# Optimizing the Management of HER2+ mBC With Current and Emerging Agents

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*Presented by*

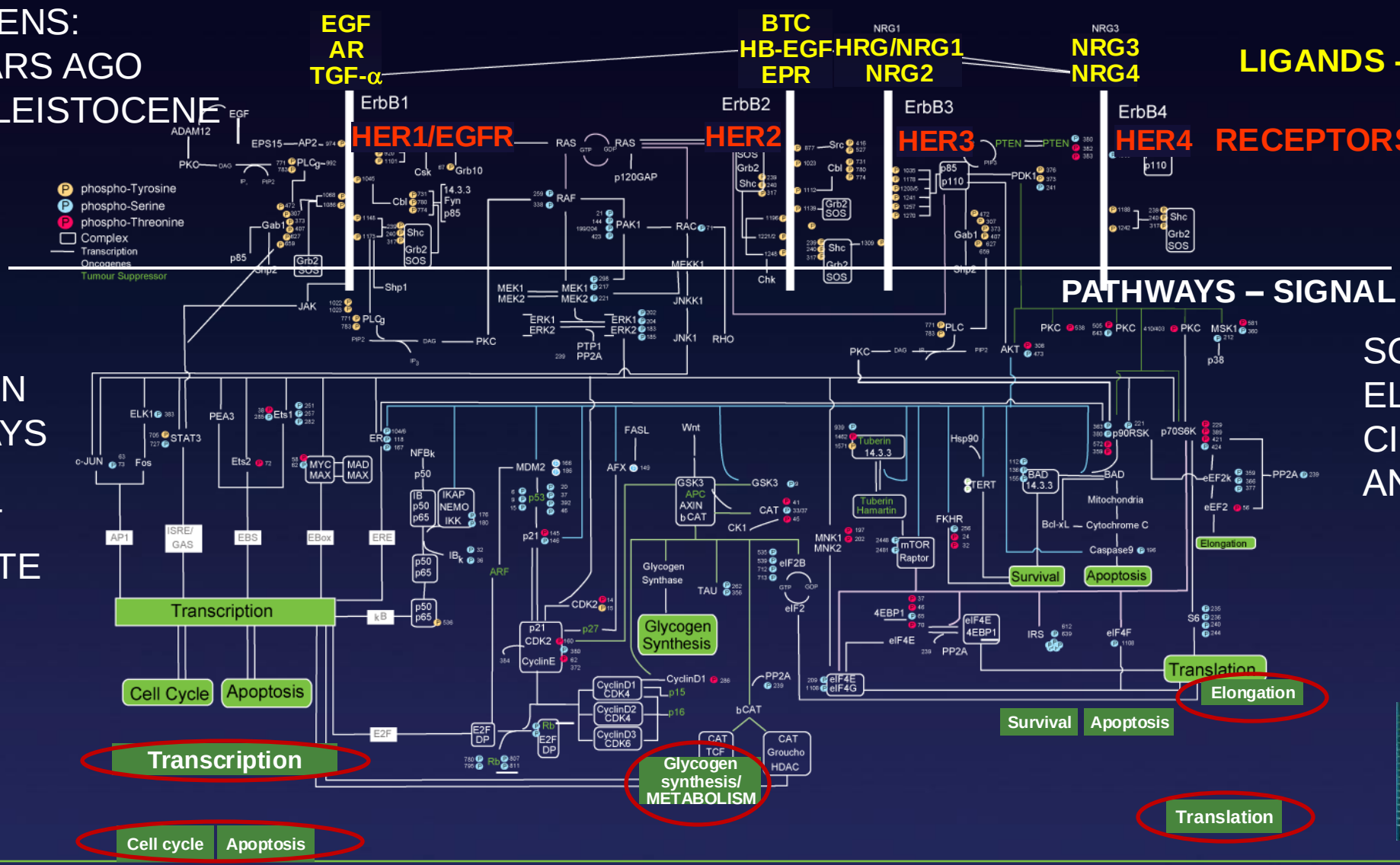
***Matthew Ellis, MBBChir | Baylor College of Medicine***

# Presentation Outline

1. Treatment of HER2+ MBC by line of therapy
2. Rationale for combining pertuzumab with trastuzumab in first-line treatment of HER2+ MBC
3. Second-line Treatment of HER2+ MBC with Fam-Trastuzumab Deruxtecan (T-DXd)
4. Third-line Treatment of HER2+ MBC with Tucatinib and/or T-DM1
5. Treatment of HER2+ MBC in the salvage setting: Margetuximab, Neratinib and others
6. ESMO 2024 Update

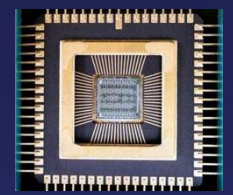
# The Human Epidermal Growth Factor Receptor (HER) Signaling Network

HOMO SAPIENS:
300,000 YEARS AGO
MID-LATE PLEISTOCENE
AFRICA




REGULATION
OF PATHWAYS
CRITICALLY
IMPORTANT
TO CELL FATE

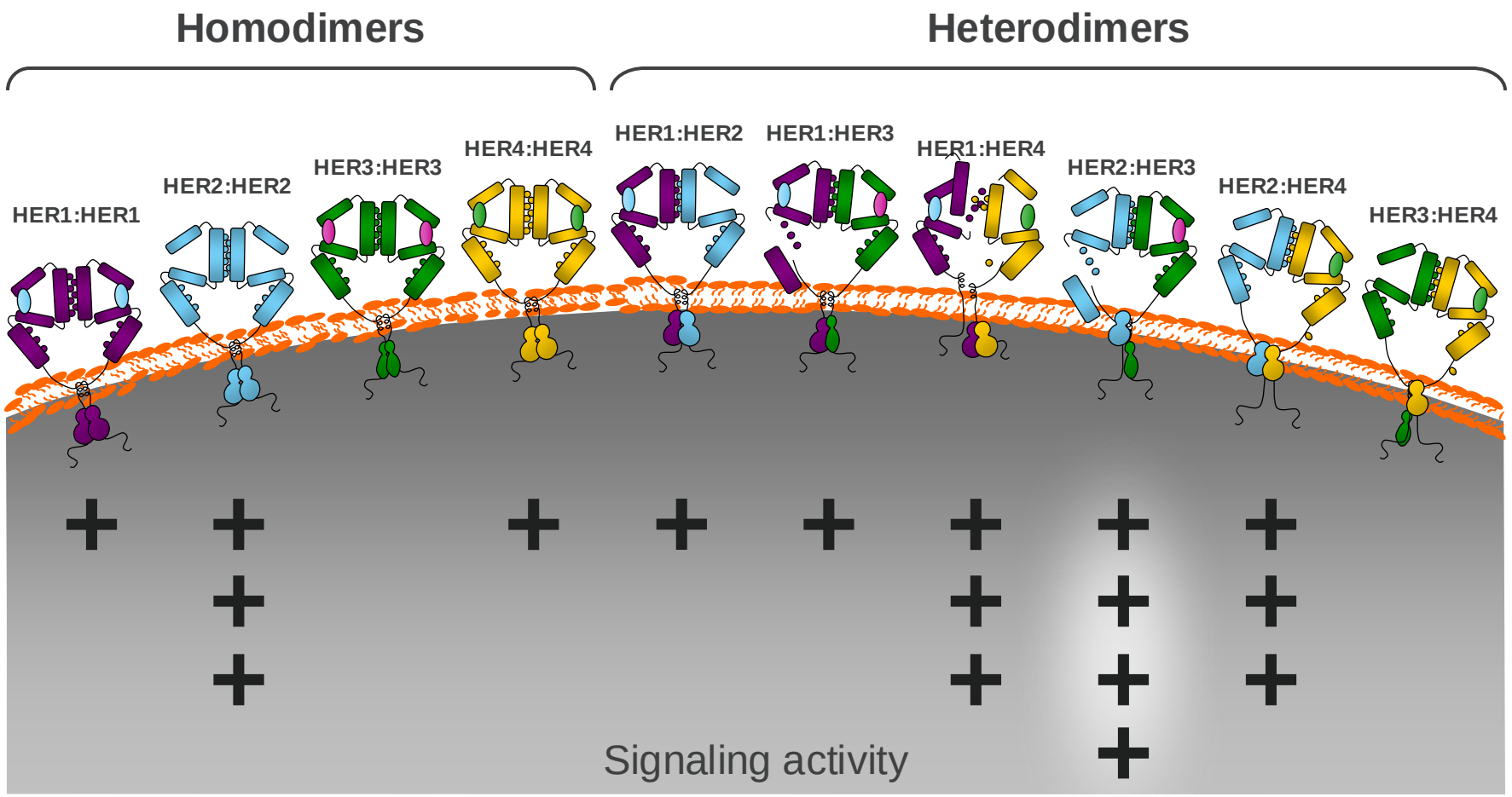
SCHEMATIC,
ELECTRICAL
CIRCUIT
ANALOGY…

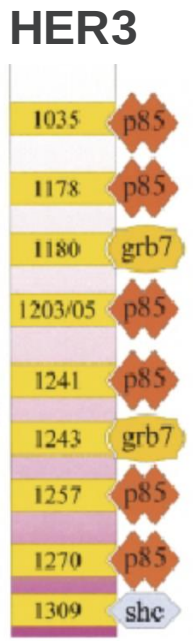


Adapted with permission from Richard Neve, M.D.
Citri A, Yosef Y. *Nat Rev Mol Cell Biol.* 2006;7:505-516.

# HER2:HER3 Dimers Initiate the Strongest Mitogenic Signaling

**SH2 domain of the p85 regulatory subunit of PI3K**




Cytoplasmic Domain aa Sequence

HER3, though a “dead kinase”, has more phosphotyrosine binding sites for the P85 regulatory subunit of PI3K than any other protein in humans

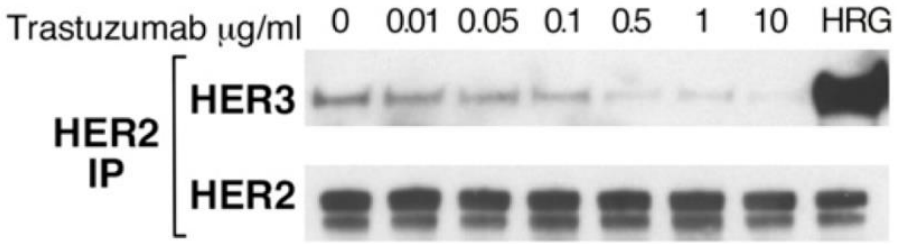
Tzahar, et al. Mol Cell Biol 1996;16:5276-5287. Citri, et al. Exp Cell Res 2003;284:54-65. Huang, et al. Cancer Res 2010;70:1204-1214.

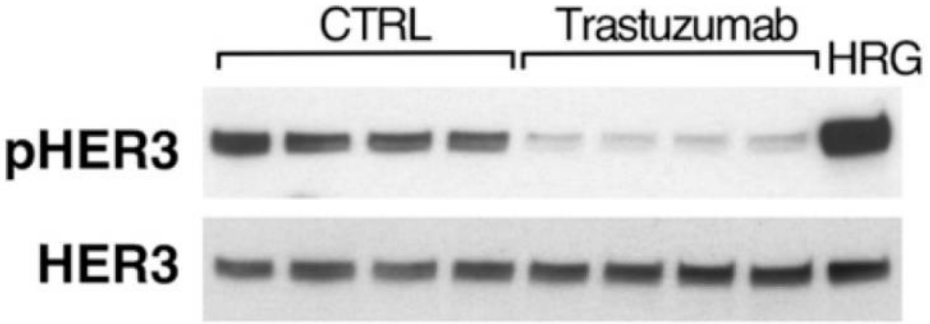
## SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[k]

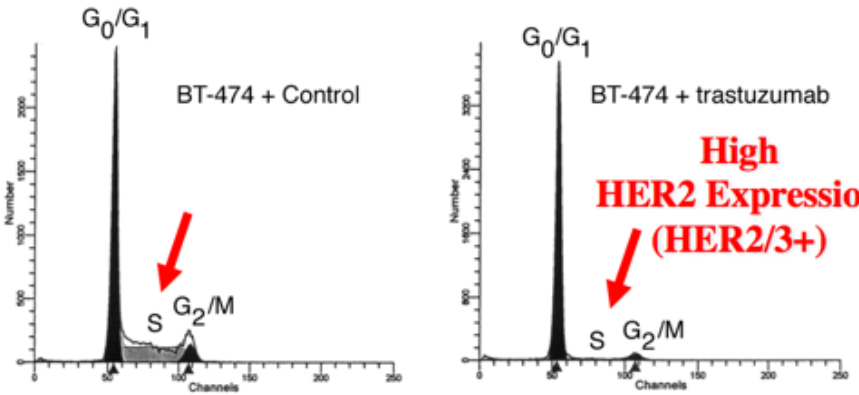
| HR-Positive or -Negative and HER2-Positive[j,k] | |
|---|---|
| **Setting** | **Regimen** |
| **First Line[l]** | Pertuzumab + trastuzumab + docetaxel (Category 1, preferred) |
| | Pertuzumab + trastuzumab + paclitaxel (preferred) |
| **Second Line[n]** | Fam-trastuzumab deruxtecan-nxki[m] (Category 1, preferred) |
| **Third Line** | Tucatinib + trastuzumab + capecitabine[n] (Category 1, preferred) |
| | Ado-trastuzumab emtansine (T-DM1)[o] |
| **Fourth Line and Beyond (optimal sequence is not known)[p]** | Trastuzumab + docetaxel or vinorelbine |
| | Trastuzumab + paclitaxel ± carboplatin |
| | Capecitabine + trastuzumab or lapatinib |
| | Trastuzumab + lapatinib (without cytotoxic therapy) |
| | Trastuzumab + other chemotherapy agents[q,r] |
| | Neratinib + capecitabine |
| | Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) |
| | Targeted Therapy Options BINV-Q (6) |

**Cancer Cell** -- Junttila TT, et al. 2009 May 5;15(5):429-40.

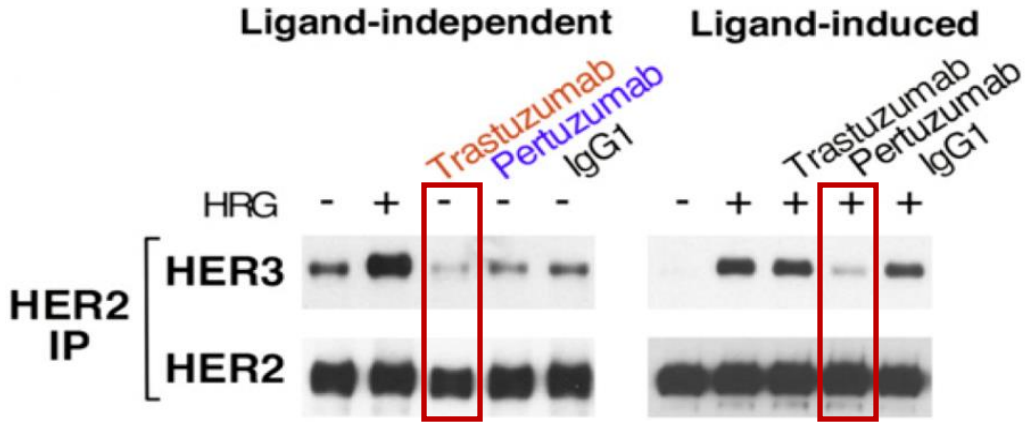
# H+P Rationale: Pertuzumab Binds Subdomain II Disrupting Ligand-Dependent HER2:HER3 Interaction, Inducing Apoptosis

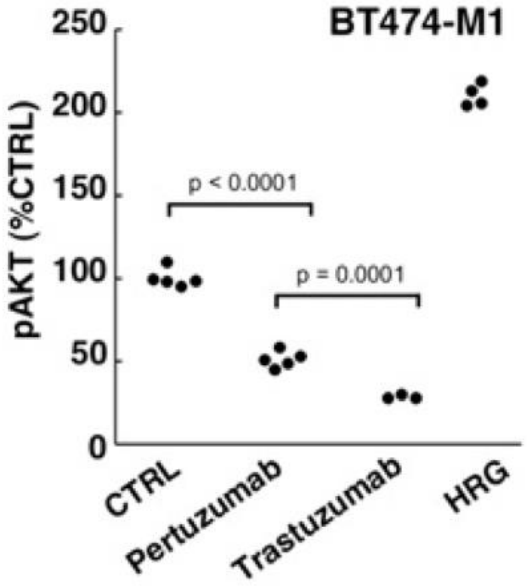


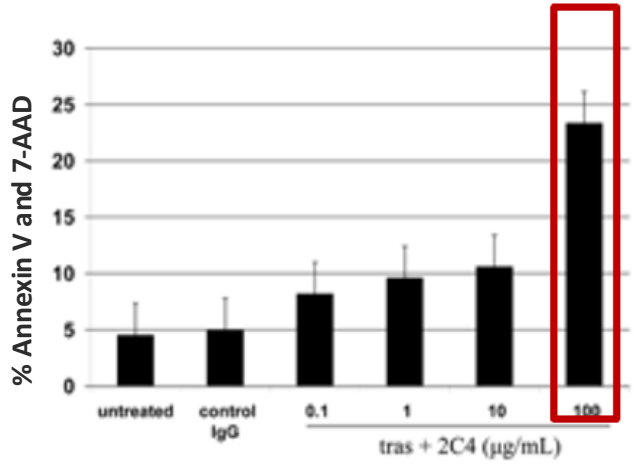




*Pegram, et al. Oncogene, 13:2241 (1997).*
*Lewis G, et al., Cancer Immunol Immunother. 1993;37(4):255-63.*

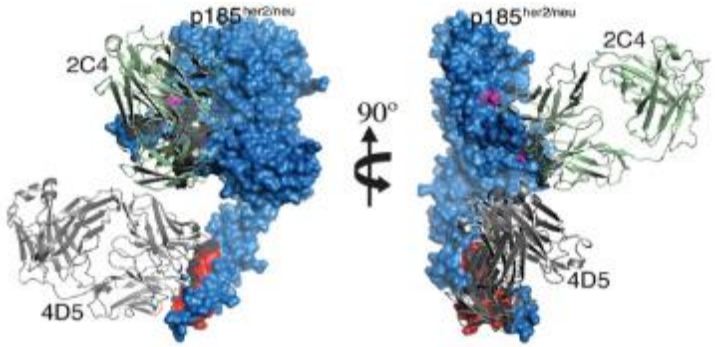


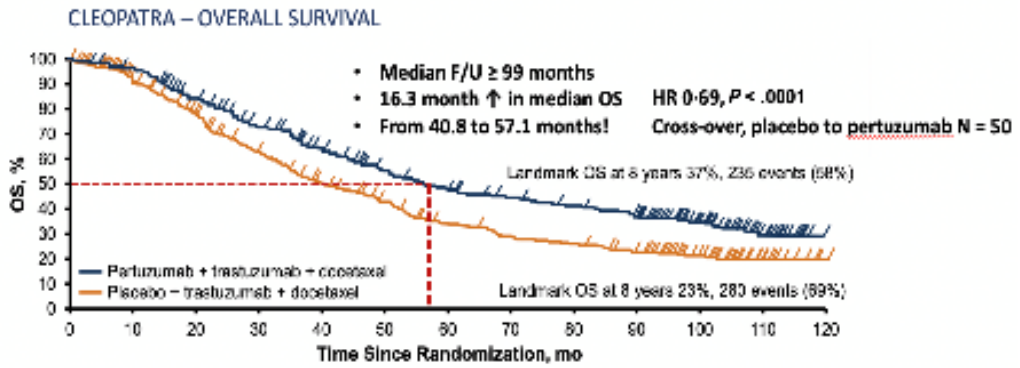

Rita Nahta, *et al*. Cancer Res 2004;64:2343-2346.

# First-line THP – Median OS Increase = 16.3 months by Adding a Second Humanized Antibody: Pertuzumab




Z Cai, et al., Oncogene (2008) 27, 3870–3874


**CLinical Evaluation Of Pertuzumab And TRAstuzumab: End of Study Results**




| | Median OS, Mos |
|---|---|
| P + H + D | 57.1 |
| PBO + H + D | 40.8 |

Most common adverse reactions (> 30%) with pertuzumab + trastuzumab and docetaxel = diarrhea, myelosuppression, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy

Swain, et al. Lancet Oncology 21(4), 519-530, 2020.

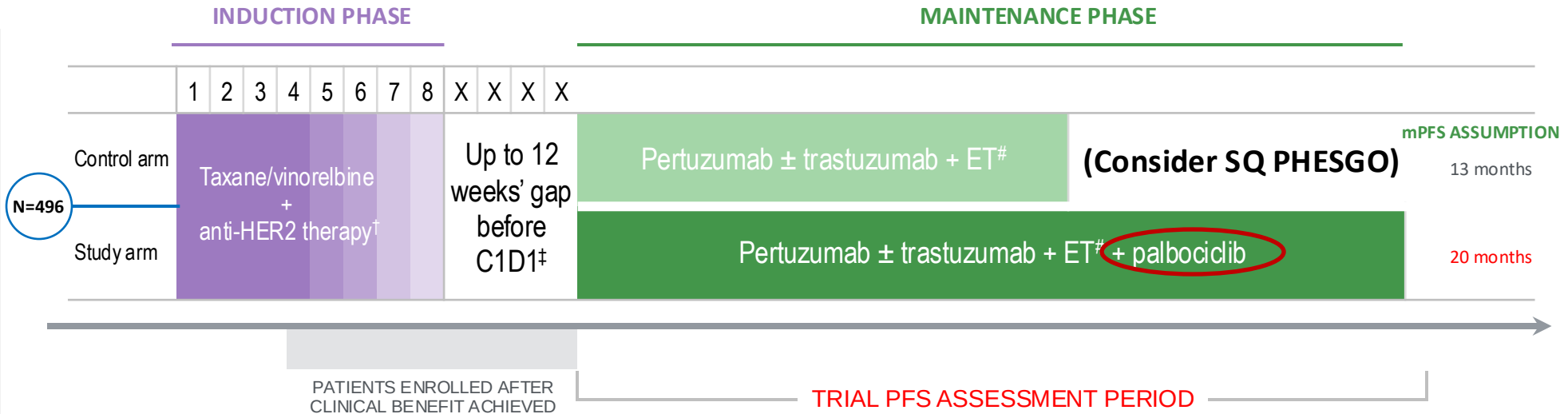
# Future Directions in First-Line HER2+ MBC: PATINA -- Palbociclib in 1st-line HR+/HER2+ mBC as Maintenance Treatment[1,2]

White paper: **M Pegram, R Pietras, C Dang, R Murthy, W Janni, P Sharma, E Hamilton, C Saura, and also please see NPJ Breast CA review on combined receptor blockade, M Pegram, C Jackisch and S Johnston**

The PATINA trial is a randomized Phase III pivotal registration trial designed to demonstrate that the combination of palbociclib with anti-HER2 therapy + endocrine therapy is superior to anti-HER2-based therapy + endocrine therapy alone in improving the outcomes of subjects with HR+/HER2+ mBC

**Key Eligibility Criteria**

- Histologically confirmed
  - HR+/HER2+ mBC
- Anti-HER2-based induction CT Tx prior to randomization*
- No prior Tx in advanced setting beyond induction Tx
- No prior Tx with a CDK4/6 inhibitor
- No evidence of disease progression after induction Tx




| Primary Endpoint | Secondary Endpoints | Other Endpoints |
|---|---|---|
| PFS | OS, 3- and 5-year survival probability, ORR, DoR, CBR, Safety, PROs | PK, PIK3CA status, Tumor tissue biomarkers |

*Patients received induction therapy for 4–8 cycles depending on tolerability. †Anti-HER2+ Therapy – Anti-HER2 treatment options are trastuzumab + pertuzumab or trastuzumab only (limited to 20% of study patients). The same anti-HER2-regimen should be used pre- and post- randomization. ‡Patients randomized immediately following completion of their induction therapy, or for those who have already completed induction, a gap of 12 weeks between their last infusion/dose of induction therapy and the C1D1 visit was permitted. Patients were eligible provided they were without evidence of disease progression by local assessment (i.e. CR, PR or SD). #Endocrine therapy options are either an aromatase Inhibitor or fulvestrant. Pre-menopausal women must receive ovarian suppression with a LHRH agonist if the patients have not documented ovarian ablation or bilateral oophorectomy before randomization or during the conduct of the study

**C1D1** = cycle 1 day 1; **CBR** = clinical benefit rate; **CDK** = cyclin-dependent kinase; **CR** = complete response; **CT** = chemotherapy; **DoR** = duration of response; **ET** = endocrine therapy; **HER2(+)** = human epidermal growth factor receptor 2 (-positive); **HR+** = hormone receptor-positive; **LHRH** = luteinizing hormone-releasing hormone; **mBC** = metastatic breast cancer; **mPFS** = median progression-free survival; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **PIK3CA** = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; **PK** = pharmacokinetic; **PR** = partial response; **PRO** = patient-reported outcome; **SD** = stable disease; **Tx** = treatment.

**1.** ClinicalTrials.gov NCT02947685. https://www.clinicaltrials.gov/ct2/show/NCT02947685. **2.** PATINA (ClinicalTrials.gov NCT02947685) Trial Protocol (data on file).

# Future Directions: DESTINY-Breast09: T-DXd ± Pertuzumab vs THP in First-line HER2+ MBC

## POPULATION

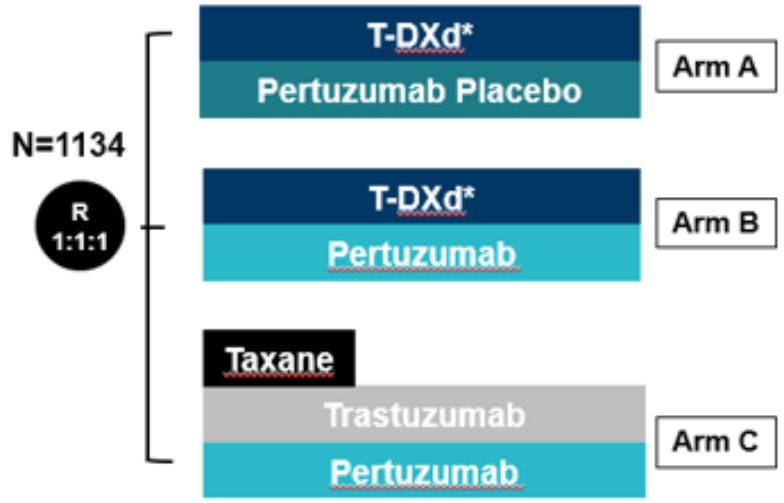
- HER2-positive mBC
- DFI >6 months from last chemotherapy or HER2-targeted therapy in neoadjuvant/adjuvant setting
- No prior systemic treatment for mBC except for endocrine therapy

**Stratification factors:**

- *De novo* vs recurrent (cap at 50% *de novo*)
- HR-positive vs negative
- *PIK3CA*m (detected vs not detected)

NCT04784715

## STUDY DESIGN




- *Participants can continue with trastuzumab if T-DXd is discontinued due to toxicity.
- Use of endocrine therapy is allowed for HR-positive participants after discontinuation of taxane or after 6 cycles of T-DXd.
- Taxane can be paclitaxel or docetaxel.
- Pertuzumab-blinded in the T-DXd arms.

## ENDPOINTS

**Primary:**

- PFS (BICR)

**Secondary:**

- OS
- PFS (Inv. assessed)
- ORR, DoR
- PFS2
- PRO/HRQoL
- PK/ADA
- Safety and tolerability

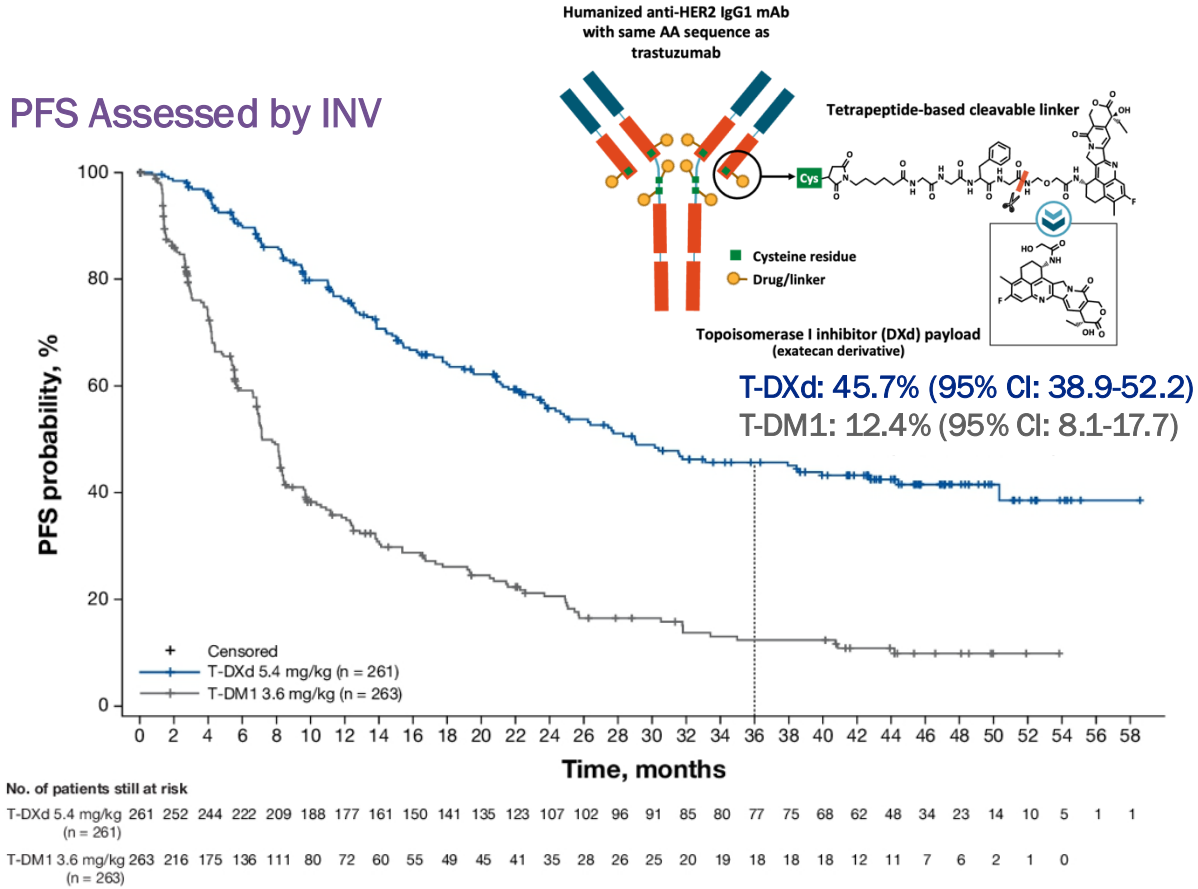
**Exploratory:**

- TTF, TFST, TSST
- BMFS, CNS-PFS
- Patient-reported tolerability
- Exploratory biomarkers

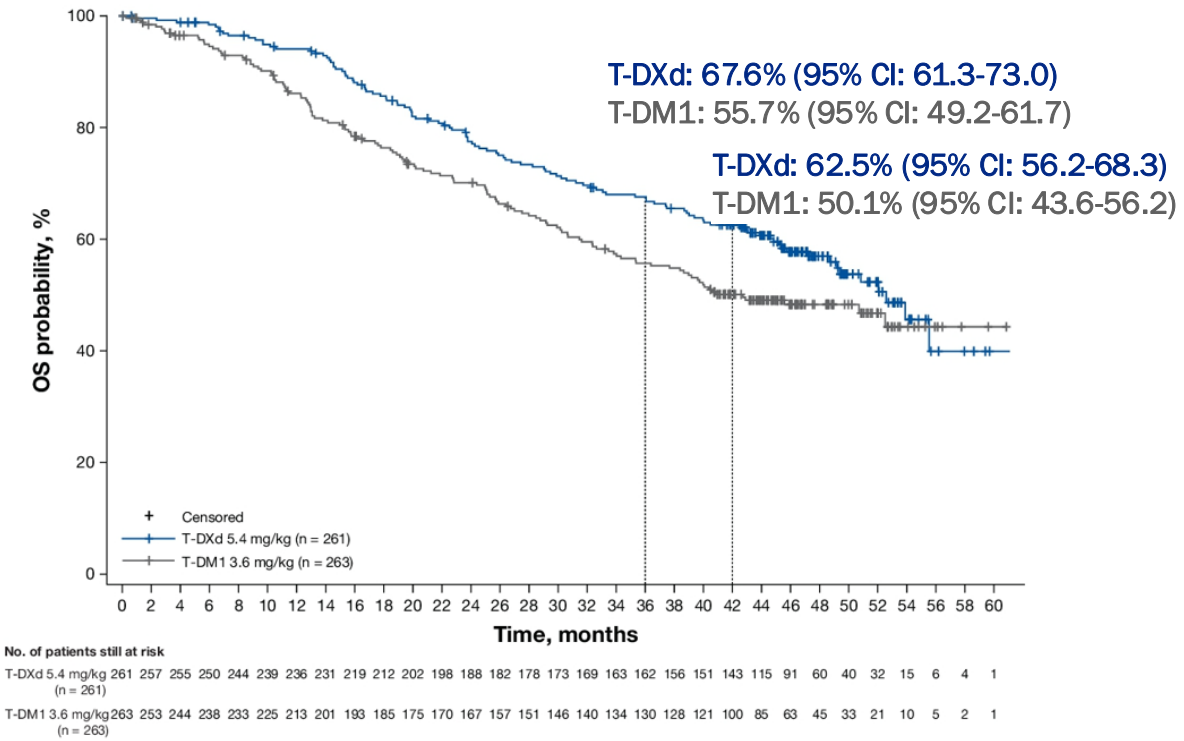
# Second-Line Rx for HER2+ MBC – T-DXd vs T-DM1 in HER2+ MBC: Updated PFS and OS Results From the Randomized Phase 3 DESTINY-Breast03 Study

## Median Follow-Up: 43.0 mo for T-DXd and 35.4 mo for T-DM1

### PFS Assessed by INV




### OS




| | T-DXd (n=261) | T-DM1 (n=263) |
|---|---|---|
| Median PFS, mo (95% CI) | 29.0 (23.7-40.0) | 7.2 (6.8-8.3) |
| HR (95% CI) | 0.30 (0.24-0.38) | |

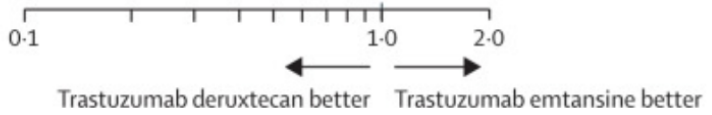
| | T-DXd (n=261) | T-DM1 (n=263) |
|---|---|---|
| Median OS, mo (95% CI) | 52.6 (48.7-NE) | 42.7 (35.4-NE) |
| HR (95% CI) | 0.73 (0.56-0.94) | |

[a] The *P* value for OS crossed the prespecified boundary (*P*=0.013) and was statistically significant.
[b] Two-sided from stratified log-rank test.

Hamilton EP, et al. ASCO 2024. Abstract 1025.

# DESTINY Breast03: Subgroup analysis of overall survival

| | Number of events | | Median overall survival time, months (95% CI) | | Hazard ratio for death (95% CI) |
|---|---|---|---|---|---|
| | Trastuzumab deruxtecan | Trastuzumab emtansine | Trastuzumab deruxtecan | Trastuzumab emtansine | |
| **All patients** | **72/261** | **97/263** | **NR (40·5–NE)** | **NR (34·0–NE)** | **0·64 (0·47–0·87)** |
| **Hormone receptor status** | | | | | |
| Positive | 42/133 | 51/139 | NR (40·5–NE) | 37·7 (34·0–NE) | 0·76 (0·50–1·14) |
| Negative | 30/126 | 45/122 | NR (NE–NE) | NR (28·5–NE) | 0·55 (0·35–0·87) |
| **Previous pertuzumab** | | | | | |
| Yes | 41/162 | 50/158 | NR (40·5–NE) | NR (37·7–NE) | 0·70 (0·46–1·06) |
| No | 31/99 | 47/105 | NR (NE–NE) | 31·5 (22·7–NE) | 0·59 (0·38–0·93) |
| **Baseline visceral disease** | | | | | |
| Yes | 64/195 | 80/189 | NR (40·5–NE) | 35·4 (29·9–NE) | 0·68 (0·49–0·95) |
| No | 8/66 | 17/74 | NR (NE–NE) | NR (NE–NE) | 0·44 (0·19–1·02) |
| **Previous lines of systemic therapy*** | | | | | |
| <3 | 44/188 | 57/191 | NR (40·5–NE) | NR (37·7–NE) | 0·70 (0·47–1·04) |
| ≥3 | 28/73 | 40/72 | NR (27·4–NE) | 22·8 (16·1–31·5) | 0·55 (0·34–0·89) |
| **Baseline brain metastases** | | | | | |
| Yes | 17/43 | 22/39 | NR (23·8–NE) | 25·1 (12·6–NE) | 0·54 (0·29–1·03) |
| No | 55/218 | 75/224 | NR (40·5–NE) | NR (37·7–NE) | 0·66 (0·47–0·94) |




Hurvitz, Sara A et al. The Lancet, Volume 401, Issue 10371, 105 – 117.

# Extended Data Table 4 Any-grade TEAEs reported in ≥20% of patients

From: Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer: long-term survival analysis of the DESTINY-Breast03 trial

| *n* (%) | T-DXd 5.4 mg/kg Q3W *n* = 257 | T-DM1 3.6 mg/kg Q3W *n* = 261 |
|---|---|---|
| **Any TEAEs** | 256 (99.6) | 249 (95.4) |
| **Blood and lymphatic system disorders** | | |
| Neutropenia[a] | 117 (45.5) | 38 (14.6) |
| Anemia[b] | 98 (38.1) | 53 (20.3) |
| Leukopenia[c] | 88 (34.2) | 25 (9.6) |
| Thrombocytopenia[d] | 81 (31.5) | 146 (55.9) |
| **Gastrointestinal disorders** | | |
| Nausea | 198 (77.0) | 79 (30.3) |
| Vomiting | 136 (52.9) | 28 (10.7) |
| Constipation | 97 (37.7) | 51 (19.5) |
| Diarrhea | 86 (33.5) | 21 (8.0) |
| Abdominal pain[e] | 64 (24.9) | 25 (9.6) |
| Stomatitis[f] | 60 (23.3) | 14 (5.4) |
| **General disorders** | | |
| Fatigue[g] | 137 (53.3) | 92 (35.2) |
| **Infections and infestations** | | |
| Upper respiratory tract infection[h] | 76 (29.6) | 41 (15.7) |
| **Investigations** | | |
| Transaminases increased[i] | 89 (34.6) | 124 (47.5) |
| **Metabolism and nutrition disorders** | | |
| Decreased appetite | 80 (31.1) | 46 (17.6) |
| Weight decreased | 61 (23.7) | 24 (9.2) |
| **Musculoskeletal and connective tissue disorders** | | |
| Musculoskeletal pain[j] | 88 (34.2) | 65 (24.9) |
| **Nervous system disorders** | | |
| Headache[k] | 69 (26.8) | 47 (18.0) |
| **Skin and subcutaneous disorders** | | |
| Alopecia | 103 (40.1) | 10 (3.8) |

Cortés, J., Nat Med 30, 2208–2215 (2024).

# Monitoring and Management of T-DXd–Induced ILD: The 5 “S” Rules

## 1 Screen

- Careful patient selection is warranted before T-DXd initiation to optimize monitoring strategies
- Continue monitoring during treatment with regular clinical assessments to exclude symptoms of ILD

## 2 Scan

- Monitor using high resolution chest CT
- Baseline scan is recommended with repeat scans every 6-12 weeks

## 3 Synergy

- Minimizing risk of ILD involves teamwork; educating patients and the care team is essential
- Multidisciplinary management is required once ILD is suspected

## 4 Suspend Treatment

- T-DXd should be interrupted if ILD is suspected
- T-DXd can be restarted only in the case of asymptomatic ILD that has fully resolved

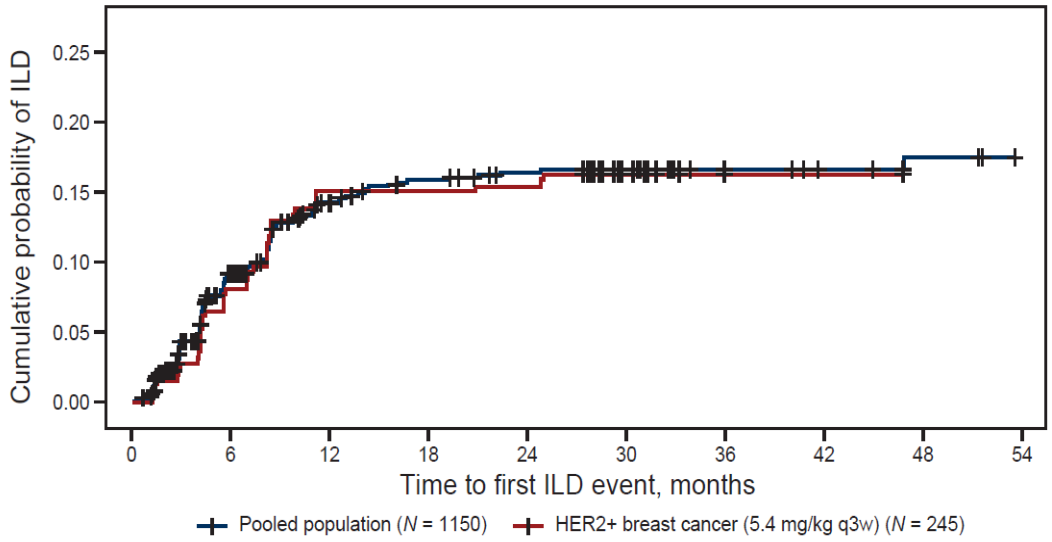
## 5 Steroids

- Corticosteroids are the mainstay of treatment, and the dose should be tailored to toxicity grade

Tarantino P, et al. *JCO Oncol Pract*. 2023;19(8)526-527.

# ILD Risk Factors: Pooled Analysis From 9 Phase 1 and Phase 2 T-DXd Monotherapy Studies

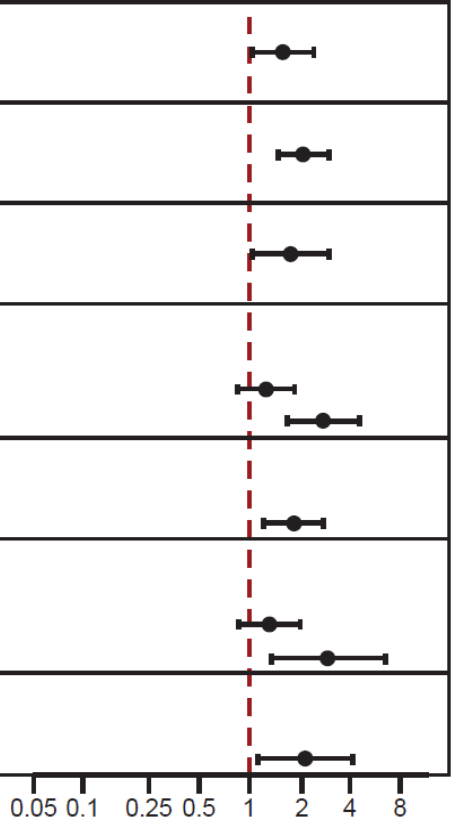
## Time to First Adjudicated Drug-Related ILD Event




| No. at risk (events) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pooled population | 1150 (0) | 547 (101) | 262 (154) | 142 (170) | 84 (174) | 35 (176) | 13 (176) | 7 (176) | 4 (177) | 0 (177) |
| HER2+ breast cancer | 245 (0) | 170 (20) | 95 (37) | 66 (37) | 45 (38) | 11 (40) | 2 (40) | 1 (40) | 0 (40) | 0 (40) |
| **ILD rate** | | | | | | | | | | |
| Pooled population | 0 | 9.2% | 14.3% | 16.0% | 16.4% | 16.6% | 16.6% | 16.6% | 17.5% | 17.5% |
| HER2+ breast cancer | 0 | 8.2% | 15.1% | 15.1% | 15.5% | 16.3% | 16.3% | 16.3% | 16.3% | 16.3% |

## Hazard Ratios[a]

| Potential risk factor | Patients, *n* (*N* = 1150) | Hazard ratio[a] (95% CI) |
|---|---|---|
| **Age group** | | |
| <65 years | 754 | 1.56 (1.02-2.38) |
| ≥65 years | 396 | Ref |
| **Country** | | |
| Japan | 506 | 2.08 (1.45-2.98) |
| Non-Japan | 644 | Ref |
| **Lung comorbidities[b]** | | |
| Yes | 81 | 1.75 (1.03-2.98) |
| No | 1069 | Ref |
| **Baseline renal function[c,d]** | | |
| Normal | 470 | Ref |
| Mild decrease | 458 | 1.24 (0.83-1.84) |
| Moderate/severe decrease | 196 | 2.73 (1.65-4.52) |
| **Time since disease diagnosis[c]** | | |
| 0 to ≤4 years | 624 | Ref |
| >4 years | 403 | 1.82 (1.20-2.75) |
| **Dose** | | |
| 5.4 mg/kg q3w | 315 | Ref |
| 6.4 mg/kg q3w | 808 | 1.30 (0.85-1.99) |
| >6.4 mg/kg q3w | 27 | 2.92 (1.32-6.42) |
| **Baseline $SpO_2$[c]** | | |
| ≥95% | 1080 | Ref |
| <95% | 57 | 2.14 (1.11-4.13) |



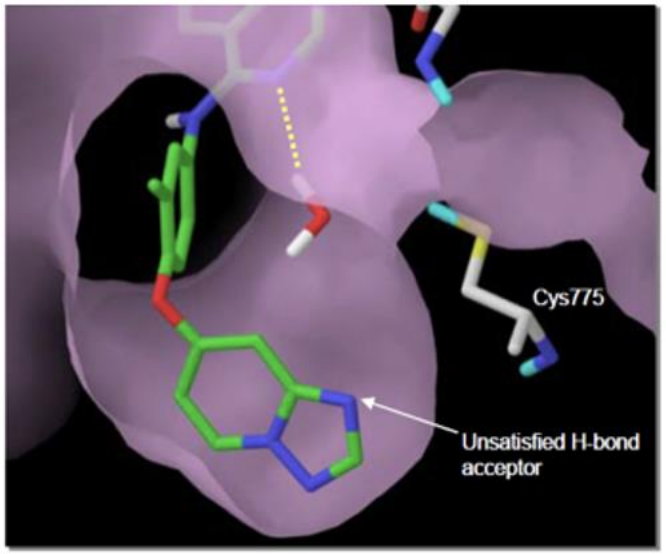

This was a retrospective review of investigator-assessed ILD/pneumonitis events across 9 phase 1 and phase 2 studies and multiple tumor types.

[a] Hazard ratios are presented relative to the reference categories indicated. [b] Includes asthma, chronic obstructive pulmonary disease, prior ILD/pneumonitis, pulmonary fibrosis, pulmonary emphysema, and radiation pneumonitis. [c] Due to differences in data collection among the studies, some data were not collected for all patients; thus, the number of patients may not add up to the total population. [d] Determined by Cockcroft-Gault formula.

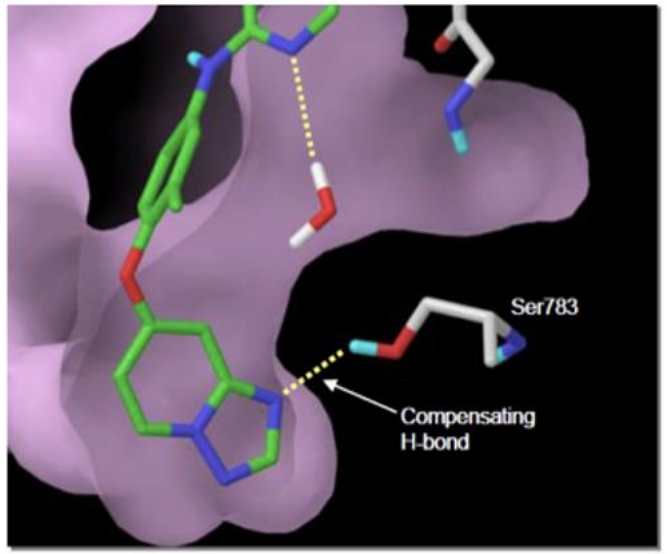
Powell CA, et al. *ESMO Open*. 2022;7(4):100554.

# Tucatinib is > 1,000X more selective for HER2 kinase than EGFR kinase in vitro[1-3]

**EGFR with tucatinib[4]**




**HER2 with tucatinib[4]**




Tucatinib targets the intracellular tyrosine kinase domain of HER2.[2]

Upon binding, tucatinib inhibits the phosphorylation of HER2 and HER3, inhibiting downstream cell signaling.[2]

Consequently, blocking HER2 signaling inhibits cell proliferation and induces cell death.[2]

Highly selective inhibition of HER2 kinase may improve tolerability[5-7]

---------- DRUG INTERACTIONS ----------•

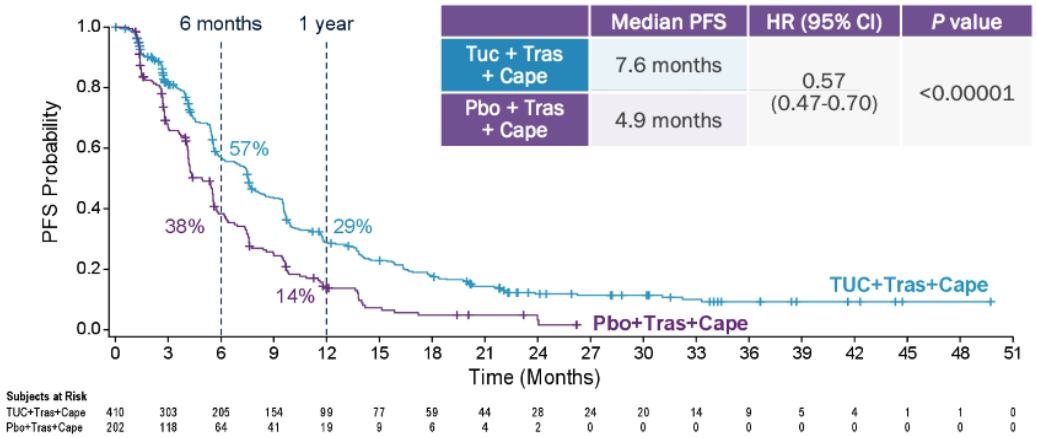
- Strong CYP3A Inducers or Moderate CYP2C8 Inducers: Avoid concomitant use.
- Strong CYP2C8 Inhibitors: Avoid concomitant use; reduce tucatinib dose if concomitant use cannot be avoided.
- CYP3A Substrates: Avoid concomitant use with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.
- P-gp Substrates: Consider reducing the dose of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

**1.** Kulukian A et al. *Mol Cancer Ther*. 2020;19:976-987. **2.** Tucatinib [Prescribing Information]. Bothell, WA: Seagen Inc. April 2020. **3.** Ruiz-Saenz A et al. *J Clin Oncol*. 2018;36:808-811. **4.** Moulder SL et al. AACR-NCI-EORTC. Nov 12-16, 2011; San Francisco, CA. Abstract #A143. **5.** Murthy R et al. *Lancet Oncol*. 2018;19:880-888. **6.** Harandi A et al. *J Oncol*. 2009;2009:567486. **7.** Li J. *J Clin Pharmacol*. 2019;59:935-946.

# The Tucatinib Regimen vs Placebo in HER2+ MBC: Results From the Randomized Phase 3 HER2CLIMB Study – PFS and OS

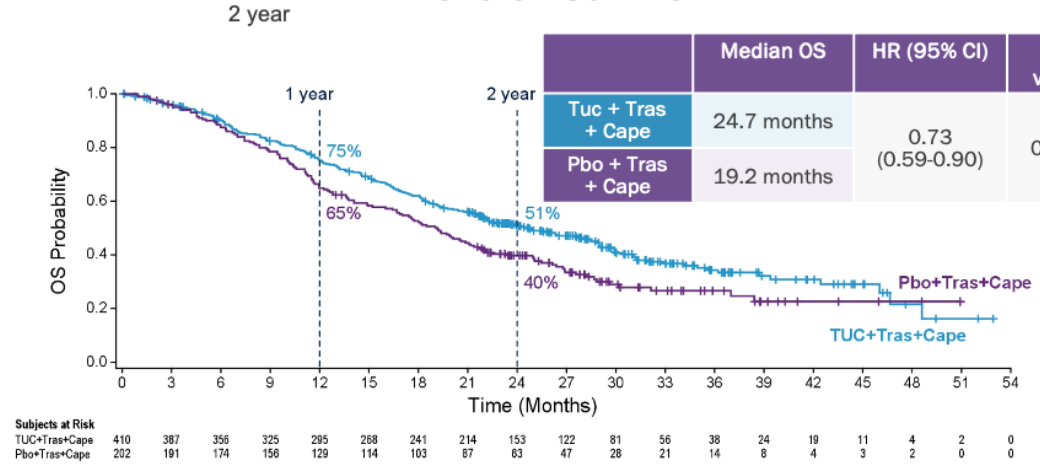
**Median Follow-Up: 29.6 mo**

## Progression-Free Survival




| | Median PFS | HR (95% CI) | *P* value |
|---|---|---|---|
| Tuc + Tras + Cape | 7.6 months | 0.57 (0.47-0.70) | <0.00001 |
| Pbo + Tras + Cape | 4.9 months | | |

## Overall Survival




| | Median OS | HR (95% CI) | *P* value |
|---|---|---|---|
| Tuc + Tras + Cape | 24.7 months | 0.73 (0.59-0.90) | 0.004 |
| Pbo + Tras + Cape | 19.2 months | | |

## Overall Survival in an Exploratory Analysis in Patients With and Without Visceral Metastases

| | Patients With Visceral Metastases (n=455) | | | Patients Without Visceral Metastases (n=157) | | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* value | Median OS | HR (95% CI) | *P* value | Median OS |
| Tuc + Tras + Cape | 0.70 (0.55-0.89) | 0.004 | 21.6 months | 0.80 (0.48-1.3) | 0.36 | 32.9 months |
| Pbo + Tras + Cape | | | 16.9 months | | | 26.9 months |

1. Curigliano G, et al. ASCO 2021. Abstract 1043. 2. Lin NU, et al. JAMA Oncol. 2023 Feb 1;9(2):197-205.

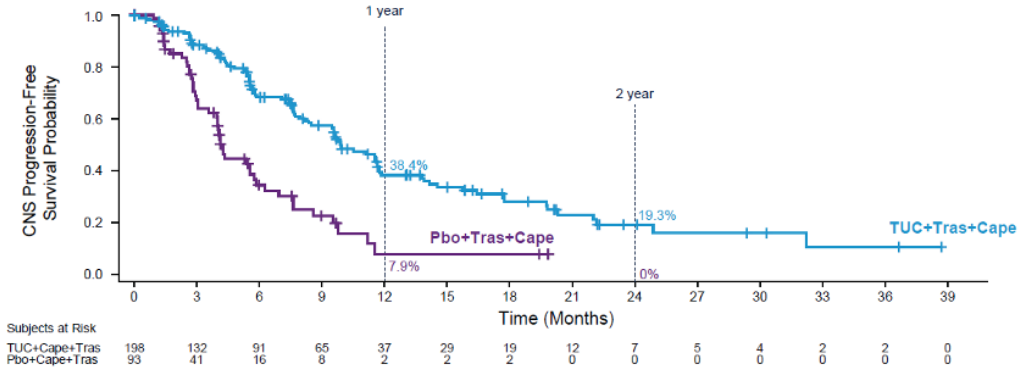
The most common adverse reactions (≥20%) are diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

# The Tucatinib Regimen vs Placebo in Patients With HER2+ MBC and Brain Metastases: Subgroup Analyses From HER2CLIMB

**Median Follow-Up: 29.6 mo**

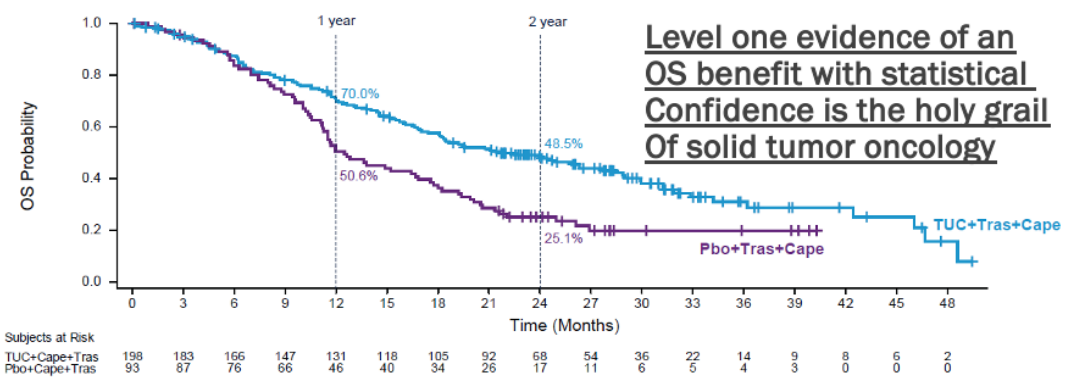
## CNS PFS for All Patients With Brain Metastases

| | Median PFS | HR (95% CI) | *P* value |
|---|---|---|---|
| Tuc + Tras + Cape | 9.9 months | 0.39 (0.27-0.56) | <0.00001 |
| Pbo + Tras + Cape | 4.2 months | | |




## OS for All Patients With Brain Metastases

| | Median OS | HR (95% CI) | *P* value |
|---|---|---|---|
| Tuc + Tras + Cape | 21.6 months | 0.60 (0.44-0.81) | 0.00078 |
| Pbo + Tras + Cape | 12.5 months | | |




Level one evidence of an OS benefit with statistical Confidence is the holy grail Of solid tumor oncology

## OS for Patients With Active Brain Metastases

| | Median OS | HR (95% CI) | *P* value |
|---|---|---|---|
| Tuc + Tras + Cape | 21.4 months | 0.52 (0.36-0.77) | 0.00087 |
| Pbo + Tras + Cape | 11.8 months | | |

## OS for Patients With Treated Stable Brain Metastases

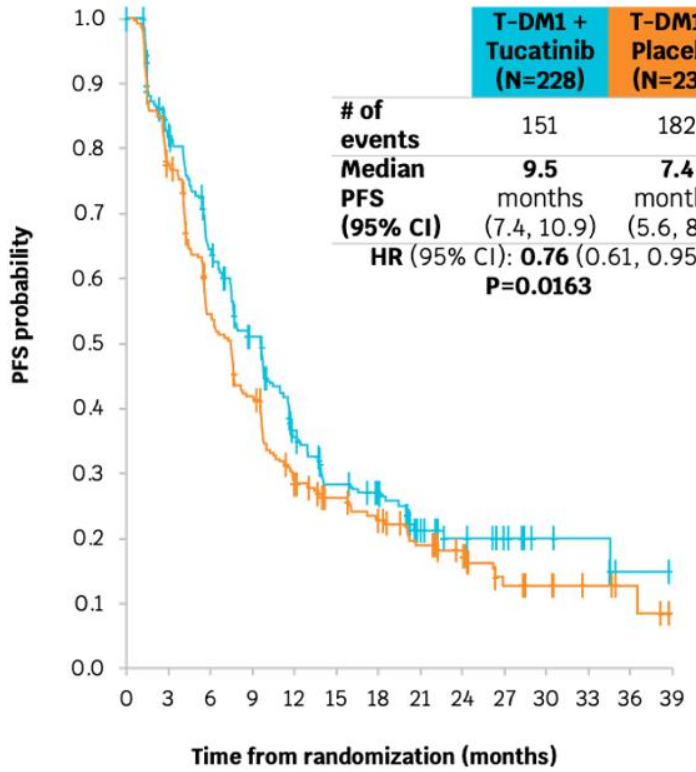
| | Median OS | HR (95% CI) | *P* value |
|---|---|---|---|
| Tuc + Tras + Cape | 21.6 months | 0.70 (0.42-1.16) | 0.162 |
| Pbo + Tras + Cape | 16.4 months | | |

1. Lin NU, et al. SABCS 2021. Abstract PD4-04. 2. Lin NU, et al. JAMA Oncol. 2023 Feb 1;9(2):197-205.

Level one evidence for OS benefit in HER2+ breast cancer brain metastases – a first.

# HER2CLIMB-02: Efficacy PFS & OS -- (T-DM1 ± Tucatinib)

## Progression-Free Survival



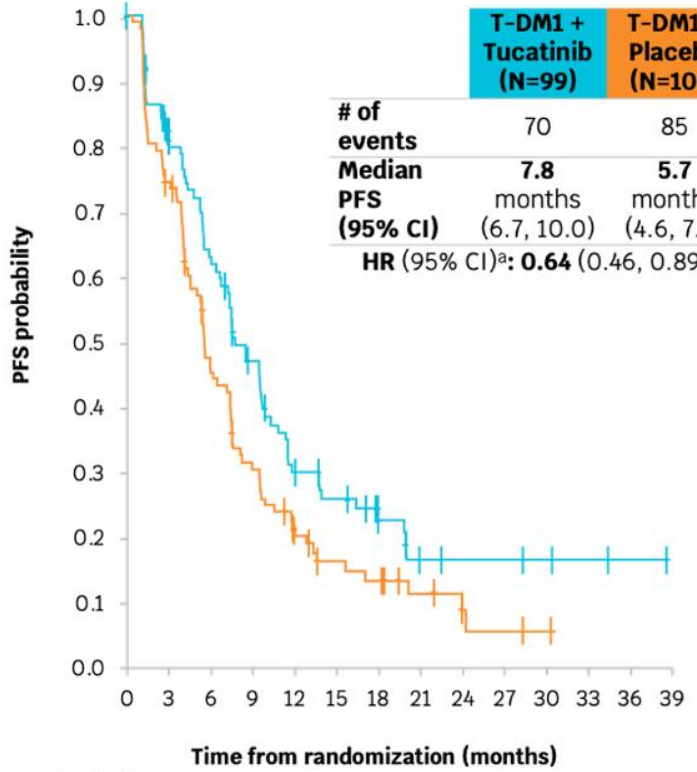

| | T-DM1 + Tucatinib (N=228) | T-DM1 + Placebo (N=235) |
|---|---|---|
| # of events | 151 | 182 |
| Median PFS (95% CI) | **9.5** months (7.4, 10.9) | **7.4** months (5.6, 8.1) |

**HR** (95% CI): **0.76** (0.61, 0.95)
**P=0.0163**

**Patients at risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DM1 + Tucatinib | 228 | 165 | 126 | 96 | 62 | 47 | 40 | 22 | 14 | 10 | 5 | 4 | 1 | 0 |
| T-DM1 + Placebo | 235 | 177 | 120 | 91 | 58 | 48 | 40 | 29 | 19 | 10 | 8 | 5 | 3 | 0 |

## PFS in Patients with Brain Metastases




| | T-DM1 + Tucatinib (N=99) | T-DM1 + Placebo (N=105) |
|---|---|---|
| # of events | 70 | 85 |
| Median PFS (95% CI) | **7.8** months (6.7, 10.0) | **5.7** months (4.6, 7.5) |

**HR** (95% CI)[a]: **0.64** (0.46, 0.89)

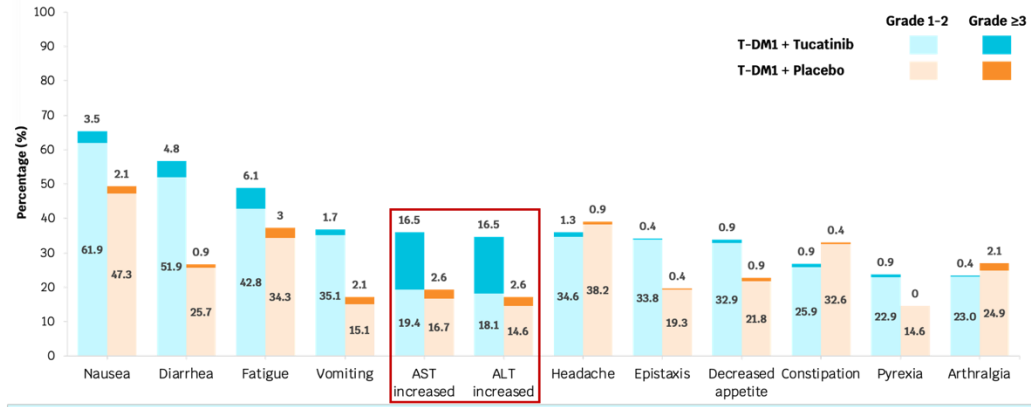
**Patients at risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T-DM1 + Tucatinib | 99 | 76 | 57 | 40 | 25 | 20 | 15 | 6 | 4 | 4 | 3 | 2 | 1 | 0 |
| T-DM1 + Placebo | 105 | 75 | 46 | 30 | 18 | 12 | 10 | 6 | 3 | 2 | 1 | 0 | 0 | 0 |

Hurvitz, S. et al. SABCS 2023

Be mindful of transaminase elevation

## HER2CLIMB-02: Most Common TEAEs (≥20%)




**Most common (≥5%) grade ≥3 TEAEs (T-DM1 + Tucatinib vs T-DM1 + Placebo)** : ALT increased (16.5% vs 2.6%), AST increased (16.5% vs 2.6%), anemia (8.2% vs 4.7%), thrombocytopenia (7.4% vs 2.1%), and fatigue (6.1% vs 3.0%)

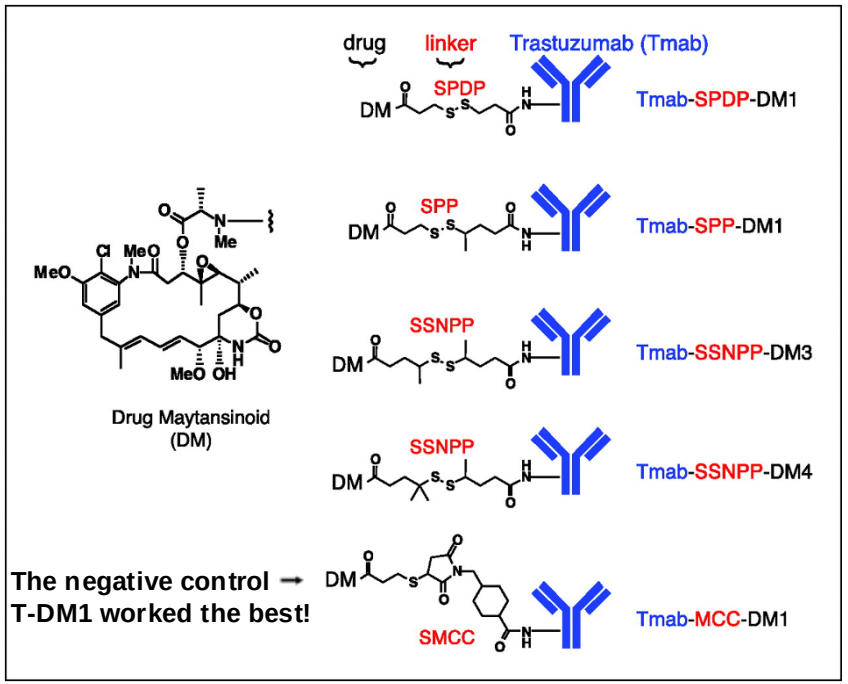
TEAEs occurring in ≥20% of patients in T-DM1 + Tucatinib arm are shown.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; T-DM1, trastuzumab emtansine; TEAEs, treatment-emergent adverse events. Date of data cutoff: Jun 29, 2023.

Hurvitz, S. et al. SABCS 2023

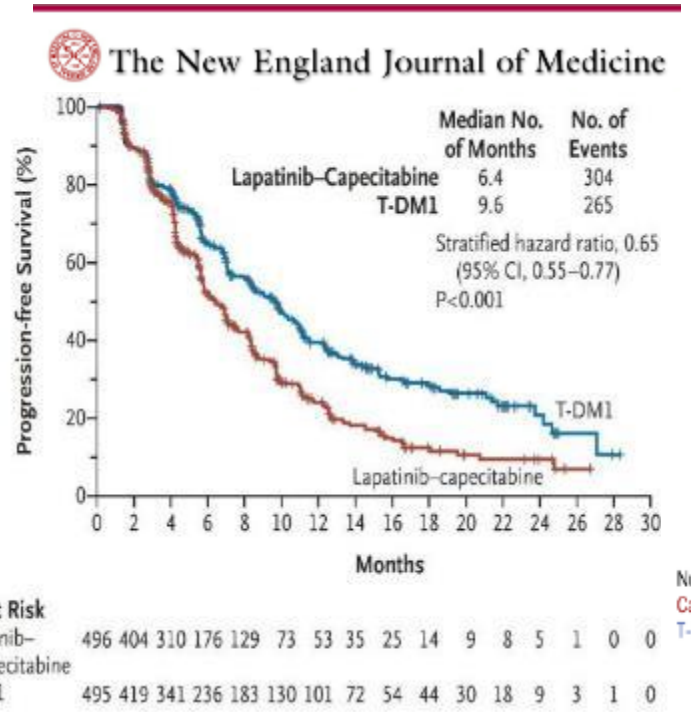
# Phase III EMILIA: T-DM1 in HER2+ MBC (prior to the T-DXd era)

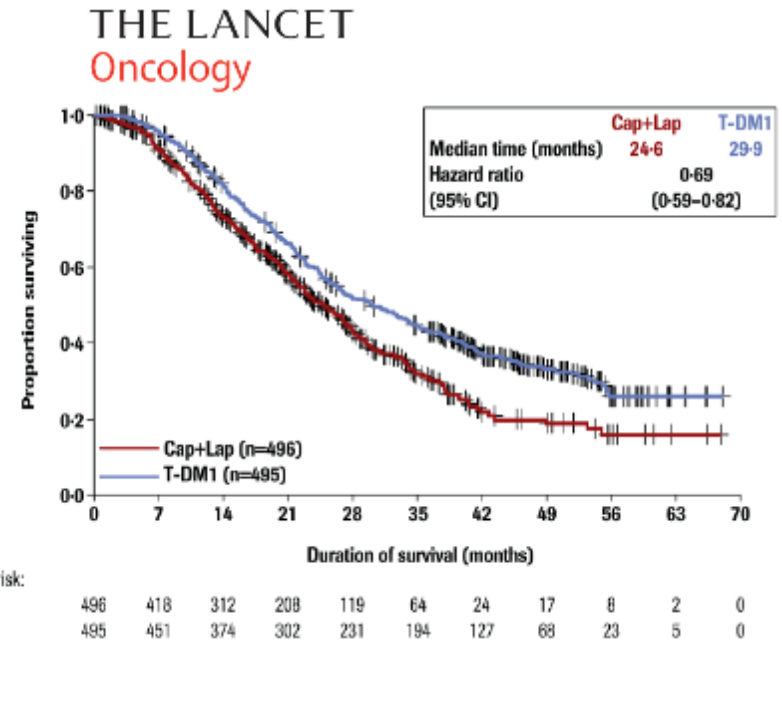
## In EMILIA, T-DM1 was superior to lapatinib + capecitabine in HER2+ mBC[1,2]

- In 991 randomized patients, median PFS was 9.6 months with T-DM1 vs 6.4 months with lapatinib + capecitabine (HR 0.65; 95% CI, 0.55 to 0.77; *P*<0.001), and median OS was 30.9 months vs. 25.1 months (HR, 0.68; 95% CI, 0.55 to 0.85; *P*<0.001).




Lewis Phillips G D et al. Cancer Res 2008;68:9280-9290



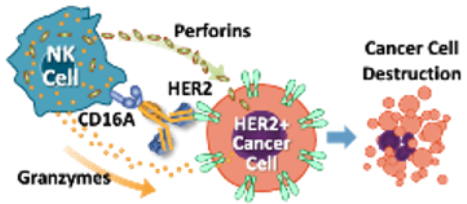

**The most common adverse drug reactions (frequency > 25%) with T-DM1 (n=884 treated patients) were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation.**

HER, human epidermal growth factor receptor; HR, hazard ratio; mBC, metastatic breast cancer; PFS, progression-free survival; OS, overall survival.

1. Verma S, et al. *N Engl J Med*. 2012;367:1783-1791. 2. Diéras V, et al. Lancet Oncol. 2017 Jun;18(6):732-742.

# Fc-Engineered HER2-Targeted Chimeric Monoclonal Antibody Margetuximab

**Increased CD16A Affinity:**
**Enhanced Innate Immunity/More Potent ADCC Stimulation**




Musolino A, Gradishar WJ, Rugo HS, Nordstrom JL, Rock EP, Arnaldez F, Pegram MD.J Immunother Cancer. 2022 Jan;10(1):e003171.

**Margetuximab: Increased affinity for activating Fcγ RIIIA (CD16A) and decreased affinity for inhibitory Fcγ RIIB (CD32B)**

FcγRIIIB

IgG1 Fc

Co-crystal structure

Locations of Fc mutations (red, blue) identified by yeast surface display identify the variant F243L/R292P/Y300L/V305I/P396L
Stavenhagen. Cancer Res. 2007;67:8882.

**SOPHIA:**
HER2+ advanced BC with ≥ 2 previous anti-HER2 therapies; prior brain metastasis allowed if treated/stable
**(N = 536)**

| Margetuximab + Chemotherapy | Trastuzumab + Chemotherapy |
|---|---|

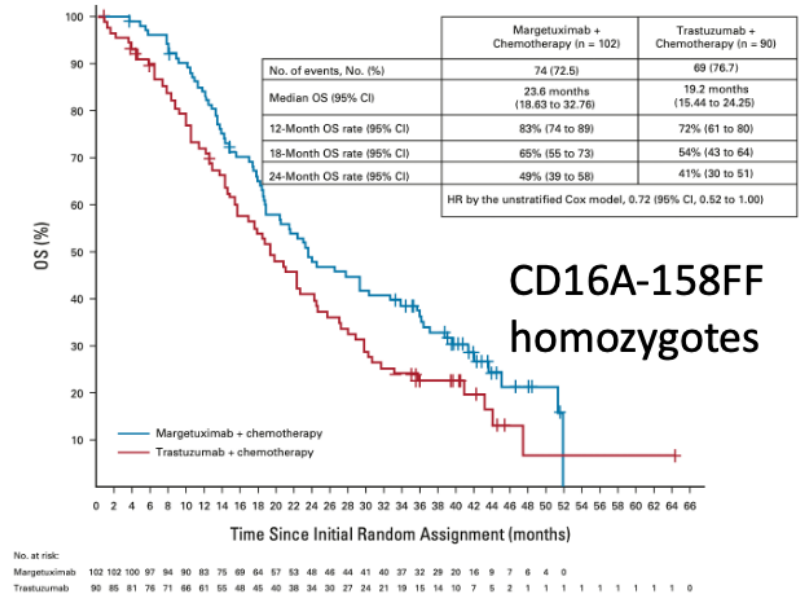
*Investigators choice of CT:
capecitabine, eribulin, gemcitabine, or vinorelbine.

**Sequential primary endpoint: PFS, OS**
**Secondary endpoints:** ORR by central blinded analysis, investigator-assessed PFS
**Tertiary and exploratory endpoints:** investigator-assessed CBR, DoR, safety, effect of CD16A, CD32A, and CD32B alleles on margetuximab efficacy

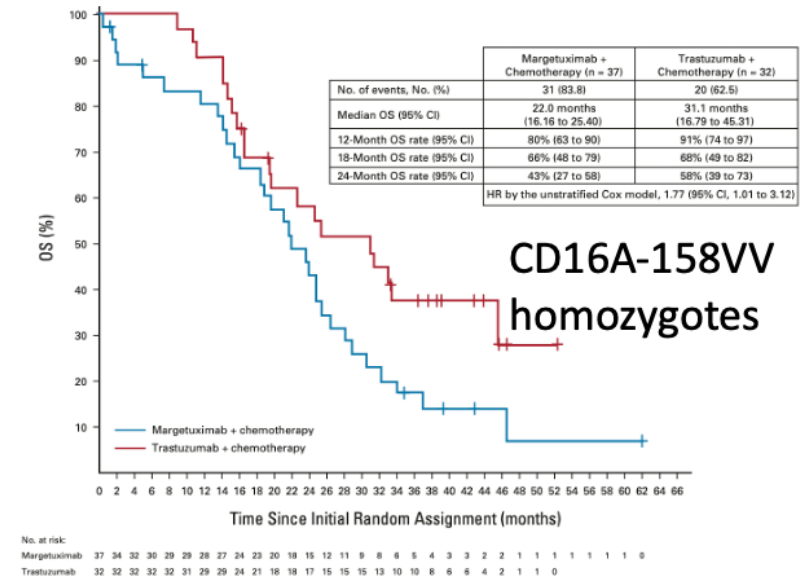
**Safety: ↑ in IRR, 14.4% vs 3.8%**

# CD16A Genotype by Treatment Group

## Prespecified Exploratory OS Analysis



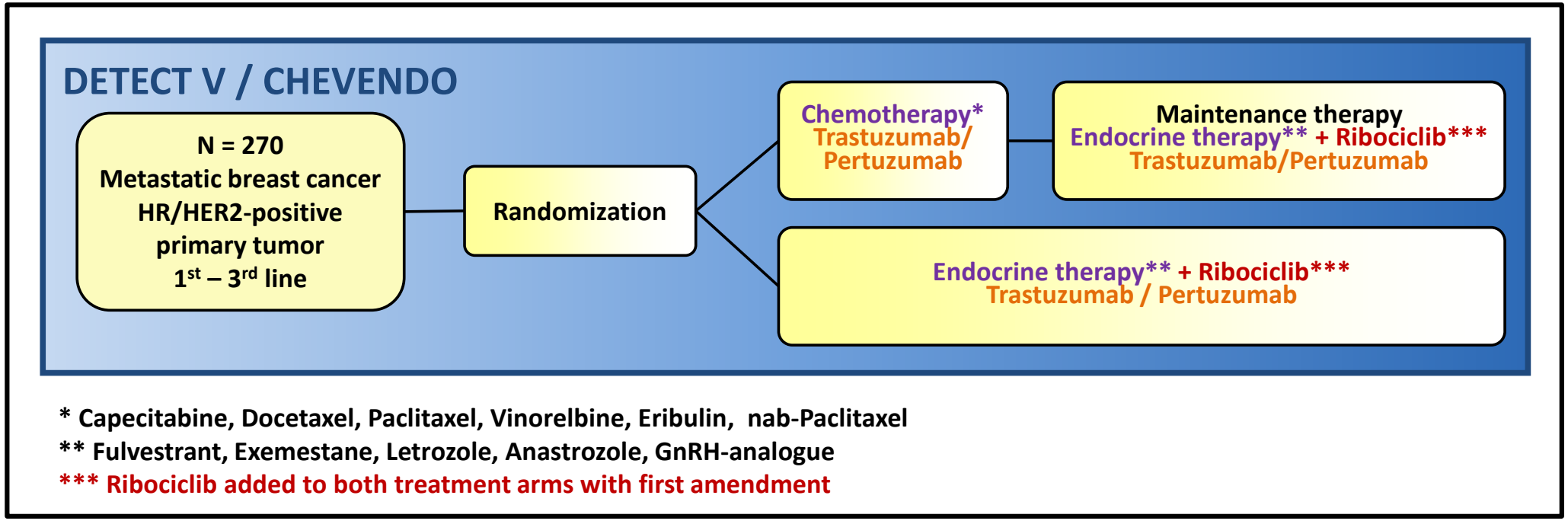

CD16A-158FF homozygotes




CD16A-158VV homozygotes

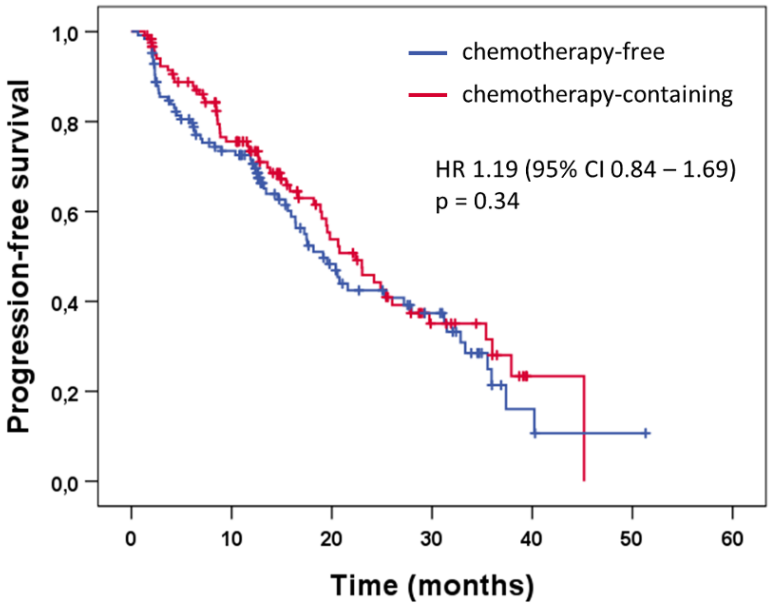
Rugo HS, et al. J Clin Oncol. 2023 Jan 10;41(2):198-205.

# METHODS: Study design Phase III RCT

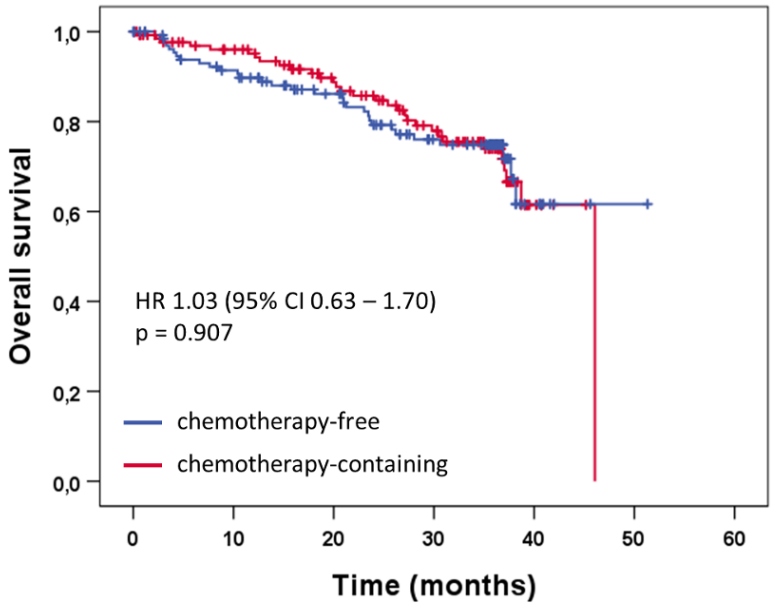



- After 124 enrolled patients, the study was amended with the addition of the CDK4/6 inhibitor **ribociclib to endocrine therapy in both arms**
- Second interim efficacy analysis with data cut off April 3rd 2024 (271 patients enrolled; 54 patients still in the follow-up period)

# RESULTS: CT-free vs CT-containing treatment - Efficacy




Adjusted multivariable analysis:
HR 1.18 (95% CI 0.81 – 1.72), p = 0.381

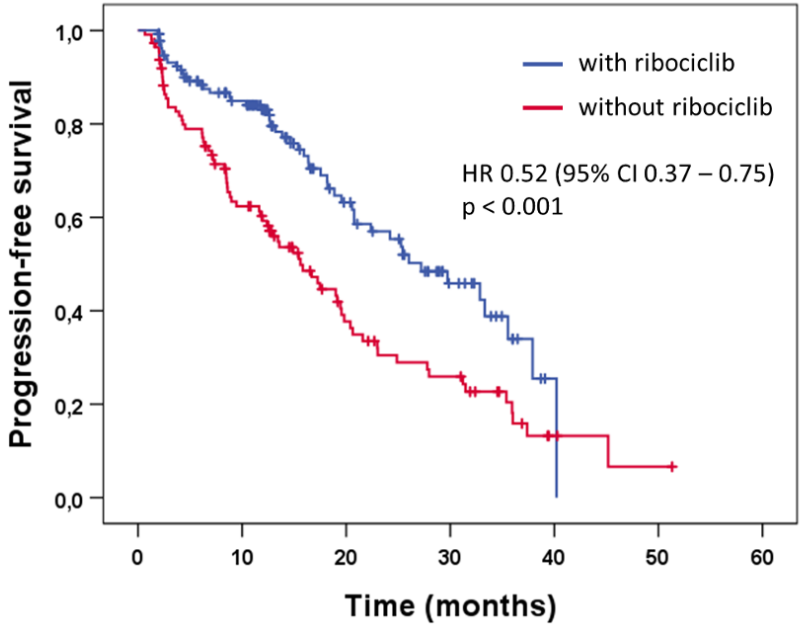


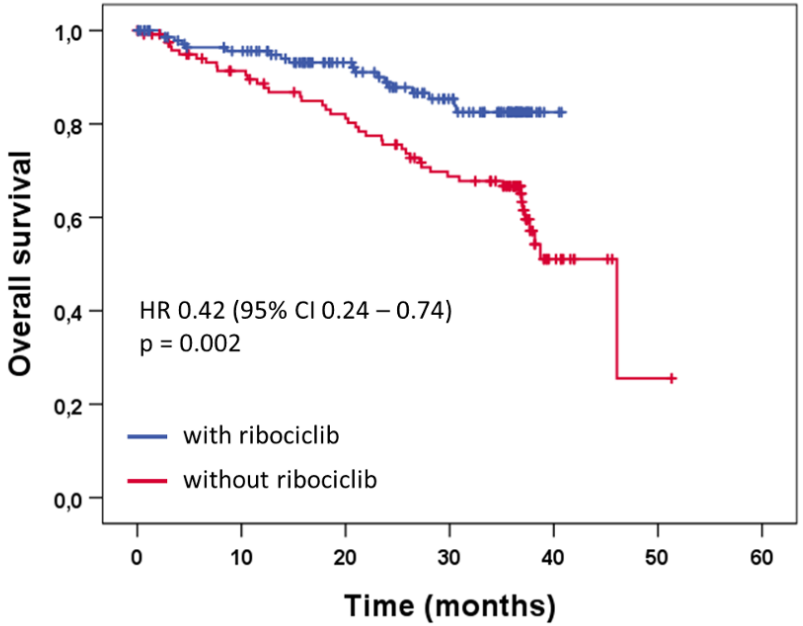

Adjusted multivariable analysis:
HR 1.07 (95% CI 0.62 – 1.82), p = 0.816

Wolfgang Janni

| SAFETY | CT-free (n = 135) | CT-containing (n = 136) | P-value |
|---|---|---|---|
| Patients with ≥ 1 SAE | 52 (38.5%) | 46 (33.8%) | 0.421 |
| Patients with ≥ 1 AEs grade 3/4/5 | 74 (54.8%) | 83 (61.0%) | 0.300 |

# RESULTS: Ribociclib vs no ribociclib – Efficacy*




Adjusted multivariable analysis:
HR 0.57 (95% CI 0.39 – 0.85), p = 0.005

Adjusted multivariable analysis:
HR 0.47 (95% CI 0.26 – 0.85), p = 0.013

*Comparison of subsequent study cohorts, no randomized comparison

Wolfgang Janni

| SAFETY | Ribociclib (n = 147) | No ribociclib (n = 124) | P-value |
|---|---|---|---|
| Patients with ≥ 1 SAE | 55 (37.4%) | 43 (34.7%) | 0.640 |
| Patients with ≥ 1 AEs grade 3/4/5 | 95 (64.6%) | 62 (50.0%) | 0.015 |

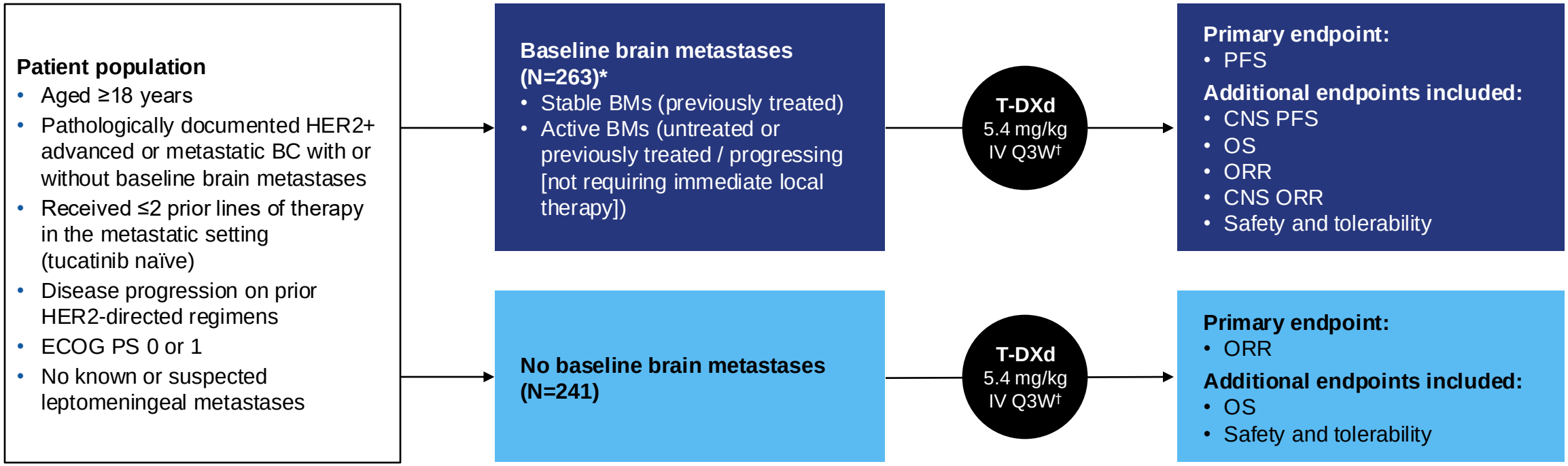
# RESULTS: Ribociclib vs no ribociclib - Safety

Most common adverse events by frequency (AEs all grades > 30 and/or AEs grade 3 or higher > 5)

| | Ribociclib (n = 147) | | No ribociclib (n = 124) | |
|---|---|---|---|---|
| | All grades | Grade 3 or higher | All grades | Grade 3 or higher |
| Diarrhea | 131 | 15 | 115 | 11 |
| Neutrophil count decreased | 100 | 74 | 17 | 10 |
| Fatigue | 67 | 4 | 41 | 3 |
| Nausea | 54 | 2 | 54 | 4 |
| White blood cell decreased | 66 | 18 | 19 | 4 |
| Anemia | 43 | 9 | 28 | 4 |
| Peripheral sensory neuropathy | 37 | 2 | 27 | 1 |
| Alanine aminotransferase increased | 50 | 21 | 6 | 1 |
| Mucositis oral | 19 | 1 | 35 | 6 |
| Alopecia | 32 | 0 | 20 | 0 |
| Vomiting | 23 | 1 | 18 | 3 |
| Aspartate aminotransferase increased | 35 | 10 | 4 | 2 |
| Dyspnea | 14 | 4 | 24 | 4 |
| Hypertension | 24 | 11 | 13 | 4 |
| Headache | 15 | 2 | 18 | 1 |
| Epistaxis | 19 | 0 | 14 | 0 |
| Dry skin | 17 | 0 | 13 | 2 |
| Hot flashes | 14 | 0 | 16 | 0 |
| GGT increased | 21 | 6 | 4 | 2 |
| Left ventricular systolic dysfunction | 4 | 4 | 4 | 4 |

# DESTINY-Breast12 study design

Phase 3b/4, multicenter, single-arm, two-cohort, open-label study of T-DXd in previously treated HER2+ mBC with and without brain metastases (BMs); the largest prospective study of T-DXd in patients with stable or active BMs



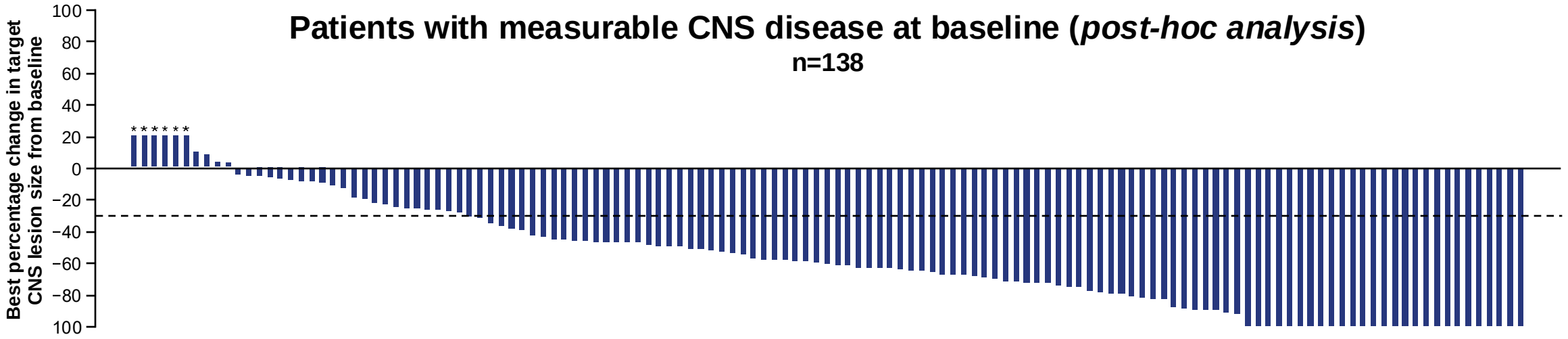

Data reported for the full analysis set (all patients enrolled in the study who received at least one treatment dose) and safety analysis set (identical to full analysis set). No hypothesis testing or comparison of cohorts. Response and progression assessed by ICR per RECIST 1.1 in both cohorts. Patients were enrolled from Australia, Canada, Europe, Japan, and United States

***Concomitant use of ≤3 mg of dexamethasone daily or equivalent allowed for symptom control of BMs (baseline BMs cohort only)**; †until RECIST 1.1-defined disease progression outside the CNS

BC, breast cancer; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; ICR, independent central review; IV, intravenous; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

NCT04739761. Updated. July 19, 2024. Available from: https://www.clinicaltrials.gov/study/NCT04739761 (Accessed September 9, 2024)

# Baseline BMs: CNS ORR



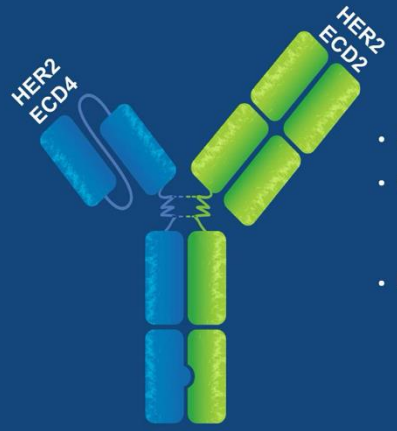

| Measurable CNS disease at baseline | All patients (n=138) | Stable BMs (n=77) | Active BMs (n=61) | Active BM subgroups: Untreated (n=23) *Post-hoc analysis* | Active BM subgroups: Previously treated / progressing (n=38) *Post-hoc analysis* |
|---|---|---|---|---|---|
| **Confirmed CNS ORR, % (95% CI)** | **71.7 (64.2, 79.3)** | 79.2 (70.2, 88.3) | 62.3 (50.1, 74.5) | 82.6 (67.1, 98.1) | 50.0 (34.1, 65.9) |

**T-DXd showed substantial CNS responses in the overall BMs population, including patients with stable and active BMs**

Dashed line indicates a 30% decrease in target tumor size (PR)
*Imputed values: a value of +20% was imputed if best percentage change could not be calculated because of missing data if: a patient had a new lesion or progression of non-target lesions or target lesions, or had withdrawn because of PD and had no evaluable target lesion data before or at PD
BM, brain metastasis; CI, confidence interval; CNS, central nervous system; ORR, objective response rate; PD, progressive disease; PR, partial response; T-DXd, trastuzumab deruxtecan

# FUTURE DIRECTIONS: HER2:HER2 BISPECIFIC ZANIDATAMAB BINDS TRASTUZUMAB AND PERTUZUMAB EPITOPES HER2 CROSSLINKING IS A POTENT STIMULUS FOR HER2 INTERNALIZATION/DOWNREGULATION

## ZW25: Azymetric™ Bispecific HER2-Targeted Antibody




- Designed using the Azymetric bispecific platform
- Biparatopic - simultaneously binds two HER2 epitopes
  - ECD4 (trastuzumab binding domain)
  - ECD2 (pertuzumab binding domain)
- Unique binding results in novel mechanisms of action



## Zanidatamab + Palbociclib + Fulvestrant in HER2+ HR+ MBC

**Select Eligibility Criteria**

- Unresectable, locally advanced and/or metastatic HER2+ HR+ BC
- Enrollment based on local HER2 assessment (reassessed using central testing)
- ECOG PS ≤1
- Prior treatment with trastuzumab, pertuzumab, and T-DM1 were required
- No prior treatment with CDK4/6 inhibitor(s)
- Previously treated, stable brain metastases allowed

**Single Arm**

**Zanidatamab**[a]
20 mg/kg IV Q2W
+
**Palbociclib**
125 mg PO daily (day 1-21)
+
**Fulvestrant**
500 mg IM Q4W[b]

Tumor assessments Q8W

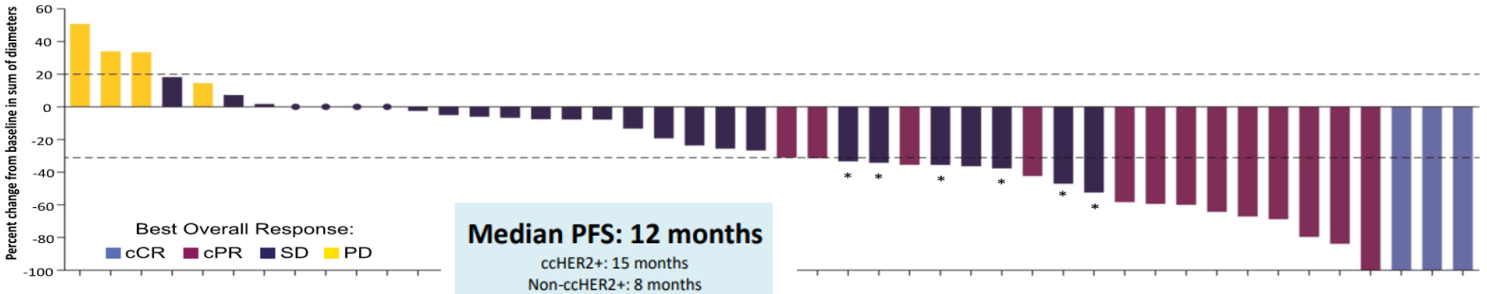
**Endpoints**

**Primary endpoints:**
- Part 1: Safety
- **Part 2: PFS6**

**Select secondary endpoints:**
- ORR
- DCR
- DOR
- PFS
- OS

**Select exploratory endpoints:**
- PAM50 subtyping

### Efficacy of Treatment by Best Overall Response (All Patients With Measurable Disease)




Escriva-de-Romani S, et al. SABCS 2023

# SOME FUTURE DIRECTIONS:

## HER2CLIMB05

**Eligibility criteria**

- Unresectable locally advanced or metastatic HER2-positive BC[1,2]
- Prior treatment with trastuzumab, pertuzumab, and taxane as 1L therapy advanced BC with no evidence of disease progression[1]
- Known HR status[1]
- ECOG PS 0–1[1]
- No evidence of BMs, or untreated asymptomatic BMs, or previously treated asymptomatic BMs[1]
- N=650[1]

**Induction therapy:** Pertuzumab + trastuzumab + taxane (4–8 cycles)[2]

R 1:1

- **Tucatinib (300 mg PO BID) + pertuzumab (420 mg IV Q3W) + trastuzumab (6 mg/kg IV or 600 mg SC Q3W)**
- **Placebo (PO BID) + pertuzumab (420 mg IV Q3W) + trastuzumab (6 mg/kg IV or 600 mg SC Q3W)**

**Study endpoints**

Primary endpoint
- PFS by IA

Secondary endpoints
- OS
- PFS by BICR
- HRQoL
- CNS PFS
- Safety
- PK of tucatinib

## herdERA

**Eligibility criteria**

- HER2-positive LA or mBC
- Maintenance phase: Complete a minimum of 4 cycles of induction therapy, achieve a minimum of stable disease
- ECOG 0–1
- Previously untreated HER2-positive ER-positive
- N=812

**Induction therapy:** Phesgo + taxane

R 1:1

- **Phesgo + giredestrant**
- **Phesgo**

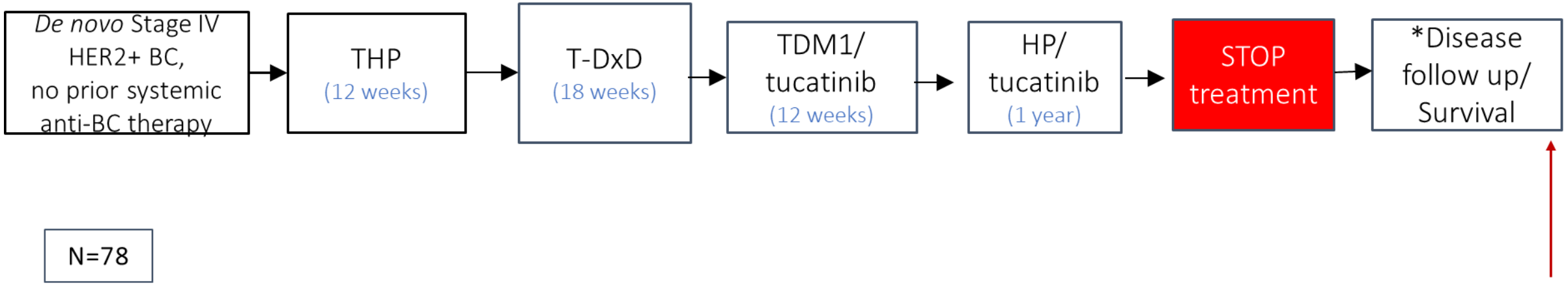
**Study endpoints**

Primary endpoint
- PFS

Secondary endpoints
- OS
- ORR
- DoR
- CBR
- Safety and HRQoL

# Future Direction…

## SAPPHO: Phase II Trial of Sequential HER2 Therapies for HER2+ Advanced Disease




N=78

**Primary endpoint: Percentage of patients progression-free at 4yrs**

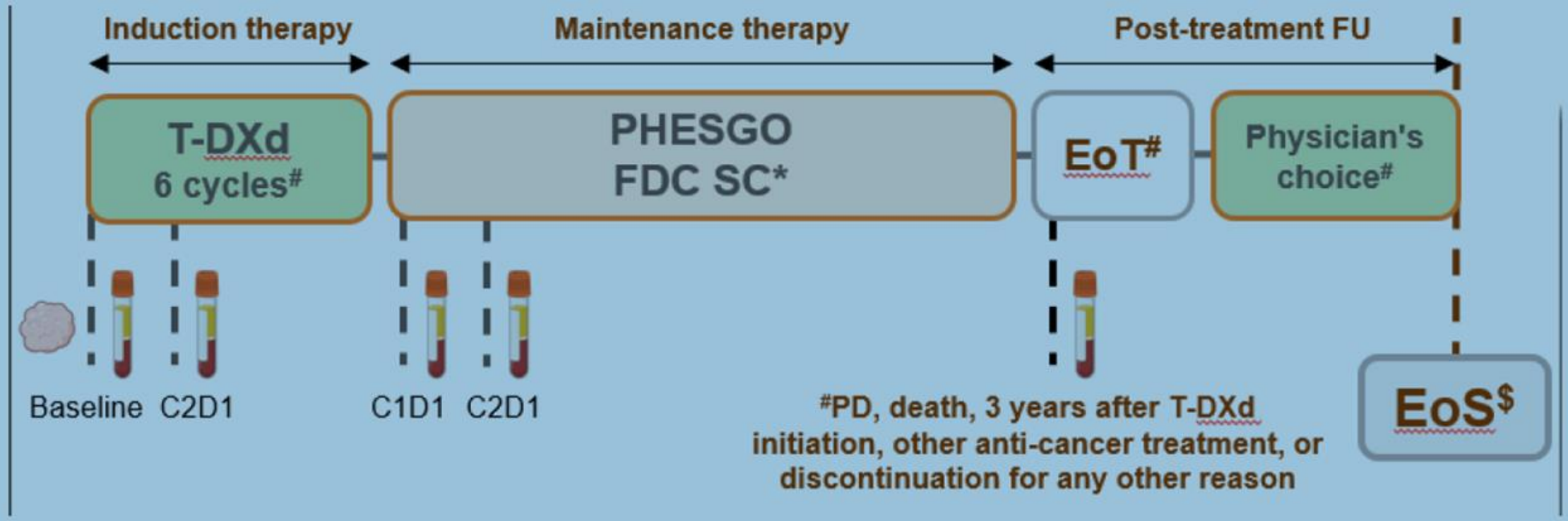
*(ER+ BC continues on HR tx)

# Future Direction… (Demether Study)

## First-line therapy HER2 positive mBC

**DEMETHER:** Optimizing the first-line treatment in patients with HER2 overexpressing breast cancer: A phase II trial exploring the maintenance of trastuzumab and pertuzumab following trastuzumab-deruxtecan as induction treatment

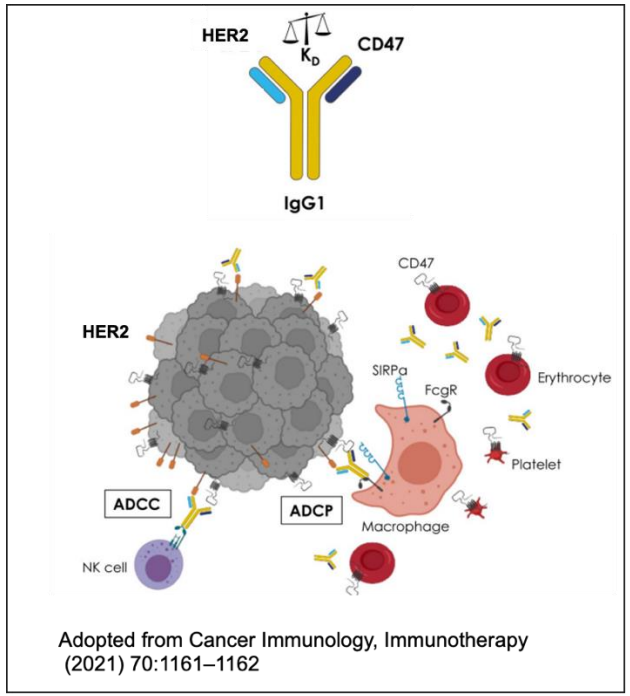
MEDSIR
MEDICA SCIENTIA INNOVATION RESEARCH



# SOME NEXT STEPS…

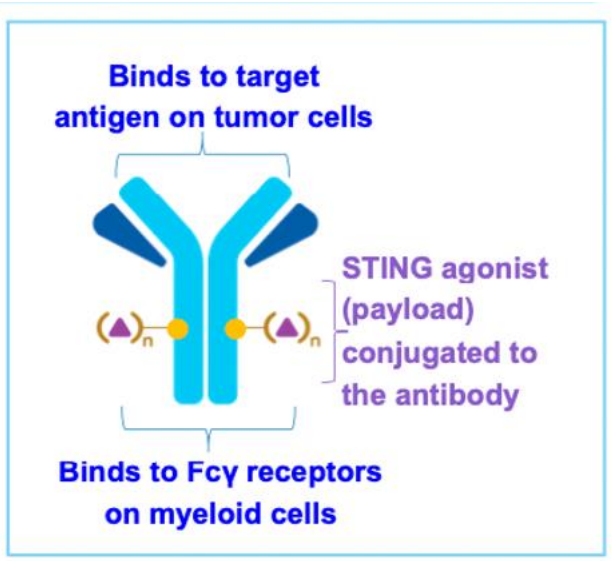
## Bispecifics:

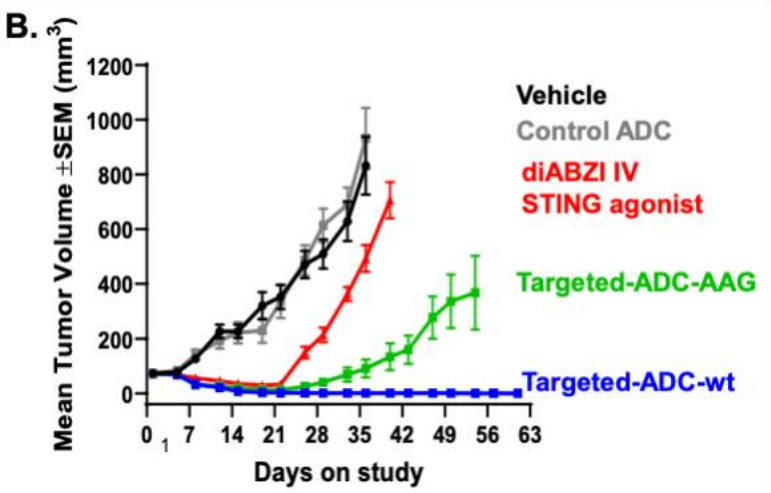
D3L-001 HER2-CD47



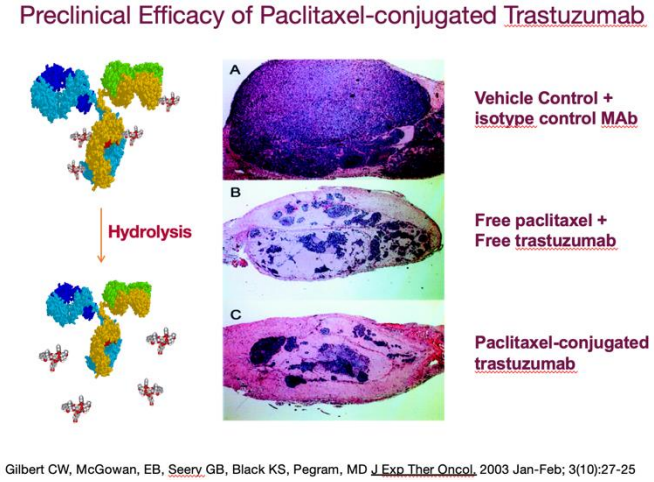

Adopted from Cancer Immunology, Immunotherapy (2021) 70:1161–1162

## ADCs with immune payloads:



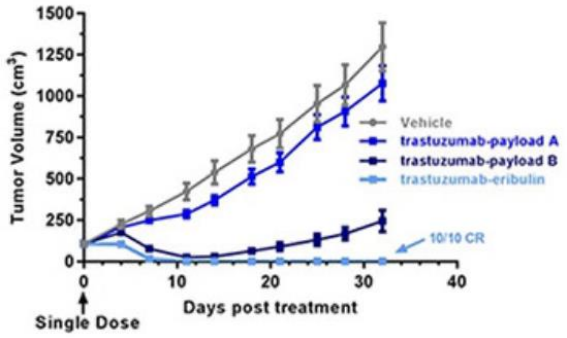




## ADCs with chemo payloads:




Gilbert CW, McGowan, EB, Seery GB, Black KS, Pegram, MD J Exp Ther Oncol. 2003 Jan-Feb; 3(10):27-25

Trastuzumab-eribulin ADC



## THE GRADUATE – 1967

- Bancroft, Hoffman, and Ross earned Oscar nominations for their performances.
- Also nominated for Best Cinematography, Best Adapted Screenplay, and Best Picture.
- Mike Nichols won the Academy Award for Best Director.
- Only film in history to win best director,…and nothing else.