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CANCER INSTITUTE

Advances in the Treatment of HER2+ Breast Cancer

February 2025

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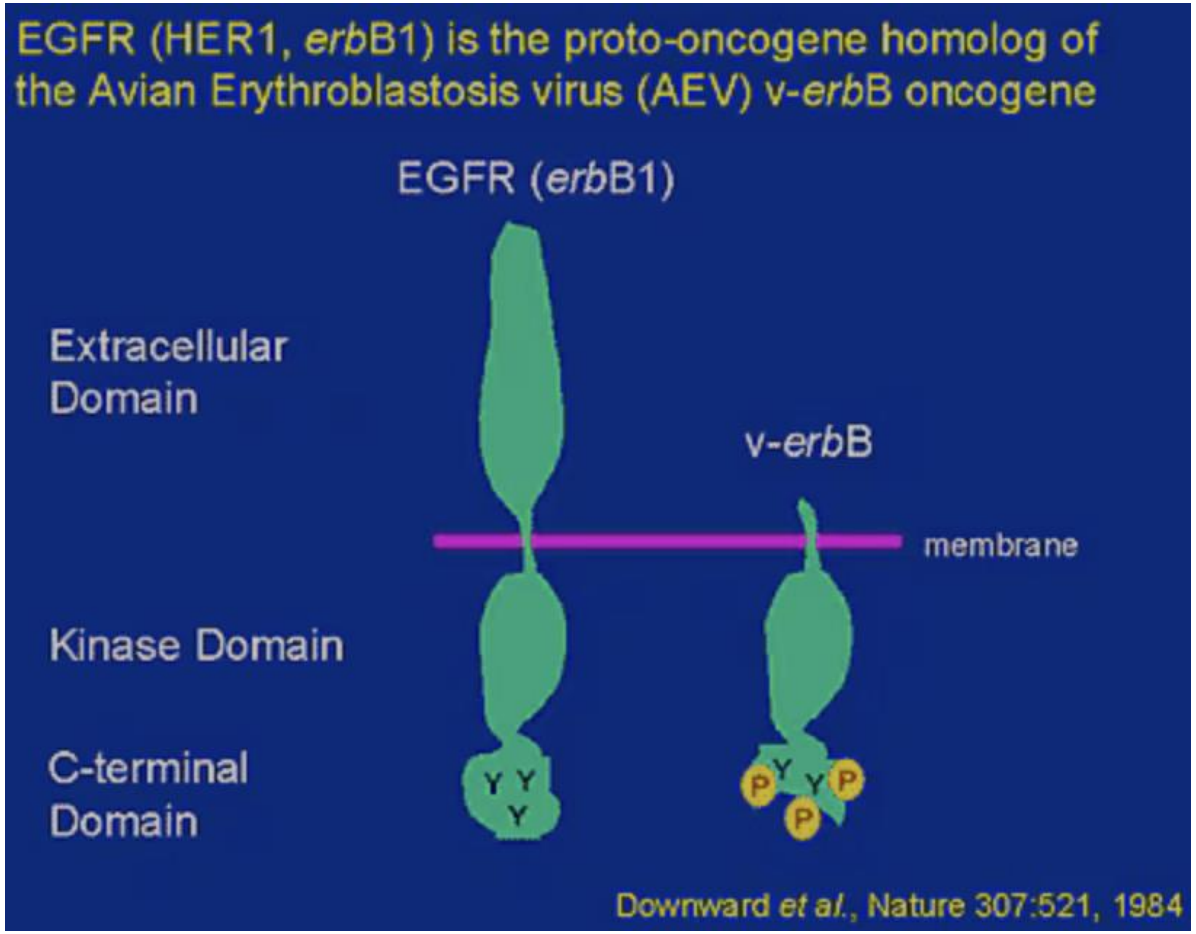
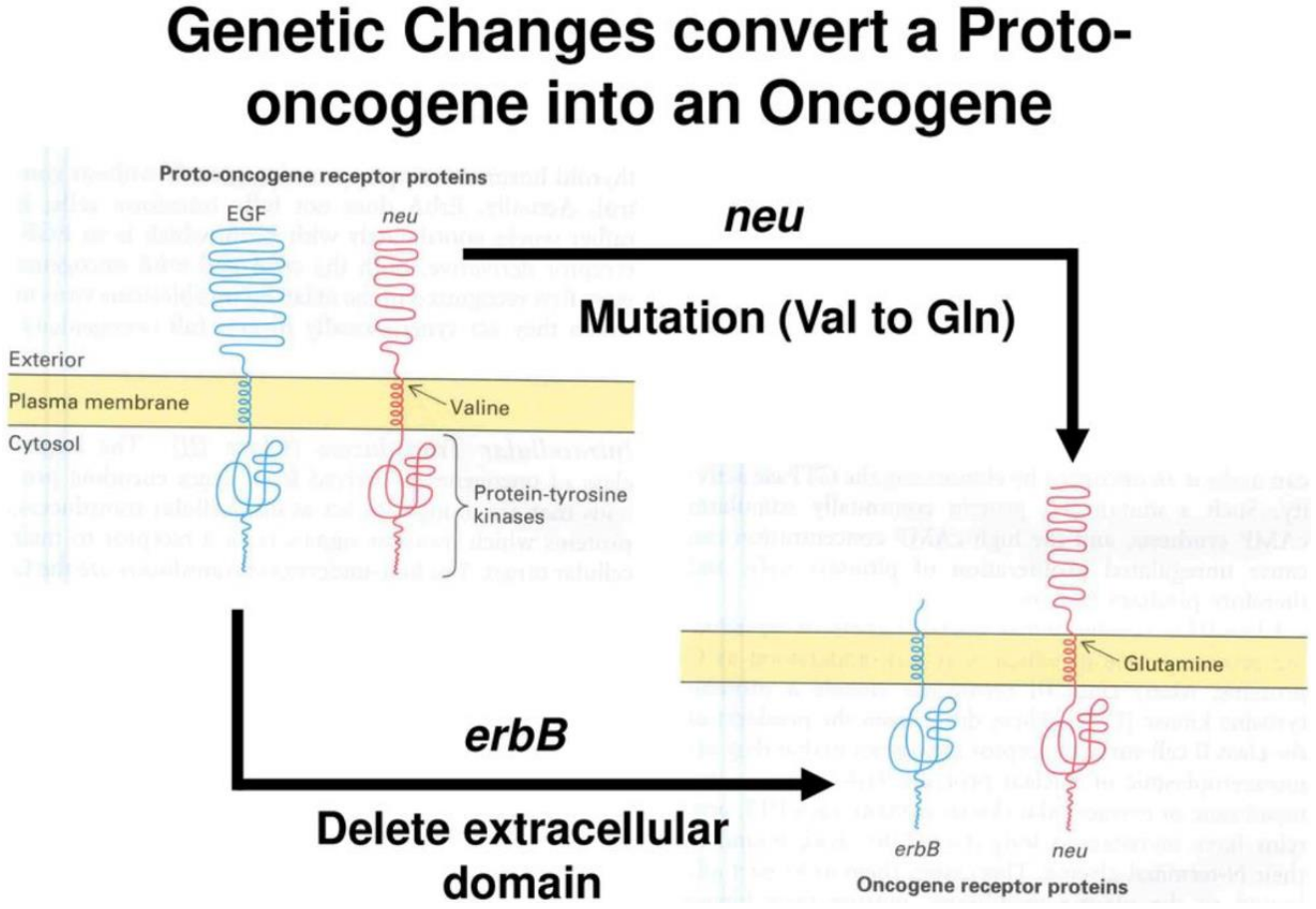
Multiple Independent Activations of the *neu* Oncogene by a Point Mutation Altering the Transmembrane Domain of p185

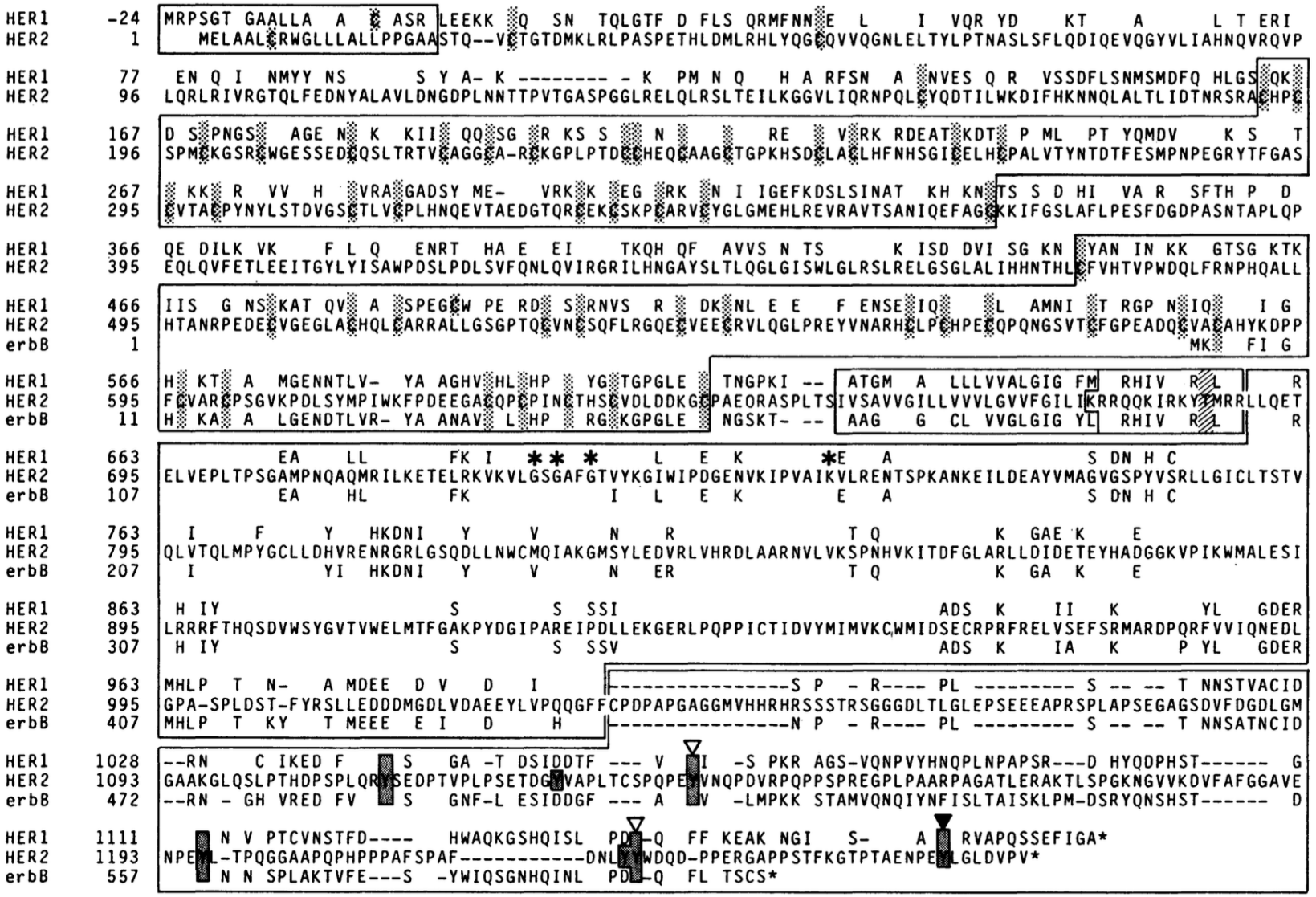




Tyrosine Kinase Receptor with Extensive Homology to EGF Receptor Shares Chromosomal Location with *neu* Oncogene

- "Using the transforming gene of the avian erythroblastosis virus, v-erbB, as a hybridization probe, we isolated genomic and cDNA sequences of an uncharacterized human gene. The 1255 amino acid polypeptide sequence derived from this cloned cDNA shows extensive homology to v-erbB and its cellular homologue, the human EGF receptor, and was therefore termed HER2".

- "Further experiments should establish the biological role of the HER2 gene, and its role in oncogenesis".



Coussens L, et al. Science. 1985 Dec 6;230(4730):1132-9.

OUTLINE

- **Discovery of HER2 using v-erbB as a low stringency hybridization probe**
- **Early-stage HER2+ treatment considerations**
- **Sequential therapeutic options for HER+ metastatic breast cancer**

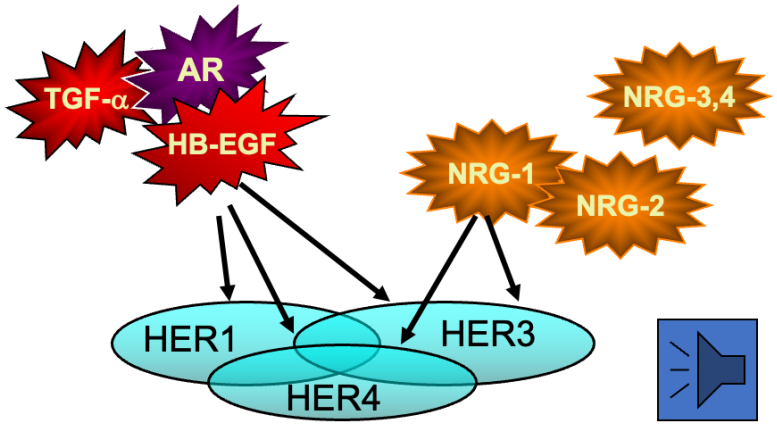
HER2 Gene Amplification in Breast Cancer: Disease Pathogenesis

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

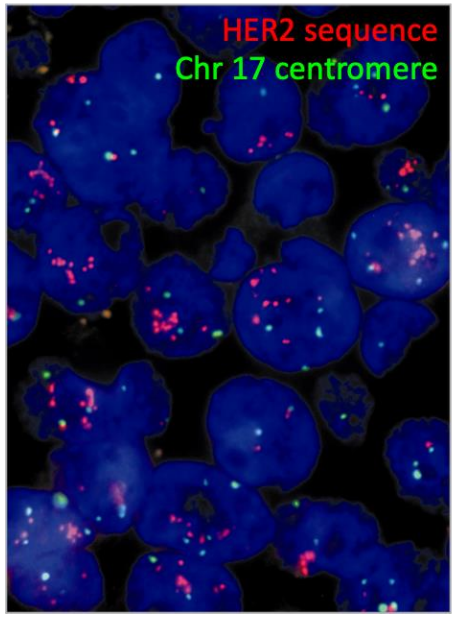


HER2

Signal Amplifier

Cell Behavior (Malignancy)

HER2 Gene Amplification

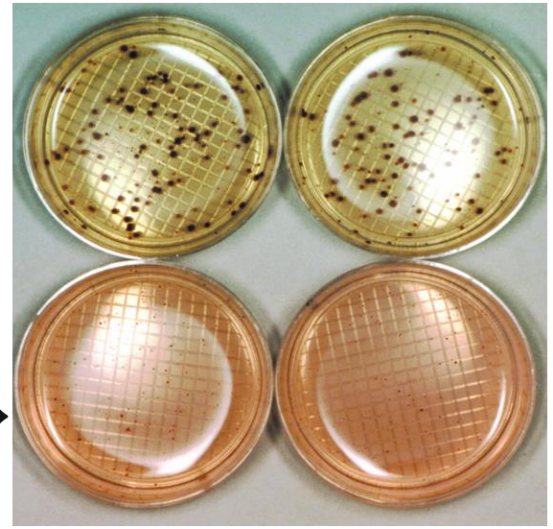


HER2-overexpression, Constitutive activation

HER2

MCF7 HER2→

MCF7 control→



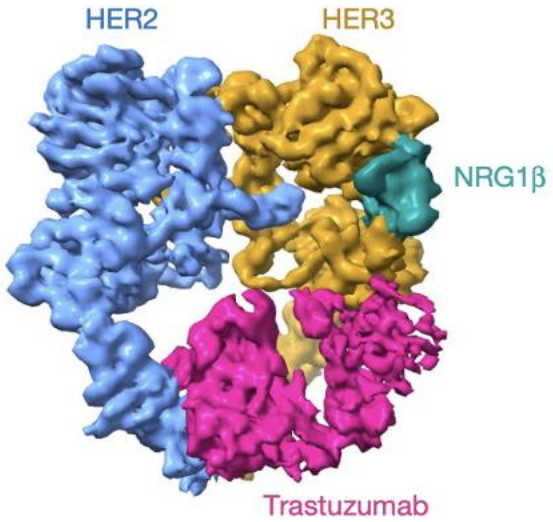
MCF7 HER2→

MCF7 control→

Pegram M, Slamon D
Semin Oncol 2000 Oct;27 (5 Suppl 9):13-9.

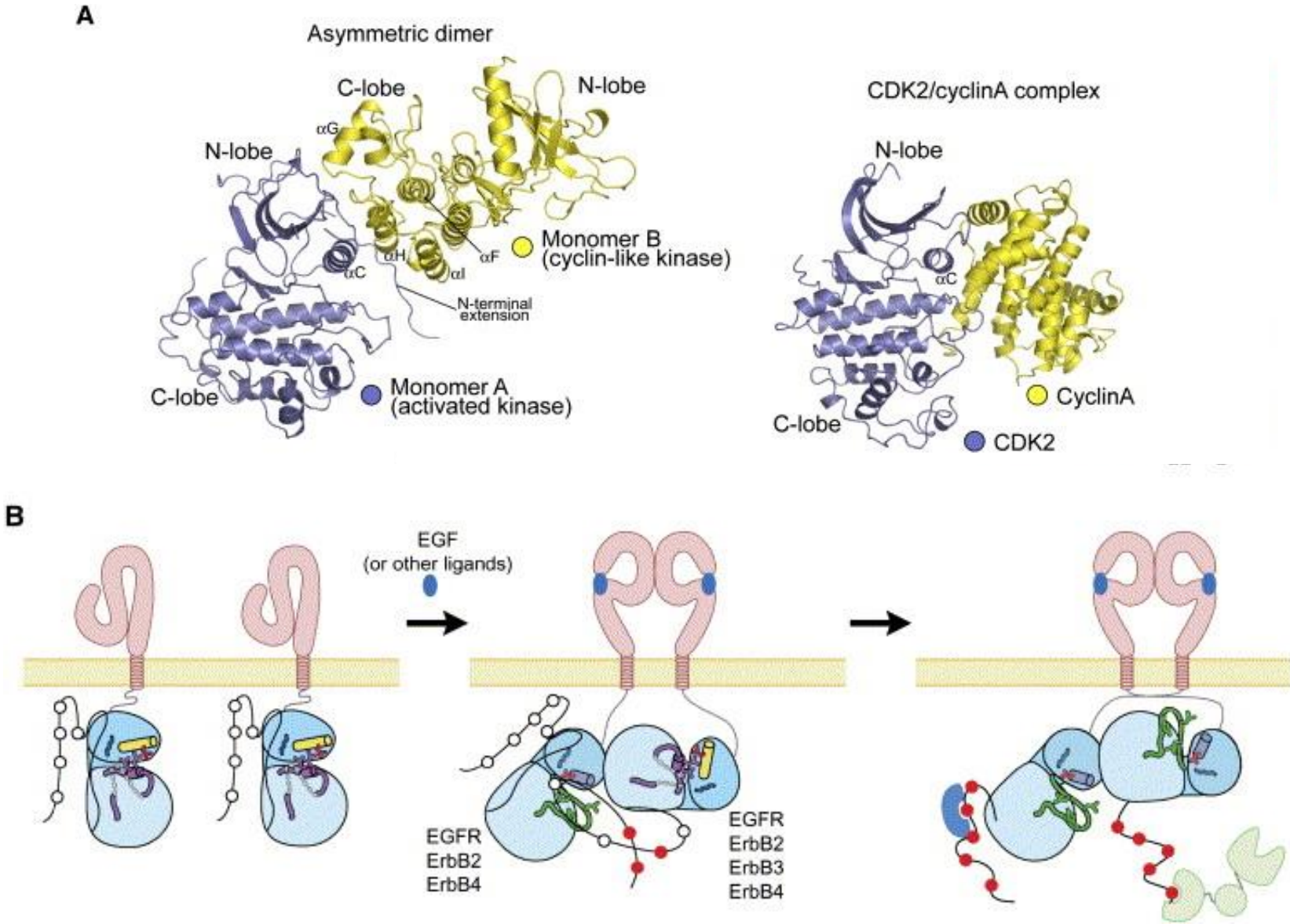
General Model for Activation of the EGFR Family

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).

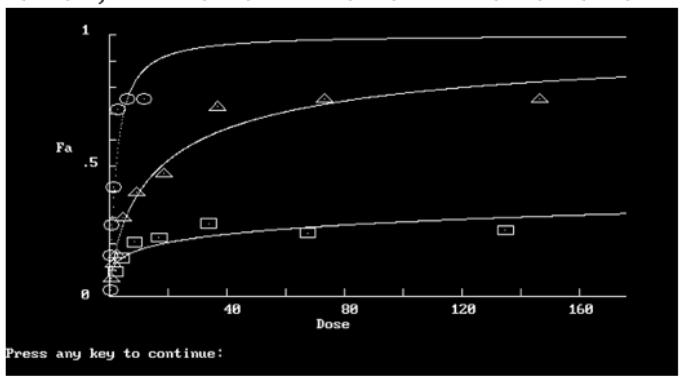


Zhang X, et al., Cell 125: 1137-49 (2006).

Trastuzumab MOA -- Synergy with Chemotherapy

Combination Index Isobologram Analysis

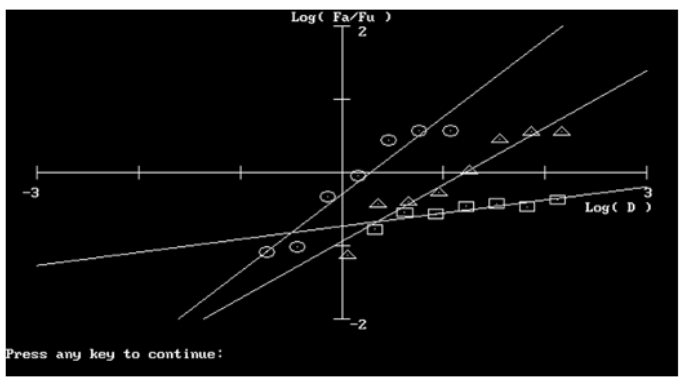
$$\frac{(fa)_{1,2}}{(fu)_{1,2}} = \frac{(fa)_1}{(fu)_1} + \frac{(fa)_2}{(fu)_2} + \frac{(fa)_1(fa)_2}{(fu)_1(fu)_2}$$



Docetaxel, trastuzumab, combination

$$\text{Dose}_1 = \text{Dose IC}_{50}[(1 - f)/f]^{1/m} \longleftarrow \text{Median Effects Principle}$$

$$\log (f_a/f_u) = m \log (D) - m \log (D_m)$$



Median Effects Plot: docetaxel, trastuzumab, combination

Pegram M,…Pietras RJ, …Slamon DJ, et al. Oncogene 18, 2241–2251 (1999).

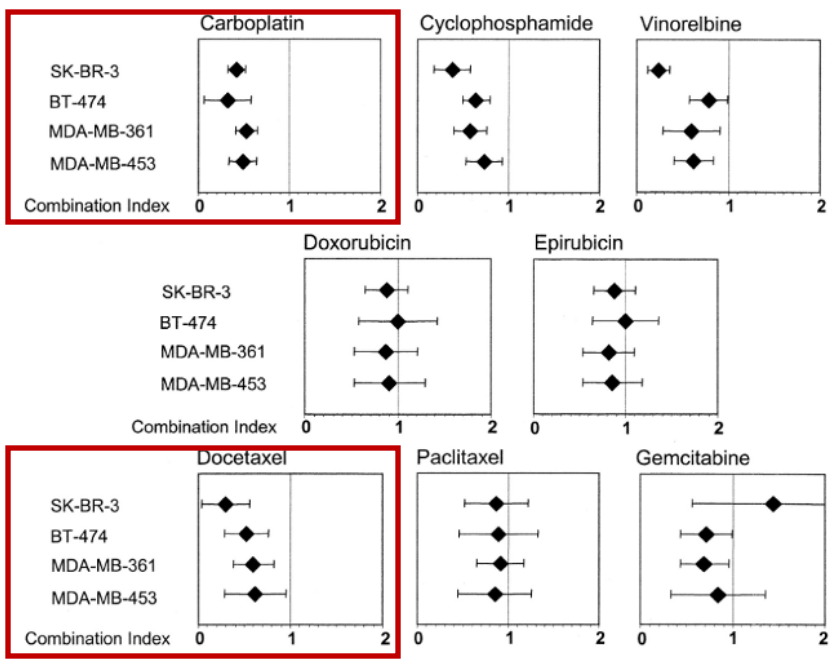
Table 1 Calculated values for the Combination Index as a function of fractional inhibition of SK-BR-3 cell proliferation by a mixture of TSPA and rhuMAb HER2

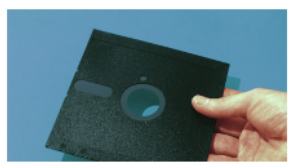
	Combination Index Values					*Parameters*		
Drug	*ED30*	*ED40*	*ED50*	*ED60*	*ED70*	*Dm*	*m*	*r*
TSPA						66.2 μM	0.81	0.99
rhuMAb HER2						675.0 nM	0.15	0.96
TSPA + rhuMAb HER2	0.52	0.37	0.41	0.49	0.60	27.1 μM	0.59	0.99
Diagnosis of combined effect	Synergy	Synergy	Synergy	Synergy	Synergy			

Table 2 Mean combination index values for chemotherapeutic drug/rhuMAb HER2 combinations *in vitro*

Drug	*rhuMAb HER2/drug molar ratio*	*Drug Dose Range (μM)*	*Combination Index (Mean±s.e.m.)*	P *value*	*Interaction*
TSPA	6.4×10^{-5}	$8.25-1.06\times10^{3}$	0.67±0.12	0.0008	Synergy
CDDP	4.0×10^{-4}	$6.5\times10^{-1}-1.7\times10^{2}$	0.56±0.15	0.001	Synergy
VP-16	9.9×10^{-4}	$2.6\times10^{-1}-6.8\times10^{1}$	0.54±0.15	0.0003	Synergy
DOX	9.8×10^{-3}	$2.7\times10^{-2}-6.9$	1.16±0.18	0.13	Addition
TAX	1.4×10^{-1}	$1.8\times10^{-3}-5.0\times10^{-1}$	0.91±0.23	0.21	Addition
MTX	3.3×10^{-1}	$8.0\times10^{-4}-2.0\times10^{-1}$	1.36±0.17	0.21	Addition
VBL	1.7	$1.6\times10^{-4}-3.9\times10^{-2}$	1.09±0.19	0.26	Addition
5-FU	8.8×10^{-5}	$3.0-7.65\times10^{2}$	2.87±0.51	0.0001	Antagonism

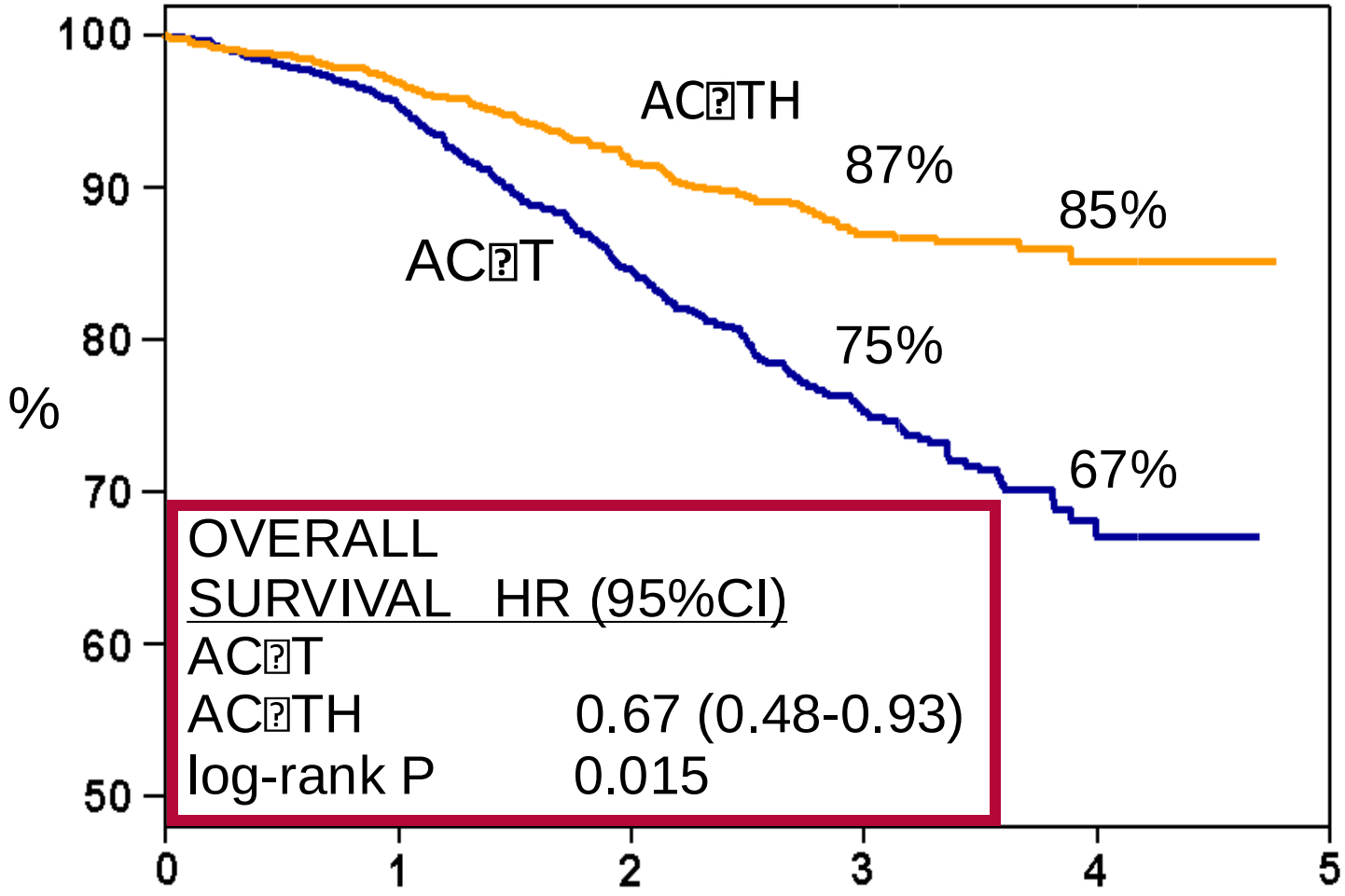
P values indicate level of significance compared to CI = 1.0





Pegram, MD, Konecny GE,… Slamon DJ, et al. JNCI 96 (10):2004, 739–49.

Analysis of Adjuvant Trastuzumab Efficacy (N = 3,351)

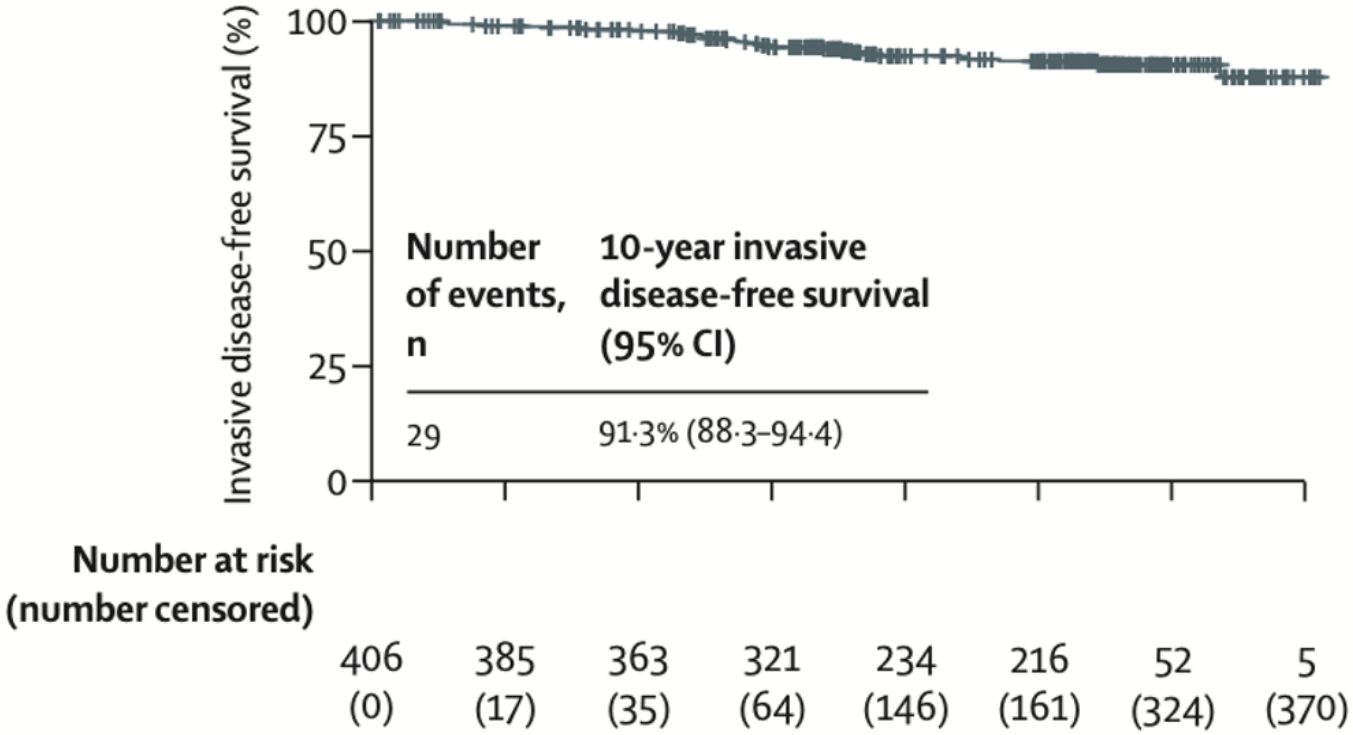


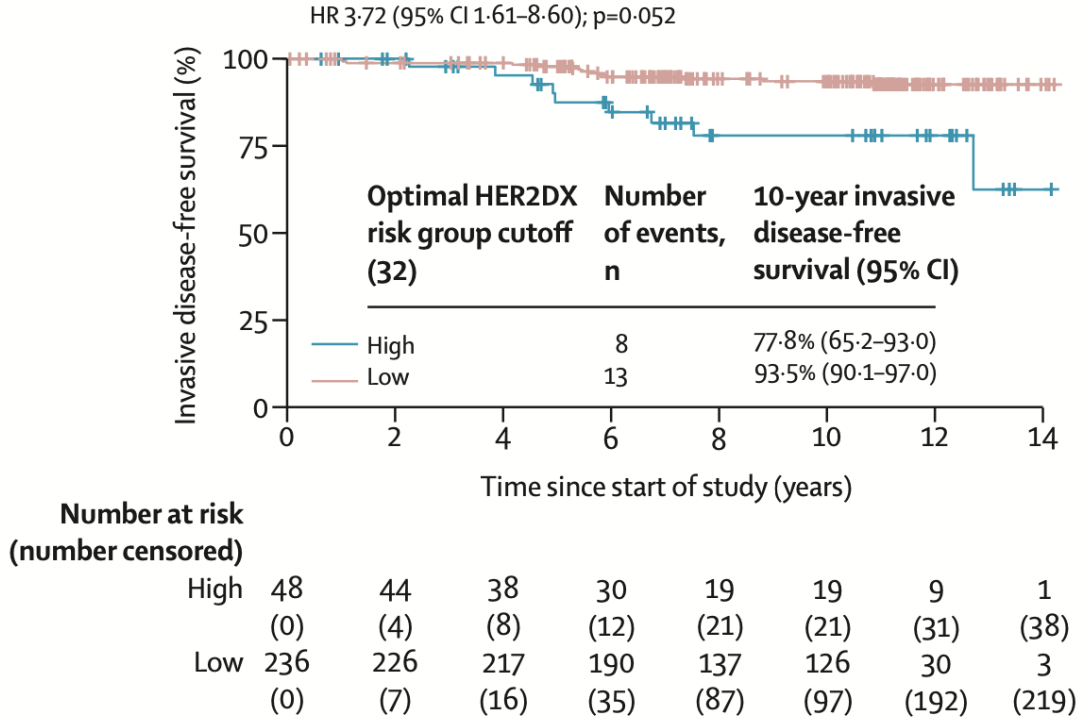
HR=0.48,
2P=3x10^{-12}

Romond, et al., New England Journal of Medicine (2005).

Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial

Sara M Tolaney, Paolo Tarantino, Noah Graham, Nabihah Tayob, Laia Parè, Guillermo Villacampa, Chau T Dang, Denise A Yardley, Beverly Moy, P Kelly Marcom, Kathy S Albain, Hope S Rugo, Matthew J Ellis, Iuliana Shapira, Antonio C Wolff, Lisa A Carey, Romualdo Barroso-Sousa, Patricia Villagrasa, Michelle DeMeo, Molly DiLullo, Jorge Gomez Tejeda Zanudo, Jakob Weiss, Nikhil Wagle, Ann H Partridge, Adrienne G Waks, Clifford A Hudis, Ian E Krop, Harold J Burstein, Aleix Prat, Eric P Winer

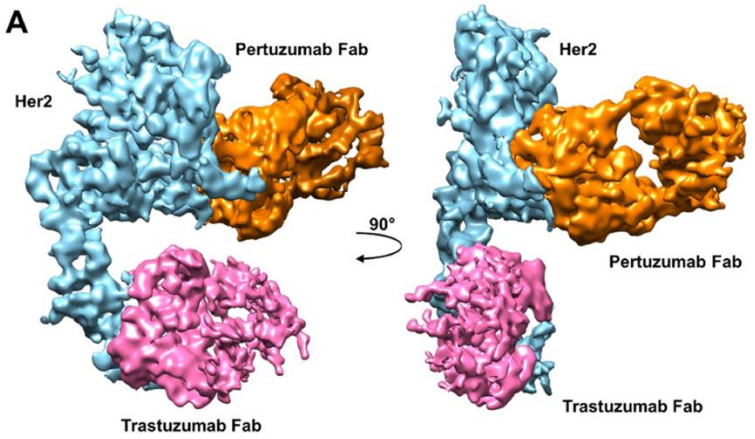




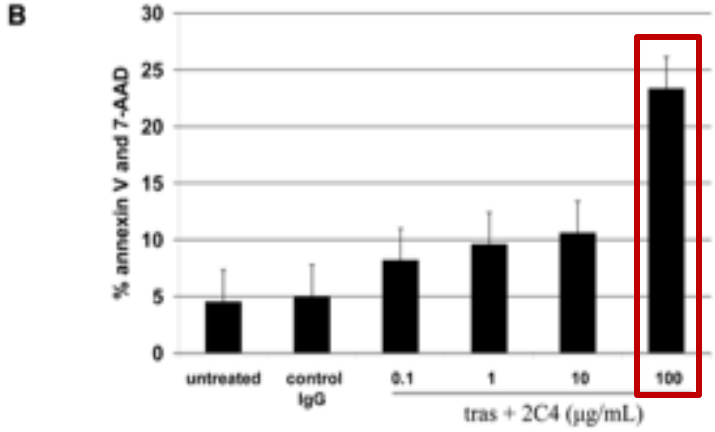
Tolaney SM, et al. Lancet Oncol 2023; 24: 273–85.

Neoadjuvant Dual HER2 MAb Therapy: Scientific Rationale and Clinical Outcomes

4.36Å resolution, cryo-EM structure

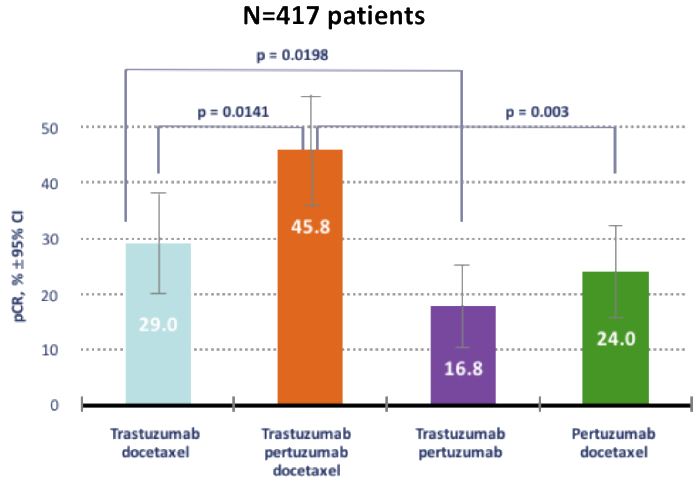


Hao Y, et al., PLoS One. 2019;14(5):e0216095.

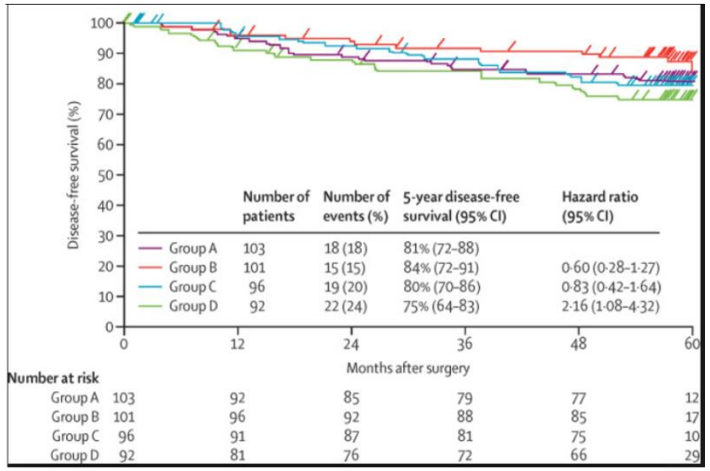


Rita Nahta, *et al*. Cancer Res 2004;64:2343-2346.

NEOSPHERE Study

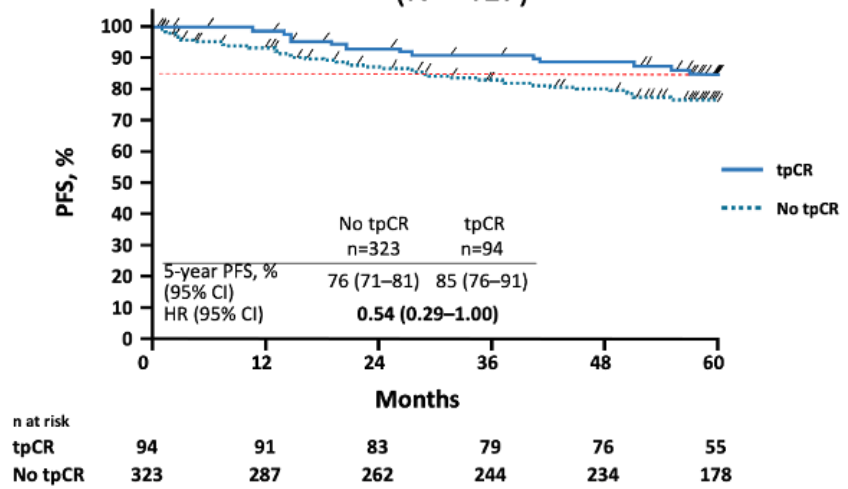


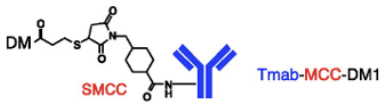
NEOSHERE Time-to-event Outcomes

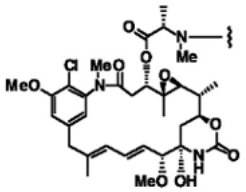


Gianni L, et al. Lancet Oncol 2016: 17(6), 791-800.

PFS by tpCR: all treatment arms combined, ITT population (N = 417)







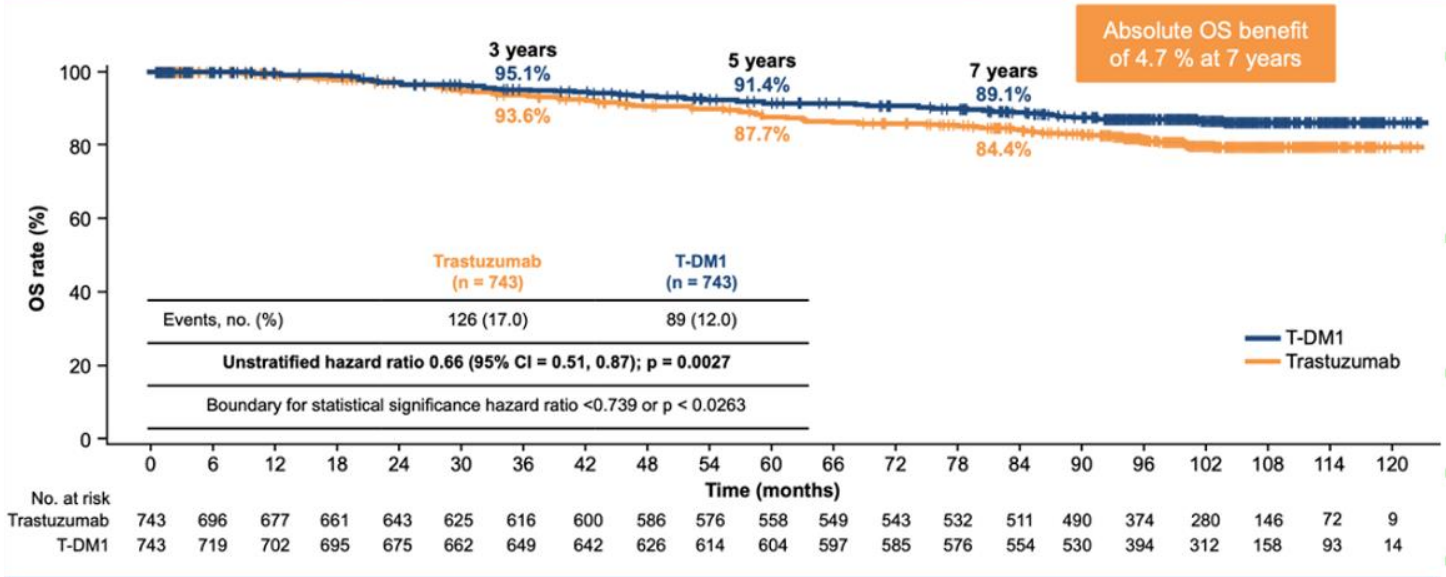
Drug Maytansinoid (DM)

Post-neoadjuvant T-DM1: Final IDFS and updated OS Analysis at 8.4 yrs

Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis

Sibylle Loibl, Max S. Mano, Michael Untch, Chiun-Sheng Huang, Eleftherios P. Mamounas, Norman Wolmark, Adam Knott, Asna Siddiqui, Thomas Boulet, Beatrice Nyawira, Eleonora Restuccia, Charles E. Geyer, Jr.

KATHERINE 2nd OS interim analysis; median follow-up 8.4 years (101 months)



Significant reduction in risk of death by 34% with T-DM1

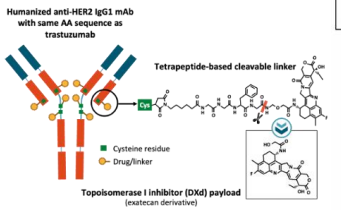
KATHERINE summary and conclusions

- After 8.4 years (101 months) median follow-up, T-DM1 significantly improved OS in patients with HER2-positive early breast cancer with residual invasive disease after neoadjuvant therapy
  - Hazard ratio 0.66 (95% CI 0.51, 0.87), p = 0.0027
  - 7-year OS rates: 89.1% (T-DM1) vs 84.4% (trastuzumab), a difference of 4.7%
- IDFS benefit of T-DM1 was sustained in the ITT population with longer follow-up with a hazard ratio of 0.54 (95% CI 0.44, 0.66) as well as in key subgroups
  - 7-year IDFS rates: 80.8% (T-DM1) vs 67.1% (trastuzumab), a difference of 13.7%
- No new safety issues emerged with longer follow-up
  - Cardiac toxicity was rare in both arms
- T-DM1 is the first therapy to show improved survival post-surgery in patients with HER2-positive early breast cancer with residual invasive disease after neoadjuvant therapy
- Follow-up is ongoing for the final OS analysis

LBA GS03-12; SABCS 2023.

DESTINY-BREAST05 and COMPASSHER2-RD: Post-neoadjuvant Trials for HER2+ RD

DESTINY-Breast05 Head-to-Head Phase 3 Trial of Trastuzumab Deruxtecan Versus T-DM1 Initiated in Patients with HER2 Positive Early Breast Cancer at High Risk* After Neo-adjuvant Therapy [NCT04622319]



Trastuzumab deruxtecan –
- Antibody Drug conjugate
- Deruxtecan payload
- Toxicity - Pneumonitis

Eligibility:
- HER2+
- Residual Dz after neoadjuvant therapy

N=1600
R
1:1

- Trastuzumab deruxtecan 5.4 mg/kg x 1 year
- Trastuzumab emtansine 3.6 mg/kg x 1 year

- Primary endpoint = IDFS
- Secondary endpoints = DFS, OS, Brain mets, Safety

***Patients will be defined as high risk based on inoperable cancer at disease presentation (clinical stages T4, N0-3, M0 or T1-3, N2-3, M0) or operable at presentation (clinical stages T1-3, N0-1, M0) with positive pathological node status (ypN1-3) after neo-adjuvant therapy. Stratification variables: operability at dx, HR status, ypN status, neoadj regimen.**

COMPASSHER2 TRIALS

Preoperative Phase: all patients

Eligibility:
Stage II or IIIA HER2+ BC (T2-3, N0-2)
- cN0 eligible if ≥ 2.0 cm
- cN1-2 eligible ≥ 1.5cm
- ER+ and ER- eligible

REGISTRATION

THP x 4 Cycles
Paclitaxel qwk x12
OR
Docetaxel q3 wk x4
with
Trastuzumab (H)
& Pertuzumab (P) q3 wk x4

* nab-pacl allowed

SURGERY

Arm A: pCR (no invasive disease)

pCR (ypT0/Tis ypN0) *40%*

EA1181
CompassHER2-pCR
- Complete 1 yr HP
- Radiation and endocrine Rx (if appropriate)

ECOG-ACRIN cancer research group

No pCR *60%*

A011801
CompassHER2-RD

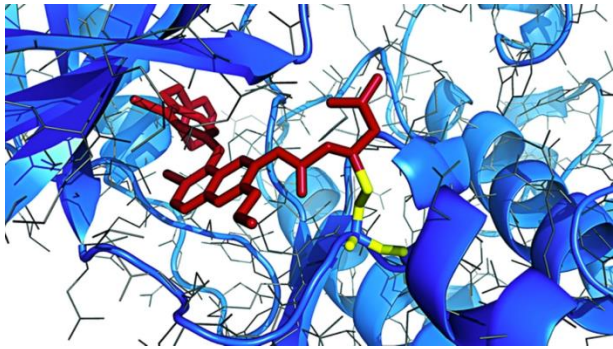
Alliance for Clinical Trials in Oncology

Grp 1: pre-op THP-> AC, Cb/HP x 4
Grp 2: pre-op TCHP, *AC-THP* -> no further chemo

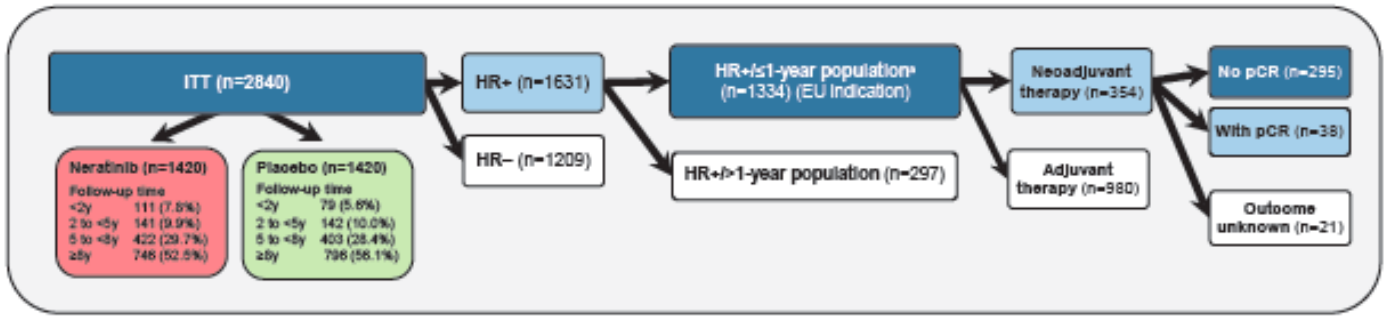
Eligibility
HER2+ RD
ER- & ER+
(ER+ must be N+)
(~30% of A011801 expected to come from EA1181)

Registration
R
- T-DM1 x 14 doses
- T-DM1/tucatinib x 14 doses

1) Screening, 2) scanning for ILD, working 3) synergistically with a care team, 4) suspending cancer treatment, and managing ILD with 5) steroids.

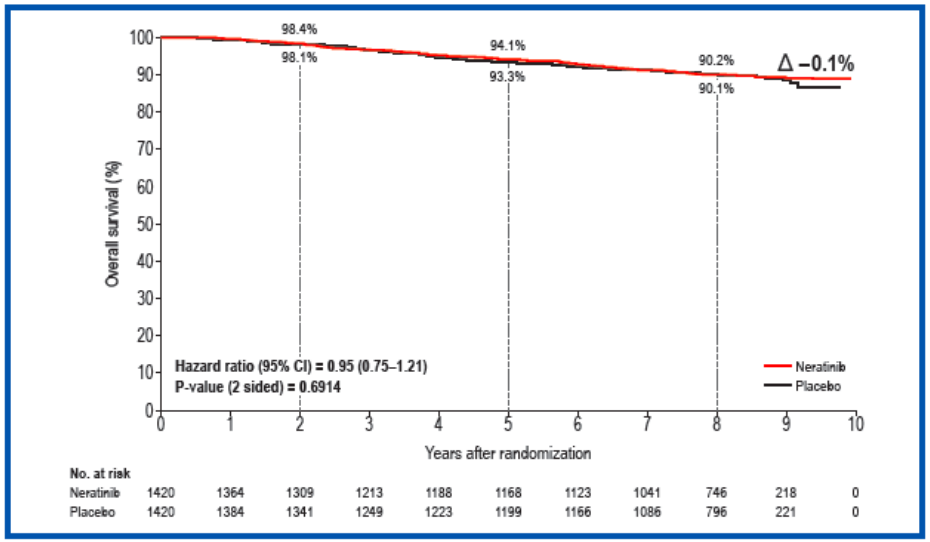


Extended Adjuvant HER2-Targeted Therapy
PD3-03 (Abstr #533): ExteNET "Final" OS



Median FU 8.1 years: **HR+/≤1 year, 8y OS: 91.5% vs, 89.4% Δ2.1%. HR 0.79 (0.55-1.13)**

Figure 2. Overall survival (ITT population)

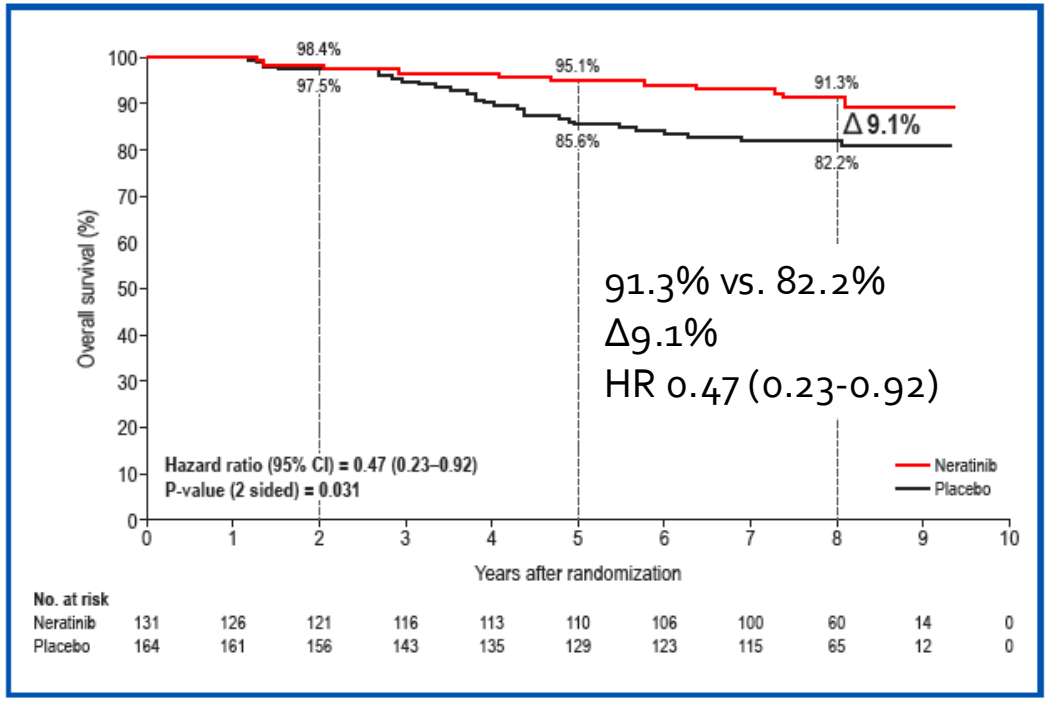


←No difference in OS for ITT population.

HR+:
91.6% vs. 90.1%
HR-:
88.1% vs. 90.3%

HR+/≤1 year/neoadjuvant Rx/non-pCR subset(s):

Figure 5. Overall survival (HR+/≤1-year no pCR)



91.3% vs. 82.2%
Δ9.1%
HR 0.47 (0.23-0.92)

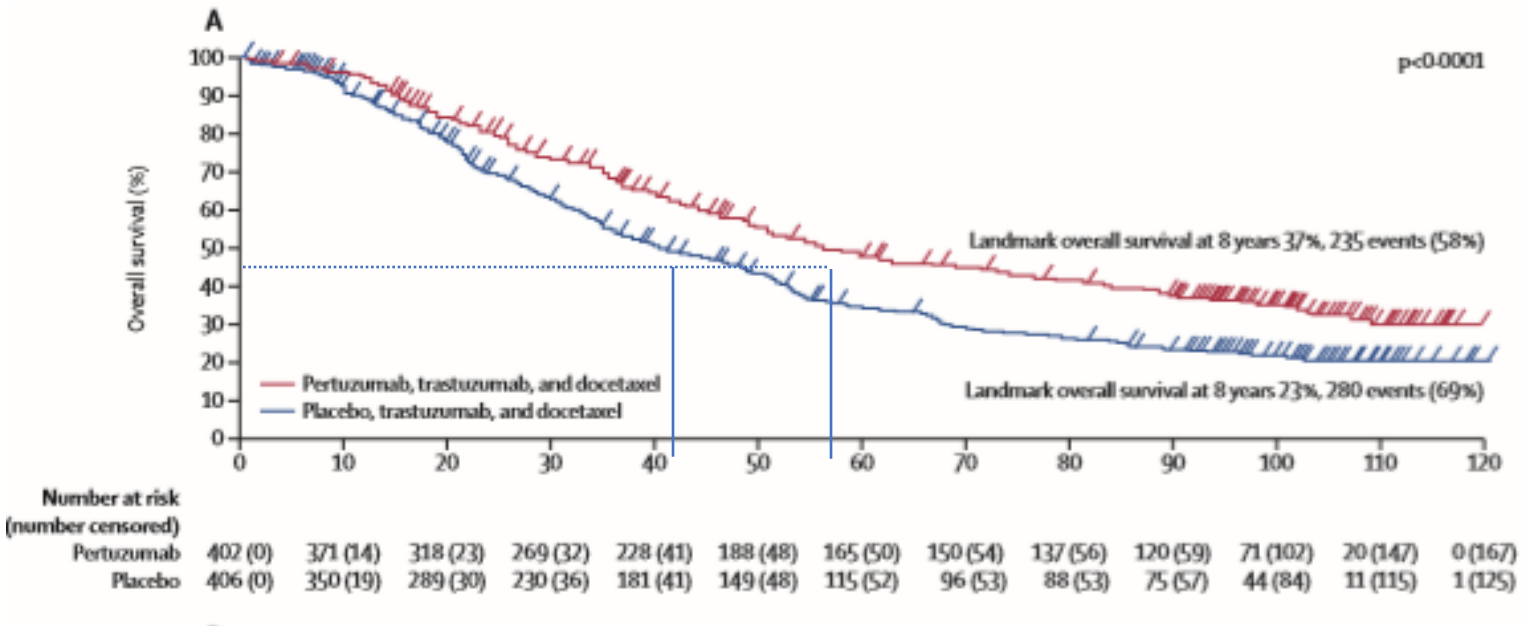
Cut-off date: July 2019

Holmes et al, Abstract #533 SABCS 2020.

First-line HER2+ MBC- CLEOPATRA: End-of Study Results

Median follow-up was 99·9 months in the pertuzumab group (IQR 92·9–106·4) and 98·7 months (90·9–105·7) in the placebo group

End-of-Study OS in ITT Population*



*Crossover patients were analyzed in the placebo arm.

	Median OS, Mos (95% CI)
Pertuzumab + Trastuzumab/Doc	**57.1**
Placebo + Trastuzumab/Doc	**40.8**

Δ16.3 months ↑ OS

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

VOLUME 27 · NUMBER 33 · NOVEMBER 20 2009

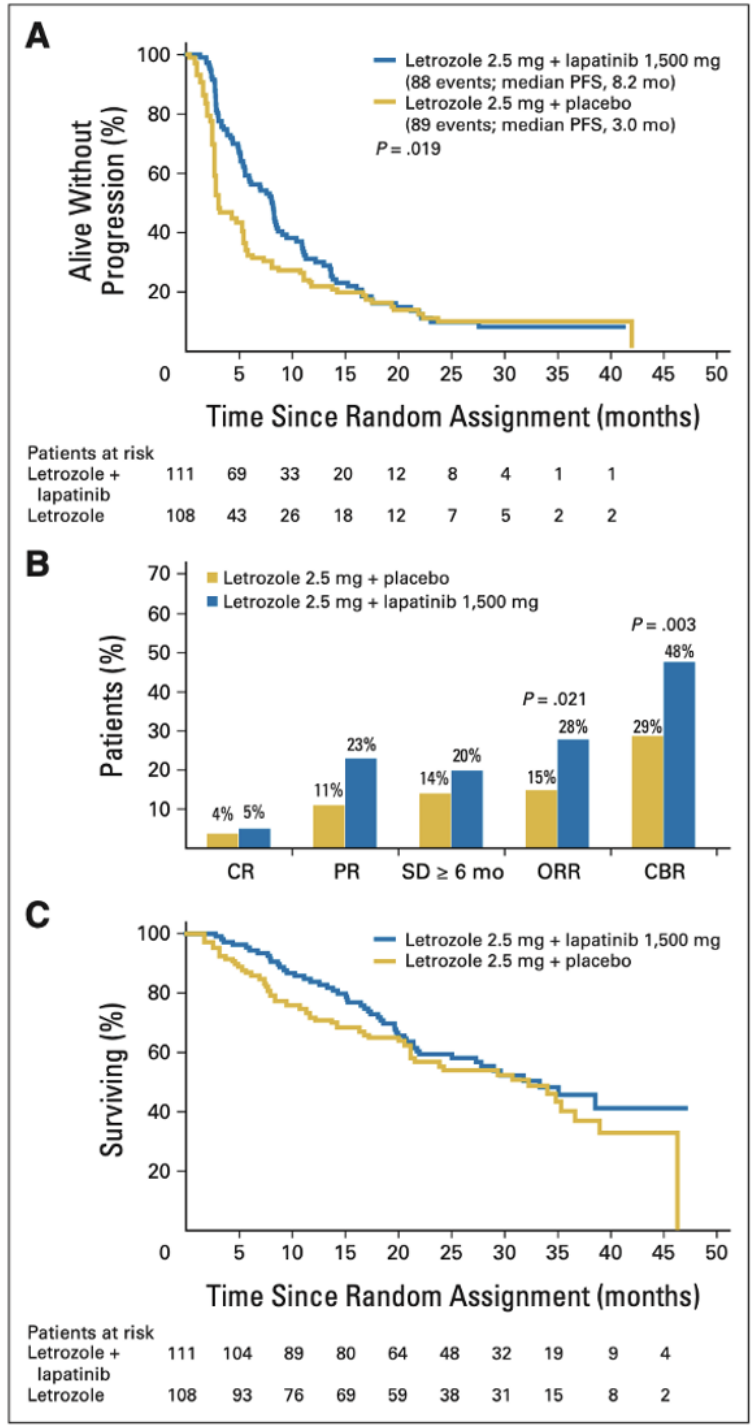
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Lapatinib Combined With Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer

Stephen Johnston, John Pippen Jr, Xavier Pivot, Mikhail Lichinitser, Saeed Sadeghi, Veronique Dieras, Henry Leonidas Gomez, Gilles Romieu, Alexey Manikhas, M. John Kennedy, Michael F. Press, Julie Maltzman, Allison Florance, Lisa O'Rourke, Cristina Oliva, Steven Stein, and Mark Pegram

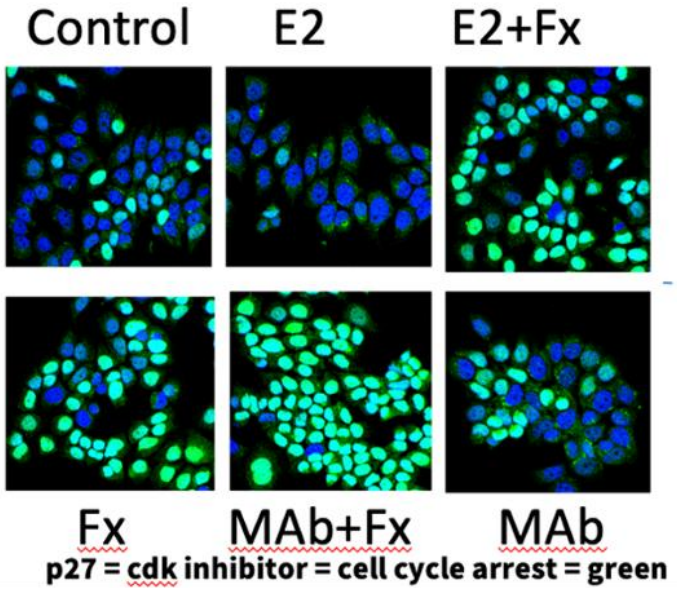
See accompanying editorial on page 5492 and article on page 5529



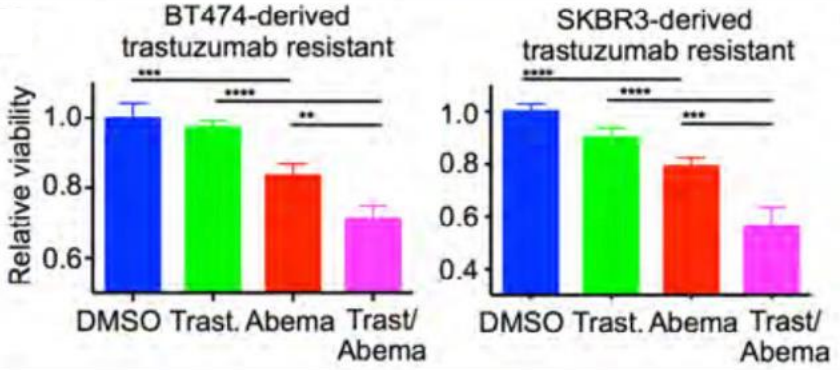
Oncogene. 1995 Jun 15;10(12):2435-46.

HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells

R J Pietras [1], J Arboleda, D M Reese, N Wongvipat, M D Pegram, L Ramos, C M Gorman, M G Parker, M X Sliwkowski, D J Slamon



Synergy between anti-HER2 and CDK 4/6i



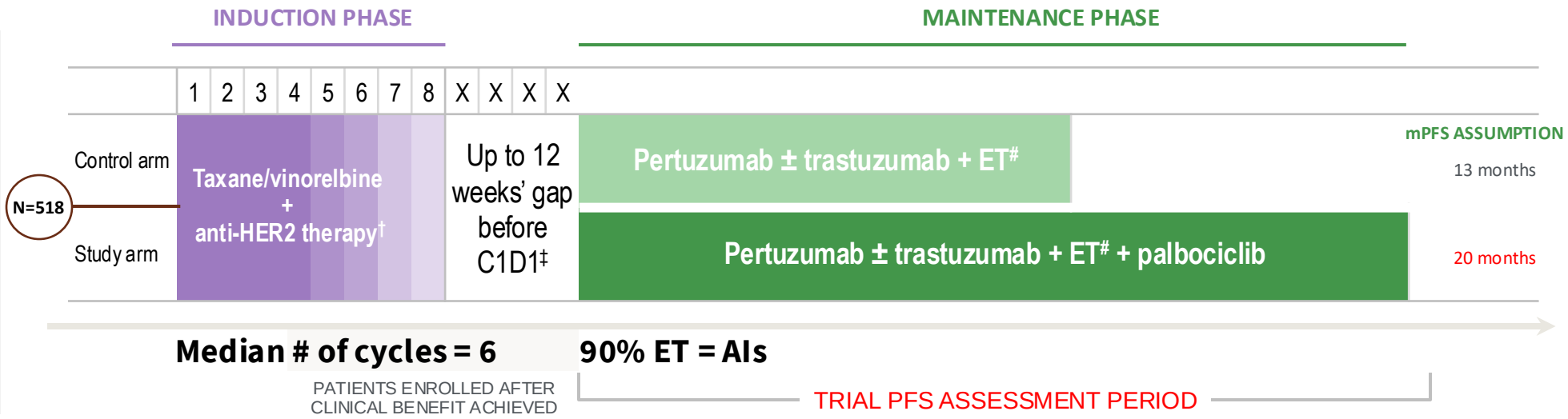
Goel S, et al. Cancer Cell. 2016; 29(3): 255-269.

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

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 – 90% power for HR 0.667	OS, 3- and 5-year survival probability, ORR, DoR, CBR, Safety, PROs	PK, PIK3CA status, Tumor tissue biomarkers

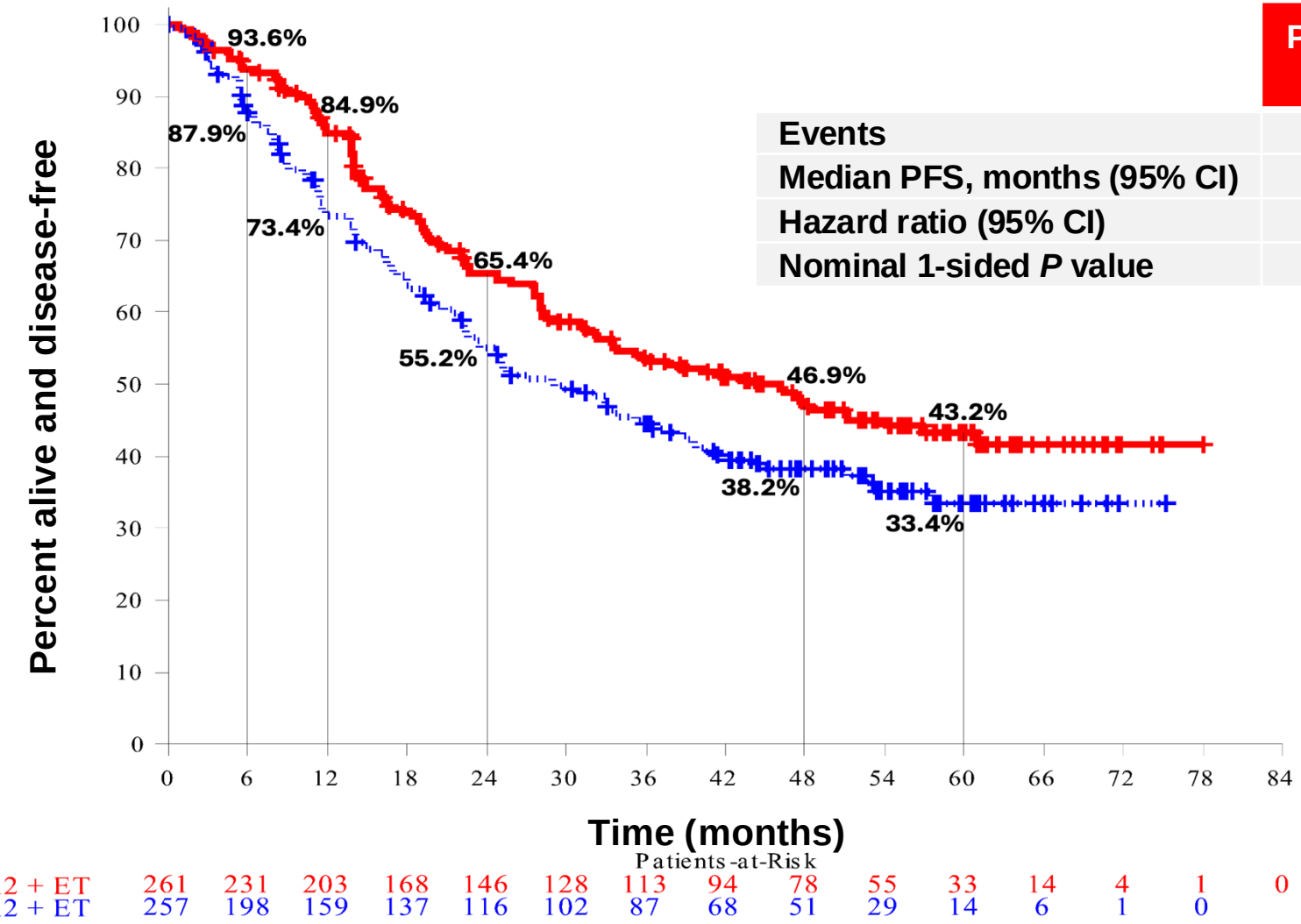
*Patients received induction therapy for 4–8 cycles depending on tolerability. †Anti-HER2+ Therapy – Anti-HER2 treatment options are trastuzumab + pertuzumab or trastuzumab only (limited to 20% of study patients). The same anti-HER2-regimen should be used pre- and post- randomization. ‡Patients randomized 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).

Primary Endpoint: PFS (Investigator-Assessed)

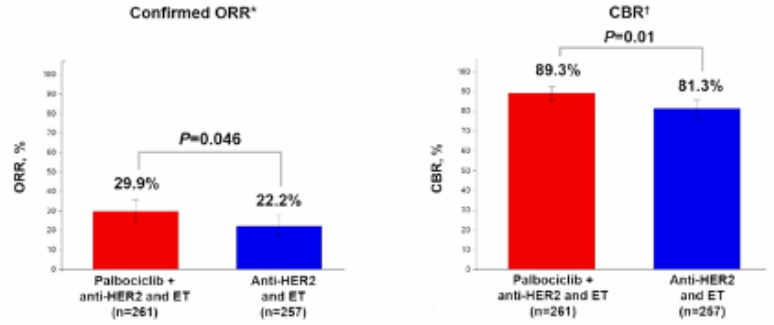
OS analysis remains immature, with only 119 of 247 planned events observed to date; median OS (control arm) = 77 mos.



	Palbo + anti-HER2 and ET	Anti-HER2 and ET
Events	126/261	136/257
Median PFS, months (95% CI)	**44.3** (32.4-60.9)	**29.1** (23.3-38.6)
Hazard ratio (95% CI)	0.74 (0.58-0.94)	
Nominal 1-sided *P* value	0.0074	

Median follow-up on patients who are alive and disease-free, 52.6 months

Secondary Endpoints: ORR and CBR (Investigator-Assessed)



CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; palbo=palbociclib.

Metzger, et al. SABCS 2024. Abstract GS1-03.

Adverse Events (Grade ≥2 in ≥10% of Patients)

Adverse Events, n (%)*	Palbociclib + anti-HER2 and ET (N=261)			Anti-HER2 and ET (N=248)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Neutropenia	52 (19.9)	165 (63.2)	12 (4.6)	10 (4.0)	11 (4.4)	0 (0.0)
White blood cell count decreased	30 (11.5)	30 (11.5)	1 (0.4)	2 (0.8)	0 (0.0)	0 (0.0)
Fatigue	60 (22.9)	14 (5.4)	0 (0.0)	32 (12.9)	0 (0.0)	0 (0.0)
Stomatitis	45 (17.2)	11 (4.2)	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)
Diarrhea	69 (26.4)	29 (11.1)	0 (0.0)	26 (10.5)	4 (1.6)	0 (0.0)
Upper respiratory tract infection	30 (11.5)	1 (0.4)	0 (0.0)	16 (6.5)	0 (0.0)	0 (0.0)
Urinary tract infection	26 (10.0)	2 (0.8)	0 (0.0)	19 (7.7)	1 (0.4)	0 (0.0)
Arthralgia	23 (8.8)	4 (1.5)	0 (0.0)	44 (17.7)	3 (1.2)	0 (0.0)
Ejection fraction decreased	22 (8.4)	1 (0.4)	0 (0.0)	21 (8.5)	8 (3.2)	0 (0.0)
Cardiac heart failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)

- The incidence of grade ≥4 adverse events regardless of treatment attribution was similar across study arms (12.3% vs 8.9% for palbociclib-containing arm vs control; *P*=0.21)
- Treatment discontinuation due to AEs were reported in 14 (7.5%) of patients in the palbociclib arm
- No treatment-related deaths were reported in either arm of the study

*Adverse events were assessed per Common Terminology Criteria for Adverse Events, version 4.0 regardless of treatment attribution. Stomatitis, mouth ulceration, mucosal inflammation, and mucositis were assessed as medical concepts using grouped terms. Fatigue and asthenia were assessed as medical concepts using grouped terms. Cardiac safety data were also included in the table above. AE=adverse events.

Metzger, et al. SABCS 2024. Abstract GS1-03.

Implications to Clinical Practice

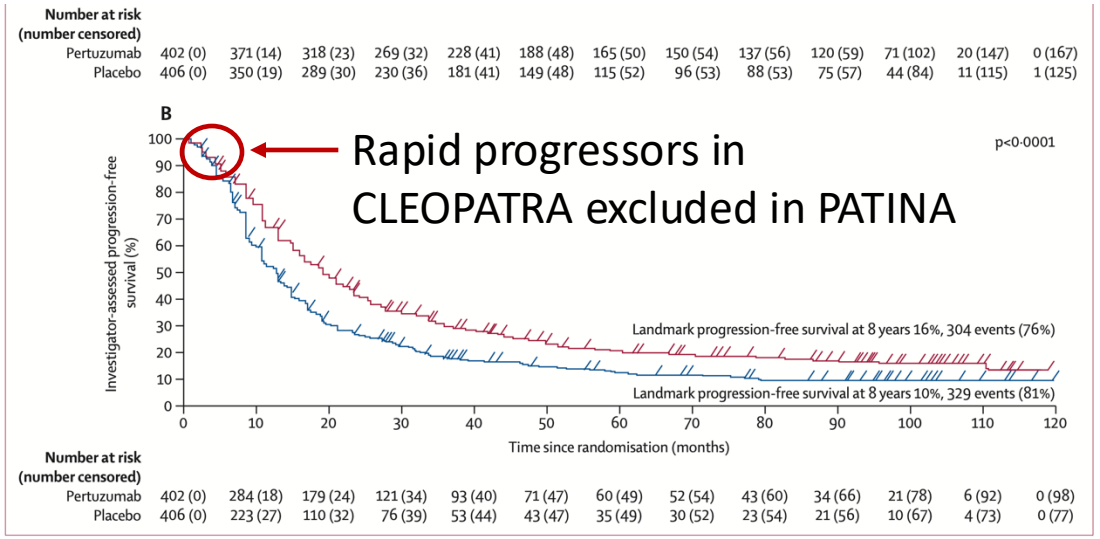
- The AFT-38 PATINA phase III study demonstrates a **clinically meaningful** improvement in PFS among patients diagnosed with HR+,HER2+ breast cancer
  - Median PFS increased from 29.1 to 44.3 months (Δ15.2 months)
  - Manageable toxicity

Palbociclib added to anti-HER2 and endocrine therapy may represent a new standard of care for patients diagnosed with HR+,HER2+ advanced breast cancer

Have we gotten it all wrong in HR+/HER2+ MBC?
Should we follow same paradigm as in HR+/HER2-neg dz?

Caveats:

1. **Randomization *after* a median of 6 cycles of chemo:**
   - **The real PFS from start of chemo would be even *longer* in PATINA**
   - **Yet, some patients progress during the chemo run-in; these patients no doubt have worse prognosis (*not* included in PATINA).**



2. **These data pre-date the anticipated results from DB-09, which has no real "maintenance" phase.**
3. **Febrile neutropenia not reported, ILD apparently not increased.**
4. **Will need FDA or guideline(s) nod for insurance authorization.**

Ongoing Trials in the First-line HER2+ Metastatic Space

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

POPULATION

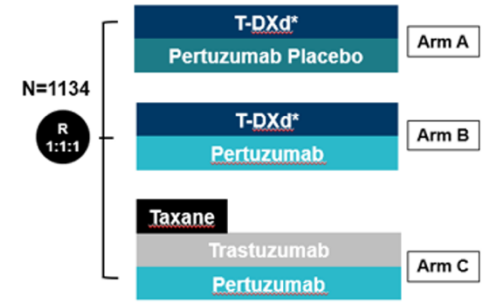
- HER2-positive mBC
- DFI >6 months from last chemotherapy or HER2-targeted therapy in neoadjuvant/adjuvant setting
- No prior systemic treatment for mBC except for endocrine therapy

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)

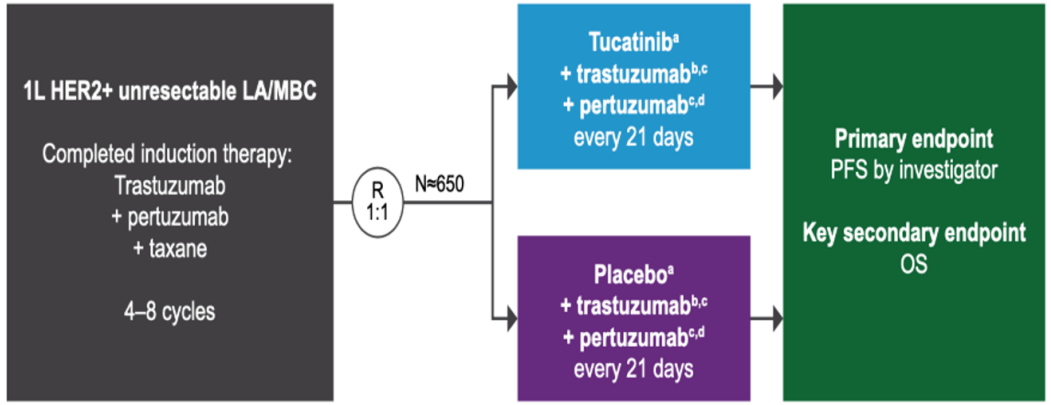
Secondary:

- 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

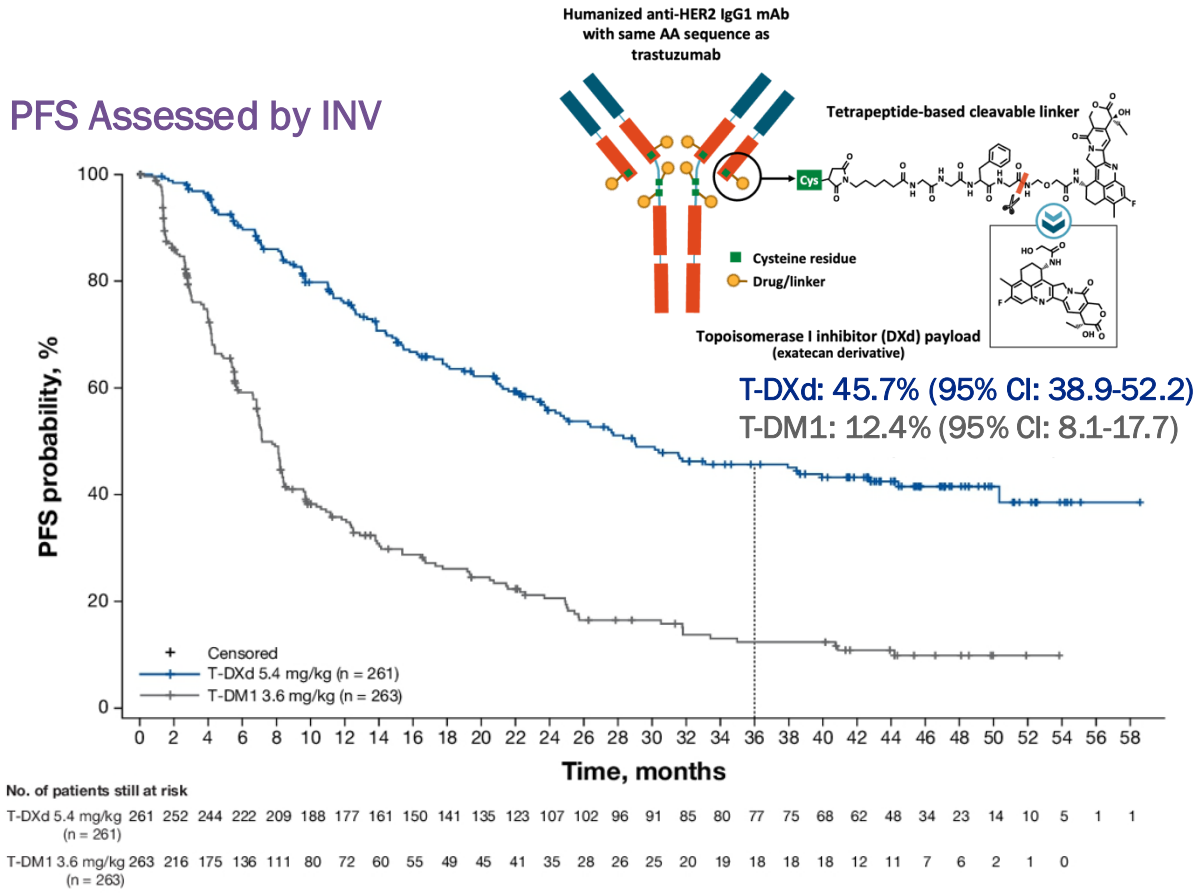
HER2CLIMB-05



HER2CLIMB-05 (NCT05132582) is a phase 3, randomized, double-blind study evaluating tucatinib or placebo in combination with trastuzumab plus pertuzumab as maintenance therapy in the 1L setting for patients with unresectable LA or metastatic HER2+ breast cancer following SOC induction therapy

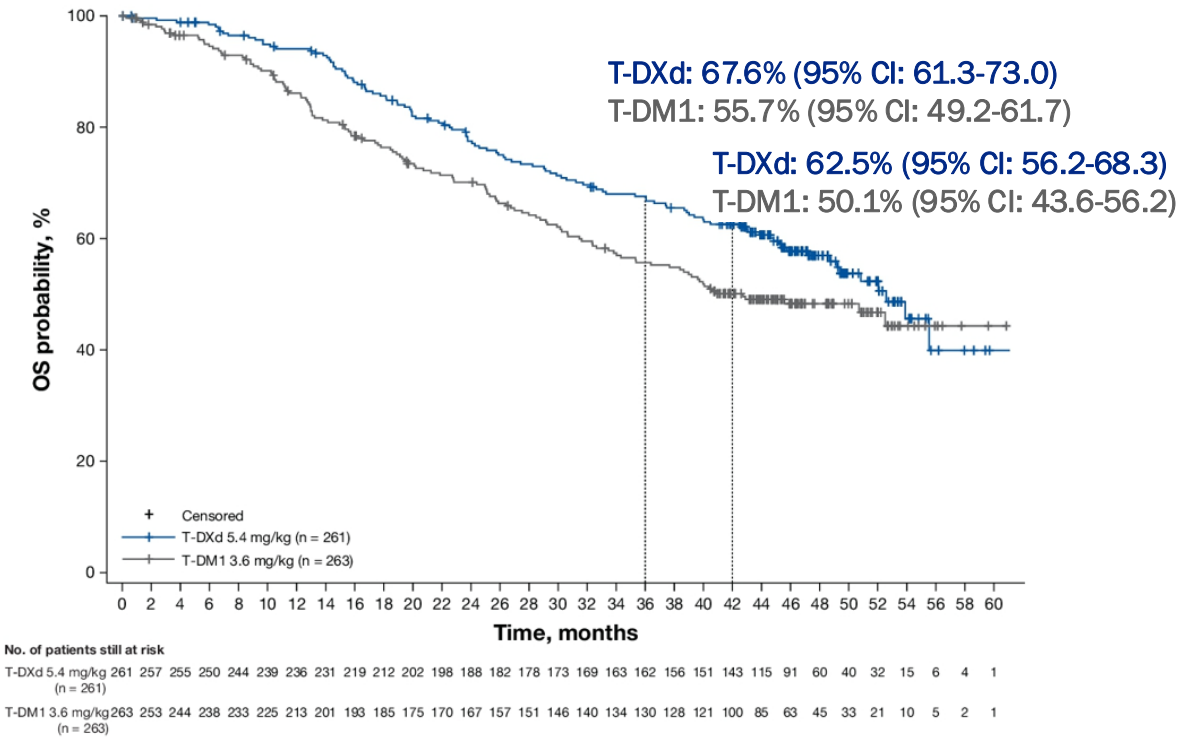
Second-Line Rx for HER2+ MBC -- T-DXd vs T-DM1 in HER2+ MBC:
Updated PFS and OS Results From the Randomized Phase 3 DESTINY-Breast03 Study
Median Follow-Up: 43.0 mo for T-DXd and 35.4 mo for T-DM1

PFS Assessed by INV



	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)	

OS



	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.

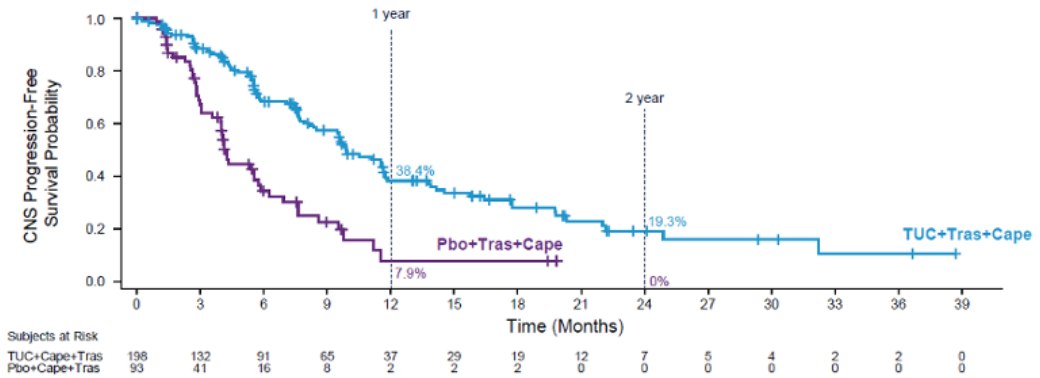
Hamilton EP, et al. ASCO 2024. Abstract 1025.

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

Median Follow-Up: 29.6 mo

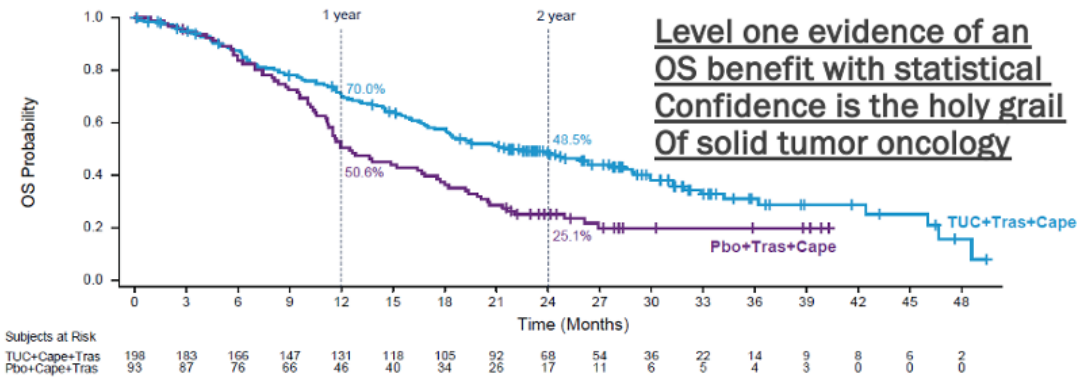
CNS PFS for All Patients With Brain Metastases

	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		

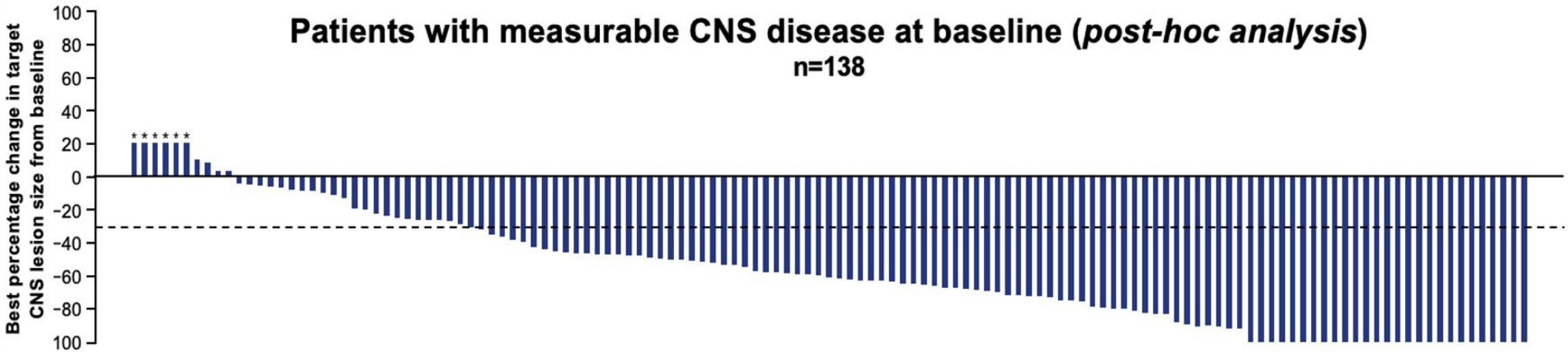
OS for Patients With Treated Stable Brain Metastases

	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.

Baseline BMs: CNS ORR

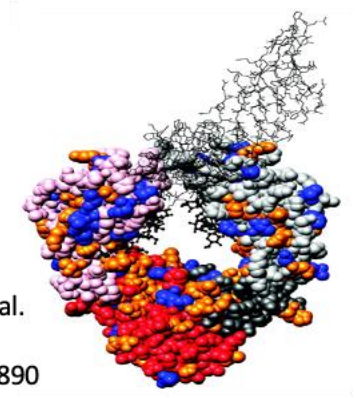


Measurable CNS disease at baseline	All patients (n=138)	Stable BMs (n=77)	Active BMs (n=61)	Active BM subgroups: Untreated (n=23) *Post-hoc analysis*	Active BM subgroups: Previously treated / progressing (n=38) *Post-hoc analysis*
Confirmed CNS ORR, % (95% CI)	**71.7 (64.2, 79.3)**	79.2 (70.2, 88.3)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

Margetuximab is a chimeric, Fc-engineered, immune-activating anti-ERBB2 immunoglobulin G1 (IgG1) monoclonal antibody that shares epitope specificity and Fc-independent antiproliferative effects with trastuzumab.



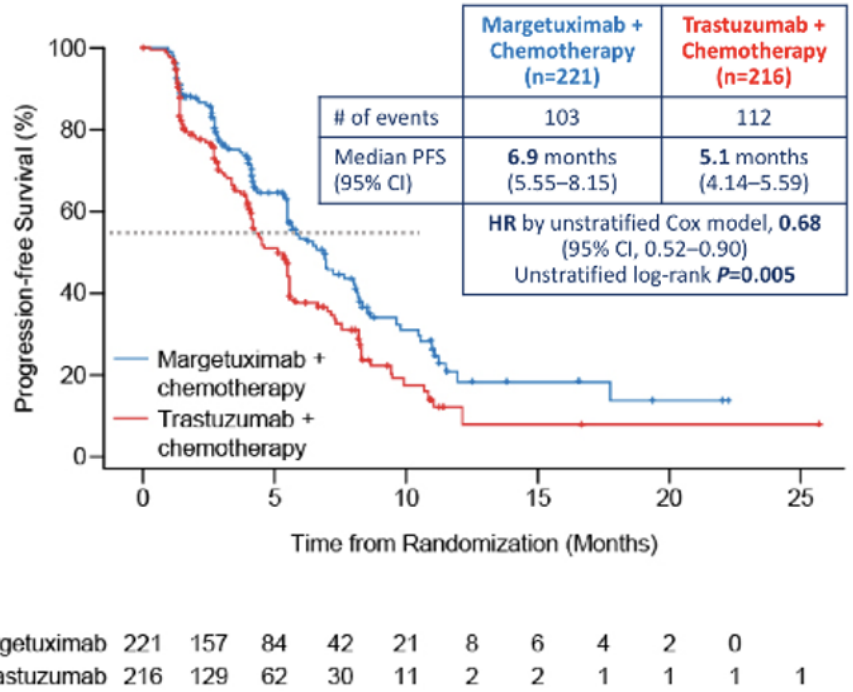
Jeffrey B. Stavenhagen et al. Cancer Res 2007;67:8882-8890

Locations of Fc mutations identified by yeast surface display identify the variant F243L/R292P/Y300L/V305I/P396L

Fc domain mutants *deliberately* introduced to increase binding affinity for activating Fc receptors and decrease binding affinity for decoy inhibitory Fc receptors

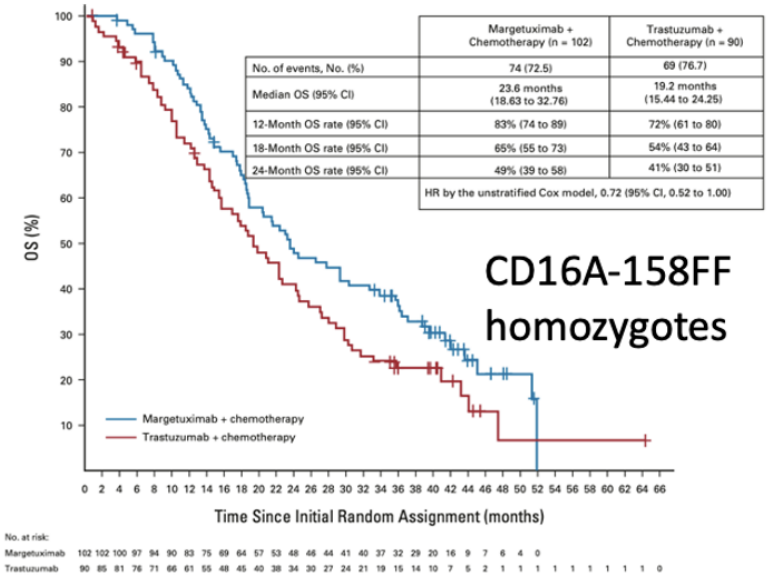
Margetuximab Versus Trastuzumab in Patients With Previously Treated HER2-Positive Advanced Breast Cancer (SOPHIA)

FF or FV (n=437; 86%)



CD16A Genotype by Treatment Group

Prespecified Exploratory OS Analysis



Planned Exploratory PFS Analysis by CD16A Genotype

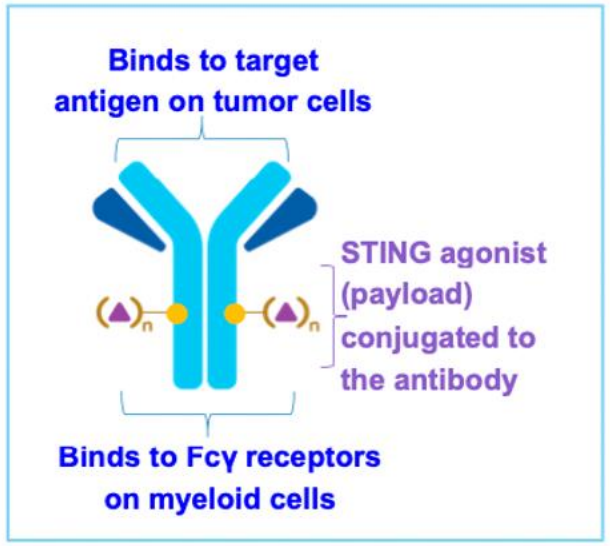
Rugo HS, et al. J Clin Oncol. 2023 Jan 10;41(2):198-205.

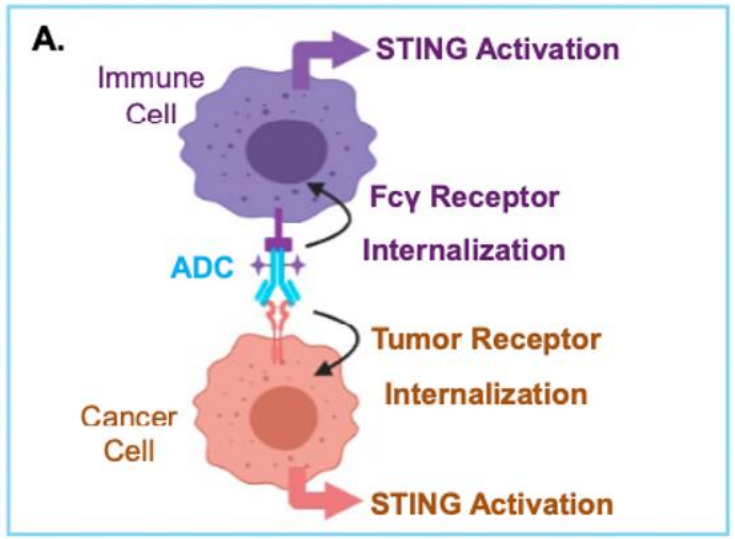
Rugo HS, et al. JAMA Oncol. 2021 Apr 1;7(4):573-584.

Two New Ongoing Phase I Studies Exploiting Immune Activation in HER2+ Tumor Microenvironments

1. HER2 ADC STING agonist payload

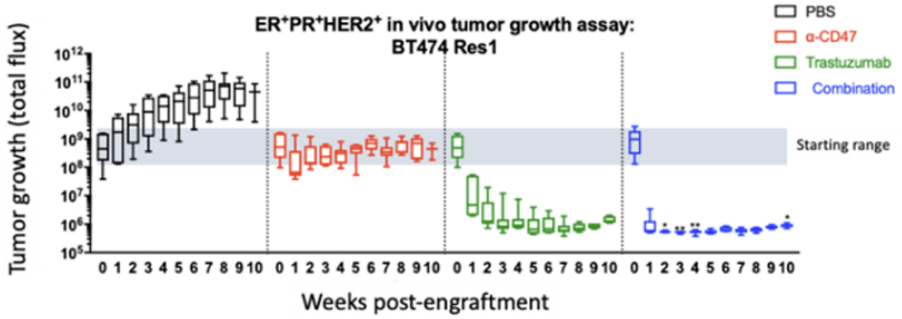
Tumor cell-intrinsic STING pathway activation leads to robust induction of Type III Interferons and contributes to the anti-tumor activity elicited by STING agonism



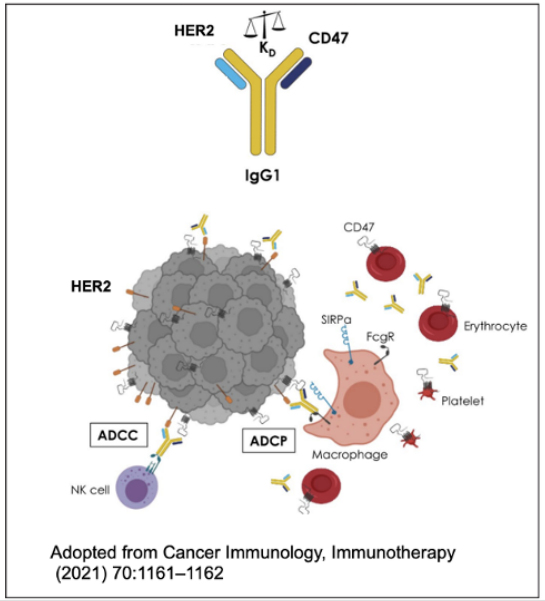


2. HER2/CD47 bispecific

Combining CD47 blockade with trastuzumab eliminates HER2-positive breast cancer cells and overcomes trastuzumab ADCC tolerance



Upton R,…Pegram MD*, Weissman IL*, et al. PNAS Jul 2021, 118 (29) e2026849118.
*Co-senior authors



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

ep·i·logue

/ˈepəˌlôg,ˈepəˌläg/

Noun, definition -- An epilogue is the final chapter at the end of a story that often serves to reveal the fates of the characters. Some epilogues may feature scenes only tangentially related to the subject of the story. They can be used to hint at a sequel or wrap up all the loose ends.

1. **HER2 structure/function relationships demonstrate high homology with EGFR, and cytoplasmic kinase domain *primordial* structural similarity to Cyclin/CDK complexes.**

2. **Combined receptor blockade with anti-HER2 and anti-estrogens is synergistic against HER2+/HR+ breast cancers.**

3. **Therapeutic strategies targeting HER2 and CDK 4/6 are also synergistic [Goel S, et al. Cancer Cell. 2016; 29(3): 255–269].**

4. **HER2-targeting ADCs with cytotoxic payloads are a new standard of care in the treatment of both HER2+ early breast cancer (with residual disease following neoadjuvant therapy), and HER2+ MBC – both with OS benefits.**

5. **Trastuzumab was the first approved immunotherapy for breast cancer. Co-targeting HER2 and immune mechanisms with HER2 ADCs or bi-specifics is an ongoing paradigm in clinical phase I investigations.**

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Questions/Comments
Debate/Discussion
Criticism

The Many *Thousands* of Patients and Their Families

ACKNOWLEDGEMENTS: Some Unsung Heroes (from my POV)

Richard Pietras – UCLA (platinum/HER2 MAb synergy, anti-estrogens + HER2 MAb)
Gottfried Konecny (UCLA faculty)
Richard Finn – UCLA (undergraduate, now faculty)
Giovani Pauletti – UCLA (HER2 amplicon mapping and FISH)
Jane Arboleda – UCLA (HER2 signaling)
Lilian Ramos – UCLA (lab manager)
Michael Press -- USC (Godfather of HER2 testing)
Mike Shepard – GNE (HER2 program leader)
Paul Carter – GNE (antibody humanization)
Leny Presta – GNE (antibody engineering)
Rafat Shalaby – GNE (preclinical group)
Dan Maneval – GNE (preclinical group)
Gail Lewis [Phillips] – GNE (preclinical group)
Robert Mass – GNE (clinical)
Stanford Stewart – GNE (clinical)

Mark Sliwkowski – GNE (head, protein chemistry)
Rob Akita – GNE (preclinical)
Teemu Juntilla – GNE (scientist)
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Larry Norton – MSKCC (trastuzumab phase 3 study design)
Michael Sela – (anti-EGFR + platinum work)
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Judith Hurley (Univ Miami, neoadjuvant TCH)
Kenneth Chien – (Harvard, HER2 cardiotoxicity)
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Vinay Jain – (support for grad student in the lab)
Susy Yuan-Huey Hung Family – (endowed professorship)
Jill and John Freidenrich – (endowed professorship)
Carl Tras – GNE (regulatory)

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Stanford Bio-X Program:
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Physics and Engineering

THANK YOU!