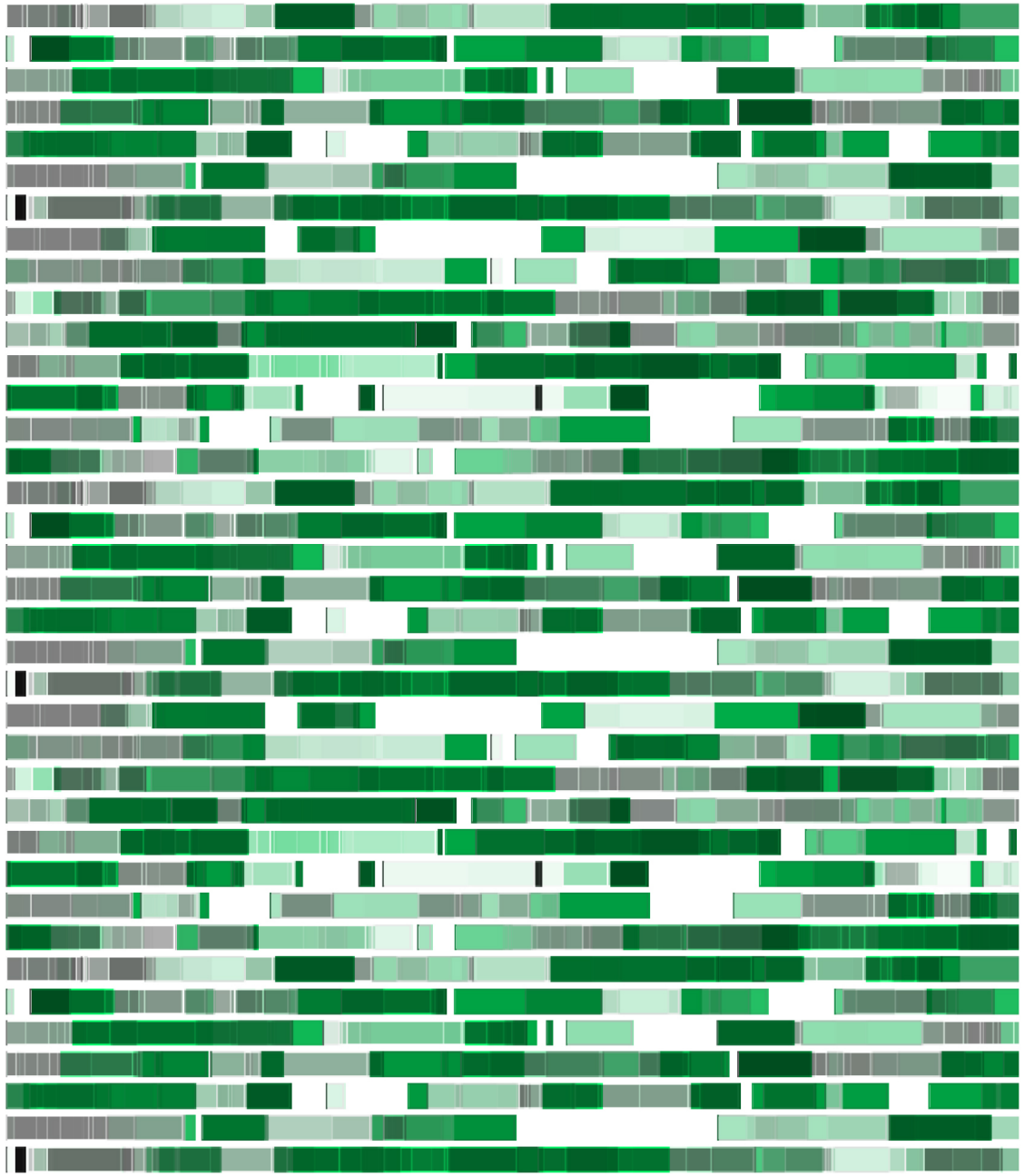
III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 12 Y 13 DE FEBRERO DE 2026



ENFERMEDAD HER2-POSITIVA: CÁNCER DE MAMA

Sonia Pernas, MD, PhD

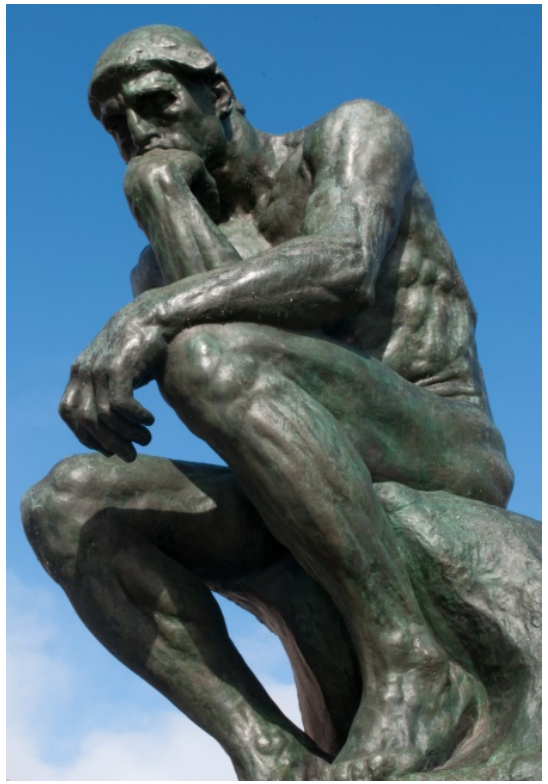
Institut Catala d'Oncologia- IDIBELL- Campus Salut Bellvitge Comprehensive Cancer Center

DISCLOSURES

- **Advisor/Consultant:** AstraZeneca-Daiichi; Eli Lilly; Novartis; Pfizer, Sea-Gen; Lilly, MSD-Merck; Gebro Pharma; Reveal; Jiangsu Hengrui Pharma
- **Speaker honoraria:** AstraZeneca-Daiichi; Gilead; Lilly; Novartis; Pfizer Roche;
- **Travel Grants** from Menarini, Novartis; Gilead; Pfizer; Roche
- **Grant/Research funding to the Institution:** Roche
- **Non-financial disclosure:** member of the SOLTI Executive Board and Scientific Committee

OUTLINE

- T-Dxd impact as 1L treatment in HER2-positive mBC (DESTINY Breast 09)
- Role of 1L Maintenance Therapy with:
  - Palbociclib + HP + ET in HR+ HER2+ mBC (PATINA)
  - Tucatinib+ HB +/- ET in HER2+ mBC (HER2CLIMB-05)
- T-DXd in the adjuvant setting following residual disease (DESTINY Breast 05)
- T-DXd in the neoadjuvant setting (DESTINY Breast 11)



The therapeutic landscape in HER2-positive breast cancer is rapidly evolving, with new agents and combinations expanding options across early and advanced disease

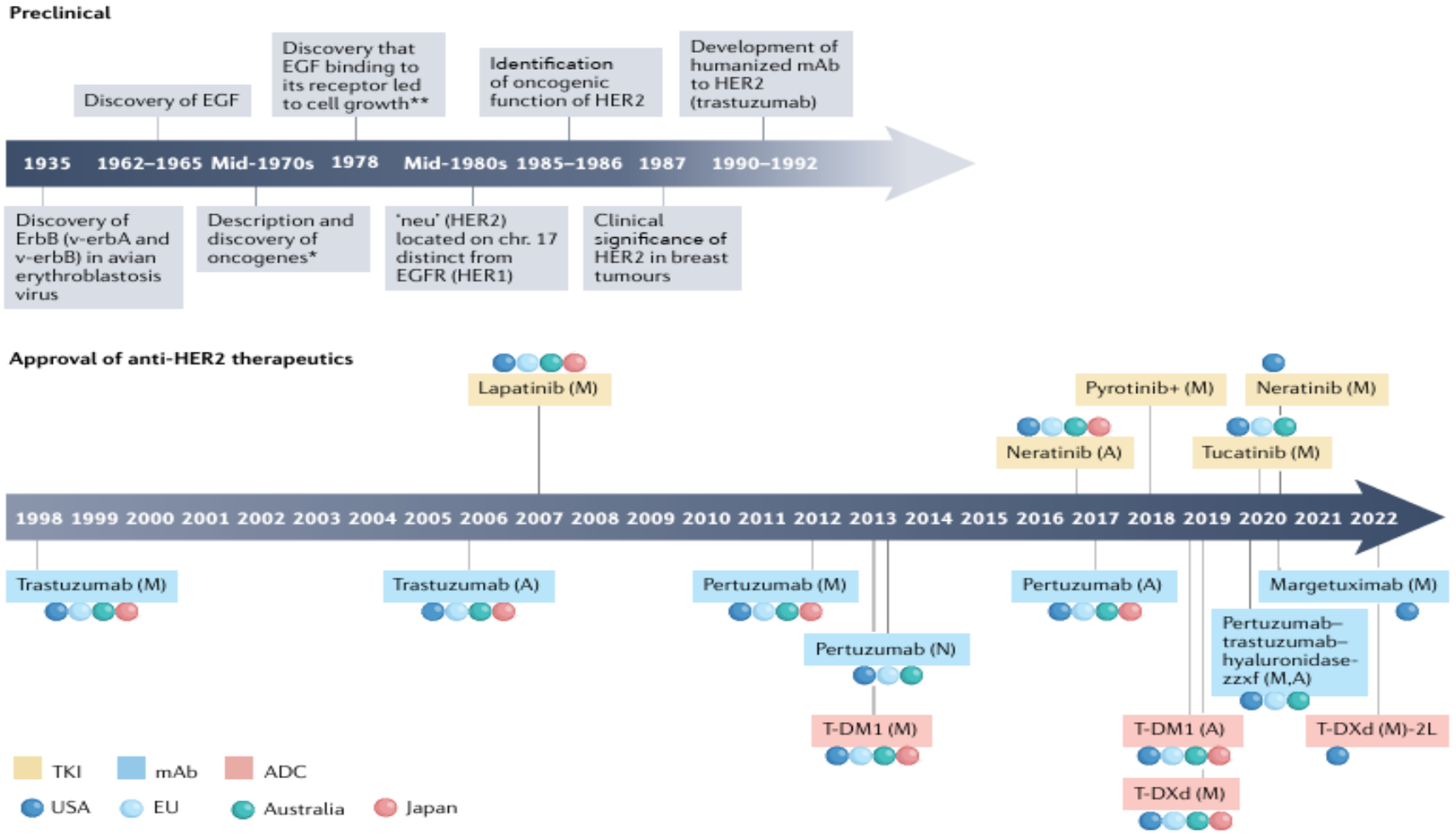


Fig. 1 | Evolution of HER2 as a biomarker and target for treatment for breast cancer. Timeline of preclinical discovery milestones for HER2 biology and regulatory approval for anti-HER2 therapies. A, adjuvant setting; M, metastatic setting; N, neoadjuvant setting; +, approved in China only; *, M. Bishop and H. Varmus awarded Nobel Prize in 1989 for this discovery; **, S. Cohen and R. Levi-Montalcini awarded Nobel Prize in 1986 for discovery of growth factors and their receptors.

Nature Reviews Drug Discovery; Vol 22; February 2023

ESMÉ
unicancer
587P

Recent nationwide overall survival trends across subtypes in 33,044 patients with metastatic breast cancer in the French ESME cohort

Paul Cottu[1], A. Antoine[2], W. Jacot[3], V. C. Diéras[4], J.-S. Frenel[5], A. Gonçalves[6], A. Mailliez[7], C. Levy[8], M. Arnedos[9], V. Massard[10], F. Dalenc[11], C. Bailleux[12], A.M. Savoye[13], M. Leheurteur[14], S. Delaloge[15], L. Bosquet[16], D. Pérol[2], T. Grinda[15]

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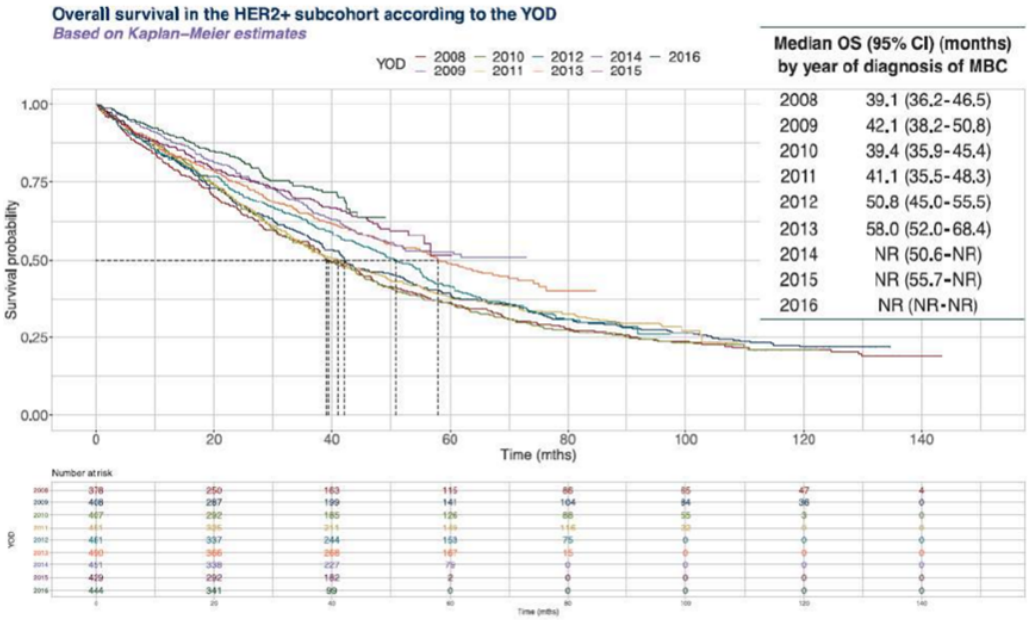
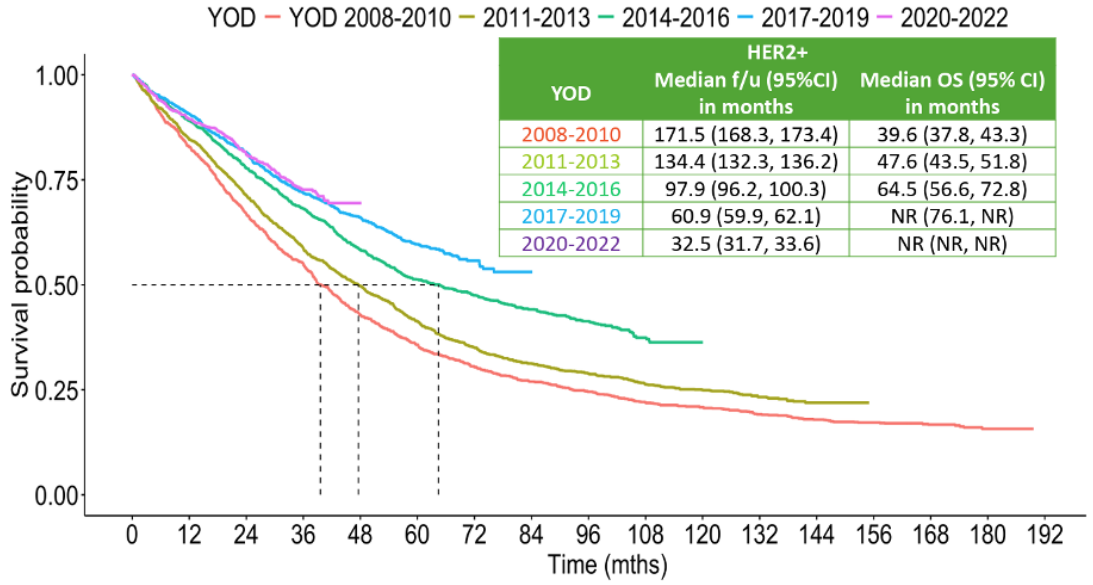
	2008-2010 (N=6382)	2011-2013 (N=7161)	2014-2016 (N=7097)	2017-2019 (N=7231)	2020-2022 (N=5173)	Total (N=33044)
• HER2+	1128 (17.7%)	1289 (18.0%)	1255 (17.7%)	1251 (17.3%)	970 (18.8%)	5893 (17.8%)

HER2+ subtype



c) HER2+ subtype according to the YOD



YOD	HER2+ Median f/u (95%CI) in months	Median OS (95% CI) in months
2008-2010	171.5 (168.3, 173.4)	39.6 (37.8, 43.3)
2011-2013	134.4 (132.3, 136.2)	47.6 (43.5, 51.8)
2014-2016	97.9 (96.2, 100.3)	64.5 (56.6, 72.8)
2017-2019	60.9 (59.9, 62.1)	NR (76.1, NR)
2020-2022	32.5 (31.7, 33.6)	NR (NR, NR)

- OS has dramatically improved in HER2-positive mBC, but unmet needs remain: resistance mechanisms, CNS progression, and treatment-related toxicities

Cottu P et al. ESMO 2025

HER2-positive mBC Treatment Landscape

First Line	Second Line	Third Line +
Docetaxel, Trastuzumab, Pertuzumab (THP)	Trastuzumab Deruxtecan	Tucatinib, Trastuzumab, Capecitabine
Maintenance:		
HP +/- ET		T-DM1

T-DXd + pertuzumab as 1L in HER2-positive mBC: DESTINY BREAST 09 results

A randomized, multicenter, open-label,* Phase 3 study (NCT04784715)

Eligibility criteria
- HER2+ a/mBC
- Asymptomatic/inactive brain mets allowed
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant/adjuvant setting
- One prior line of ET for mBC permitted
- **No other prior systemic treatment for mBC†**

Stratification factors
- De-novo vs recurrent mBC
- HR+ or HR−
- *PIK3CA*m (detected vs non-detected)

R 1:1:1

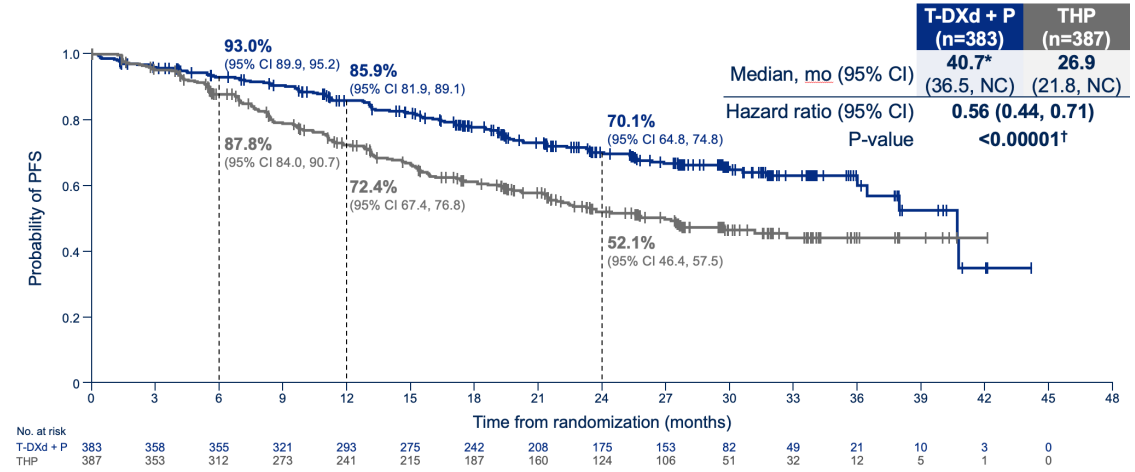
- n=387 — T-DXd‡ + placebo (Blinded until final PFS analysis)
- n=383 — T-DXd‡ + pertuzumab§
- n=387 — THP (Taxane (paclitaxel or docetaxel)¶ + trastuzumab‖ + pertuzumab§)

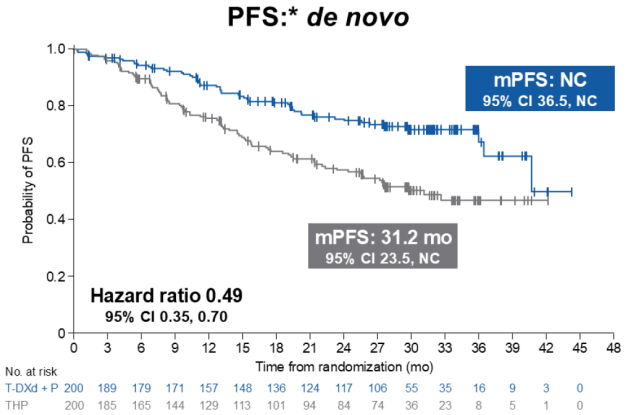
Endpoints

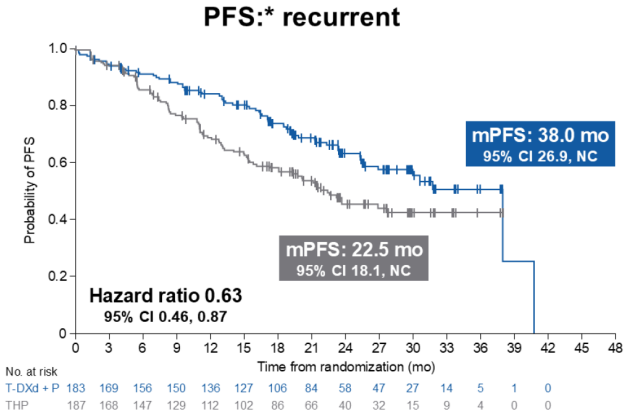
Primary
- PFS (BICR)

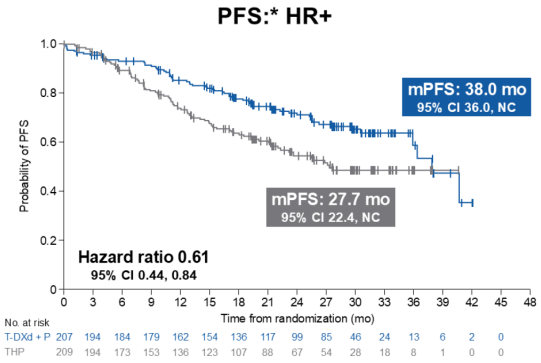
Key secondary
- OS

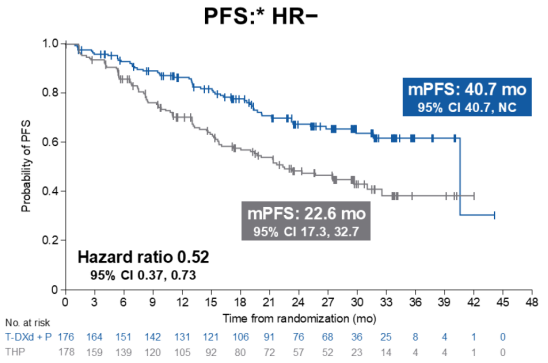
Secondary
- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety and tolerability











Patients with HR+ disease could receive concurrent ET after six cycles of T-DXd or discontinuation of taxane, which occurred in **13.5% (T-DXd + P)** versus **38.3% (THP)** of patients

T-DXd + pertuzumab represents an effective 1L treatment for patients with HER2+ mBC, regardless of prior treatment, HR, or PIK3CAm status

Tolaney SM, et al. ASCO 2025 (LBA 1008); Loibl S, et al. ESMO 2025; Tolaney SM et al. NEJM 2025

T-DXd + pertuzumab: Potential New 1L in HER2-positive mBC

	DESTINY Breast-09
Arms	T-DXd + P vs. THP
De-novo disease at diagnosis	~50%
mPFS (mo) *HR*	40.7 versus 26.9 *0.56*
mOS (mo) *HR*	NR (Immature) *0.84*
Grade ≥ 3 AE ***ILD** (Any grade)*	63.5 vs. 62.3% ***12.1 vs. 1%***
PRO	Similar between arms

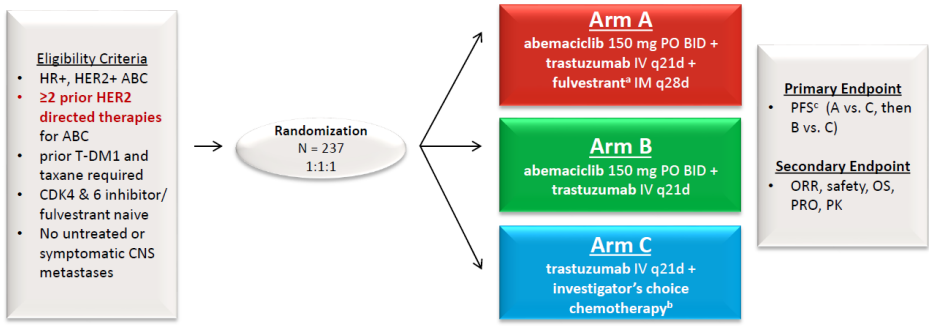
Tolaney SM et al. NEJM 2025; Rimawi et al SABCS 2025; Reid S, SABCS 2025

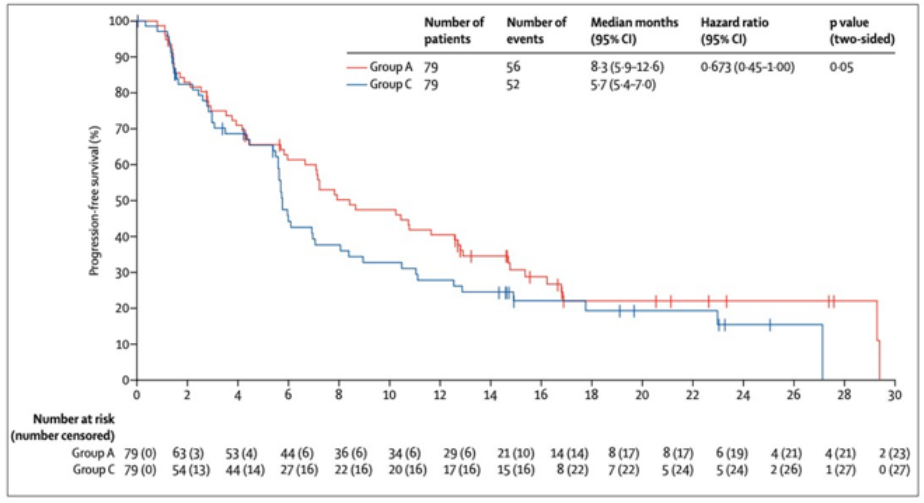
CDK4/6i +ET in ER+/HER2-positive aBC

ABEMACICLIB + FULVESTRANT + TRASTUZUMAB VS QT + TRASTUZUMAB

CDK4/6 Inhibition in ER+ HER2+ MBC: monarcHER Trial

Randomized Phase 2



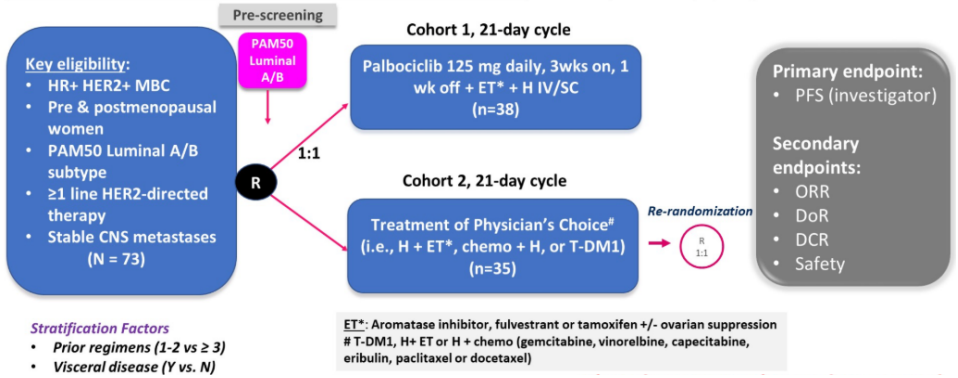


Luminal subtypes[a] were associated with longer PFS and OS compared to non-luminal.

PALBOCICLIB + LETROZOL + TRASTUZUMAB VS QT/HT + TRASTUZUMAB

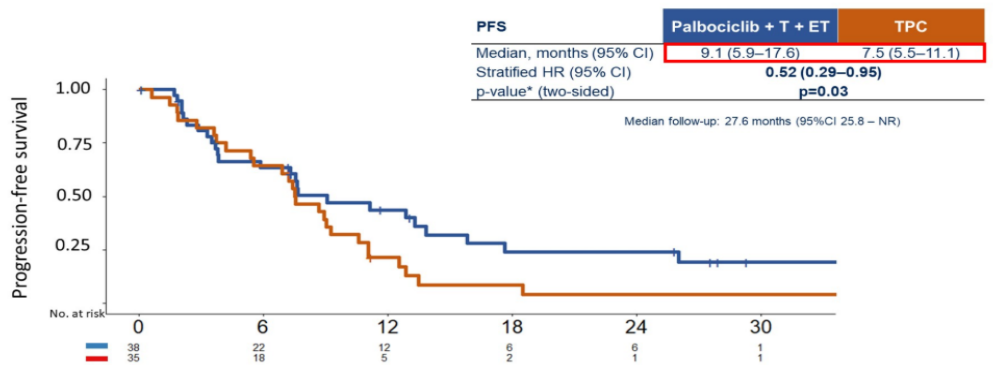
PATRICIA Trial (Cohort C): Design

Multicenter, open-label, randomized phase II trial (SOLTI-1303) **Enrollment:** 8/19-8/23



PATRICIA Cohort C: Longer PFS with Palbociclib + H + ET vs. TPC

PFS (Investigator Assessed)



Tolaney et al. Clin Cancer Res 2024; Ciruelos et al Clin Cancer Res 2025

1L Maintenance Therapy with Palbociclib + HP + ET in HR+ HER2+ mBC: PATINA

Objective: To evaluate the addition of palbociclib to anti-HER2 and ET for patients with HR+/HER2+ breast cancer

REGISTRATION
- Histologically confirmed HR+/HER2+ mBC
- No prior treatment in the advanced setting beyond induction treatment
- 6–8 cycles of treatment, including trastuzumab ± pertuzumab and taxane/vinorelbine

KEY ELIGIBILITY CRITERIA
- Completion of induction chemotherapy and no evidence of disease progression (ie, CR, PR, or SD)
- Patients with a history or presence of asymptomatic CNS metastases were eligible

R 1:1, N = 518

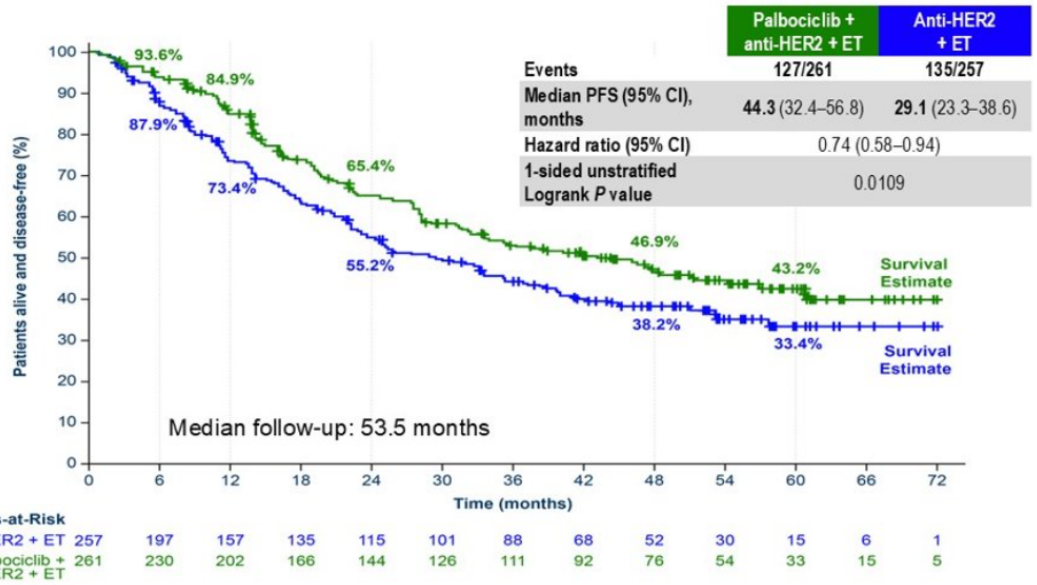
- Palbociclib + Trastuzumab ± pertuzumab + ET[†,‡] n = 261
- Trastuzumab ± pertuzumab + ET[†,§] n = 257

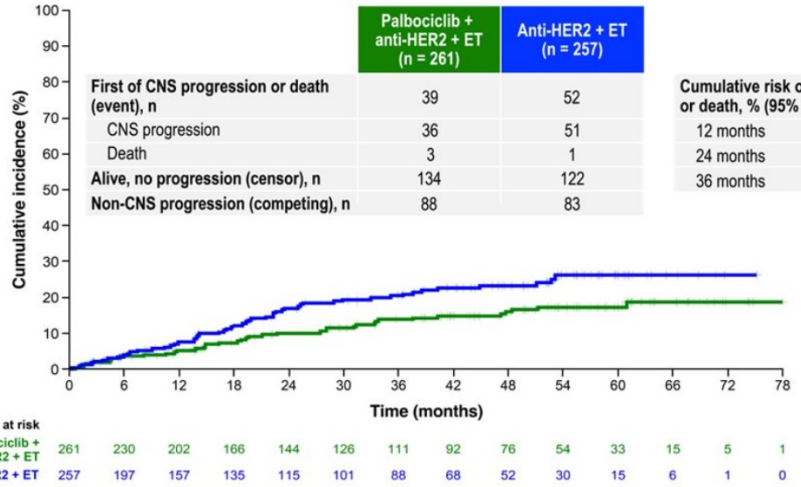
Until PD or toxicity → Survival follow-up

Primary Outcome
- Investigator-assessed PFS

Secondary Outcomes
- OS
- 3- and 5-year survival probabilities
- ORR / DOR / CBR
- Safety
- PRO
- Incidence of CNS metastases

Stratification Factors
- Pertuzumab use (yes vs no)
  - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (yes vs no, including de novo)[‖]
- Response to induction therapy (CR or PR vs SD) by investigator assessment[‖]
- Type of ET (fulvestrant vs aromatase inhibitor)





	Palbociclib + anti-HER2 + ET (n = 261)	Anti-HER2 + ET (n = 257)
First of CNS progression or death (event), n	39	52
CNS progression	36	51
Death	3	1
Alive, no progression (censor), n	134	122
Non-CNS progression (competing), n	88	83

	Palbociclib + anti-HER2 + ET (n = 261)	Anti-HER2 + ET (n = 257)
Cumulative risk of CNS progression or death, % (95% CI)		
12 months	5.2 (2.9–8.5)	7.5 (4.6–11.5)
24 months	10.1 (6.7–14.3)	17.0 (12.3–22.3)
36 months	13.8 (9.7–18.6)	20.4 (15.3–26.1)

- At 36 months, the cumulative incidence of CNS progression or death was 13.8% vs 20.4% for palbociclib vs control (Gray's test $P = 0.0404$).

- Baseline CNS involvement: 4%
- Median of cicles of induction treatment: 6-7
- De novo M1 disease 54%
- Prior neo/adj anti-HER2 therapy: 32% (?)
- Type of ET: 91% aromatase inh.

Vaz Luis et al ESMO 2025; Metzger et al SABCS 2025; Metzger et al N Engl J Med 2026

1L Maintenance Therapy with Tucatinib + HP +/-ET in HER2positive mBC: HER2CLIMB-05

HER2CLIMB-05 is a randomized, double-blind, placebo-controlled, international, phase 3 trial (NCT05132582)

Key Eligibility Criteria

- Centrally confirmed HER2+ MBC
- No evidence of progression after THP (4 to 8 cycles)
- ECOG PS of 0 or 1
- No or asymptomatic BM confirmed by contrast-enhanced MRI at screening

R 1:1

Randomization was stratified by:
- Diagnosis: *de novo* or recurrent
- HR status: positive or negative
- Presence or history of BM: yes or no

1L Maintenance Therapy

TUC 300 mg PO BID + **HP*** Once every 21 days ± ET (**n = 326**)

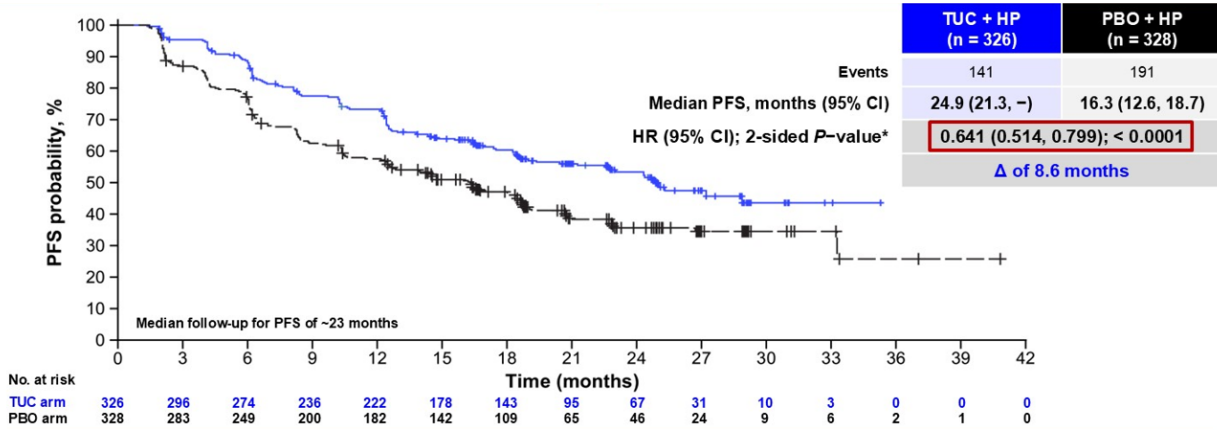
PBO PO BID + **HP*** Once every 21 days ± ET (**n = 328**)

Study treatment continues until unacceptable toxicity, disease progression, consent withdrawal, or study closure. No crossover from PBO to TUC was allowed.

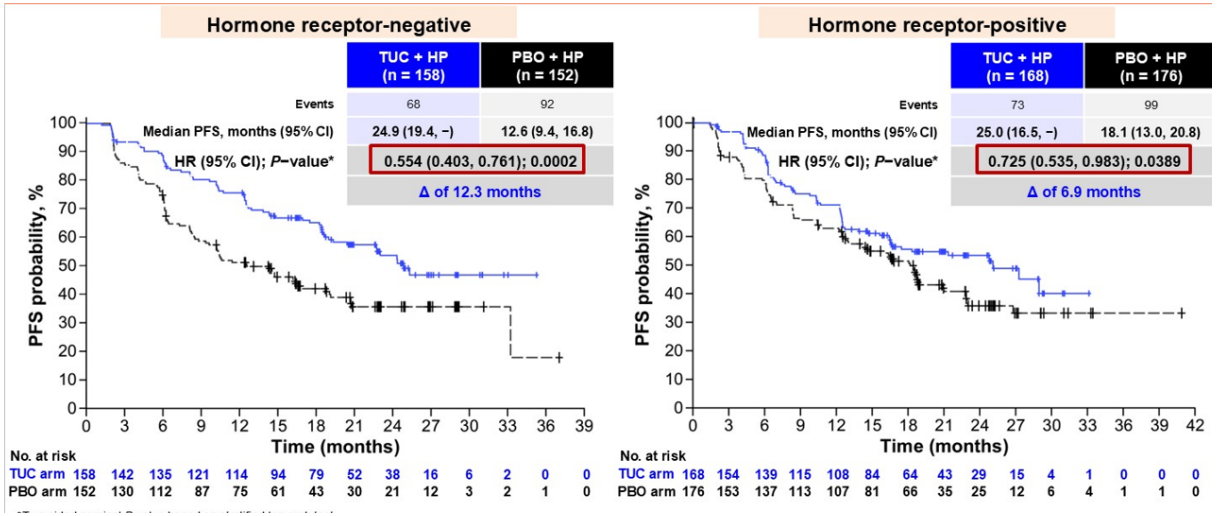
Endpoints

Primary
- Investigator-assessed PFS per RECIST v1.1

Secondary
- OS (key secondary)
- PFS per BICR
- CNS-PFS
- Safety
- HRQoL
- Pharmacokinetics



Addition of TUC to 1L maintenance therapy extended median PFS to over 2 years in patients with HER2+ MBC, an **8.6-month** improvement over HP, the standard-of-care.



- 51.5% HR+
- Only 50% of HR+ pts received ET
- G3 AEs were more common in the HP + Tucatinib arm where GI and Hepatic Adverse events were the most commonly reported AE

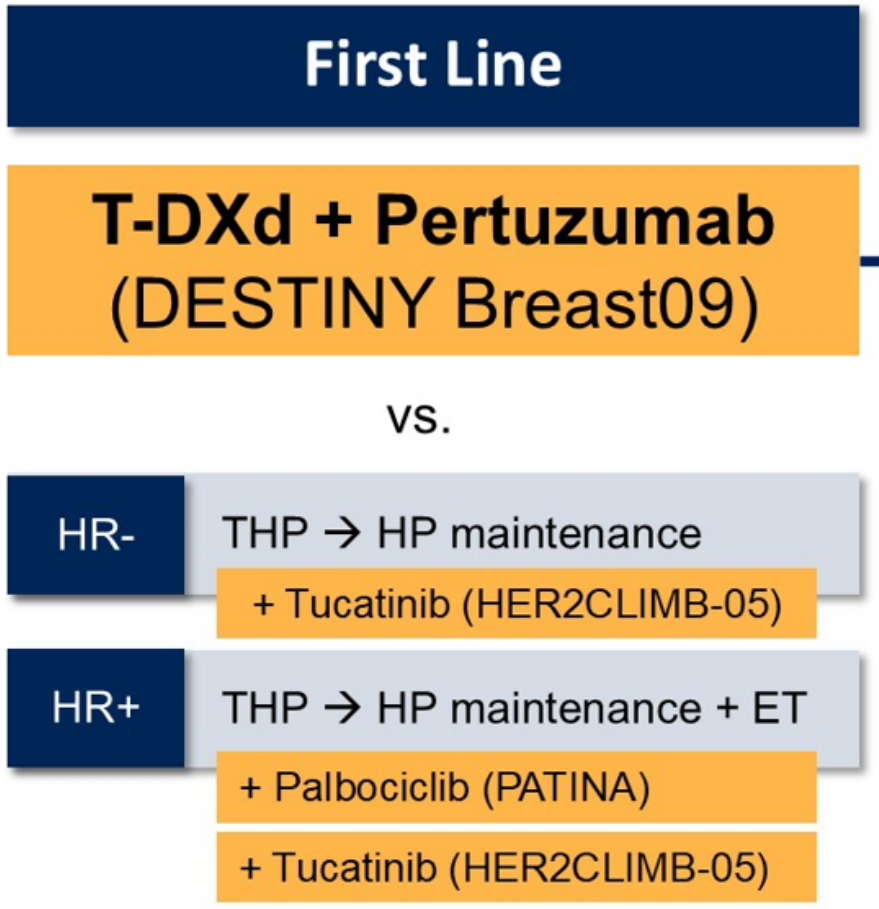
Hamilton E, et al SABCS 2025

1L HER2positive mBC Maintenance Clinical Trials

	HER2CLIMB-05		PATINA
Arms	Tucatinib + HP +/- ET vs. HP +/- ET		Palbociclib + HP + ET vs. HP + ET
De-novo disease	70%		52%
HR+ subgroup	51.5% (<50% received ET)		All
mPFS (mo) *HR*	24.9 vs. 16.3 *0.64*		44.3 vs. 26.9 *0.74*
mPFS (mo), by subtype *HR*	**HR+:** 25.0 vs. 18.1 *0.725*	**HR-:** 24.9 vs. 12.6 *0.554*	-
Adverse events (Grade ≥ 3)	42% vs. 24%		Neutropenia 63.2 % vs. 4.4% Diarrhea 11.1% vs. 1.6%

Metzger et al SABCS 2024; Metzger et al 2026; Hamilton et al SABCS 2025; Reid S SABCS 2025

Potential 1st line HER2-positive m BC Treatment Landscape and Unanswered Questions



Maintenance ?

- Treatment of Recurrent disease after neo/adjuvant T-Dxd (DB-05; DB-11)
- Balancing Efficacy vs Tolerability
  - Is there a role of T-DXd +P induction followed by HP maintenence +/- palbo or tucatinib?
  - Can some pts still be treated with THP?

Swain et al. Lancet 2020; Hurvitz et al. Lancet 2023; Metzger et al SABCS 2024; Metzger et al 2026; Hamilton et al SABCS 2025; Reid S SABCS 2025

Novel approaches being assessed

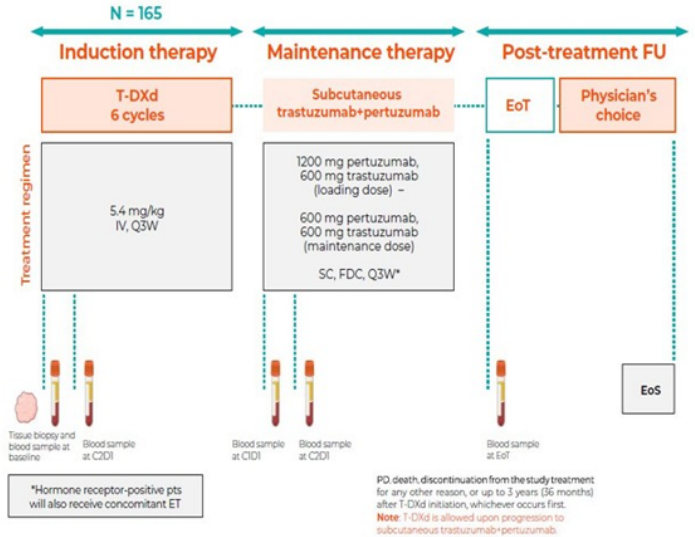
DEMETHER CLINICAL TRIAL

The DEMETHER study is an international, multicenter, open-label, single-arm phase II trial (NCT06172127).

KEY INCLUSION CRITERIA

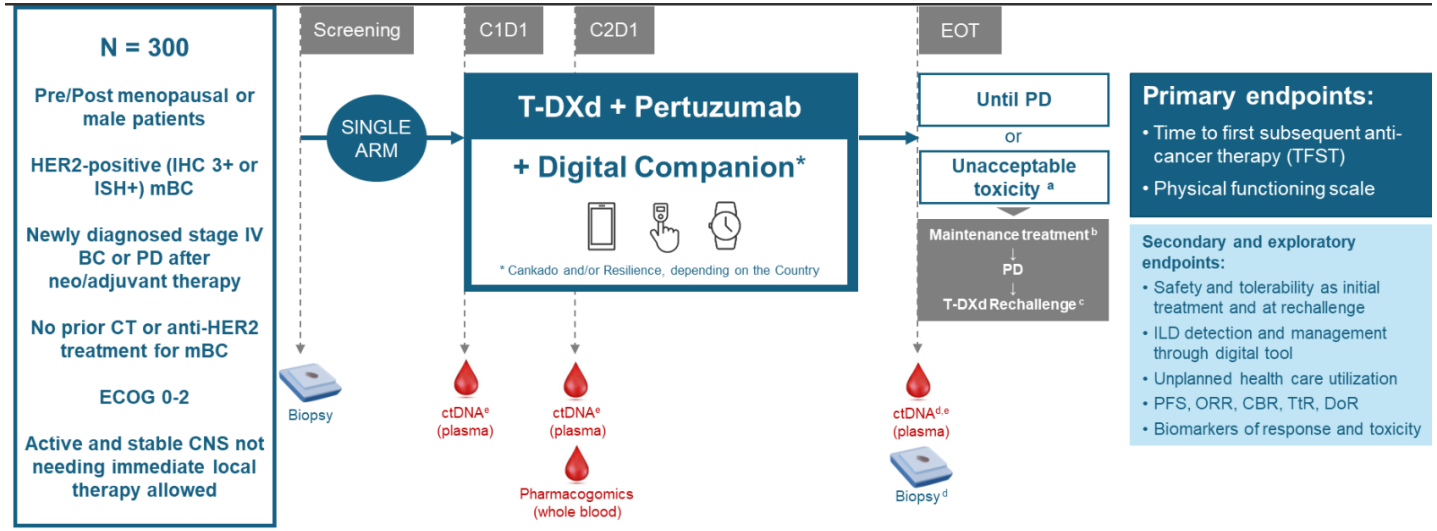
- ≥18 years of age.
- Centrally-confirmed HER2[+] (IHC 3+, IHC 2+ & ISH+) ABC.
- Stable brain metastasis allowed.
- No prior systemic treatment for advanced disease (one prior line of ET is allowed for ABC).
- Participants may have received CT or HER2-targeted therapy in the (neo)adjuvant setting with a disease-free interval from completion of the systemic treatment (excluding ET) to metastatic diagnosis ≥ 12 months.
- No prior treatment with T-DXd in the (neo)adjuvant setting.
- Evaluable disease according to RECIST v1.1
- ECOG PS 0-1.
- LVEF ≥ 55% (ECHO or MUGA scan)
- Adequate hematologic and organ function

*An interim analysis will be performed on the first 62 pts with measurable lesions; if at least 44 pts show objective response, the trial will continue.



TOP-REAL CLINICAL TRIAL

Broader eligibility criteria; emphasizing patient-centered outcomes; and exploring the feasibility of rechallenging patients with T-DXd



DESTINY-Breast05-T-DXd in the Adjuvant Setting: Potential new standard of care

High risk population with residual invasive disease following NAT

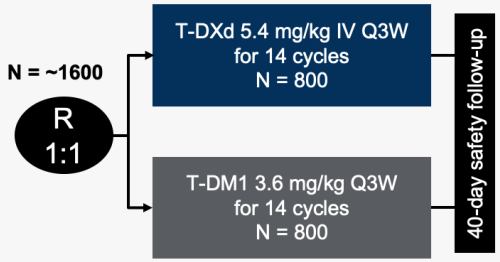
A global, multicenter, randomized, open-label, phase 3 trial (NCT04622319)

Population

- Residual invasive disease in the breast and/or axillary lymph nodes after neoadjuvant chemotherapy and HER2-directed treatment[a]
- **High-risk**
  - **Inoperable eBC (cT4, N0-3, M0 or cT1-3, N2-3, M0) at presentation before NAT or**
  - **Operable eBC (cT1-3, N0-1, M0) with axillary node-positive disease (ypN1-3) after NAT**
- Centrally confirmed HER2+ (IHC 3+ or ISH+) eBC
- ECOG PS 0 or 1

Stratification factors

- Extent of disease status at presentation[b]
- HER2-targeted NAT (single, dual)
- Hormone receptor status (positive, negative)
- Post-NAT pathologic nodal status (positive [ypN1-3], negative [ypN0])



Primary endpoint
- IDFS

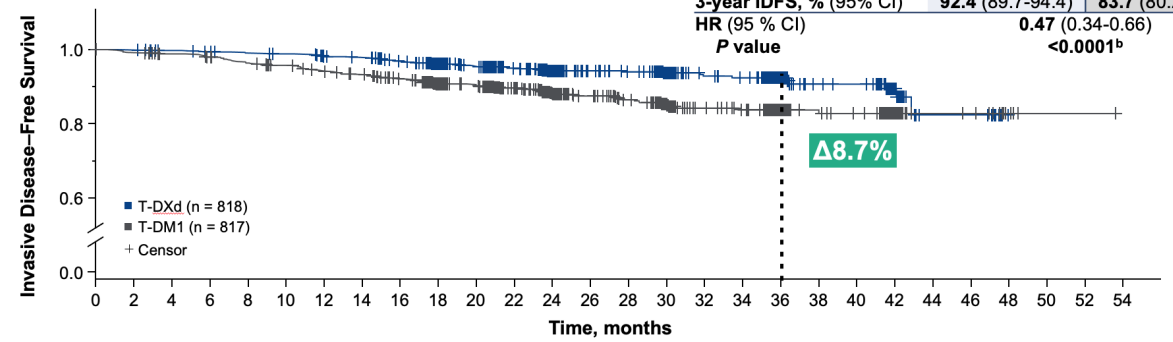
Key secondary endpoint
- DFS

Other secondary endpoints
- OS
- DRFI
- BMFI
- Safety

- **Concomitant adjuvant ET was allowed per local practices**
- **Adjuvant RT and ILD monitoring program:**
  - All patients receiving RT had chest CT scans prior to start of RT, 6 weeks after start of study treatment, then every 12 weeks while on treatment, and at 40-day follow-up
  - Patients completing RT prior to start of study medication (sequential) had an additional chest CT scan prior to start of study treatment

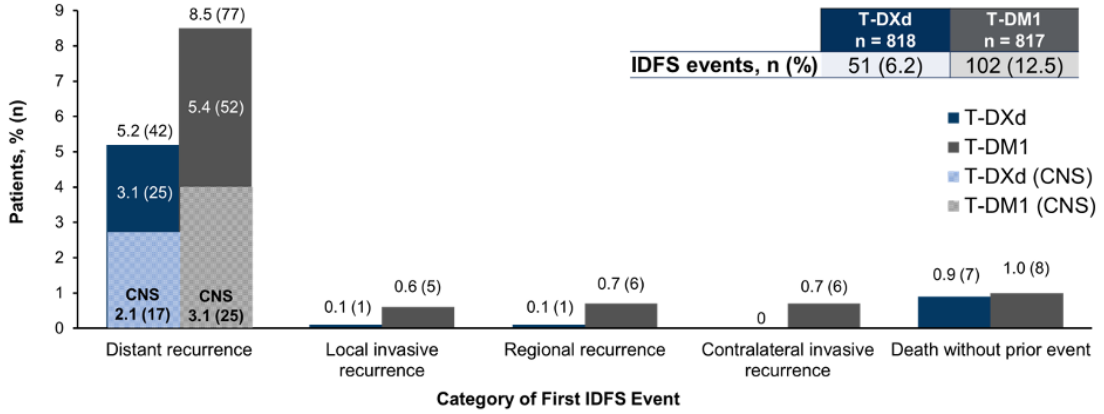
- HR+72%
- IHC 3+ 82%
- Inoperable 52%
- ypN+ 81%
- Neaodjuvant trastuzumab + pertuzumab 78%

	T-DXd n = 818	T-DM1 n = 817
Patients with events, n (%)	**51** (6.2)	**102** (12.5)
3-year IDFS, % (95% CI)	**92.4** (89.7-94.4)	**83.7** (80.2-86.7)
HR (95 % CI)		**0.47** (0.34-0.66)
***P* value**		**<0.0001**[b]



Number at Risk:

T-DXd	818	788	781	776	771	768	758	753	731	684	634	544	440	380	370	275	218	212	129	92	90	46	14	14	0	0	0	0
T-DM1	817	781	769	760	745	734	719	708	687	632	599	527	417	355	337	233	186	177	120	84	79	38	14	13	4	1	1	0

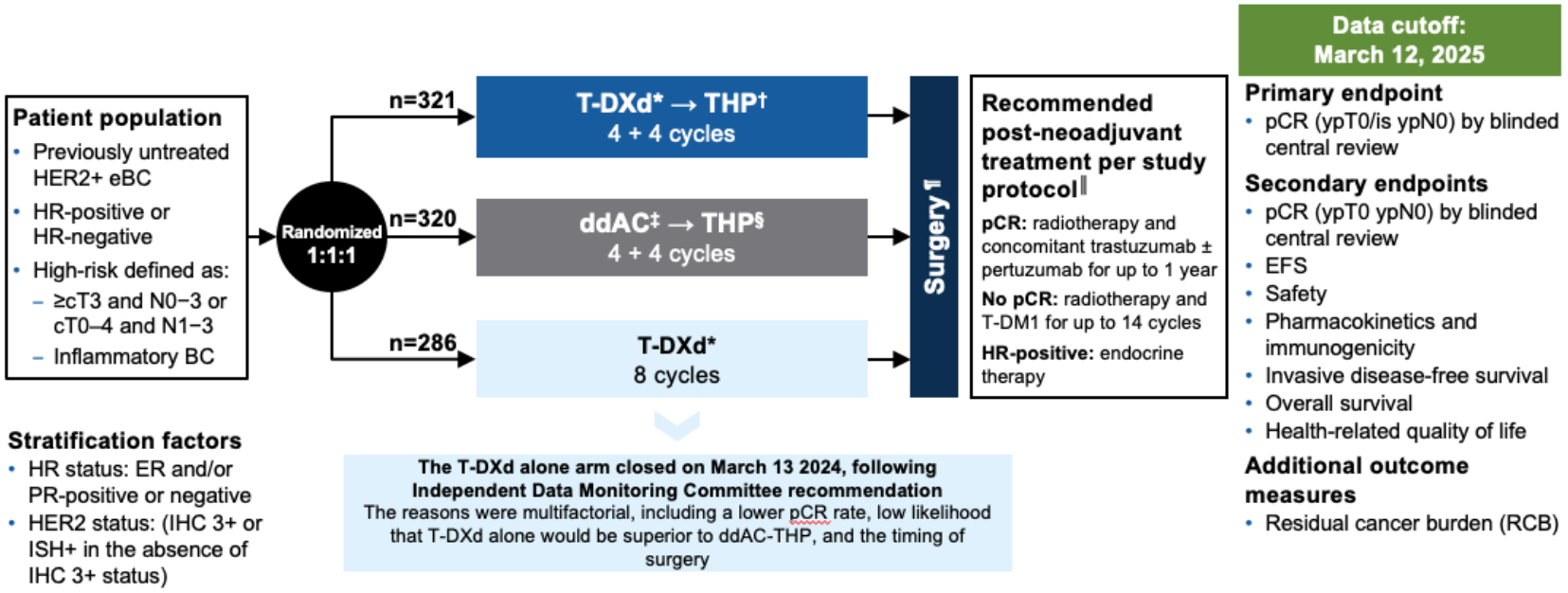


IDFS events, n (%)	T-DXd n = 818	T-DM1 n = 817
	51 (6.2)	102 (12.5)

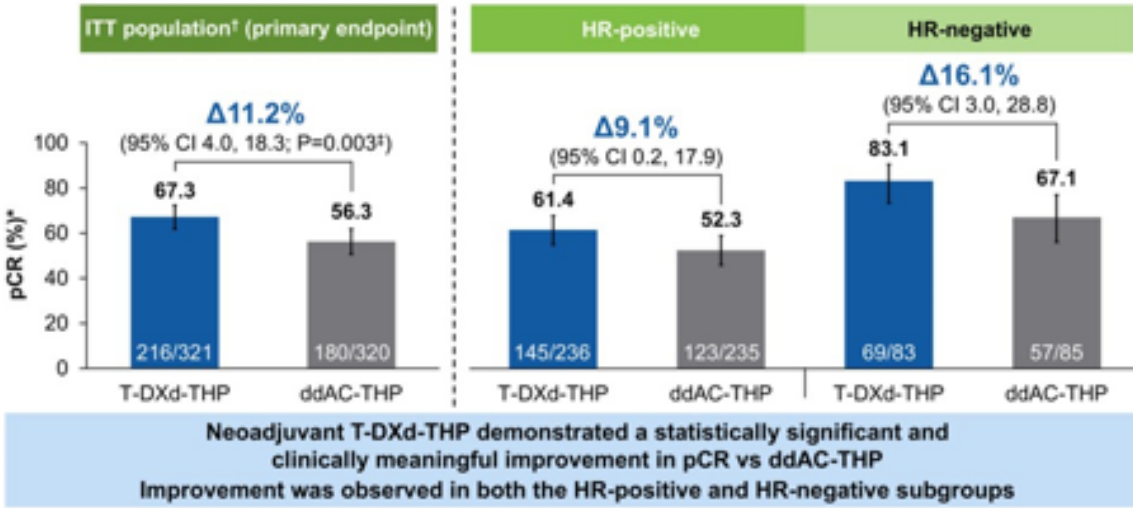
53% reduction in the risk of invasive disease recurrence or death for T-DXd compared with T-DM1
Drug related ILD/pneumonitis 11 vs 2.5%

Geyer C, et al. ESMO 2025

DESTINY-Breast11: T-DXd in the Neoadjuvant Setting



- HR+73%
- IHC 3+ 88%
- N+88%
- DXd monotherapy arm closed early due to lower pCR (43%)

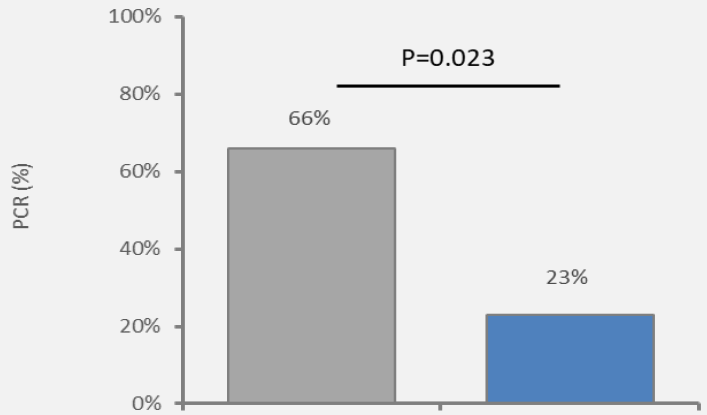


- pCR higher for T-DXd in all groups (61.4% in HR+!!)
- EFS immature but favorable trend: HR 0.56 (95% CI 0.26-1.17)
- Lower rates of Grade ≥3AEs, serious AEs and AEs leading to dose interruptions
- ILD rates were low and similar between arms

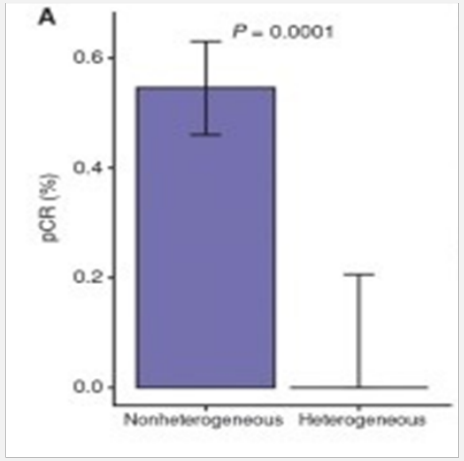
Harbeck N, et al. ESMO 2025; Harbeck N, et al. Ann Oncol 2025

Many biomarkers based on retrospective analysis…

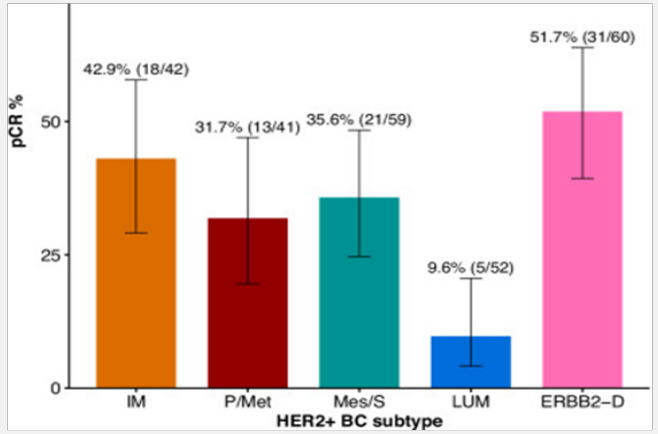
HER2 3+ vs. HER2 2+/ISH+



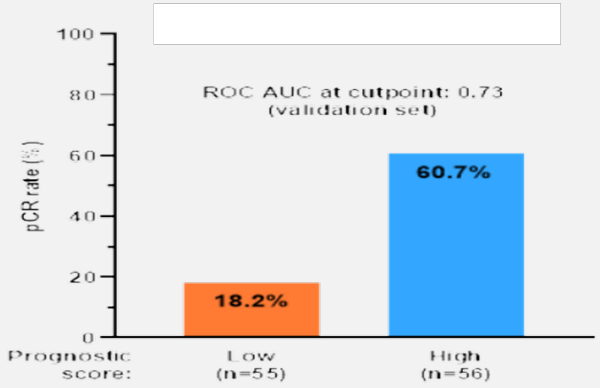
Intratumoral heterogeneity (ITH)



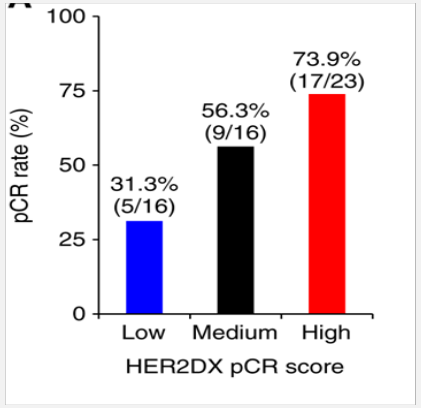
HER2 molecular subtypes



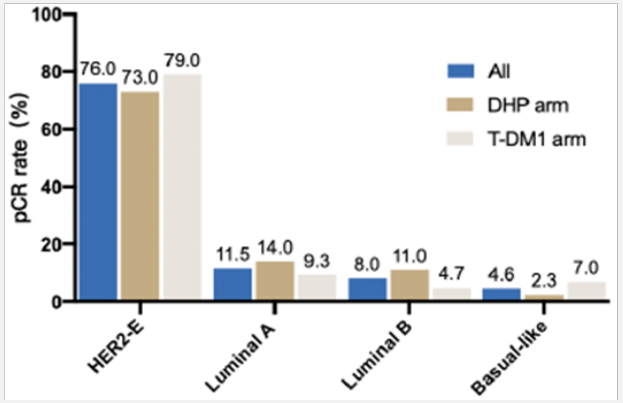
WSG ADAPT prognostic score



HER2DX PCR score



PAM50

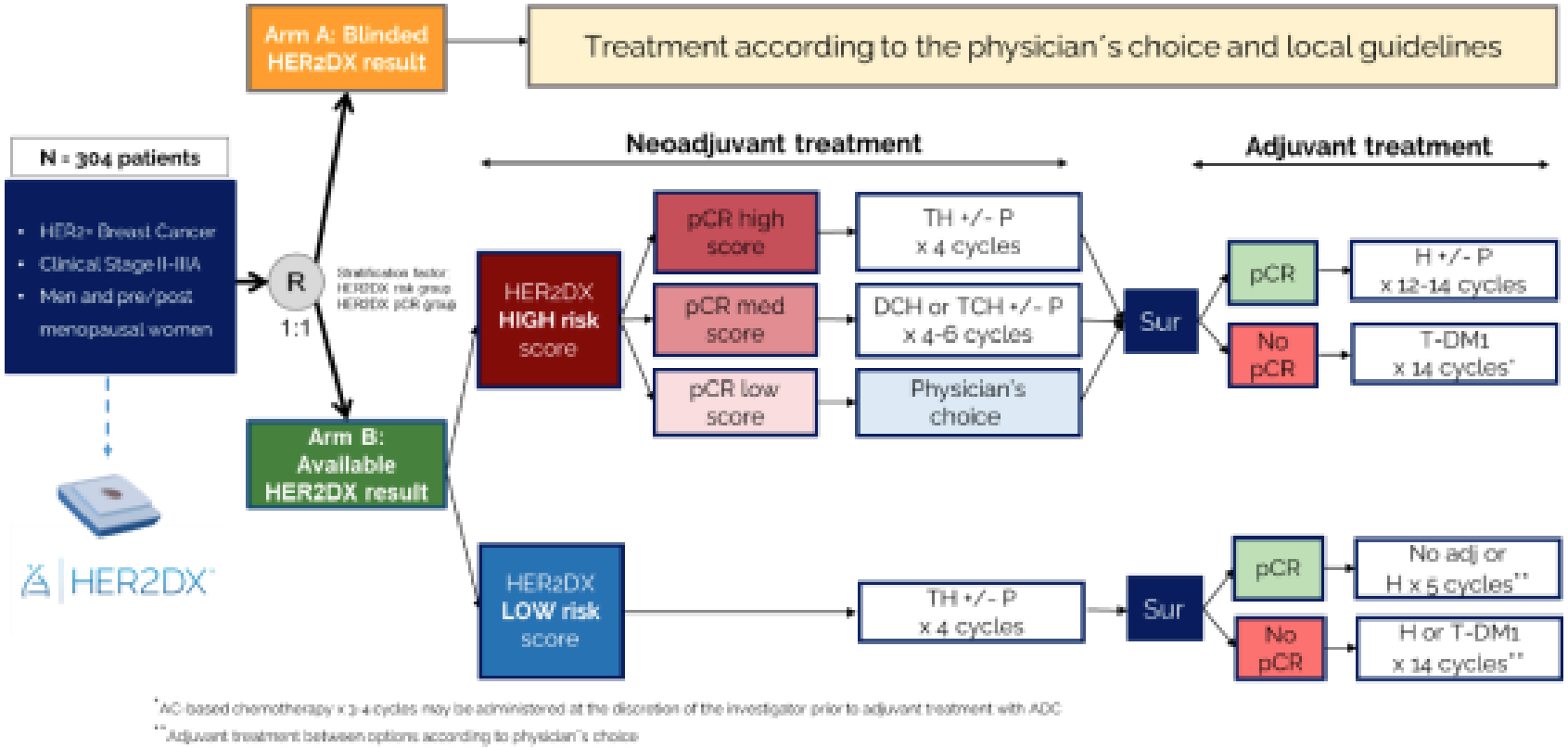


Sonke G. SABCS 2024

Pérez-García. ASCO 2024; Pérez-García. Lancet 2024; Metzger-Filho. Cancer Discovery 2021; Llombart-Cussac Clin Cancer Res. 2024; Redit. Nat Commun 2024; Aranzaru. JAMA Oncol. 2024; Graeser. SABCS 2023

Prospective validation of the HER2DX: DEFINITIVE trial

Figure 3. Trial design.



*AC-based chemotherapy x 3-4 cycles may be administered at the discretion of the investigator prior to adjuvant treatment with ADC

**Adjuvant treatment between options according to physician´s choice

AC: anthracyclines and cyclophosphamide; C: carboplatin; D: Docetaxel; H: trastuzumab; pCR: pathologic complete response; P: pertuzumab; Sur: surgery; T: paclitaxel; T-DM1: trastuzumab-emtansine; Adj: adjuvancy.

Conclusions

- T-DXd is reshaping HER2-positive breast cancer across all disease settings
- With T-DXd as potential new 1L in HER2-positive mBC and novel efficacy approaches for maintenance therapy: how to optimally integrate all these strategies?
- Post-T-Dxd sequencing represents the major upcoming challenge
- Precision biology-driven treatment decisions to guide the next era

GRACIAS!

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

SEVILLA, 6 Y 7 DE FEBRERO DE 2025