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# Reducing Risk of Recurrence in HER2+ Early Breast Cancer

Miami, FL April 2024

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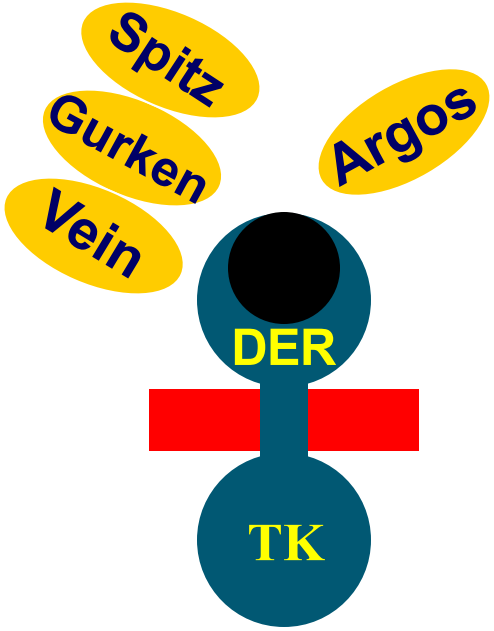
Associate Dean for Clinical Research Quality
Stanford University School of Medicine

# Evolution of Epidermal Growth Factor Receptors From ~600M Years Ago

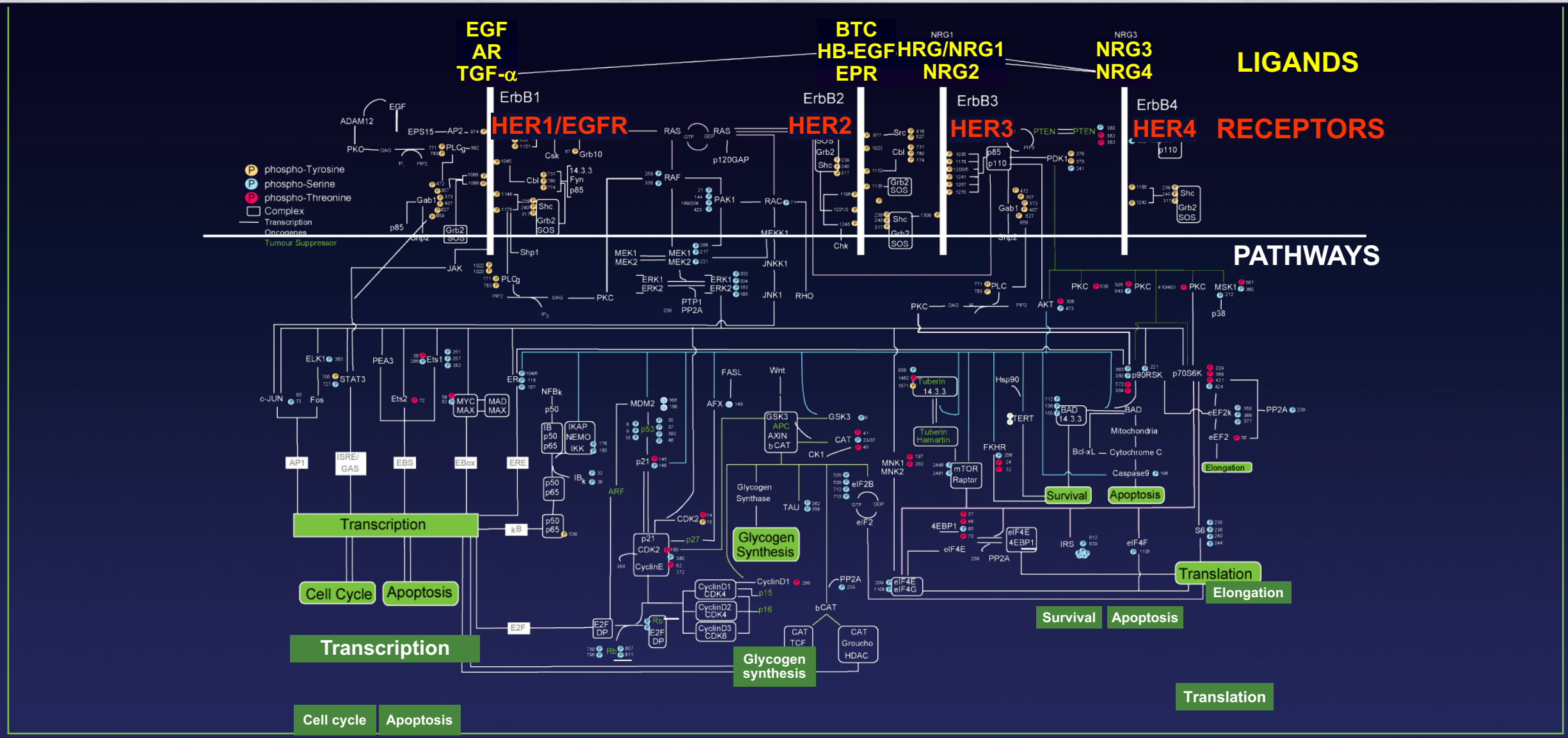
C-elegans


Drosophila



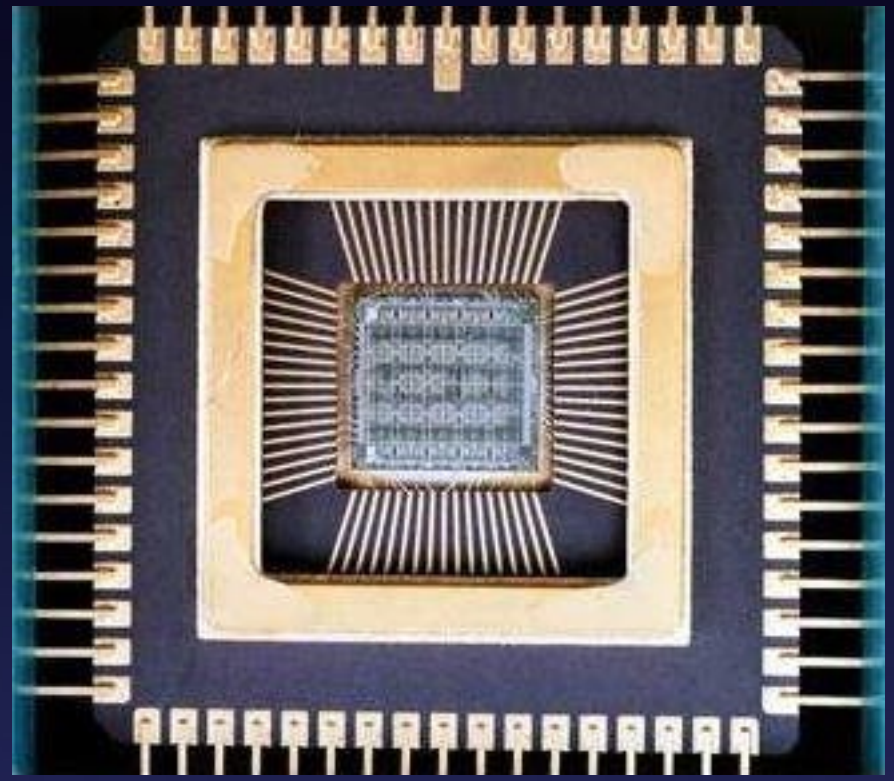

(Courtesy Prof. Yosef Yarden; Weizmann Institute of Science)

# The Human Epidermal Growth Factor Receptor (HER) signaling network

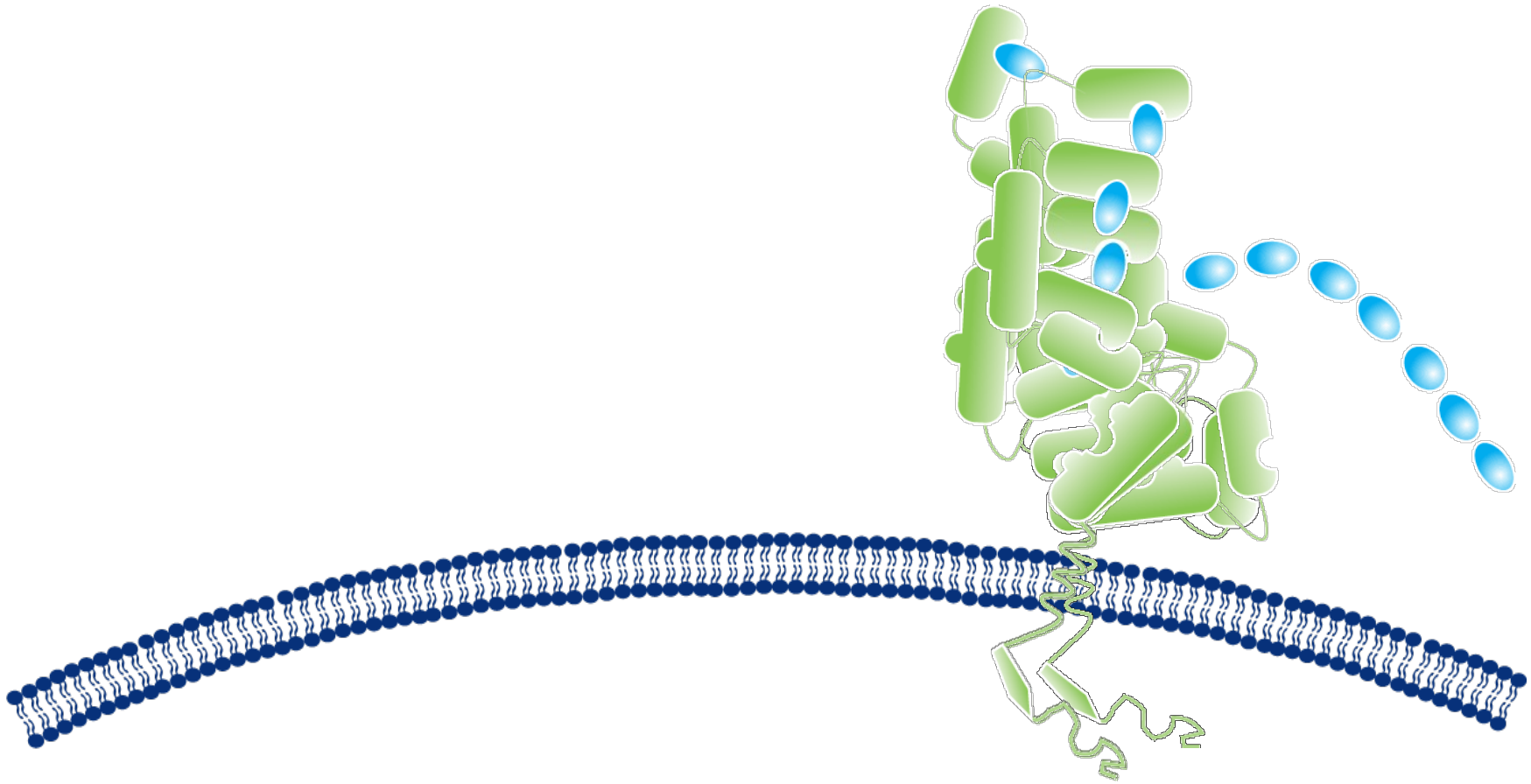



Adapted with permission from Richard Neve, M.D.
Citri A, Yosef Y. *Nat Rev Mol Cell Biol.* 2006;7:505-516.

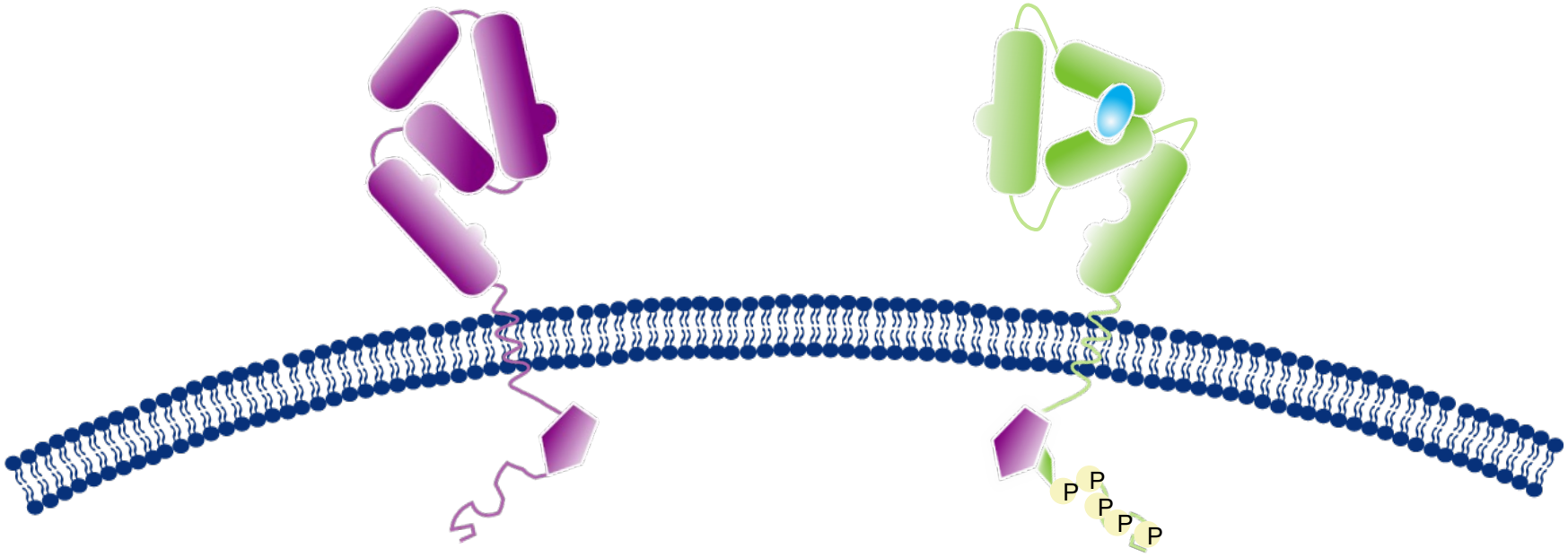
# Analogy to Signaling Networks in Biological Systems



# Ligand binding to HER receptors changes conformation from closed “tethered” to “open” form, exposing dimerization interface

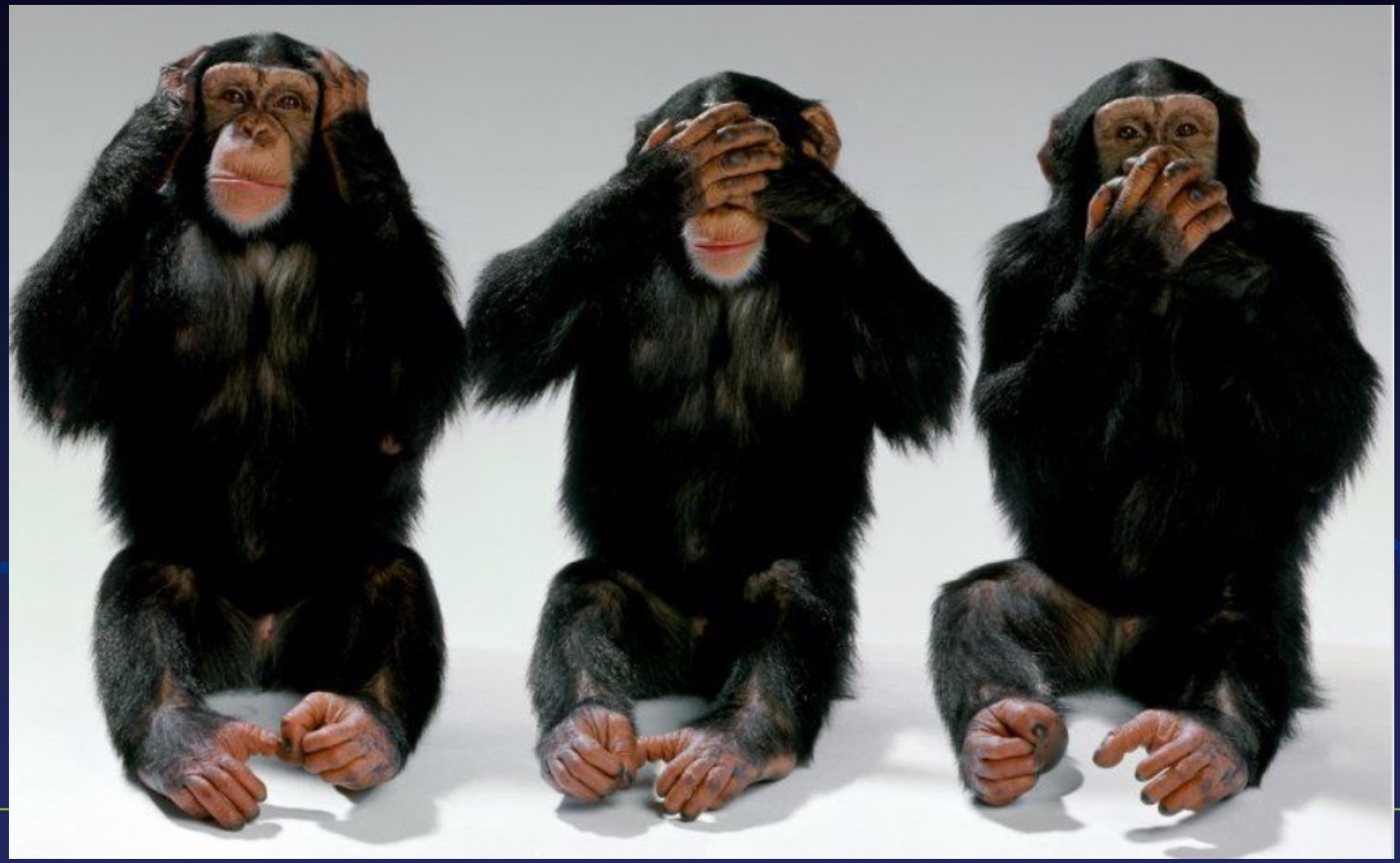


# HER dimerization is key to signaling activity



# Human Epidermal Receptors: Structure/Function Relationships

HER1/EGFR HER2 HER3



# Ligand Activation of HER-Family Receptors

## Growth Factors

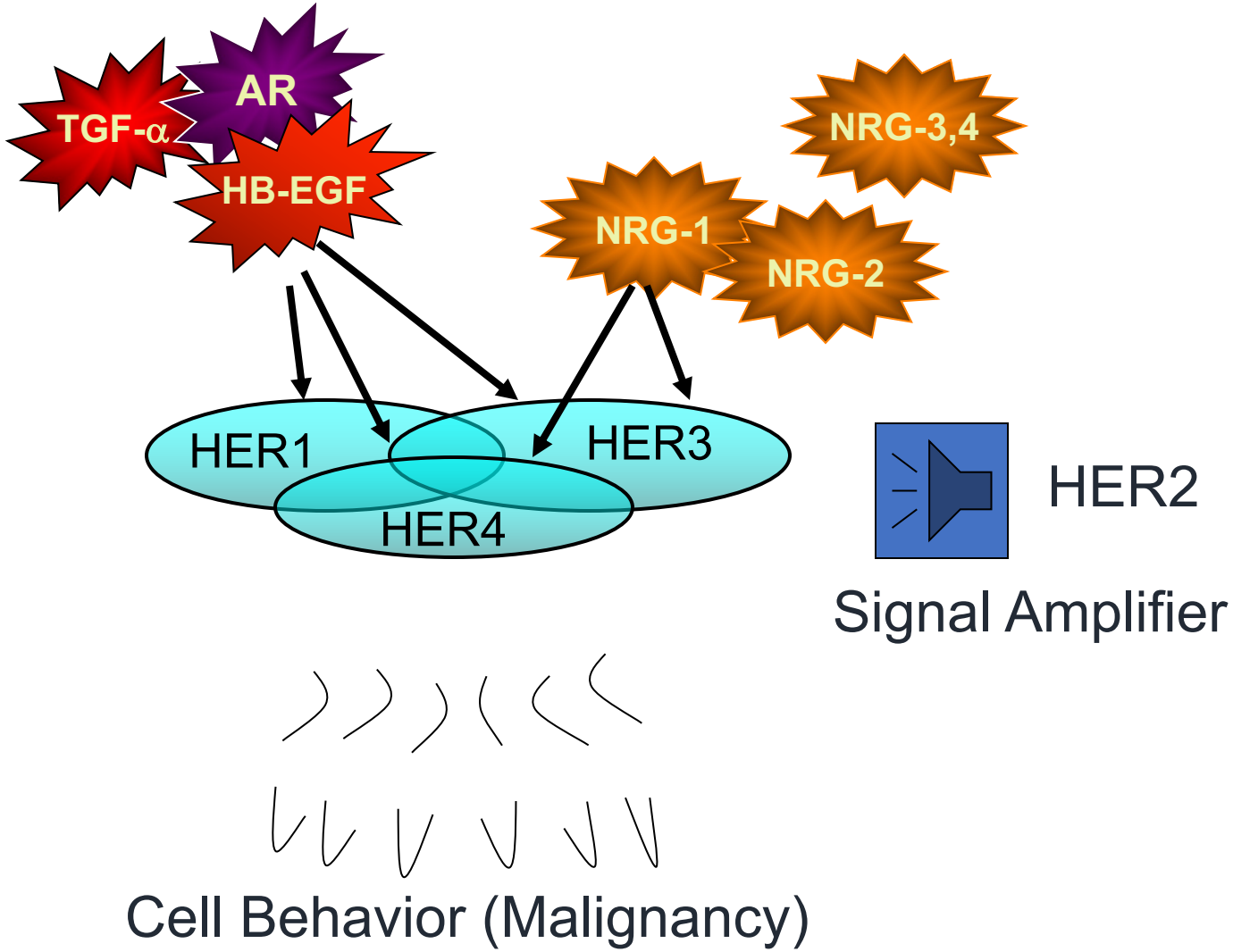
Diversity of GFs initiates HER combinatorial signaling and drug resistance

## Receptors

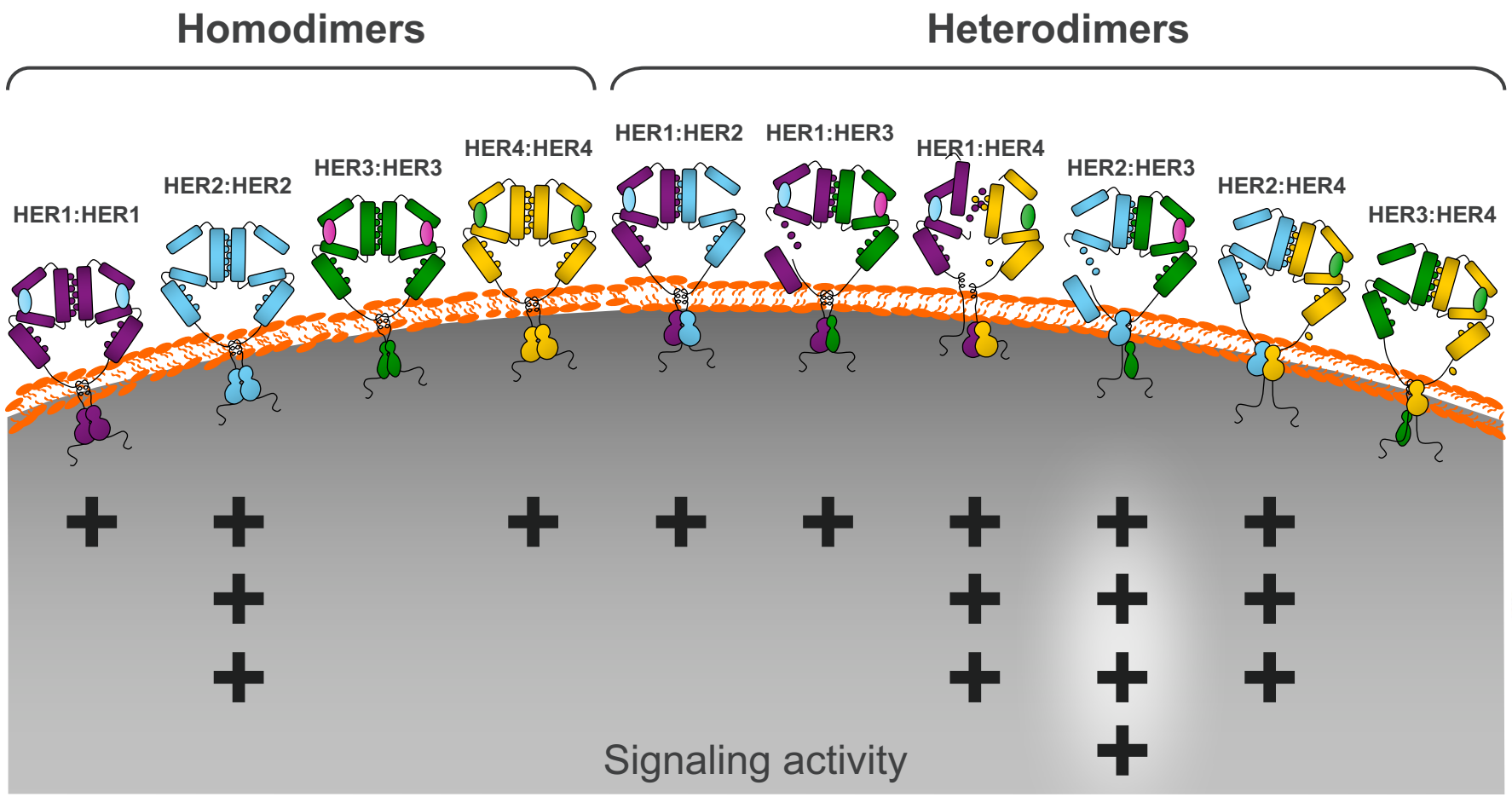
Signal Integrators

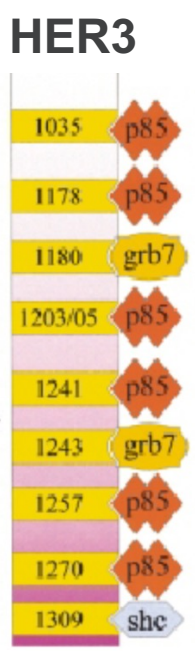
## Signaling Proteins

Diversity of Response



# HER2:HER3 Dimers Initiate the Strongest Mitogenic Signaling



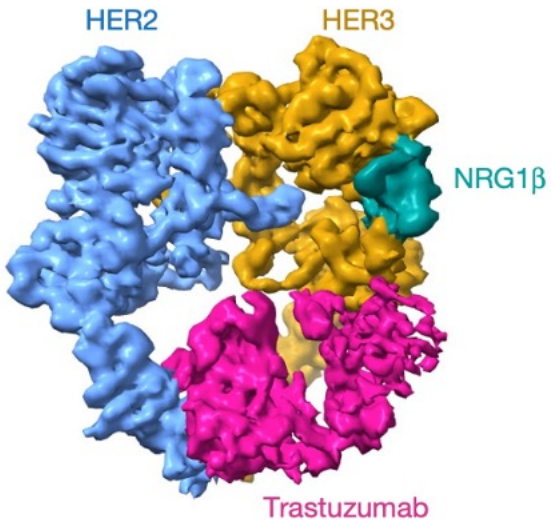




Cytoplasmic Domain aa Sequence

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.

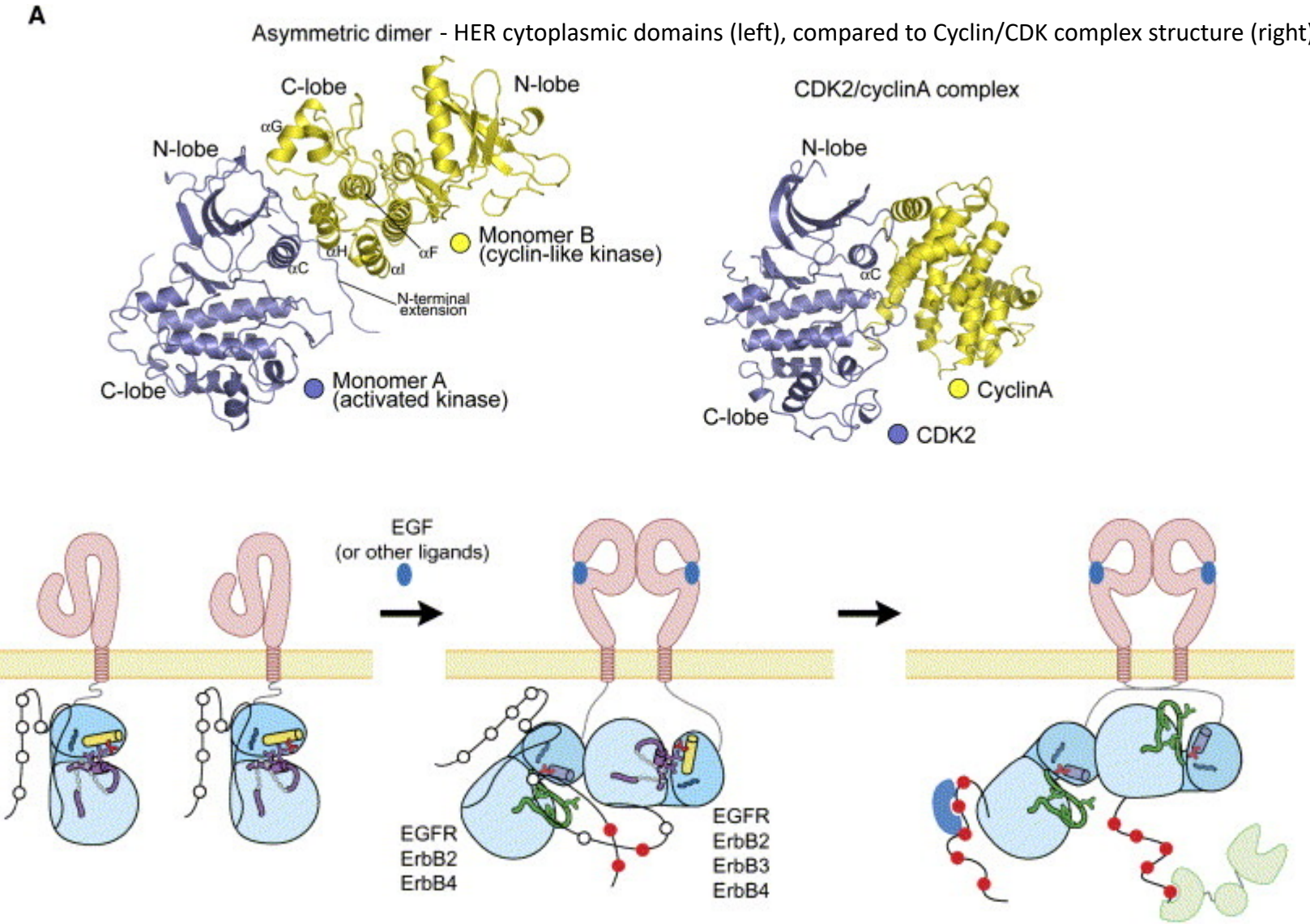
# General Model for Activation of the EGFR Family

## The HER2–HER3–NRG1β cryo-EM structure accommodates trastuzumab binding




Five-Ångstrom lowpass-filtered density of the HER2(S310F)–HER3–NRG1β heterocomplex bound to trastuzumab Fab

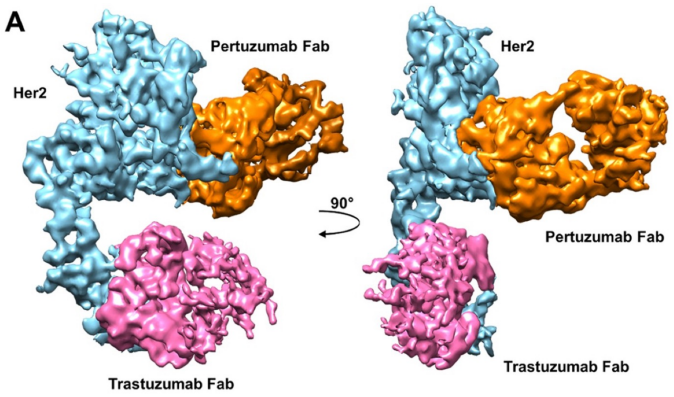
Diwanji, D., Trenker, R., Thaker, T.M. *et al. Nature* **600**, 339–343 (2021).



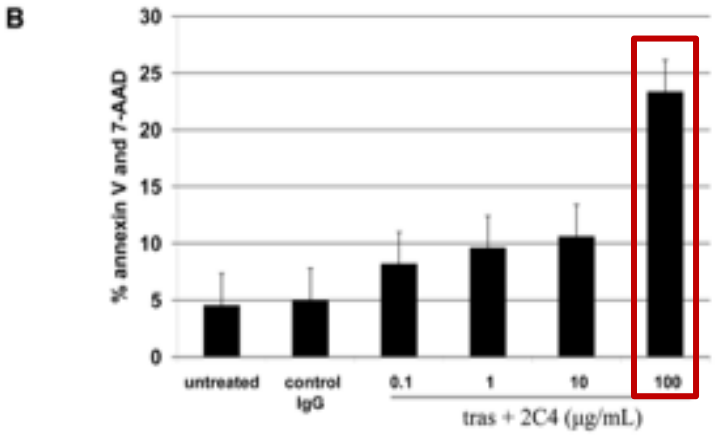

Zhang X, et al., Cell 125: 1137-49 (2006).

# Pertuzumab Binds Subdomain II and Disrupts Ligand-*Dependent* HER2:HER3 Interaction; Trastuzumab + Pertuzumab Induces Apoptosis

4.36Å resolution, cryo-EM

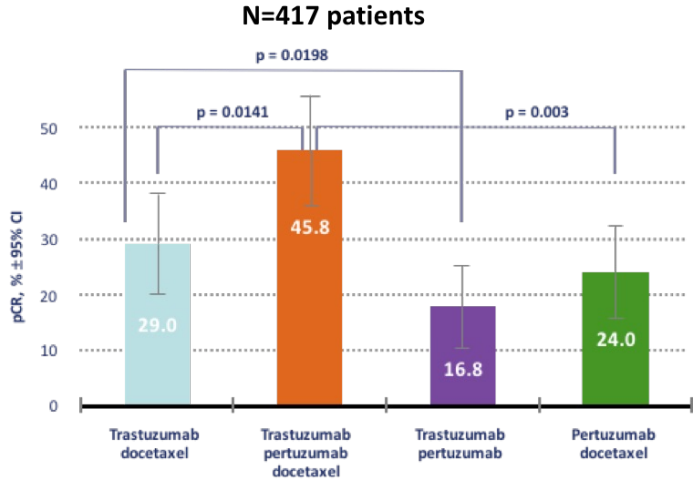



Hao Y, et al., PLoS One. 2019;14(5):e0216095.

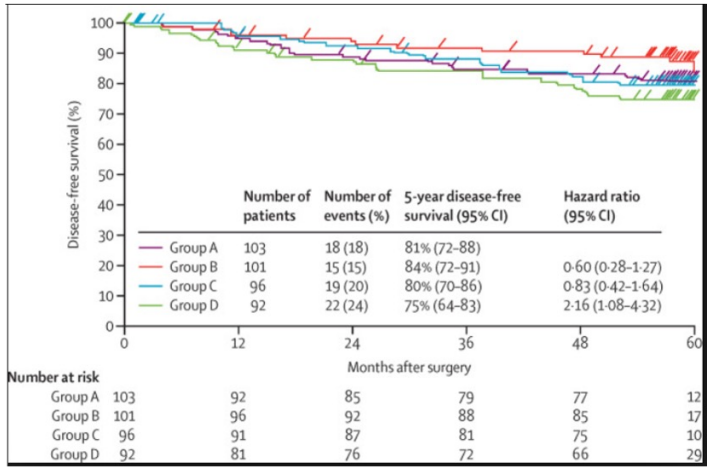



Rita Nahta, *et al*. Cancer Res 2004;64:2343-2346.

## NEOSPHERE Study



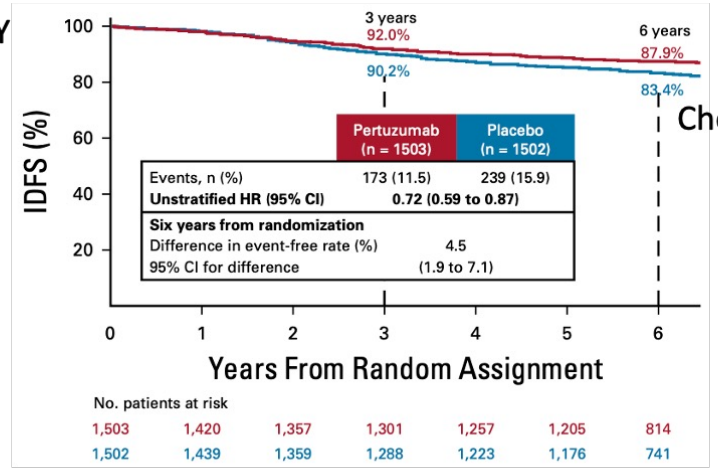

## NEOADJUVANT HP




Gianni L, et al. Lancet Oncol 2016: 17(6), 791-800.

## ADJUVANT HP

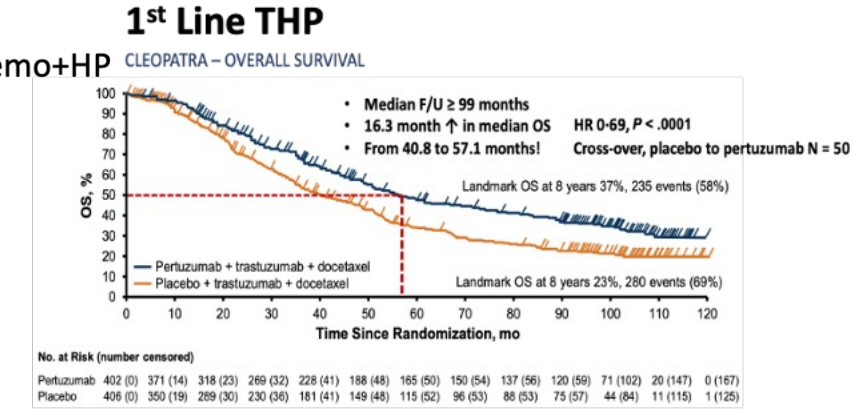
APHINITY




Piccart M, et al. J Clin Oncol 2021 39:13, 1448-1457.

## 1ST-LINE METASTATIC HP

Chemo+HP




Swain SM et al. Lancet Oncol 2020; 21: 519–30.

# ASCO 2024 – HER2+ MBC

## Optimal 1st L chemotherapy partner (#1007 - EMERALD)

### Study design

**Patients with HER2+ LABC or MBC**

- Age 20–70 years
- No prior use of chemotherapy (excluding T-DM1) for LABC/MBC
- Hormonal or anti-HER2 therapy alone, or their combination as treatment for recurrence, were allowed
- ECOG performance status score 0/1
- Left ventricular ejection fraction (LVEF) ≥50%
- Major organ function preserved
- At least 6 months since prior neoadjuvant or adjuvant cytotoxic chemotherapy

R 1:1

**Eribulin group (21-day cycle)**
Eribulin 1.4 mg/m²
days 1, 8
+
H + P[a] day 1

**Taxane group (21-day cycle)**
Docetaxel 75 mg/m² day 1 or
Paclitaxel 80 mg/m² days 1, 8, 15
+
H + P[a] day 1

**Primary endpoint :**
- Progression-free survival (PFS), investigator-assessed

**Secondary endpoints**
- Objective response rate (ORR)
- Duration of response
- Overall survival (OS)
- Patient-reported outcomes (QoL and neuropathy)
- Safety and biomarker
- New metastases−free survival
- Duration of next treatment

**Translational research**
- Search for biomarker to improve individual precision therapy

**Stratification factors for randomization**
- History of perioperative use of taxane
- Prior treatment with HER2-targeting antibody-drug conjugate after recurrence
- Presence of visceral metastases

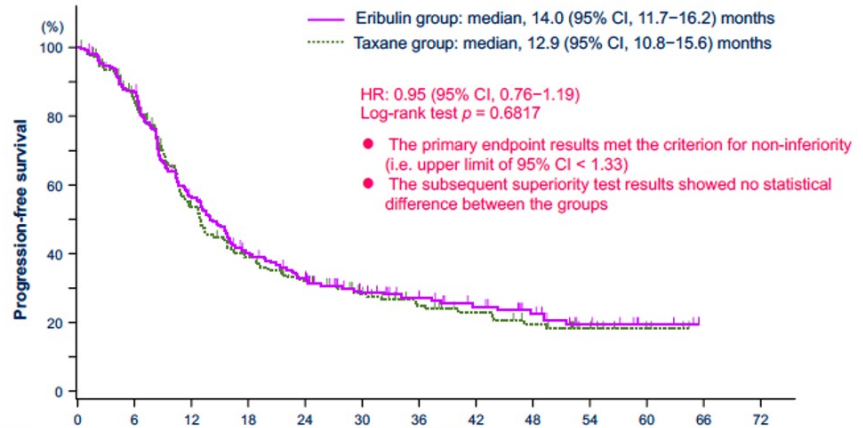
[a]Trastuzumab (H) : 8 mg/kg loading dose, 6 mg/kg subsequent doses + pertuzumab (P): 840 mg/body loading dose, 420 mg/body subsequent doses
Treatment continued to disease progression or unmanageable toxicity

JBCRG-M06/EMERALD: A multicenter, randomized, non-inferiority phase 3 trial
(UMIN000027938; ClinicalTrials.gov identifier, NCT03264547)

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Toshinari Yamashita MD, PhD

ASCO KNOWLEDGE CONQUERS CANCER

### PFS (primary endpoint)



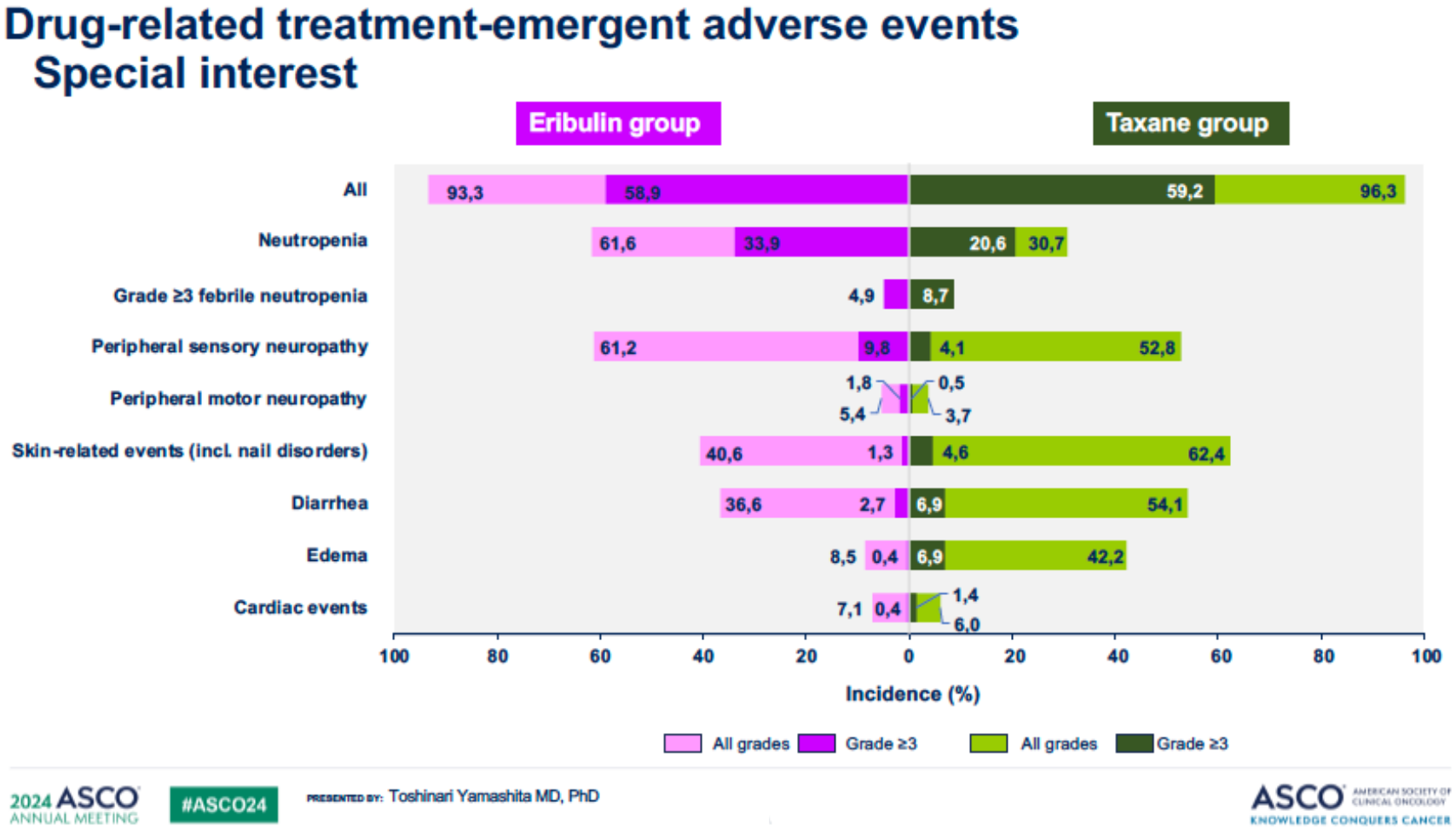

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Toshinari Yamashita MD, PhD

ASCO KNOWLEDGE CONQUERS CANCER

Yamashita et al, ASCO 2024

# ASCO 2024 – HER2+ MBC

## Optimal 1st L chemotherapy partner (#1007 - EMERALD)






Yamashita et al, ASCO 2024.

# CDK 4/6 inhibition + endocrine therapy + Tras Versus TPC (T-DM1, or Endocrine Rx + Tras, or Chemo* + Tras)

*GEM, NAV, CAPE, PAC, DOC or Eribulin

## PATRICIA Cohort C: Study design

Open-label, multicenter, randomized phase II trial

- ✓ Male or Pre and postmenopausal women
- ✓ **HR+/HER2+ ABC**
- ✓ **PAM50 Luminal A or B subtype** by Prosigna® (research use only)
- ✓ **At least 1L for ABC**[1]
- ✓ **Baseline LVEF** ≥ 50%
- ✓ **Stable CNS metastasis allowed**[2]
- ✓ **No prior CDK4/6i**

Pre-screening

PAM50 Luminal A/B[3] → R 1:1 → N=73

- **Palbociclib 125 mg QD 3W + Trastuzumab* + Endocrine therapy****
- **Treatment of physician's choice (TPC)*****

*Re-randomization*[4] → R 1:1

**Stratification factors:**

- Number of previous regimens (1-2 vs ≥ 3)
- Visceral disease (yes vs no)

* Trastuzumab: loading dose of 8mg/kg followed by 6 mg/kg IV or 600 mg SC administration.
** Aromatase inhibitor, fulvestrant or tamoxifen +/- gonadal suppression
*** T-DM1, any endocrine therapy or chemotherapy (gemcitabine, vinorelbine, capecitabine, eribulin, paclitaxel or docetaxel) plus trastuzumab.

**Primary endpoint**

- Investigator-assessed PFS (RECIST 1.1)

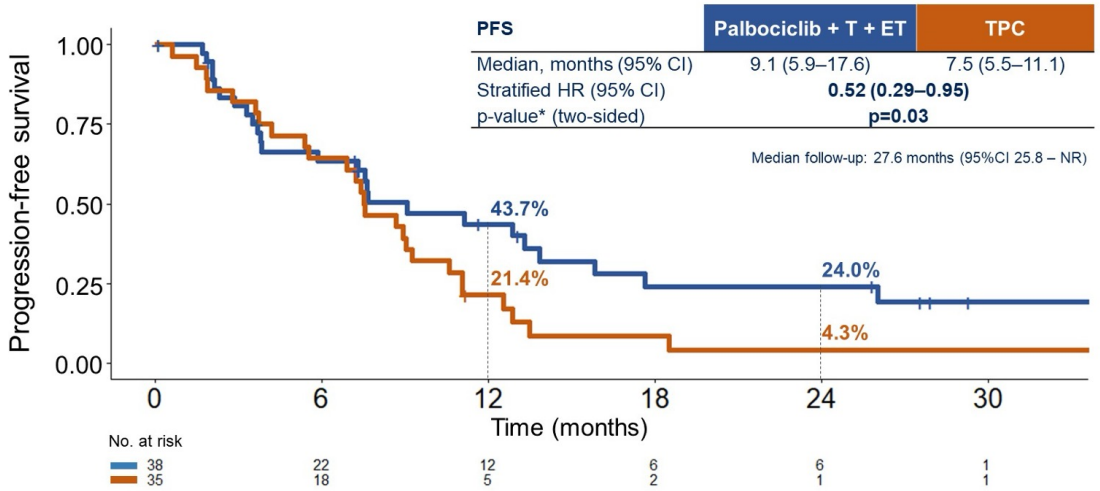
**Secondary endpoints**

- Overall response rate (ORR)
- Disease control rate (DCR)
- Duration of response
- Safety profile

(1) Including trastuzumab and/or anti-HER2 ADC for ABC ;or recurrence during or within 12 months after completing adjuvant trastuzumab and/or anti-HER2 ADCs and metastatic disease diagnosis.
(2) No evidence of progression, ≥3 wks between completion of local therapy study treatment initiation, and stable doses or no need of corticosteroids.
(3) Evaluated in primary or metastatic (preferred) sample.
(4) Patients that are initially allocated in the TPC i) have a documented disease progression and ii) meet inclusion criteria after progression, can be re-randomized to receive the experimental or control treatment.



## Primary objective: Investigator-assessed PFS




| PFS | Palbociclib + T + ET | TPC |
|---|---|---|
| Median, months (95% CI) | 9.1 (5.9–17.6) | 7.5 (5.5–11.1) |
| Stratified HR (95% CI) | **0.52 (0.29–0.95)** | |
| p-value* (two-sided) | **p=0.03** | |

Median follow-up: 27.6 months (95%CI 25.8 – NR)

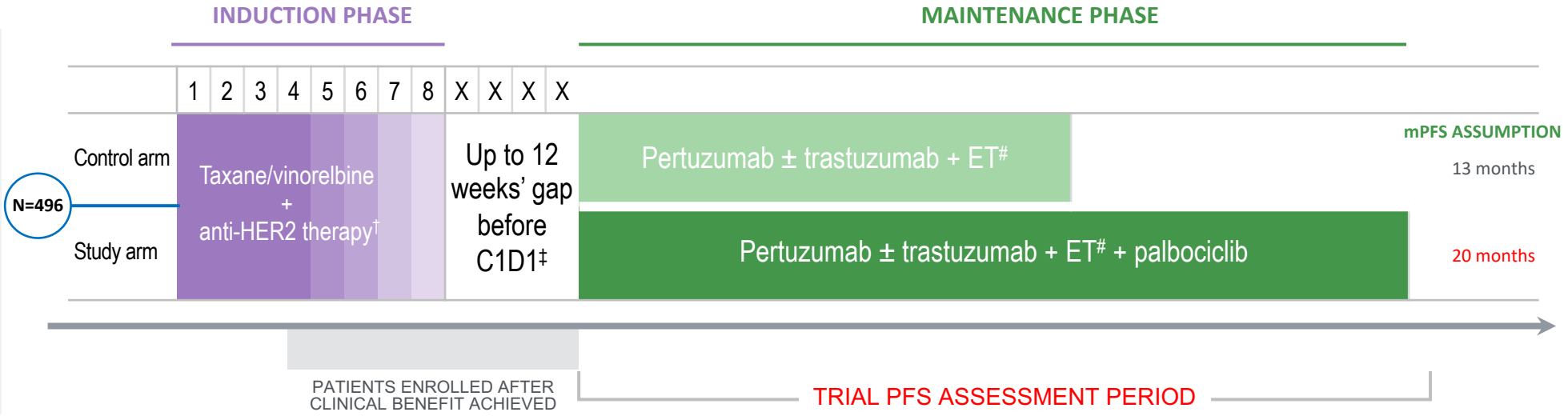
*p-value was estimated using a stratified mixed effect Cox model

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

The PATINA trial is a randomized Phase III 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).

# Study design

## DESTINY-Breast07: a Phase 1b/2, multicenter, open-label, two-part, modular study (NCT04538742)

**PATIENT POPULATION**

- Locally assessed HER2+ (IHC 3+, IHC 2+/ISH+) advanced/mBC, with measurable disease per RECIST 1.1
- Either no brain metastases or previously treated stable brain metastases
- ECOG PS of 0 or 1

**Prior lines of therapy**

- No prior therapy for mBC was allowed
- A disease-free interval of ≥12 months from adjuvant HER2-directed therapy or chemotherapy was required
- Prior taxane, trastuzumab, and pertuzumab exposure was allowed in the (neo)adjuvant setting

**This is the first dataset of T-DXd monotherapy and T-DXd + pertuzumab as first-line treatment for HER2+ mBC**

Randomized

**Module 0: T-DXd monotherapy (n=75)**
(T-DXd 5.4 mg/kg IV Q3W)*

Module 1: T-DXd + durvalumab

**Module 2: T-DXd + pertuzumab (n=50)**
(T-DXd 5.4 mg/kg IV Q3W + pertuzumab 420 mg IV Q3W, with an 840-mg loading dose)†

**Stratification factors**

- HR status
- Disease status
- PD-L1 status

**Endpoints for the P dose-expansion ph**

**Primary**
Safety and tolerability including AEs and SA

**Key secondary**
ORR, PFS (evaluated investigator per RECIST 1.1), and DC

**DCO: December 22, 2**

**Results reported here are from an interim analysis of the Part 2 dose-expansion phase for Modules 0 and 2 only; the Part 1 dose-finding phase of the study has been described previously[1]**

*Patients in Module 0 received the approved T-DXd dose for HER2+ breast cancer; †patients received the RP2D from the study's dose-finding phase; ‡the corresponding abstract reported data from the August 1, 2023, DCO
AE, adverse event; DCO, data cutoff; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HER2+, human epidermal growth factor receptor 2–positive; HR, hormone receptor; IHC, immunohistochemistry; ISH+, in situ hybridization–positive; IV, intravenous; mBC, metastatic breast cancer; ORR, objective response rate; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RP2D, recommended Phase 2 dose; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan
1. André F, et al. Poster presented at ASCO 2022 (Abstract 3025)





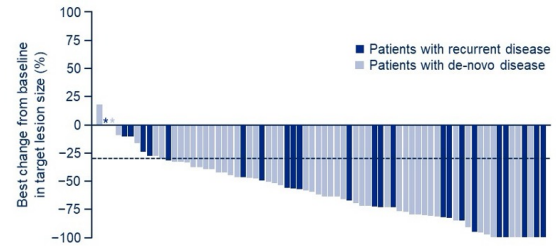






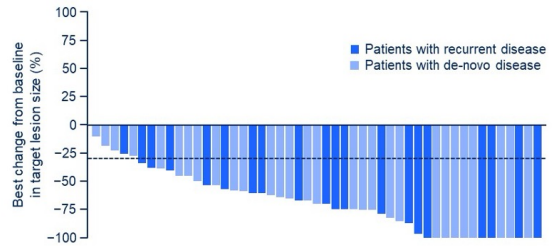
# Response to treatment per RECIST 1.1 by investigator

**T-DXd monotherapy (n=75)**




| Confirmed ORR, % (80% CI) | 76.0 (68.5–82.4) |
|---|---|
| Complete response, n (%) | 6 (8.0) |
| Partial response, n (%) | 51 (68.0) |
| Median DOR, months (range) | NE (2.1–28.5) |

**T-DXd + pertuzumab (n=50)**




| Confirmed ORR, % (80% CI) | 84.0 (75.3–90.5) |
|---|---|
| Complete response, n (%) | 10 (20.0) |
| Partial response, n (%) | 32 (64.0) |
| Median DOR, months (range) | NE (4.5–28.3) |

Dashed reference line at −30% indicates the threshold for partial response
Responses are captured for patients with baseline data and at least one follow-up assessment
DCO was December 22, 2023. Median duration of follow up was 23.9 months for T-DXd monotherapy and 25.3 months for T-DXd + pertuzumab
*Patients had 0% change from baseline
CI, confidence interval; DCO, data cutoff; DOR, duration of response; NE, not evaluable; ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan



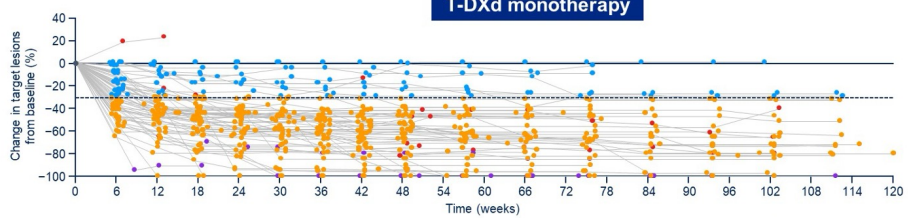




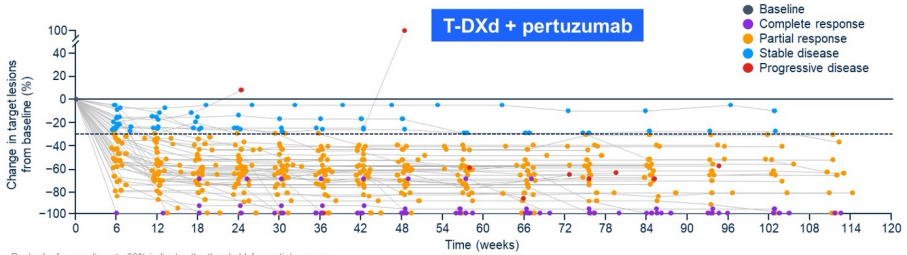


# Percentage change in target lesion size from baseline

**T-DXd monotherapy**




**T-DXd + pertuzumab**




**The majority of responses were observed by the 12-week scan and were durable**

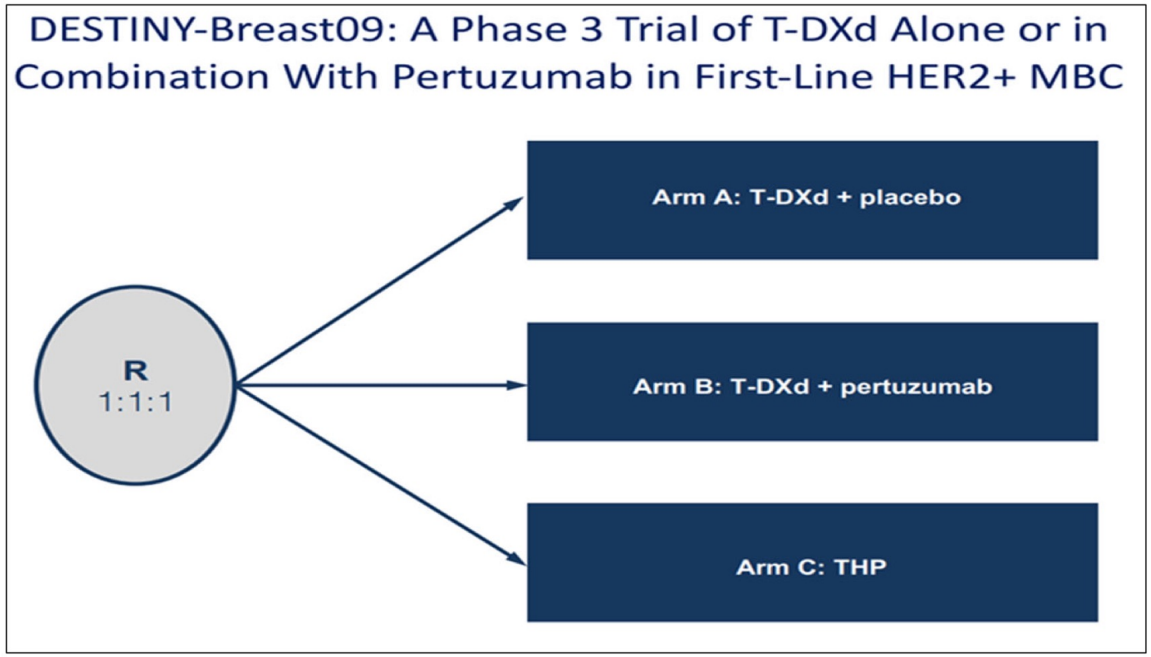
Dashed reference line at −30% indicates the threshold for partial response
DCO was December 22, 2023. Median duration of follow up was 23.9 months for T-DXd monotherapy and 25.3 months for T-DXd + pertuzumab. DCO, data cutoff; T-DXd, trastuzumab deruxtecan





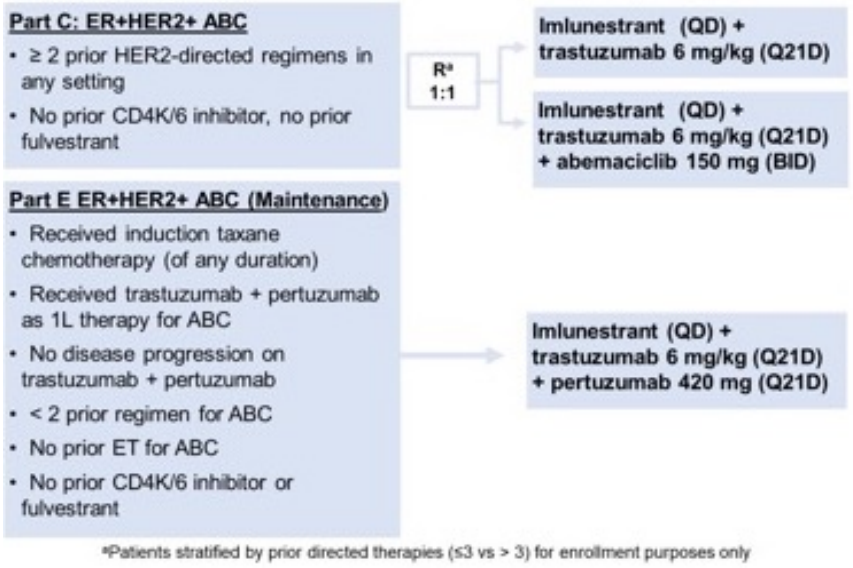
**Will DB-07 Foreshadow DB-09?** ⇒

## DESTINY-Breast09: A Phase 3 Trial of T-DXd Alone or in Combination With Pertuzumab in First-Line HER2+ MBC



# ASCO 2024

## Oral SERD + anti-HER2 therapy (#1027)




*Patients stratified by prior directed therapies (≤3 vs > 3) for enrollment purposes only

**Grade 3 TREAs:**
Diarrhea 19%
Neutropenia 24%
Thrombocytopenia 14%
Anorexia 5%

## Conclusions

- **Imlunestrant combined with trastuzumab +/- abemaciclib, or trastuzumab + pertuzumab:**
  - **Was well tolerated, with AEs consistent with the known safety profiles of single-agents**
  - **Demonstrated preliminary antitumor activity in patients with ER+, HER2+ ABC**
  - **Showed no drug-drug interactions**
- **The prevalence of *ESR1*-mutations in this ER+ HER2+ cohort was relatively high and likely reflects the heavily pre-treated nature of the trial population with previous AI exposure**
- **Taken together, these findings highlight a potential for imlunestrant as a clinically meaningful addition to existing therapy for patients with ER+, HER2+ ABC**

### Table 3. Efficacy

| | Imlunestrant + trastuzumab | Imlunestrant + trastuzumab + abemaciclib | Imlunestrant + trastuzumab + pertuzumab |
|---|---|---|---|
| | n=18 | n=21 | n=6 |
| **ORR** (CR+PR), n/N* (%) | 1/14 (7) | 5/20 (25) | 1/3 (33) |
| **CBR** (CR+PR+SD≥24 weeks), n (%) | 8 (44) | 10 (48) | 6 (100) |
| **Disease Control Rate** (CR+PR+SD), n (%) | 11 (61) | 13 (62) | 6 (100) |

*ORR evaluable population: patients who have measurable disease

Bhave et al, ASCO 2024

# ASCO 2024
# T-DXd and brain mets (#1032)

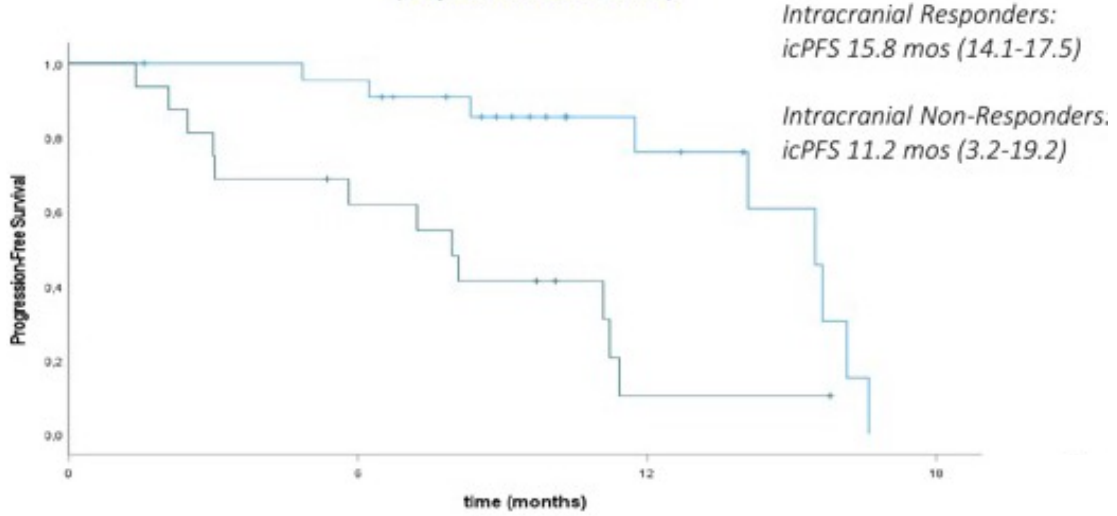
*Tab.1 Intracranial Efficacy of T-Dxd*

| | |
|---|---|
| mPFS (months) | 15.6 (95% CI: 10.5-20.8) |
| Disease Control Rate (%) | 94.9 (87.9-100.0) |
| Duration of Response (months) | 11.9 (10.1-13.7) |
| Clinical Benefit (%) 6 months<br>12 months | 27 (69.2)<br>23 (59.0) |
| Overall Survival at 12 months (%) | 76.6 |

*Tab.2* Intracranial and Global best responses with T-DxD

| *Response to T-Dxd* | *Intracranial Best Response n. (%)* | *Global Best Response n. (%)* |
|---|---|---|
| Complete Response | **1(2.6)** | **0** |
| Partial Response | **22(56.4)** | **27(69.2)** |
| *Overall Response rate* | **23(59)** | **27(69.2)** |
| Stable Disease | **14(35.9)** | **10(25.6)** |
| Progressive disease | **2(5.1)** | **2(5.1)** |

*Fig.1 : Progression Free Survival of Intracranial Responders vs no Responders (Kaplan-Meier Curve)*



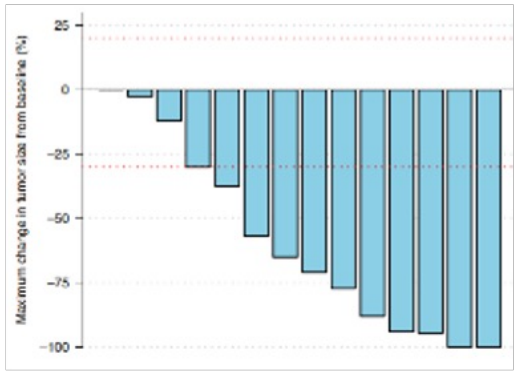

*Responders : patients achieving intracranial complete or partial response (total 23).*

*Non-Responders: patients with an intracranial stable disease or progression (total 16).*

Fabi et al, ASCO 2024

# Trastuzumab Deruxtecan in pts with active brain mets

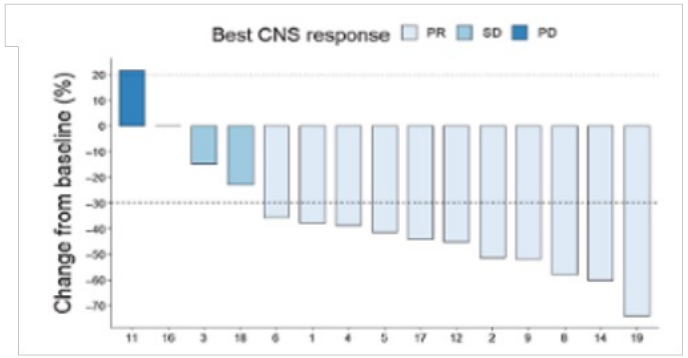
## TUXEDO-1 study (n=15)




Intracranial RR = 73.3%

## DFCI/MDACC/Duke (n=15*)

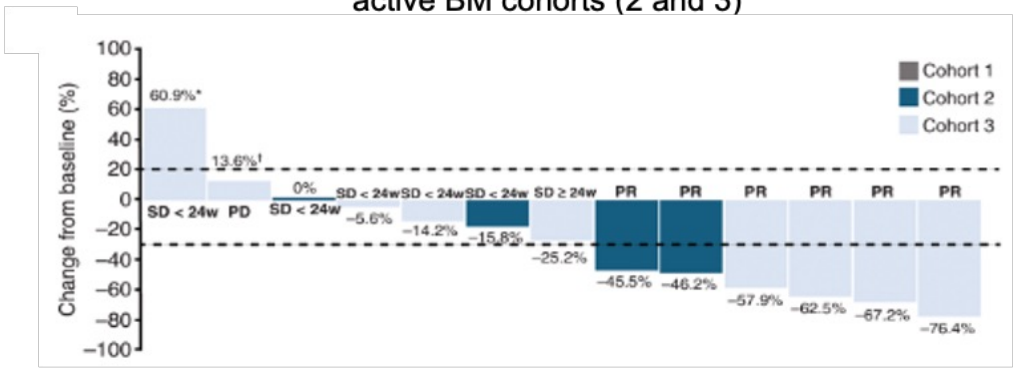
*15/17 with evaluable intracranial RR




Intracranial RR = 73%

## DEBBRAH (n=13*)

*active BM cohorts (2 and 3)




Overall intracranial RR = 46.2%
(asymptomatic untreated + progressing BMs)

MADRID 2023 ESMO congress

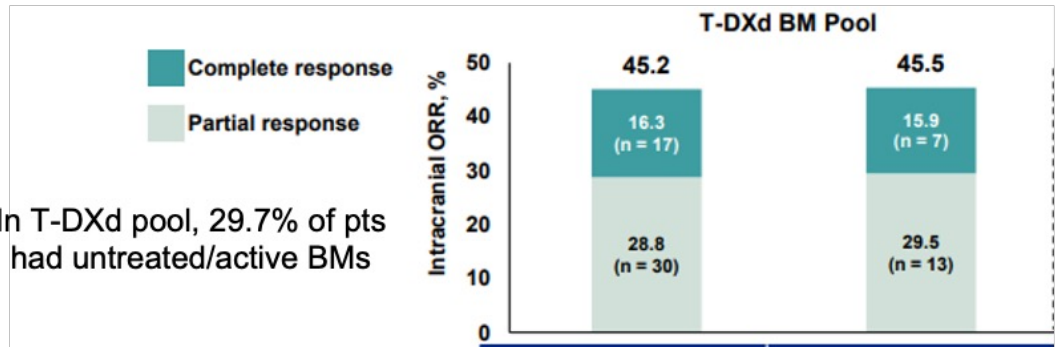
**A Pooled Analysis of Trastuzumab Deruxtecan in Patients With HER2-Positive Metastatic Breast Cancer With Brain Metastases (BMs) from DESTINY-Breast01, -02, and -03**

Presentation 3770

**Sara A. Hurvitz[1],** Shanu Modi, Wei Li, Yeon Hee Park, Wei-Pang Chung, Sung-Bae Kim, Javier Cortes, Toshinari Yamashita, Jose Luiz Pedrini, Seock-Ah Im, Ling-Ming Tseng, Nadia Harbeck, Ian Krop, Giuseppe Curigliano, Elton Mathias, Jillian Cathcart, Antonio Cagnazzo, Shahid Ashfaque, Anton Egorov, Fabrice André

**On behalf of the DESTINY-Breast01, -02, and -03 pooled investigators**

In T-DXd pool, 29.7% of pts had untreated/active BMs




| | Treated/stable BMs (n = 104) | Untreated/active BMs (n = 44) |
|---|---|---|
| **Best overall IC response, n (%)** | | |
| Stable disease | 48 (46.2) | 15 (34.1) |
| Progressive disease | 3 (2.9) | 1 (2.3) |
| Not evaluable/Missing | 6 (5.8) | 8 (18.2) |
| **IC-DoR, median, months (95% CI)** | 12.3 (9.1-17.9) | 17.5 (13.6-31.6) |

Bartsch R et al, Nature Medicine 2022; Kabraji S et al, CCR 2023; Pérez-García JM et al, Neuro-Oncology 2023; Hurvitz S et al, ESMO 2023

## HER2CLIMB-02 Study Design

- HER2+ LA/MBC with progression after trastuzumab and taxane in any setting[a]
- ECOG PS ≤1
- Previously treated stable, progressing, or untreated brain metastases not requiring immediate local therapy

N≈460

R 1:1

**Stratification factors:**
- Line of treatment for metastatic disease (1L vs other)
- Hormone receptor status (positive vs negative)
- Presence or history of brain metastases (yes vs no)
- ECOG PS (0 vs 1)

**Tucatinib (TUC) + T-DM1**

Tucatinib 300 mg PO BID and T-DM1 3.6 mg/kg IV

**Placebo (PBO) + T-DM1**

Placebo PO BID and T-DM1 3.6 mg/kg IV

**Outcomes**

Primary
- PFS by investigator assessment per RECIST v1.1

Key Secondary (hierarchical)
- OS
- PFS in patients with brain metastases
- cORR per RECIST v1.1
- OS in patients with brain metastases

The primary analysis for PFS was planned after ≈331 PFS events to provide 90% power for hazard ratio of 0.7.
The first of two interim analysis for OS was planned at the time of the primary PFS analysis, if the PFS result was significantly positive.[b]

Hurvitz S, et al. SABCS2023

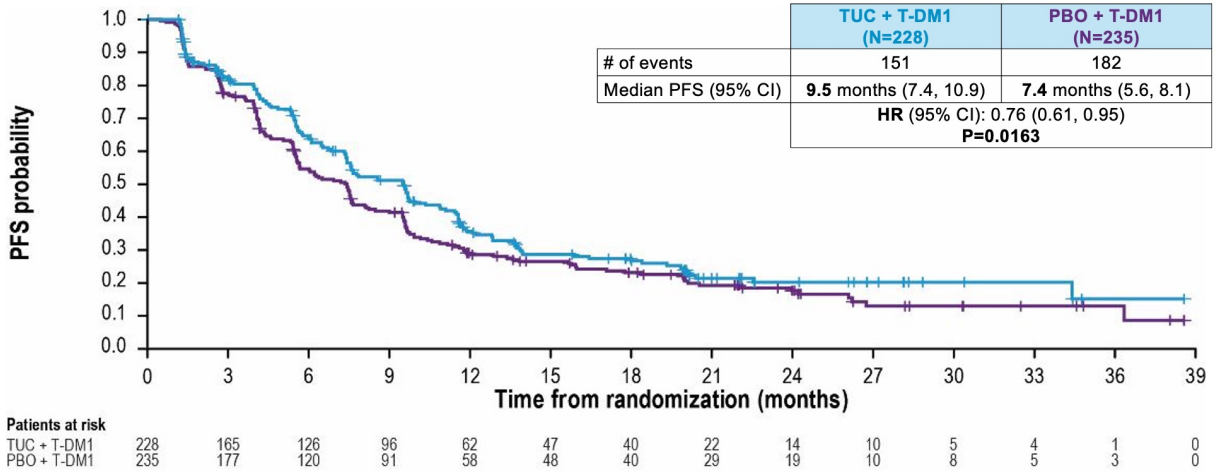
NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647. Accessed Oct 5, 2023. Date of data cutoff: Jun 29, 2023. Patients were enrolled from Oct 8, 2019, to Jun 16, 2022.

a Patients who received prior tucatinib, afatinib, T-DXd, or any investigational anti-HER2, anti-EGFR, or HER2 TKIs were not eligible. Patients who received lapatinib and neratinib were ineligible if the drugs were received within 12 months of starting study treatment, and patients who received pyrotinib for recurrent or metastatic breast cancer were not eligible. These patients were eligible if the drugs were given for ≤21 days and were discontinued for reasons other than disease progression or severe toxicity.

b Subsequent OS analyses are planned upon 80% and 100% of events.1L, first-line; BID, twice daily; cORR, confirmed objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; LA/MBC, locally advanced or metastatic breast cancer; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, orally; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKIs, tyrosine kinase inhibitors; TUC, tucatinib.



## HER2CLIMB-02: Progression-Free Survival




| | TUC + T-DM1 (N=228) | PBO + T-DM1 (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** | |

Hurvitz S, et al. SABCS 2023

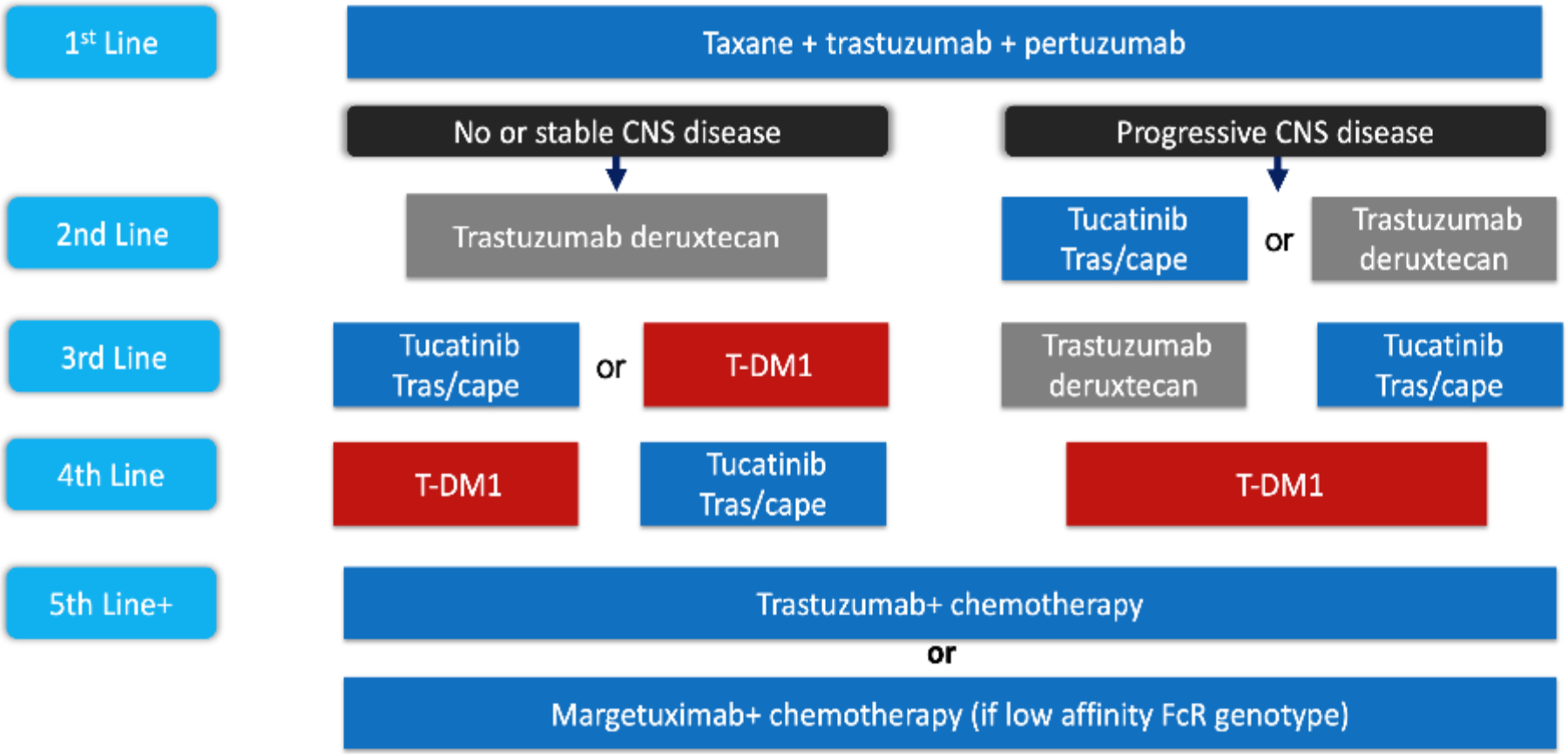
HR, hazard ratio; PBO, placebo; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TUC, tucatinib. Date of data cutoff: Jun 29, 2023.



Groups were well-balanced for: age (53-55), world region, HR status (60%HR+), ECOG PS (60% = 0), brain mets (~44%), and de novo stage IV presentation (~42-45%)

**Hepatic TEAEs:**
- Grade ≥3 hepatic TEAEs greater in TUC + T-DM1 arm (28.6% vs 7.3%), primarily due to AST/ALT elevations
- No Hy's law cases were identified

# Approach to Therapy for Metastatic HER2+ disease 2024




Multiple lines of concurrent CT with HER2-directed therapy offers clinical benefit for patients with recurrent HER2+ MBC, but optimal sequencing is not known

Adapted from Modi et al, ESMO 2021

# First Depiction of HER family Dimers Circa 3,000 B.C.E.

**ACKNOWLEDGEMENTS:**
**Prof. Yosef Yarden; Weizmann Institute of Science)**
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**Ralf Landgraf – University of Miami, study of HER3 complexes**
**Hyun-Soo Cho and Dan Leahy – Hopkins, HER2/3 crystal structures**
**Devan Diwanji – UCSF, cryoEM structure of HER2/HER3/HRG heterodimer(s)**
**Luca Gianni, Sandra Swain, Martine Piccart – Pertuzumab clinical development**
**Shom Goel – CDK4/Cyclin D1 and HER2 resistance**
**Fabrice Andre – DB-07 data; Fabi, et al. TDX-d brain met data, ASCO 2024; Sara Hurvitz, et al. HER2Climb-02; Shanu Modi – Rx paradigm, HER2+ MBC**