch R. <i>Nat Med</i> 2022: iORR in 73.3% of the population and a mPFS of 14 months)
2022-0315	M.D. Anderson Cancer Center	NCI-2022-09968 (NCI-CTRP Clinical Trial Registry)	HER2 Low/Ultra-low/Null Metastatic Breast Cancer	Phase 1b, single-center, dose-escalation and expansion study
HERB	National Cancer Center Hospital (NCCH)	NCCH1805	Unresectable or recurrent HER2+ biliary tract cancers refractory or intolerant to treatment including gemcitabine	Phase 2, open-label, single-arm
HERALD Study	National Cancer Center Hospital East	JapicCTI-194707	Solid malignancies with HER2 amplified in circulating tumor DNA refractory or intolerant to standard chemotherapy	Phase 2, multicenter, open-label, single-arm
HERALD-TR Study	National Cancer Center Hospital East	JapicCTI-194758	Solid malignancies with HER2 amplified in circulating tumor DNA refractory or intolerant to standard chemotherapy	Biomarker study
STATICE	National Cancer Center Hospital (NCCH)	NCCH1615	HER2+ metastatic/recurrent uterine carcinosarcoma	Phase 2, multicenter, open-label, single-arm

Thank you for the attention



Contacts



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