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CANCER INSTITUTE

New Developments in HER2+ Breast Cancer

San Francisco, CA February 2023

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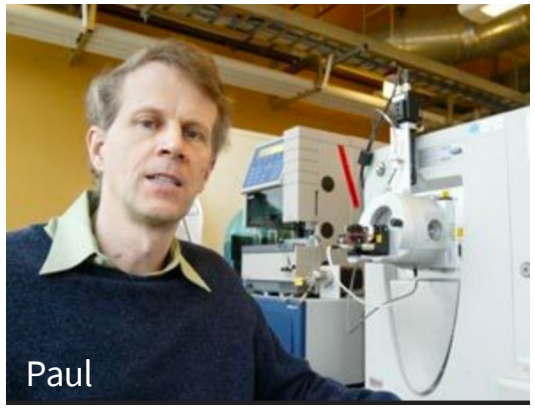
Susy Yuan-Huey Hung Professor of Oncology
Medical Director, Clinical and Translational Research Unit
Associate Dean for Clinical Research Quality
Stanford University School of Medicine

PNAS 30TH ANNIVERSARY: "GENE CONVERSION MUTAGENESIS"

Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 4285–4289, May 1992
Immunology


Paul


Leny

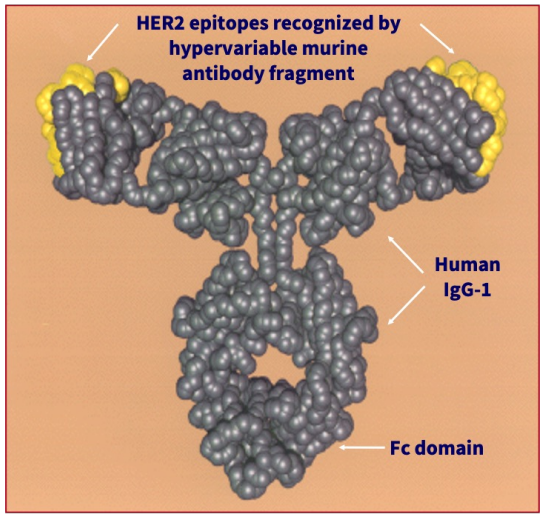

Mike

Humanization of an anti-p185^{HER2} antibody for human cancer therapy

(antibody engineering/site-directed mutagenesis/c-*erbB-2*/*neu*)

PAUL CARTER*, LEN PRESTA*, CORNELIA M. GORMAN†, JOHN B. B. RIDGWAY†, DENNIS HENNER†, WAI LEE T. WONG‡, ANN M. ROWLAND‡, CLAIRE KOTTS‡, MONIQUE E. CARVER‡, AND H. MICHAEL SHEPARD§

Departments of *Protein Engineering, †Cell Genetics, ‡Medicinal and Analytical Chemistry, and §Cell Biology, Genentech Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080

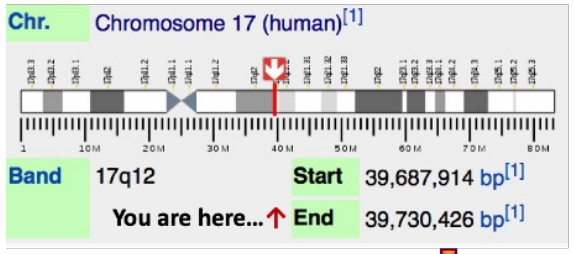


huMAb4D5-8;
AKA: rhuMAb-HER2
Kd = 0.1nM;
95% human AA sequence

Molecular Modeling. Models of mumAb4D5 V_H and V_L domains were constructed by using seven Fab crystal structures from the Brookhaven Protein Data Bank (entries 2FB4, 2RHE, 2MCP, 3FAB, 1FBJ, 2HFL, and 1REI) (29). V_H and V_L of each structure were superimposed on 2FB4 by using main-chain atom coordinates (INSIGHT program, Biosym Technologies, San Diego). The distances from each 2FB4 Cα to the analogous Cα in each of the superimposed structures was calculated. For residues with all Cα–Cα distances $\leq$1Å, the average coordinates for individual N, Cα, C, O, and Cβ atoms were calculated and then corrected for resultant deviations from standard bond geometry by 50 cycles of energy minimization (DISCOVER program, Biosym Technologies) using the AMBER forcefield (30) and fixed Cα atoms. Side chains of FR residues were then incorporated, followed by inclusion of five of the six CDR loops (except V_H–CDR3) using tabulations of CDR conformations (23) as a guide. Side-chain conformations were chosen on the basis of Fab crystal structures, rotamer libraries (31), and packing considerations. Three possible conformations of V_H–CDR3 were taken from a search of similar sized loops in the Brookhaven Protein Data Bank or were modeled by using packing and solvent exposure considerations. Models were then subjected to 5000 cycles of energy minimization.

Lasker DeBakey Clinical Medical Research Award

"For invention of a targeted antibody therapy for breast cancer"



Size: 185,000 Da

Length: 1234 aa

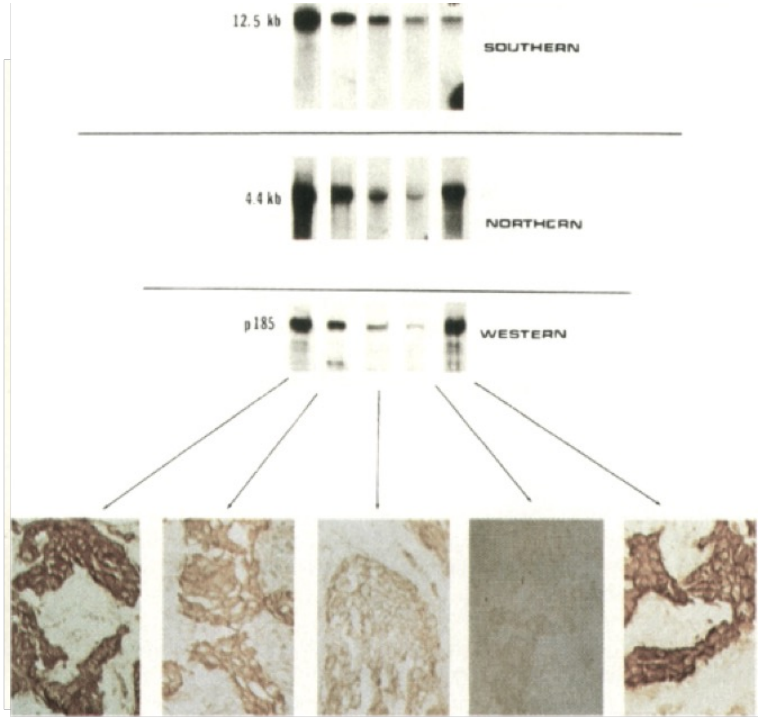
136,000 MW

mRNA: 4.8 kb

Axel Ullrich

Max Planck Institute of Biochemistry

Coussens L, Yang-Feng TL, Liao YC, Chen E, Gray A, McGrath J, Seeburg PH, Libermann TA, Schlessinger J, Francke U, Levinson A, and Ullrich A. (1985) Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal localization with neu oncogene. *Science* 230, 1132-1139

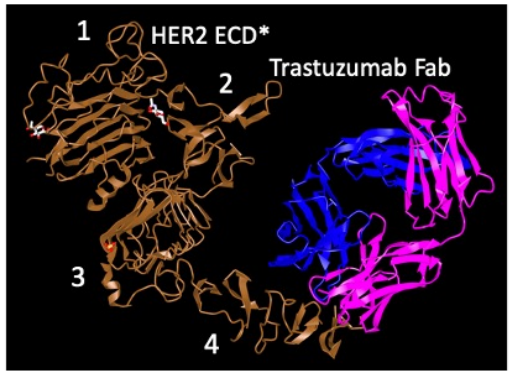


Dennis J. Slamon

University of California, Los Angeles

Slamon *et al*. Science 1987 & 1989

Structure of the extracellular region of HER2 in complex with the trastuzumab Fab



Cho HS1, Mason K, Ramyar KX, Stanley AM, Gabelli SB, Denney DW Jr, Leahy DJ.
Nature. 2003 Feb 13;421(6924):756-60.

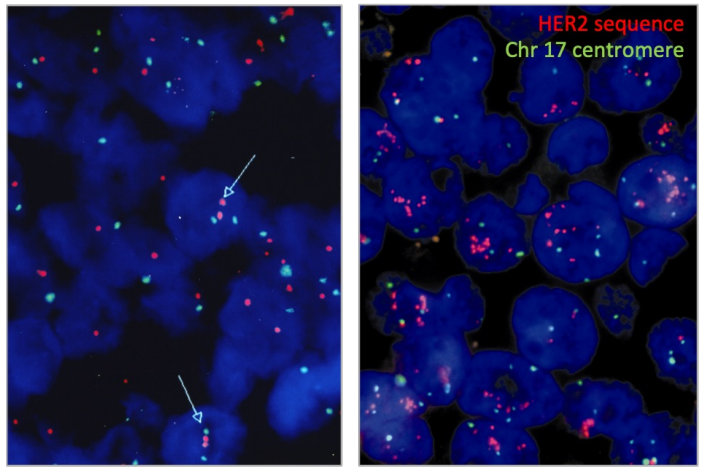
ECD* = Extracellular Domain

H. Michael Shepard

Genentech

2023 = 25th Anniversary of 1st FDA Approval of Trastuzumab

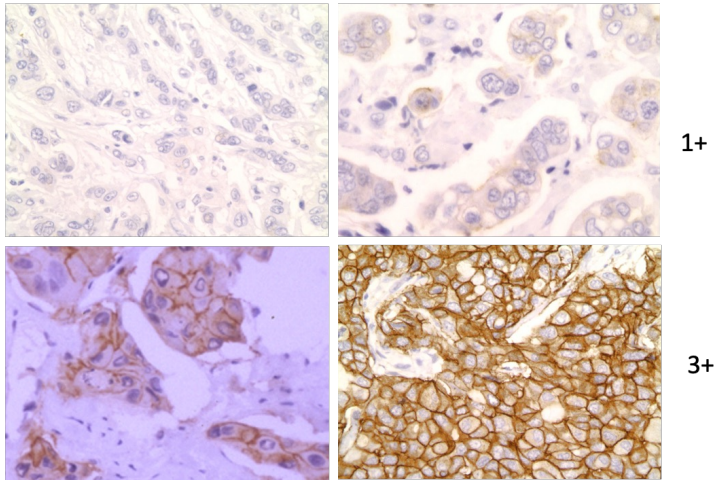
HER2 Gene Assessment by FISH

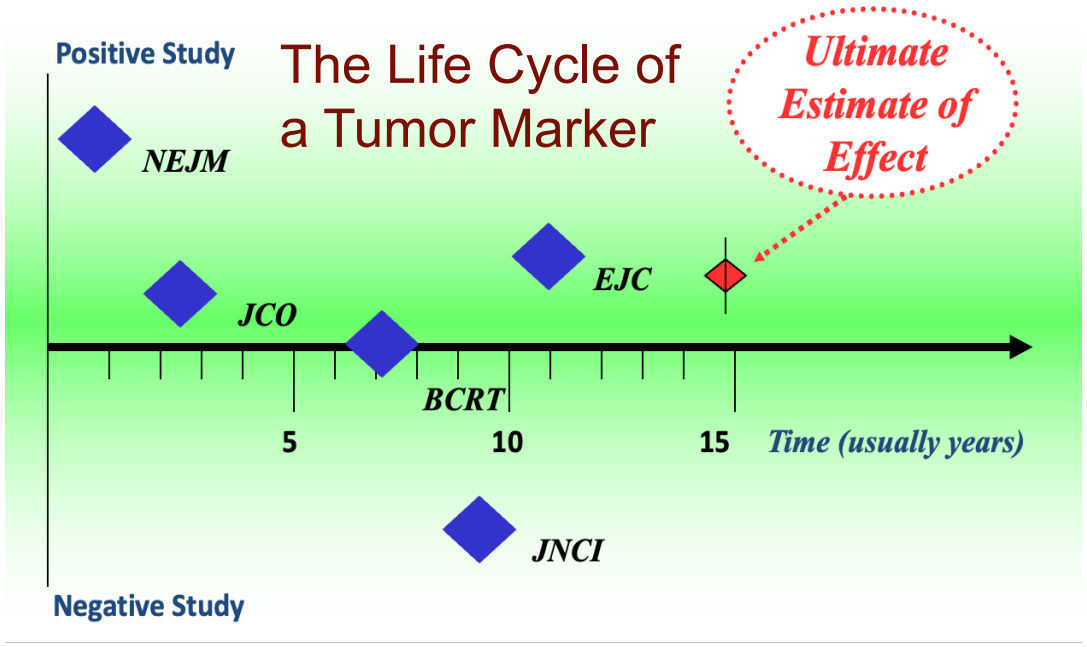


Ratio < 2.0 Not Amplified (FISH-)

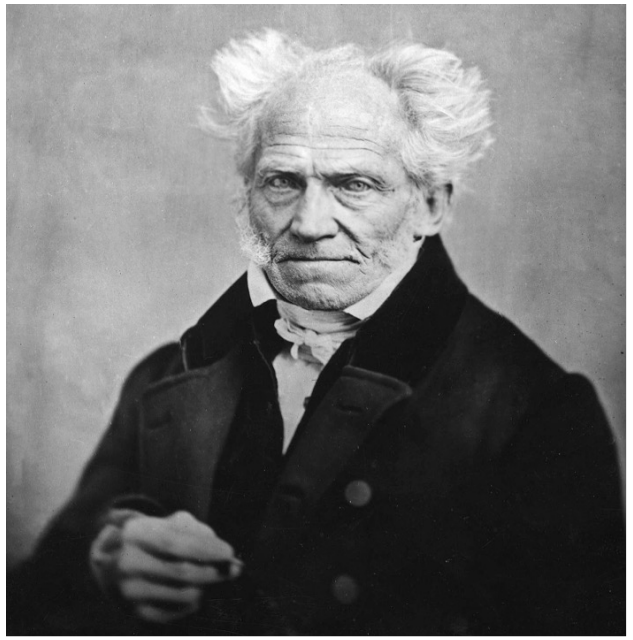
Ratio ≥ 2.0 Amplified (FISH+)

HER2 Overexpression Detection by IHC





(Courtesy Daniel Hayes, U Mich.)



Arthur Schopenhauer in 1859

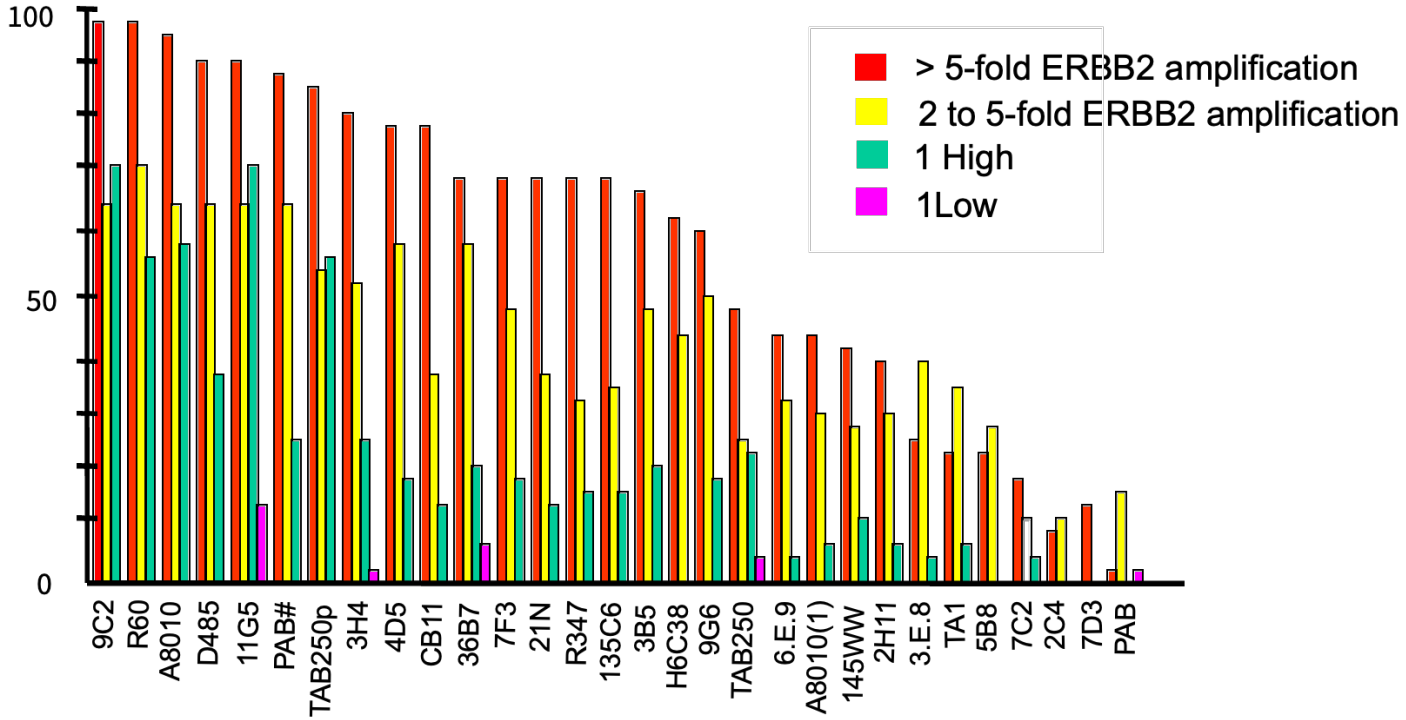
All truth passes through 3 stages:

- **Ridicule/Dismissal**
  - as if it doesn't exist
- **Opposition**
  - sometimes violent
- **Claim credit**
  - those most opposed say they discovered it first

HER2 Testing Error:

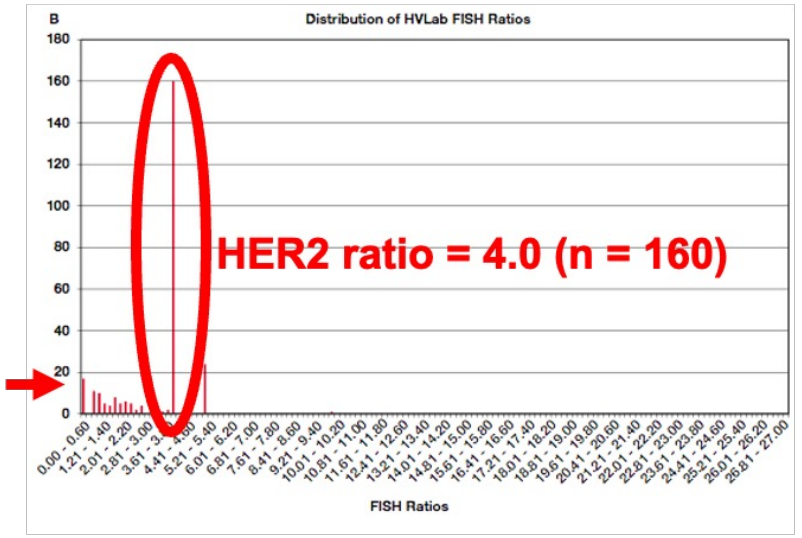
Sensitivity of HER-2 Antibodies in Archival Tissues

[Adapted from Press, MF, *et al.*, Cancer Research (1994)]

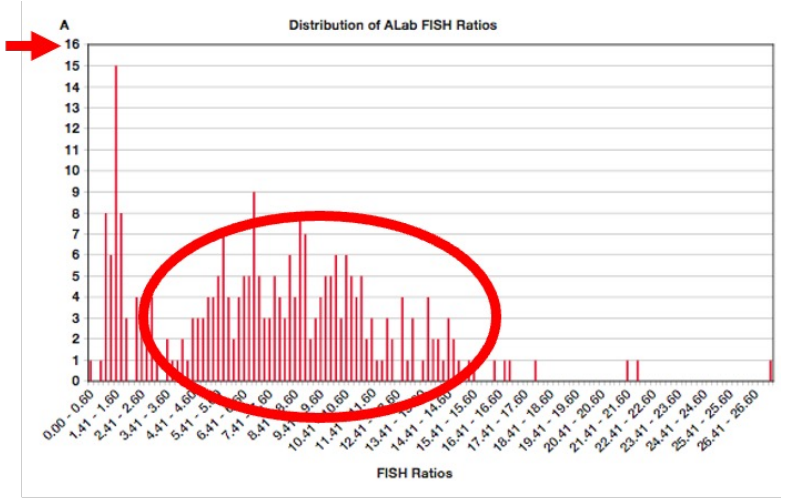


Press MF et al. HER2 Gene Amplification, HER2 and EGFR mRNA and Protein Expression, and Lapatinib Efficacy in Women With Metastatic Breast Cancer. Clinical Cancer Res. 14: 7861-7870, 2008.

Frequency and Distribution of HER2 FISH Ratios Between 2 Central Laboratories

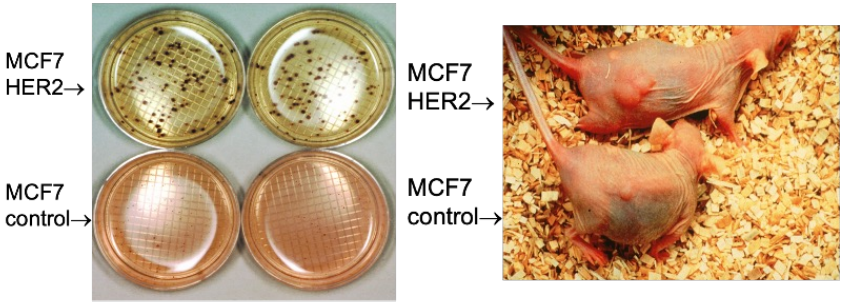


High Volume Commercial Lab:
Med Tech Assessment



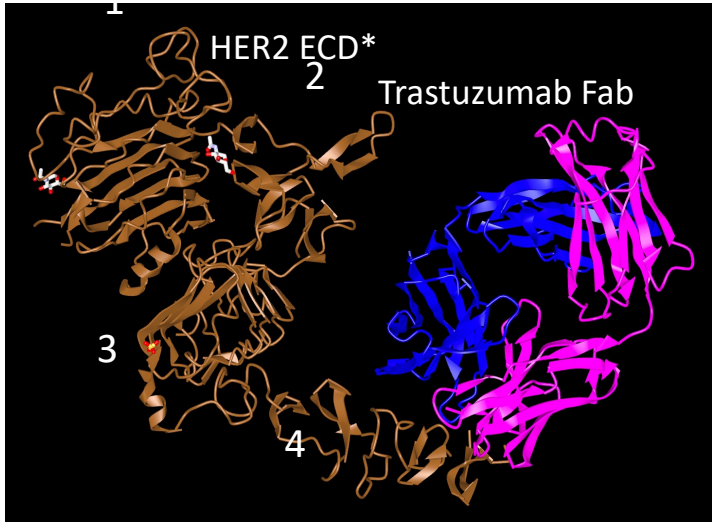
Academic Lab:
Pathologist Assessment

Crystal Structure of Trastuzumab Fab Fragment Binding HER2 Extracellular Domain (left); Trastuzumab Blocks Ligand-*independent* HER2|HER3 Association (right), Reducing S-phase Fraction (lower right)

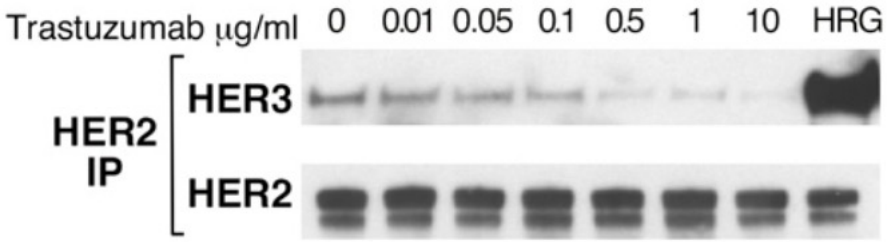


Pegram M, Slamon D, Semin Oncol 2000 Oct;
27(5 suppl 9):13-19.

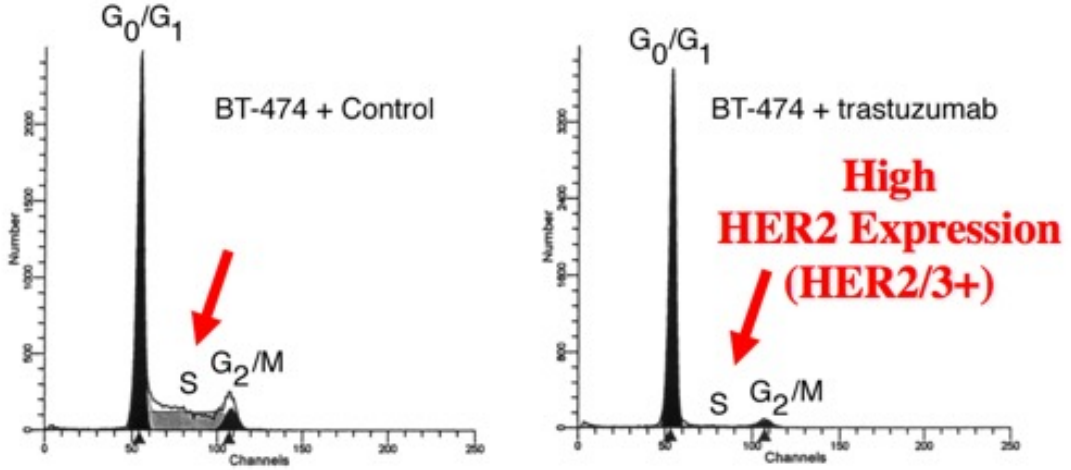
Structure of the extracellular region of HER2 in complex with the trastuzumab Fab



Cho HS1, Mason K, Ramyar KX, Stanley AM, Gabelli SB, Denney DW Jr, Leahy DJ.
Nature. 2003 Feb 13;421(6924):756-60.
ECD* = Extracellular Domain



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



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

Trastuzumab MOA: Synergistic Combinations with Chemotherapy

Calculated values for the Combination Index: Fractional inhibition of SK-BR-3 cell proliferation by a mixture of alkylating agent and trastuzumab

	Combination Index Values at:					Parameters:		
Drug	**IC_{30}**	**IC_{40}**	**IC_{50}**	**IC_{60}**	**IC_{70}**	**Dm**	**m**	**r**
Alkylating Agent						**66.2uM**	**0.81**	**0.99**
rhuMAb HER2						**675.0nM**	**0.15**	**0.96**
Alk + MAb HER2	**0.52**	**0.37**	**0.41**	**0.49**	**0.60**	**27.1uM**	**0.59**	**0.99**
Combined effect	**Synergy**	**Synergy**	**Synergy**	**Synergy**	**Synergy**			

$$CI = \frac{(D)_1}{(Dx)_1} + \frac{(D)_2}{(Dx)_2} + \frac{\alpha(D)_1(D)_2}{(Dx)_1(Dx)_2}$$

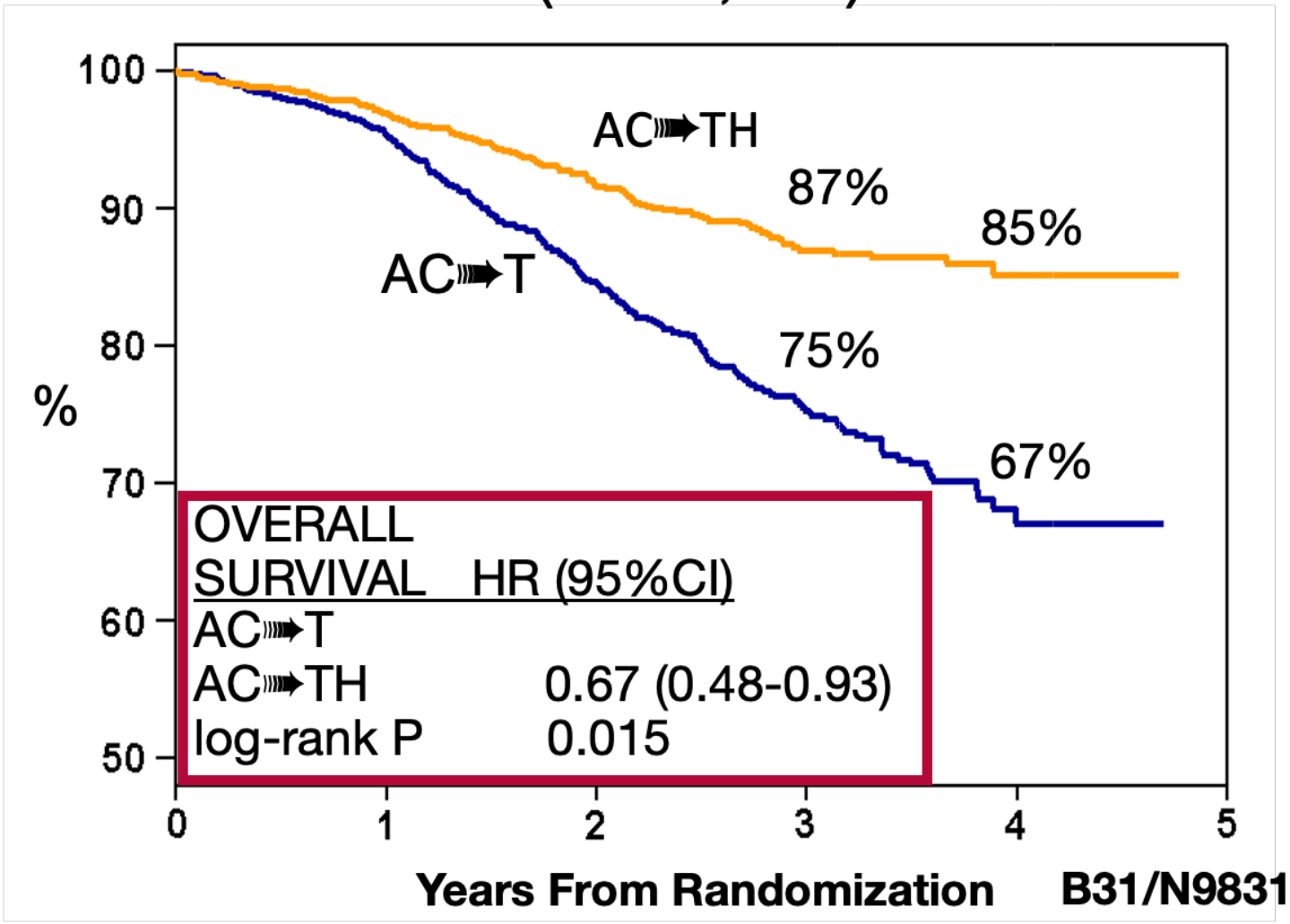
CI = 1, Interaction is SUMMATION
CI < 1, Interaction is SYNERGY
CI > 1, Interaction is ANTAGONISM

T.C. Chou and P. Talalay (1984)
Adv. Enz. Regul. 22, 27-55.

Pegram, et al., Oncogene 18: 2241-2251,1999.

Analysis of Adjuvant Trastuzumab Efficacy

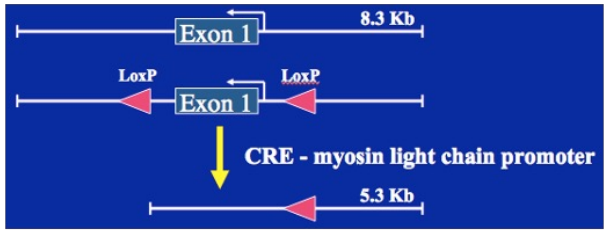
(N = 3,351)



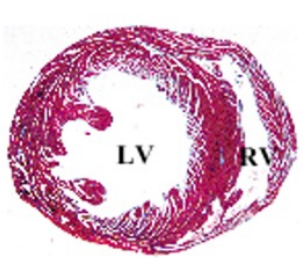
HR=0.48,
2P=3x10^{-12}

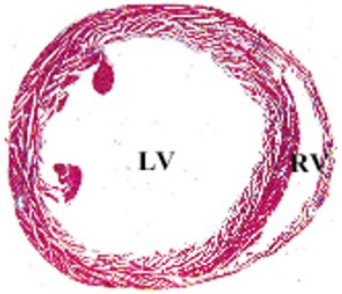
Romond, et al., New England Journal of Medicine (2005).

Phenotypic Analysis of erbB2 Conditional Knock-out Mouse Myocardium

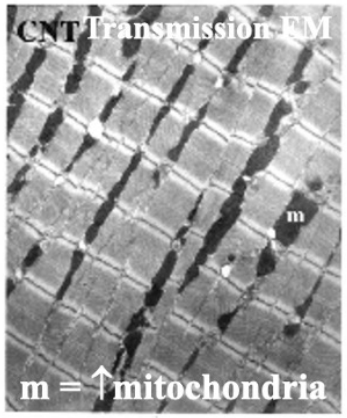


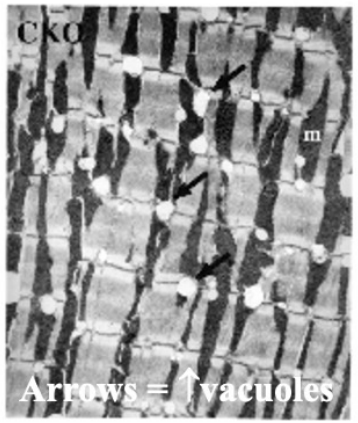
erbB2-floxed **erbB2-CKO**





Trichrome staining



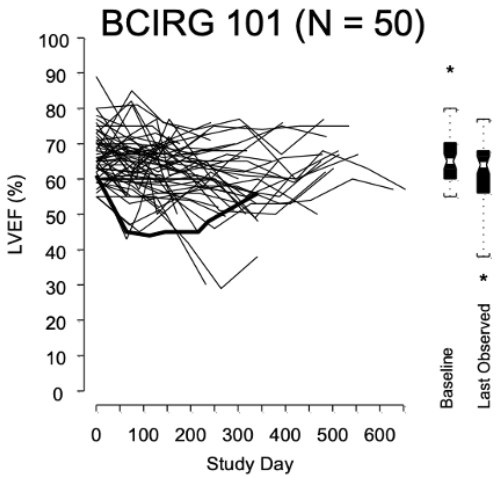


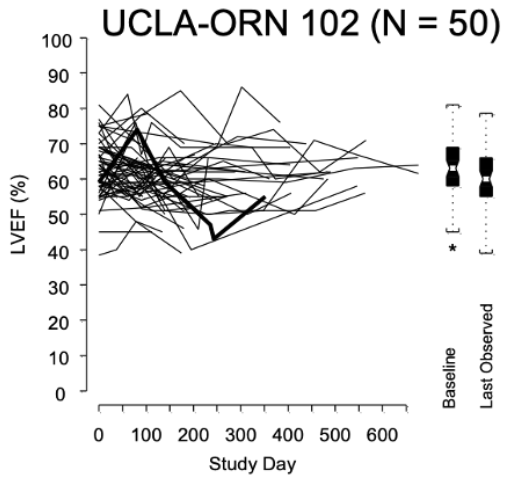
Crone SA, et al., Nature Medicine 8: 459-465 (2002).

TCH Pilot Metastatic Trials, Efficacy and Cardiac Safety

	Paclitaxel + Trastuzumab	TCisH	TCarboH
N (FISH+)	**69**	**35**	**38**
ORR [95%CI]	**49%** [38-61]	**77%** [59-90]	**64%** [46-79]
Median TTP [95%CI]	**7.1** [3.9-14.1]	**12.7** [9.2-13.1]	**17.0** [9.1-NE*]

NE* = Not Estimable





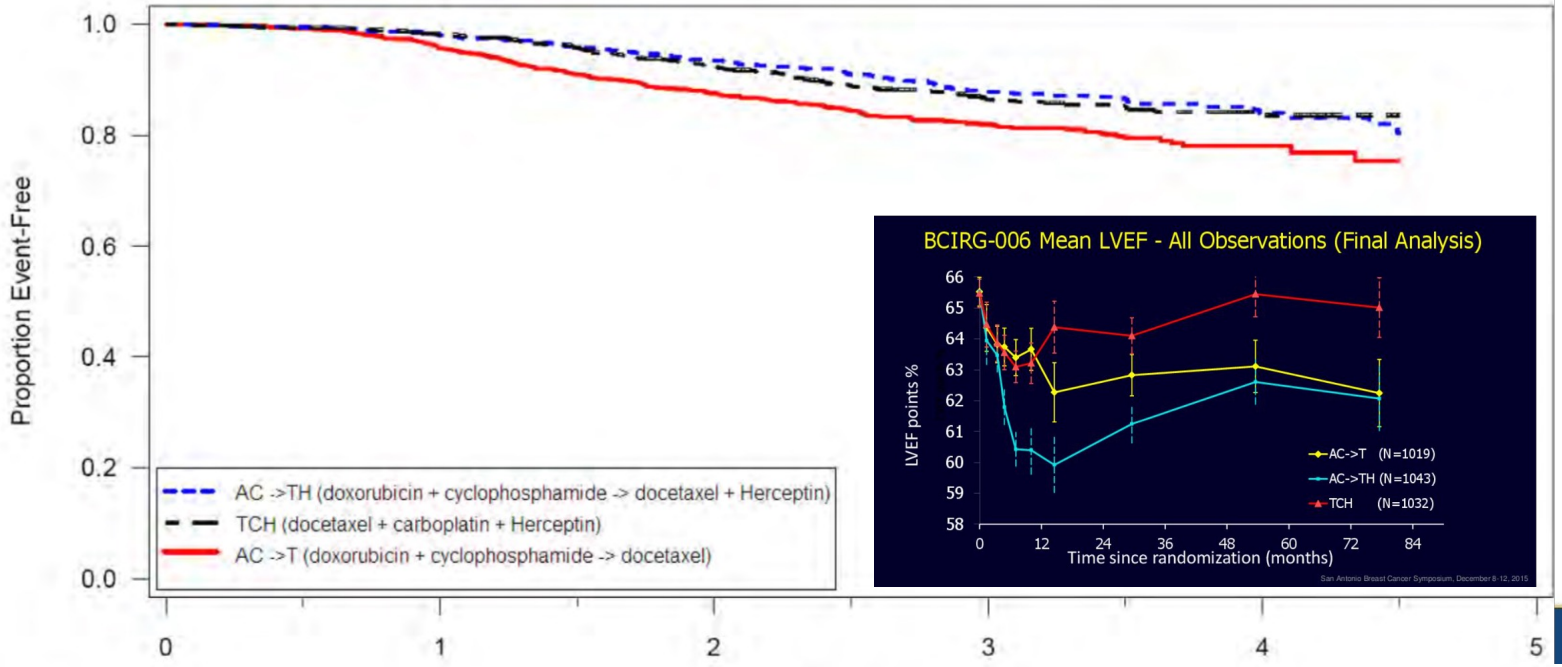
Pegram, et al., J Natl Cancer Inst. 96:759-69 (2004).

1. BCIRG 006 Study – Adjuvant TCH vs. AC-TH vs. AC-T control in HER2-amplified EBC
2. TRAIN-2 Study – Anthracycline vs. non-anthracycline chemotherapy + HP

1.

Figure 5

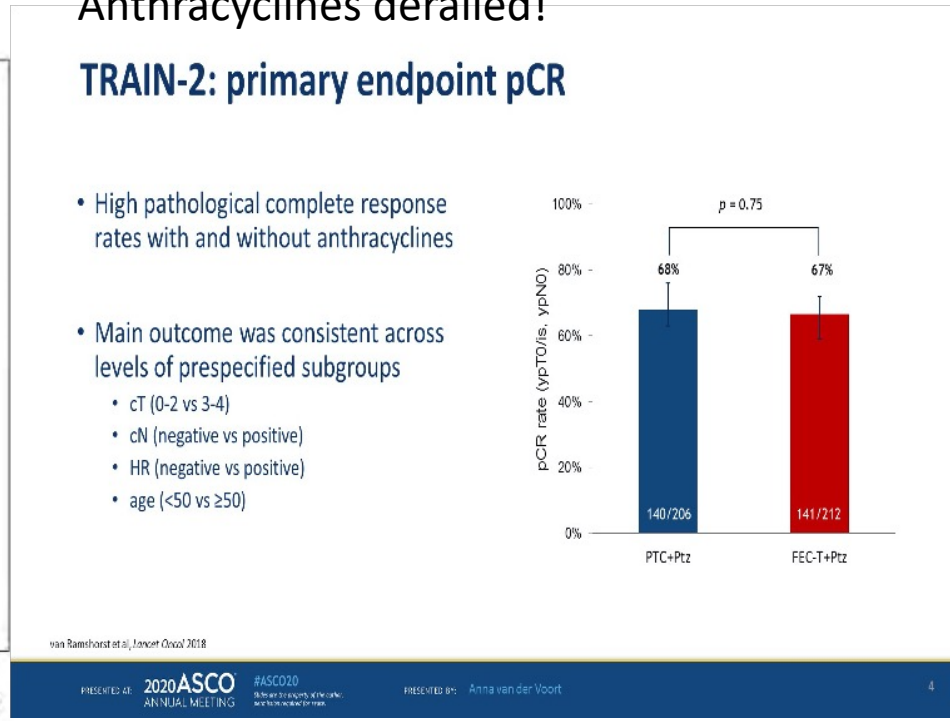
Duration of Disease-Free Survival in Patients with Adjuvant Treatment of Breast Cancer (Study 4)



Number at risk					
AC->T	1073	971	802	417	103
AC->TH	1074	1023	885	457	126
TCH	1075	1018	877	447	126

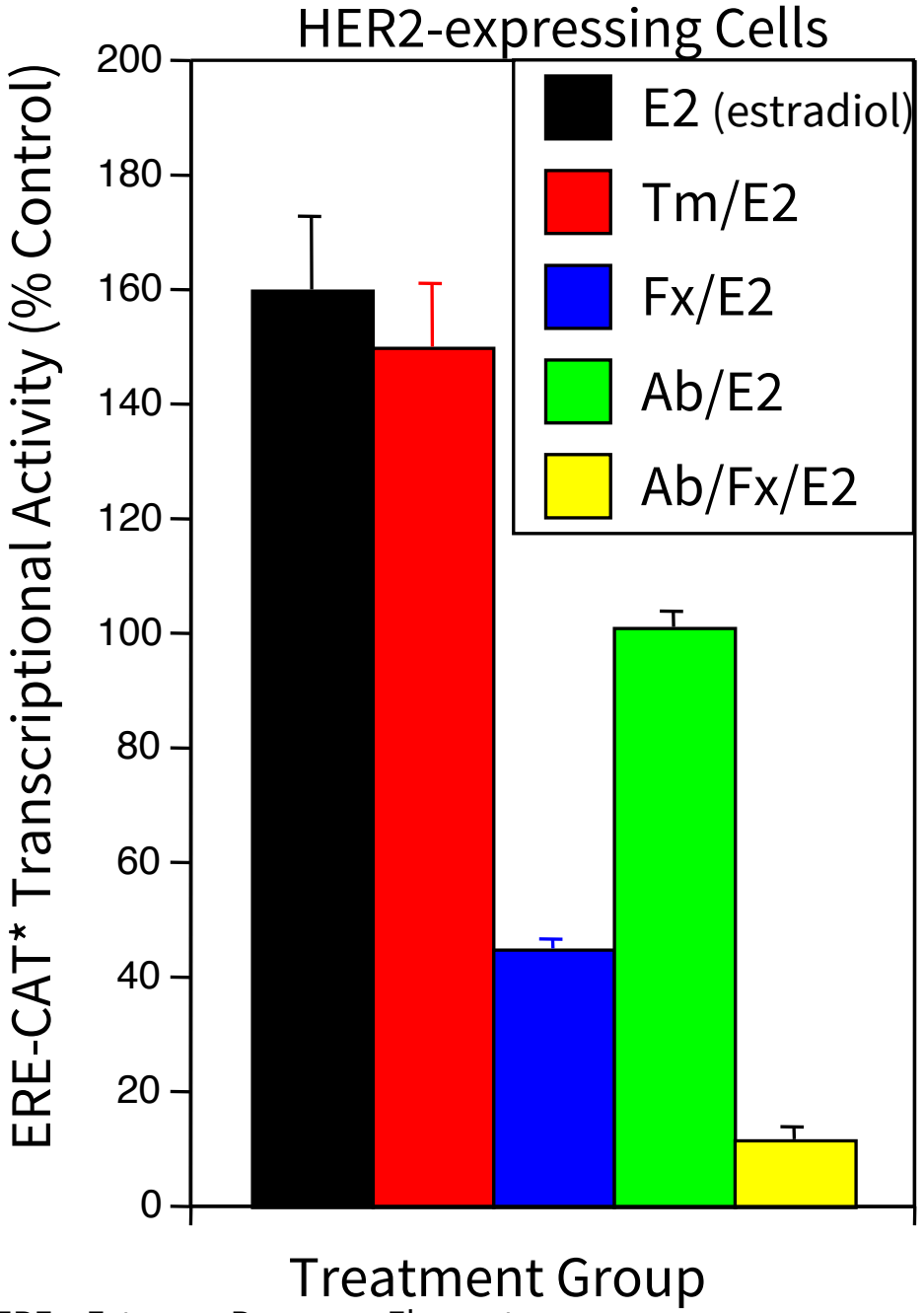
AC=doxorubicin and cyclophosphamide; T=docetaxel; TCH=docetaxel, platinum salt, and Herceptin; TH=docetaxel and Herceptin.
Kaplan-Meier estimates are shown.

2. TRAIN-2 Neoadjuvant Study: N = 438
Anthracyclines derailed!

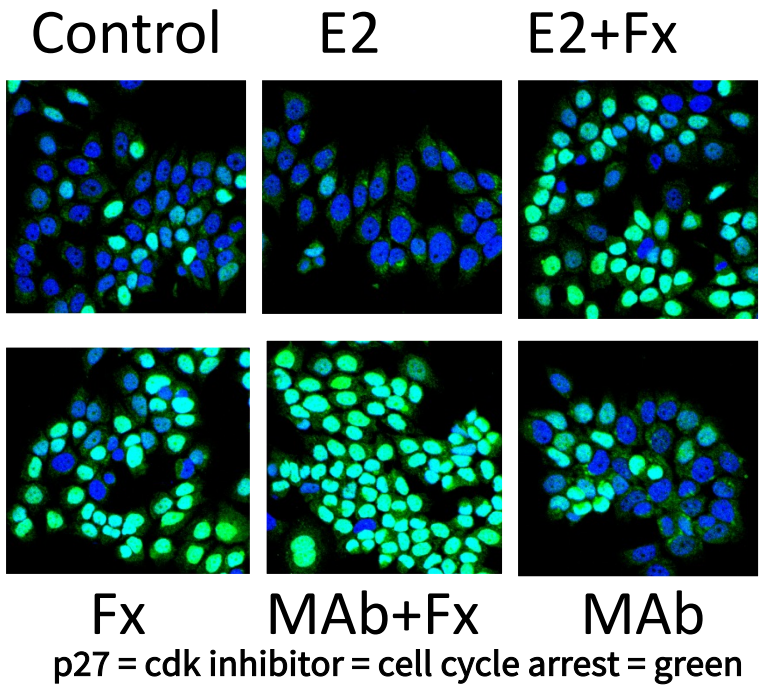


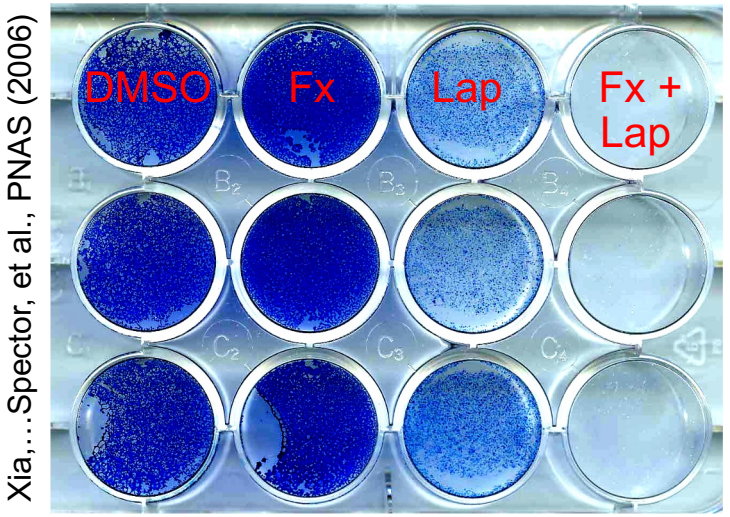
- "No *hint* of advantage of anthracyclines, even in high risk subgroups (cN2/3; EFS HR=0.75 with trend *favoring* non-anthracycline Rx)".
- LVEF did not recover to normal in ~1/3 of anthracycline-treated patients.

Trastuzumab Intravenous Infusion, FDA prescribing information.



*ERE = Estrogen Response Element
CAT = Chloramphenicol Acetyl Transferase
Fx = Fulvestrant





Tandem – AI ± tras

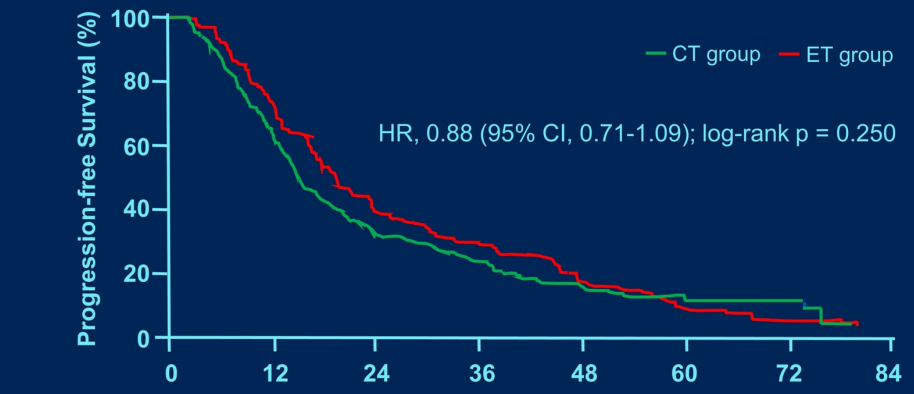
ALTERNATIVE – AI + tras + lapat

PERTAIN – AI + tras + pertuzumab

Pietras RJ, Arboleda J, Reese DM, Wongvipat N, Pegram MD, Ramos L, Gorman CM, Parker MG, Sliwkowski MX, Slamon DJ. Oncogene. 1995 Jun 15;10(12):2435-46.

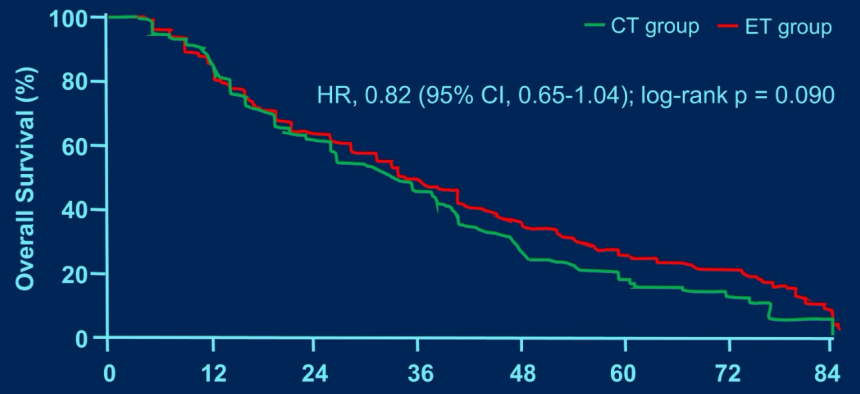
Trastuzumab plus endocrine therapy or chemotherapy as first-line treatment for HER2+/ER+ metastatic breast cancer: SYSUCC-002 randomized clinical trial

Progression-Free Survival (primary endpoint)



No. at risk								
CT group	196	124	61	33	16	9	5	0
ET group	196	142	73	50	28	11	4	0

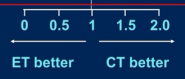
Overall Survival



No. at risk								
CT group	196	166	114	66	28	16	6	0
ET group	196	166	118	78	49	33	22	2

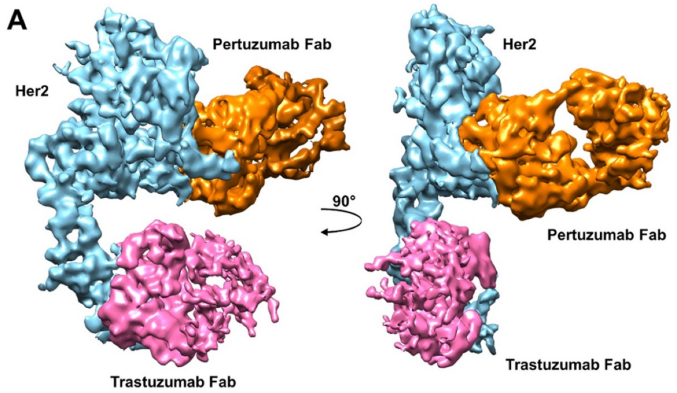
Subgroup Analyses of PFS

Subgroup	ET group (events/ n)	CT group (events/ n)	Hazard Ratio (95% CI)	p value
Age, years				0.146
≤ 40	29/31	30/42	1.14 (0.67, 1.91)	
> 40	151/165	135/154	0.80 (0.63, 1.00)	
Receptor status				0.099
ER and PR positive	143/157	128/157	0.90 (0.71, 1.15)	
ER or PR positive	37/39	37/39	0.76 (0.48, 1.20)	
Visceral involvement				0.487
Yes	106/114	103/119	0.95 (0.72, 1.25)	
No	74/82	62/77	0.80 (0.57, 1.12)	
Previous adjuvant endocrine therapy				0.904
AIs	74/83	66/83	0.98 (0.69, 1.15)	
ORMs	56/59	51/59	0.97 (0.70, 1.36)	
Metastasis number				0.851
< 2	127/140	111/139	0.89 (0.69, 1.15)	
≥ 2	53/56	54/57	0.86 (0.59, 1.27)	
Disease-free interval				0.016
≤ 24 months	59/64	64/78	1.39 (0.97, 1.98)	
> 24 months	71/78	53/64	0.77 (0.53, 1.10)	

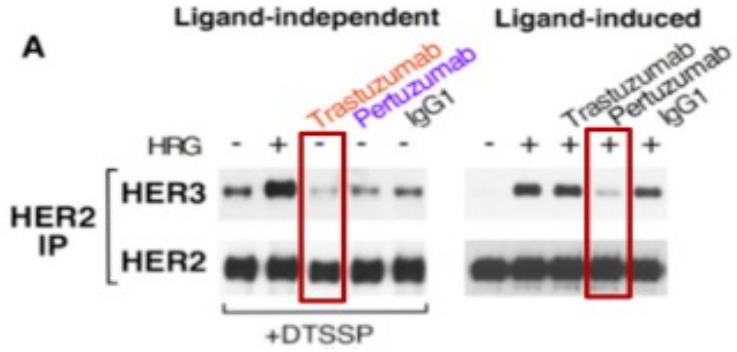


- **Trastuzumab plus endocrine therapy was non-inferior to, and had fewer toxicities than trastuzumab plus chemotherapy in patients with HR+/HER2+ MBC**
- **Exploratory subset analysis suggests endocrine therapy plus trastuzumab was likely more beneficial for patients with DFI >24 months**
- **Question remains -- does this principle apply to the pertuzumab era?**

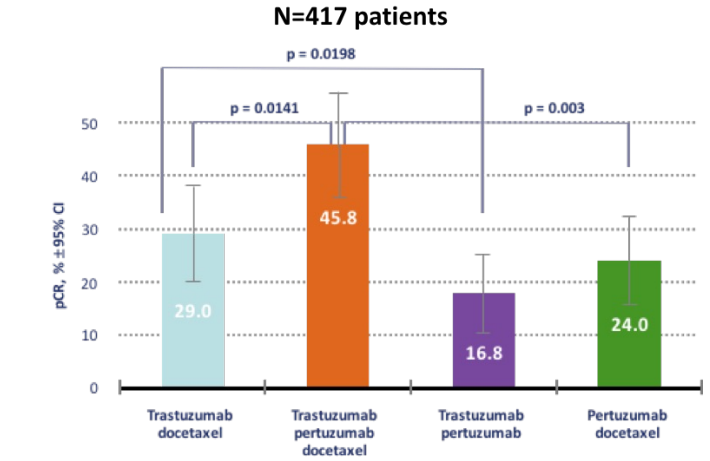
Pertuzumab Binds Subdomain II and Disrupts Ligand-Dependent HER2:HER3 Interaction; Trastuzumab + Pertuzumab Induces Apoptosis

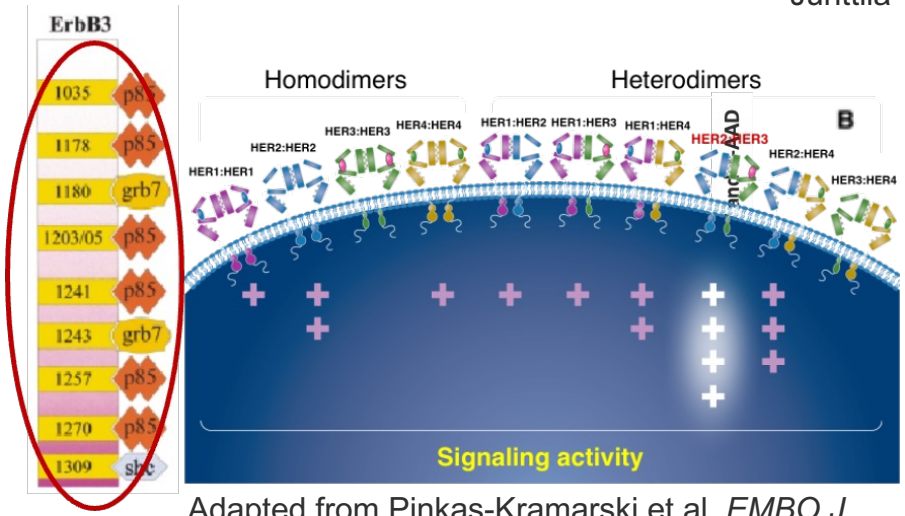


Hao Y, et al., PLoS One. 2019;14(5):e0216095.

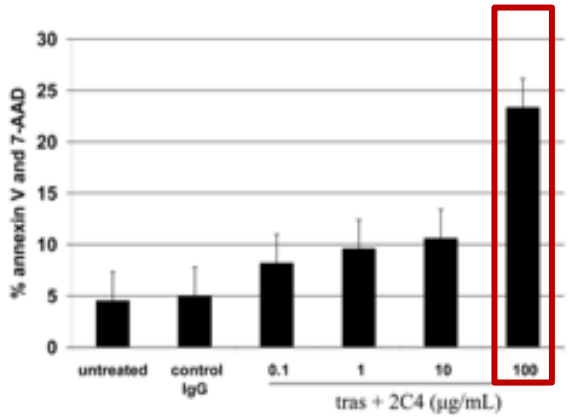


Junttila TT, et al., Cancer Cell. 2009 May 5;15(5):429-40.

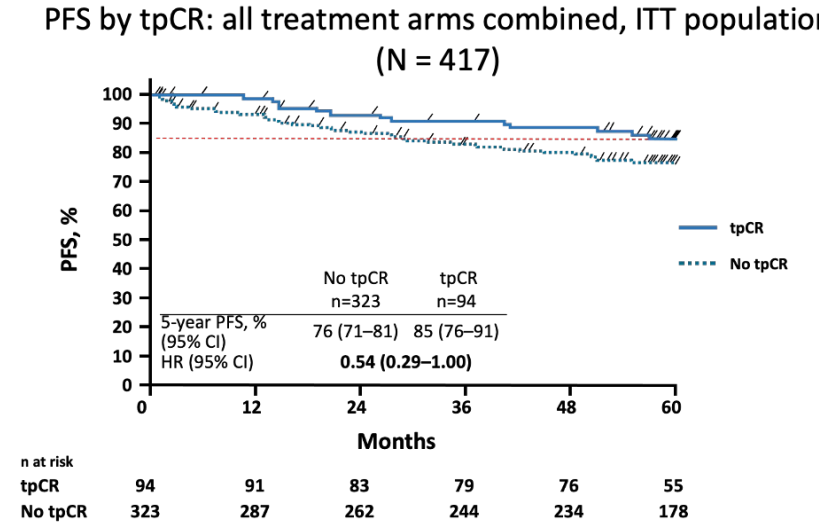




Adapted from Pinkas-Kramarski et al. *EMBO J.* 1996;15:2452, and Tzahar et al. Mol Cell Biol. 1996;16:5276-5287.

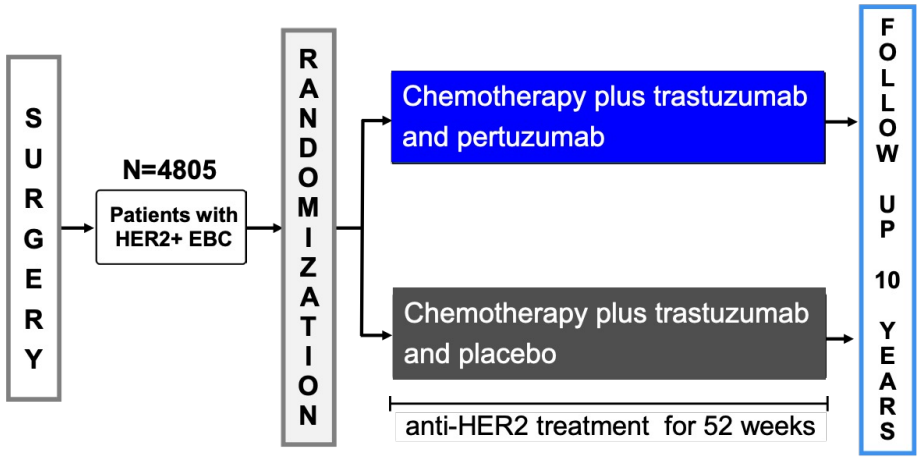


Rita Nahta, *et al*. Cancer Res 2004;64:2343-2346.



Gianni L, et al., Lancet Oncol. 2012 Jan;13(1):25-32.

APHINITY: Phase III Adjuvant Study

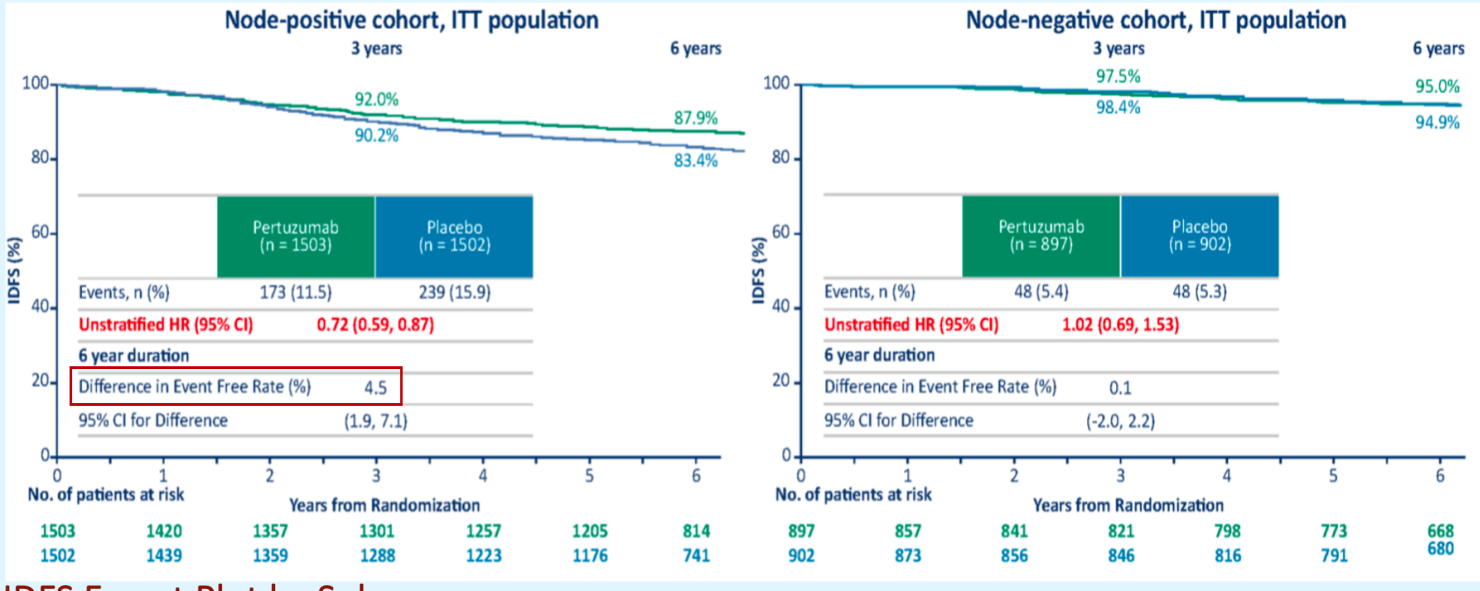


Primary endpoint: iDFS

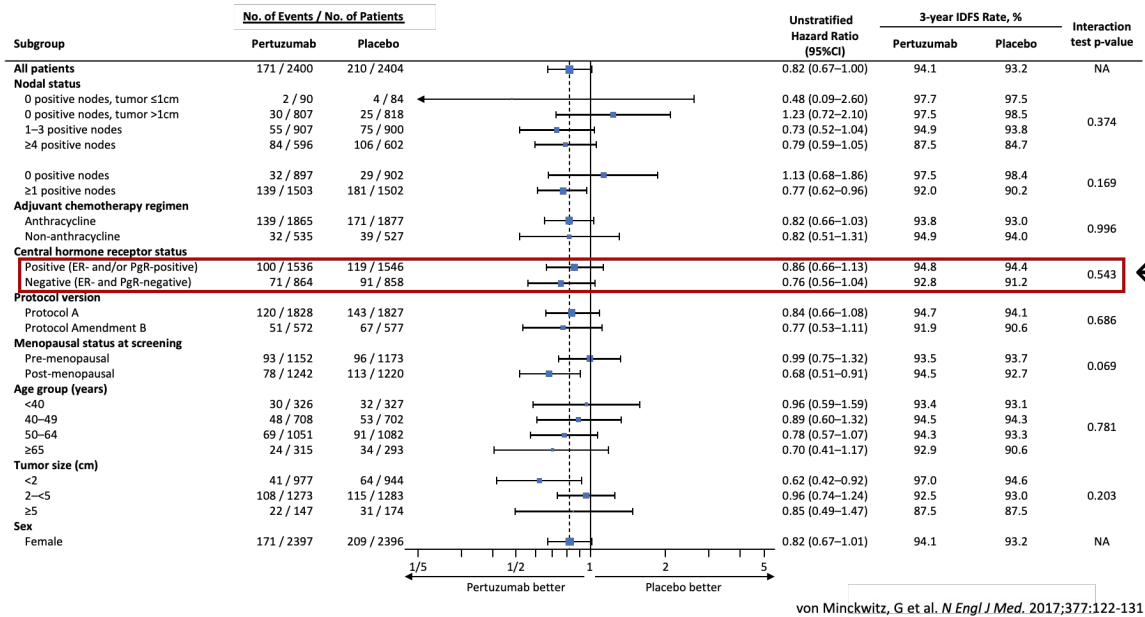
- Large Global trial: US highest enrolling country
- Anthracycline or non-anthracycline based chemo allowed
- IDMC and Independent Cardiac Review Committee

APHINITY Updated descriptive analysis 74.1 months median FU
Time to first IDFS event by treatment regimen and nodal status

The node positive cohort continues to derive clear benefit from addition of pertuzumab.



APHINITY: IDFS Forest Plot by Subgroups

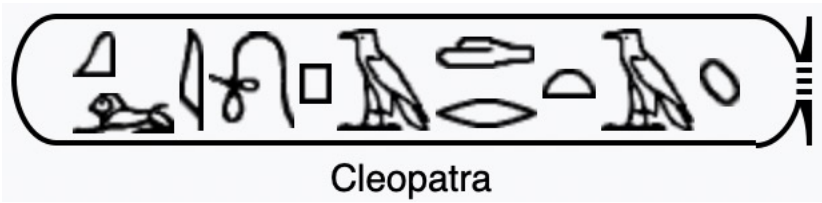


Subgroup	No. of Events / No. of Patients: Pertuzumab	Placebo	Unstratified Hazard Ratio (95%CI)	3-year IDFS Rate, %: Pertuzumab	Placebo	Interaction test p-value
All patients	171 / 2400	210 / 2404	0.82 (0.67–1.00)	94.1	93.2	NA
Nodal status						
0 positive nodes, tumor ≤1cm	2 / 90	4 / 84	0.48 (0.09–2.60)	97.7	97.5	
0 positive nodes, tumor >1cm	30 / 807	25 / 818	1.23 (0.72–2.10)	97.5	98.5	0.374
1–3 positive nodes	55 / 907	75 / 900	0.73 (0.52–1.04)	94.9	93.8	
≥4 positive nodes	84 / 596	106 / 602	0.79 (0.59–1.05)	87.5	84.7	
0 positive nodes	32 / 897	29 / 902	1.13 (0.68–1.86)	97.5	98.4	0.169
≥1 positive nodes	139 / 1503	181 / 1502	0.77 (0.62–0.96)	92.0	90.2	
Adjuvant chemotherapy regimen						
Anthracycline	139 / 1865	171 / 1877	0.82 (0.66–1.03)	93.8	93.0	0.996
Non-anthracycline	32 / 535	39 / 527	0.82 (0.51–1.31)	94.9	94.0	
Central hormone receptor status						
Positive (ER- and/or PgR-positive)	100 / 1536	119 / 1546	0.86 (0.66–1.13)	94.8	94.4	0.543
Negative (ER- and PgR-negative)	71 / 864	91 / 858	0.76 (0.56–1.04)	92.8	91.2	
Protocol version						
Protocol A	120 / 1828	143 / 1827	0.84 (0.66–1.08)	94.7	94.1	0.686
Protocol Amendment B	51 / 572	67 / 577	0.77 (0.53–1.11)	91.9	90.6	
Menopausal status at screening						
Pre-menopausal	93 / 1152	96 / 1173	0.99 (0.75–1.32)	93.5	93.7	0.069
Post-menopausal	78 / 1242	113 / 1220	0.68 (0.51–0.91)	94.5	92.7	
Age group (years)						
<40	30 / 326	32 / 327	0.96 (0.59–1.59)	93.4	93.1	0.781
40–49	48 / 708	53 / 702	0.89 (0.60–1.32)	94.5	94.3	
50–64	69 / 1051	91 / 1082	0.78 (0.57–1.07)	94.3	93.3	
≥65	24 / 315	34 / 293	0.70 (0.41–1.17)	92.9	90.6	
Tumor size (cm)						
<2	41 / 977	64 / 944	0.62 (0.42–0.92)	97.0	94.6	0.203
2–<5	108 / 1273	115 / 1283	0.96 (0.74–1.24)	92.5	93.0	
≥5	22 / 147	31 / 174	0.85 (0.49–1.47)	87.5	87.5	
Sex						
Female	171 / 2397	209 / 2396	0.82 (0.67–1.01)	94.1	93.2	NA

von Minckwitz, G et al. *N Engl J Med.* 2017;377:122-131

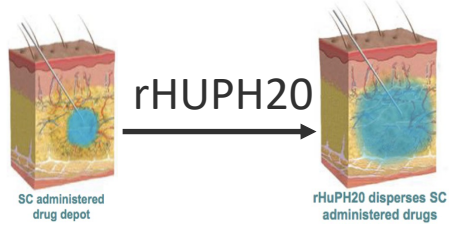
← Interaction p-value for steroid receptor expression = 0.543 (N.S.)

Piccart M, et al. 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. Abstract GS1-04.



: End of Study Results

نتائج نهاية الدراسة



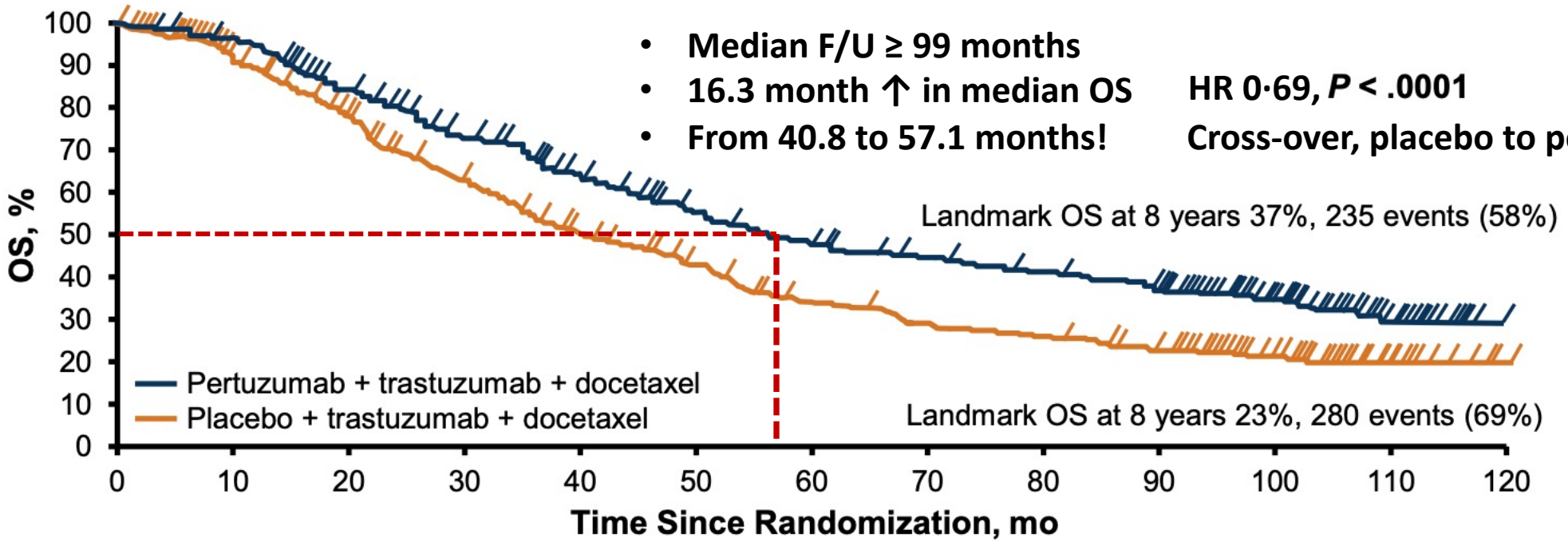
New formulation:
T + P + recombinant hyaluronidase SQ

CLEOPATRA – OVERALL SURVIVAL

- **Median F/U ≥ 99 months**
- **16.3 month ↑ in median OS**
- **From 40.8 to 57.1 months!**

HR 0·69, *P* < .0001

Cross-over, placebo to pertuzumab N = 50



No. at Risk (number censored)

Pertuzumab	402 (0)	371 (14)	318 (23)	269 (32)	228 (41)	188 (48)	165 (50)	150 (54)	137 (56)	120 (59)	71 (102)	20 (147)	0 (167)
Placebo	406 (0)	350 (19)	289 (30)	230 (36)	181 (41)	149 (48)	115 (52)	96 (53)	88 (53)	75 (57)	44 (84)	11 (115)	1 (125)

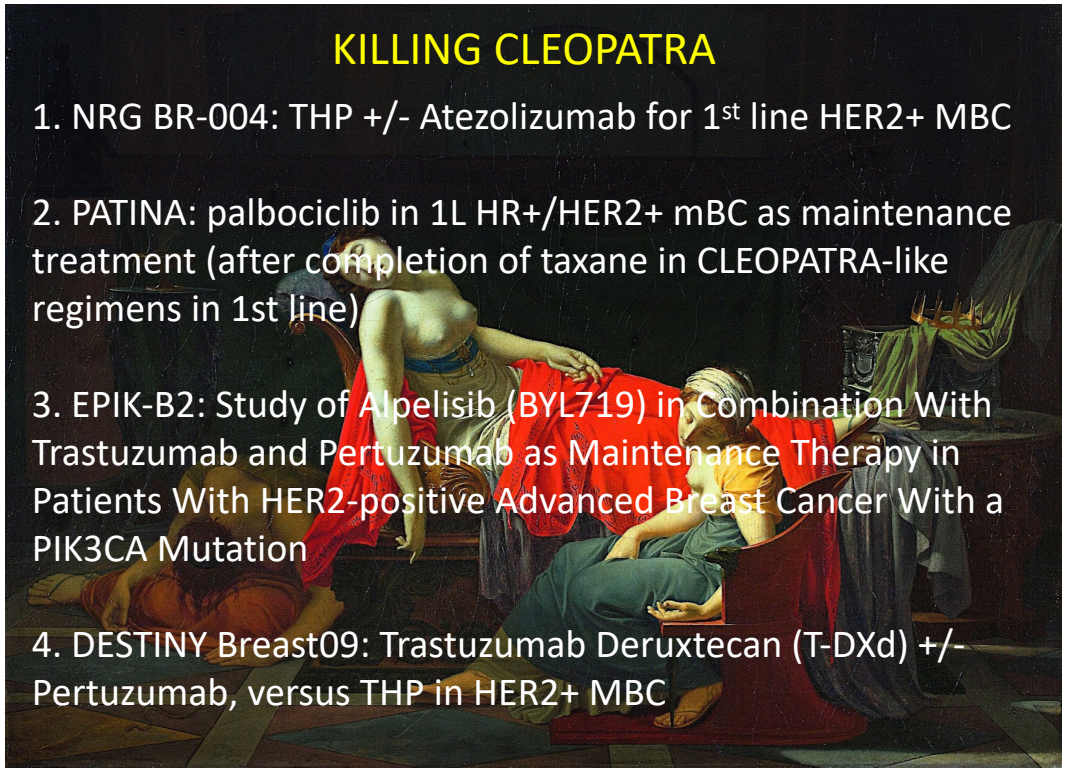
- **Most common adverse reactions (> 30%) with pertuzumab + trastuzumab and docetaxel = diarrhea, myelosuppression, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy.**

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

The death of Cleopatra VII (by suicide, age 39): the last ruler of Ptolemaic Egypt -- 10 August 30 BCE

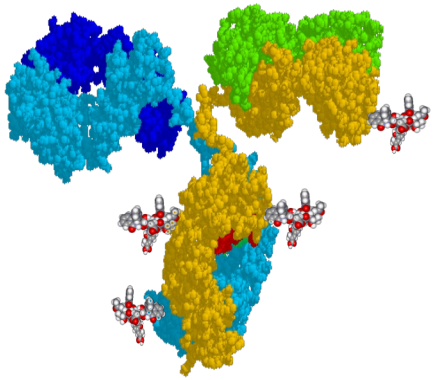
Cleopatra [a true trialist] Testing Poisons on Condemned Prisoners (?propaganda), by Alexandre Cabanel (1887)

In violation of Title 45 CFR 46, subpart C:
"Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects"

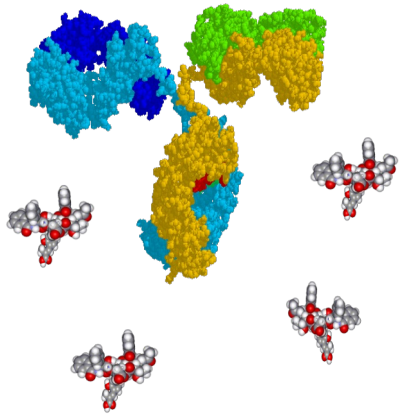


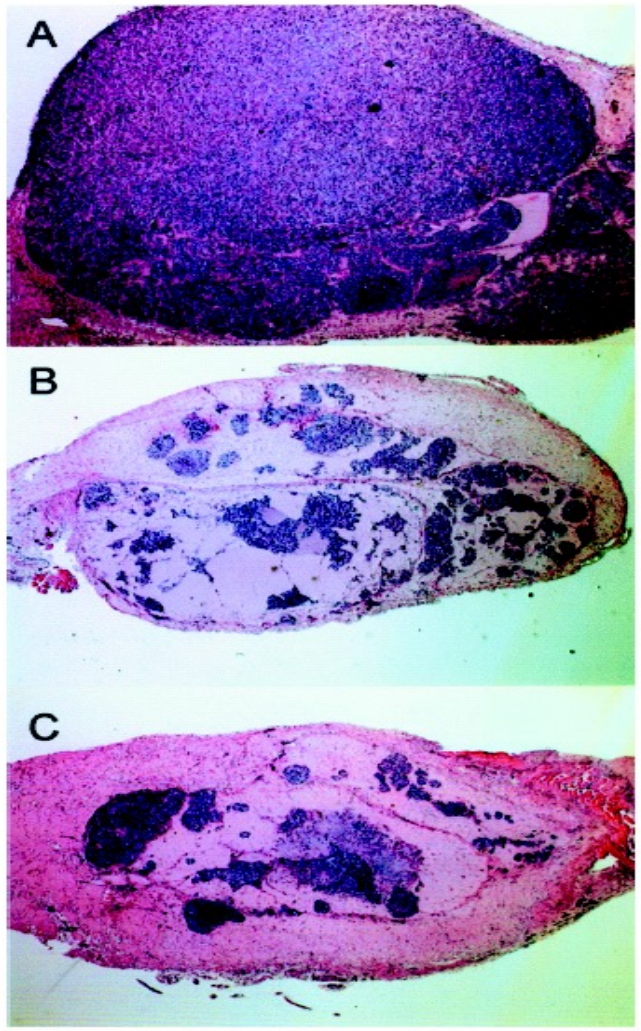
Death of Cleopatra (and her servants Eiras and Charmion, who also took their own lives – *by asp venom injection*), by Jean-Baptiste Regnault (1796–1797)

Preclinical Efficacy of Paclitaxel-conjugated Trastuzumab



Hydrolysis





Vehicle Control + isotype control MAb

Free paclitaxel + Free trastuzumab

Paclitaxel-conjugated trastuzumab

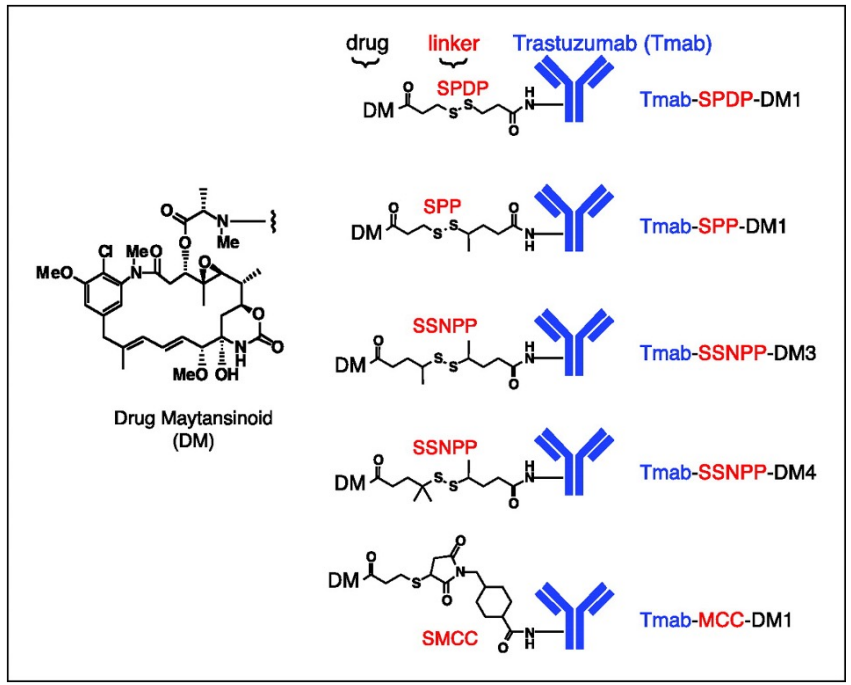
Human HER2+ breast carcinoma xenografts, athymic mice, H&E stain

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

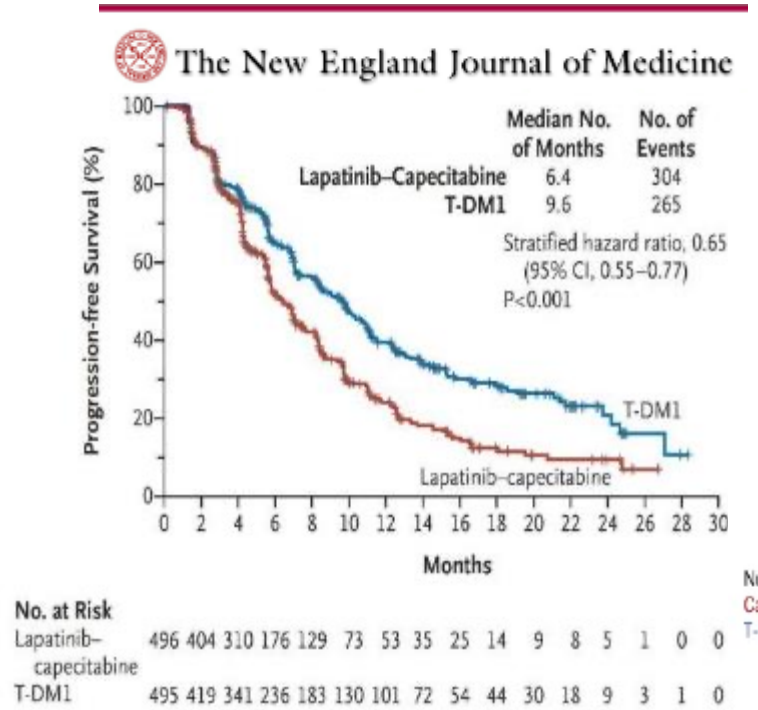
Phase III EMILIA: T-DM1 in HER2+ MBC

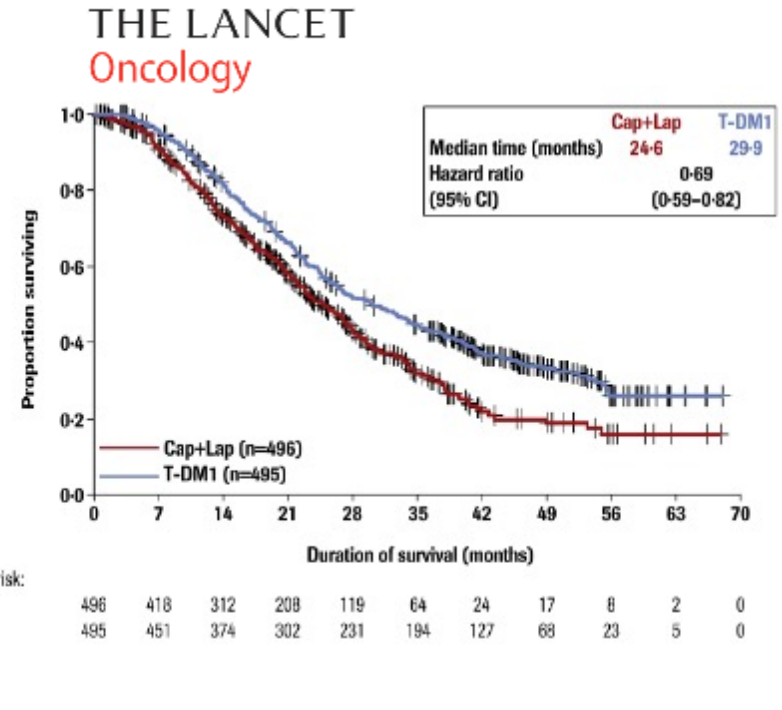
In EMILIA, T-DM1 was superior to lapatinib + capecitabine in HER2+ mBC[1,2]

- 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





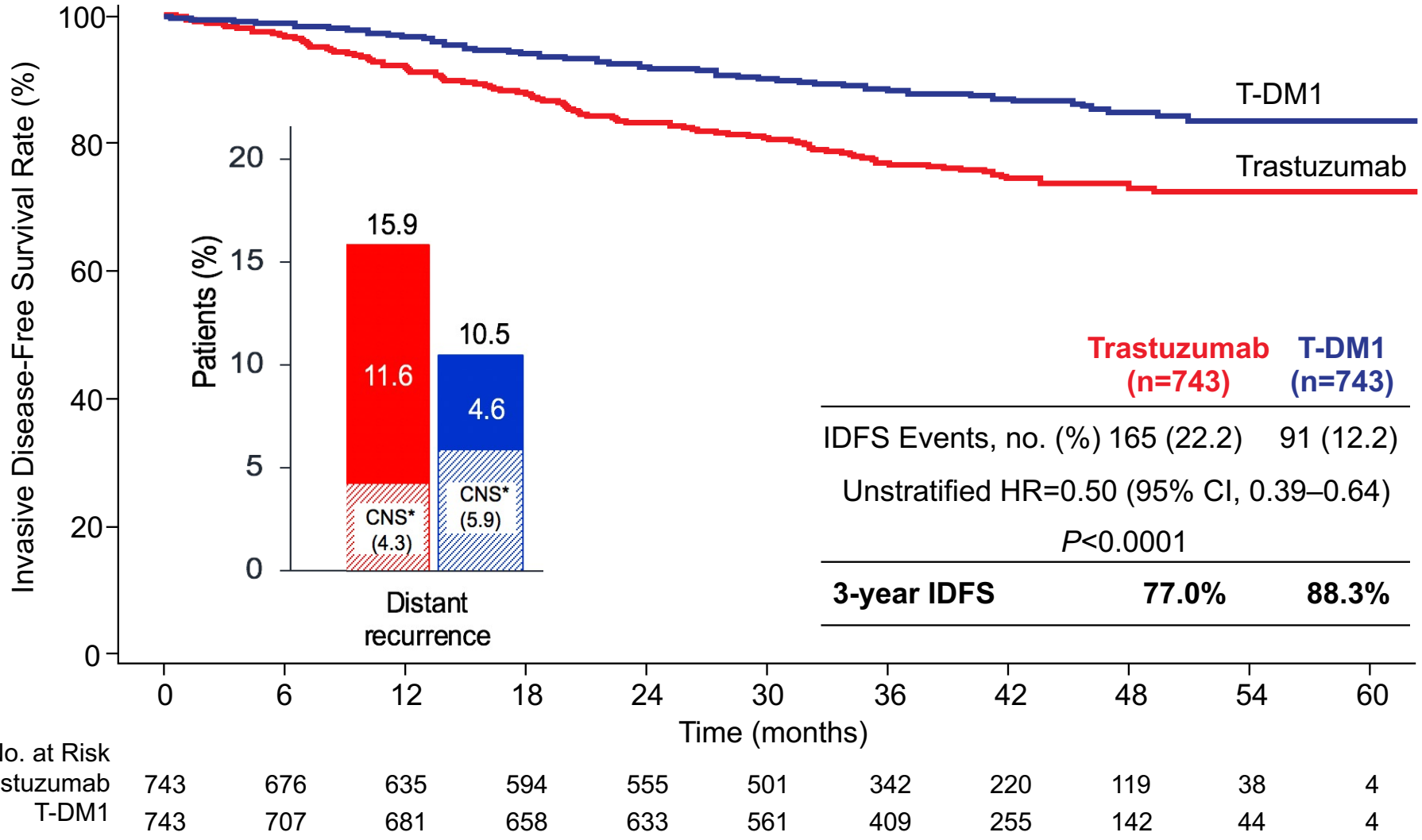
The most common adverse drug reactions (frequency > 25%) with T-DM1 (n=884 treated patients) were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation.

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.

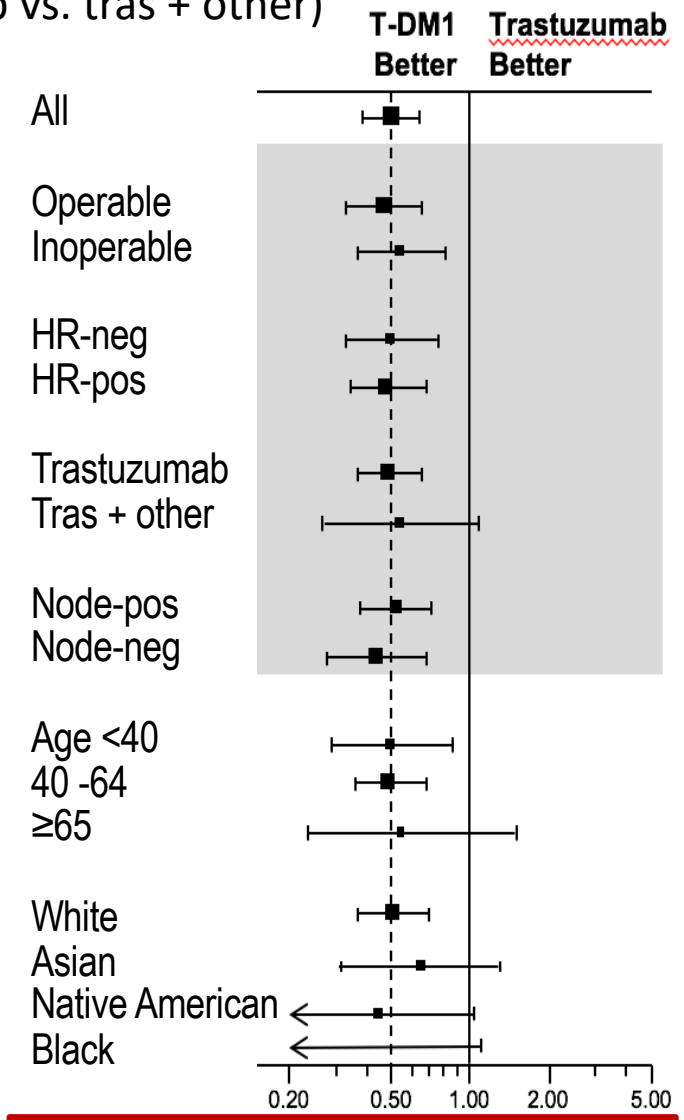
KATHERINE non-pCR Trial: T-DM1 vs. Trastuzumab, Invasive Disease-Free Survival

(Stratification factors: operability, hormone receptor status, ypN status, trastuzumab vs. tras + other)



	Trastuzumab (n=743)	T-DM1 (n=743)
IDFS Events, no. (%)	165 (22.2)	91 (12.2)
Unstratified HR=0.50 (95% CI, 0.39–0.64)		
P<0.0001		
3-year IDFS	**77.0%**	**88.3%**

No. at Risk											
Trastuzumab	743	676	635	594	555	501	342	220	119	38	4
T-DM1	743	707	681	658	633	561	409	255	142	44	4



Groups well balanced for age (median 49), race, world region (54% western Europe), operable BC (75%), ER+ (72%), prior pertuzumab (18%), LN+ (46%), residual primary tumor stage (~50% ypT1-2), and residual LN (ypLN0 ~45%). 71.4% of T-DM1-treated patients completed all 14 cycles (vs 81% trastuzumab arm); 85.7% in T-DM1 arm had no dose reduction.

Primary T stage at definitive surgery
ypT0, ypT1a., ypT1b, ypT1mic, ypTis
iDFS HR = 0.66 (95% CI 0.44 – 1.0)

Von Minckwitz G, et al. *N Engl J Med.* 2019; 380:617-628.

DESTINY-Breast03: TDX-d versus T-DM1 in HER2+ MBC (previously treated with a taxane and trastuzumab)

DESTINY-Breast03 San Antonio Breast Cancer Symposium – December 6-10, 2022

Updated OS Analysis of DESTINY-Breast03

Randomized, open-label, multicenter study (NCT03529110)

Patients (N = 524)

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and a taxane in metastatic or (neo)adjuvant setting with recurrence within 6 months of therapy[b]

R 1:1

T-DXd 5.4 mg/kg Q3W (n = 261)

T-DM1 3.6 mg/kg Q3W (n = 263)

Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS[c]

Secondary endpoints

- ORR (BICR and investigator)
- DoR (BICR)
- Safety

Stratification factors

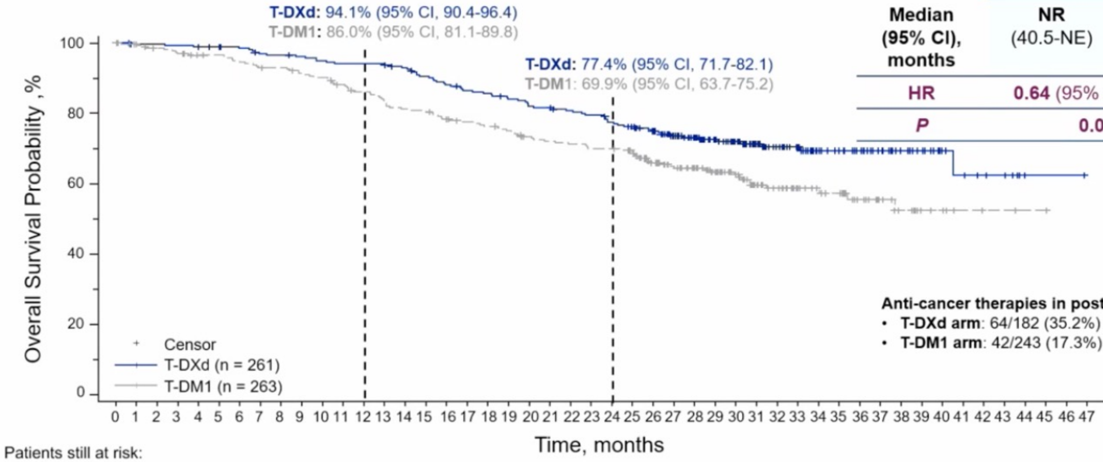
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

The prespecified OS interim analysis was planned with 153 events.[d] At the time of data cutoff (July 25, 2022), 169 OS events were observed and the *P* value to achieve statistical significance was 0.013

BICR, blinded independent central review; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]HER2 IHC 3+ or IHC 2+/ISH+ based on central confirmation. [b]Progression during or within 6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]80% powered at 2-sided significance level of 5%. [d]Information fraction of 61%, with a *P* value boundary to reach statistical significance of 0.008. The *P* value was recalculated based on the actual OS events at the data cutoff.

DESTINY-Breast03 San Antonio Breast Cancer Symposium – December 6-10, 2022

Key Secondary Endpoint: Overall Survival



	T-DXd	T-DM1
Median (95% CI), months	NR (40.5-NE)	NR (34.0-NE)
HR	0.64 (95% CI, 0.47-0.87)	
P	0.0037[a,b]	

Anti-cancer therapies in post-trial setting:

- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

Patients still at risk:

T-DXd 261 256 256 255 254 251 249 244 243 241 238 236 236 236 231 224 218 213 211 206 201 200 196 193 187 182 173 156 142 124 109 91 73 64 51 44 38 30 22 18 11 9 7 6 1 1 1 0

T-DM1 263 257 252 248 243 242 237 233 232 227 224 217 211 203 199 197 191 186 183 179 172 169 167 164 164 158 140 129 117 106 90 70 59 45 41 38 27 20 15 8 7 4 3 3 1 1 0

HR, hazard ratio; mOS, median overall survival; NE, not estimable; NR, not reached; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
There were 19 patients (7.3%) treated with T-DXd and 28 patients (10.6%) treated with T-DM1 who were lost to follow-up.
[a]The *P* value for overall survival crossed the prespecified boundary (*P* = 0.013) and was statistically significant. [b]Two-sided from stratified log-rank test.

Adjudicated Drug-Related Interstitial Lung Disease/Pneumonitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

"Updated results demonstrate remarkable OS and PFS benefit with T-DXd, further supporting the use of T-DXd as the second-line standard of care in patients with HER2+ mBC."

Fam-Trastuzumab Deruxtecan-nxki vs Physician's Choice in Patients With HER2+ Unresectable and/or Metastatic Breast Cancer Previously Treated With Ado-Trastuzumab Emtansine: Primary Results of the Randomized Phase 3 Study DESTINY-Breast02

DESTINY-Breast02: Study Design

A randomized phase 3, open-label, multicenter study (NCT03523585)

Key eligibility criteria[a]
- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

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

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
or
- Lapatinib / Capecitabine

Primary endpoint
- PFS (BICR[b])

Key secondary endpoint
- OS

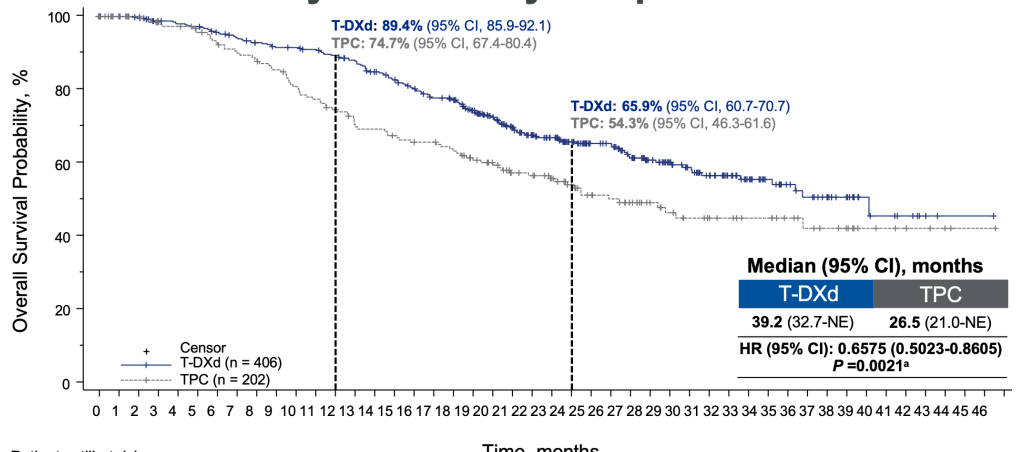
Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

Protocol-prespecified statistical analysis plan
- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:
- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm

DESTINY-Breast02: Key Secondary Endpoint - OS



In the TPC arm
- **69.3% (140/202) of patients received a new systemic anticancer treatment**
- **25.7% (52/202) of patients received T-DXd in the post-trial setting**

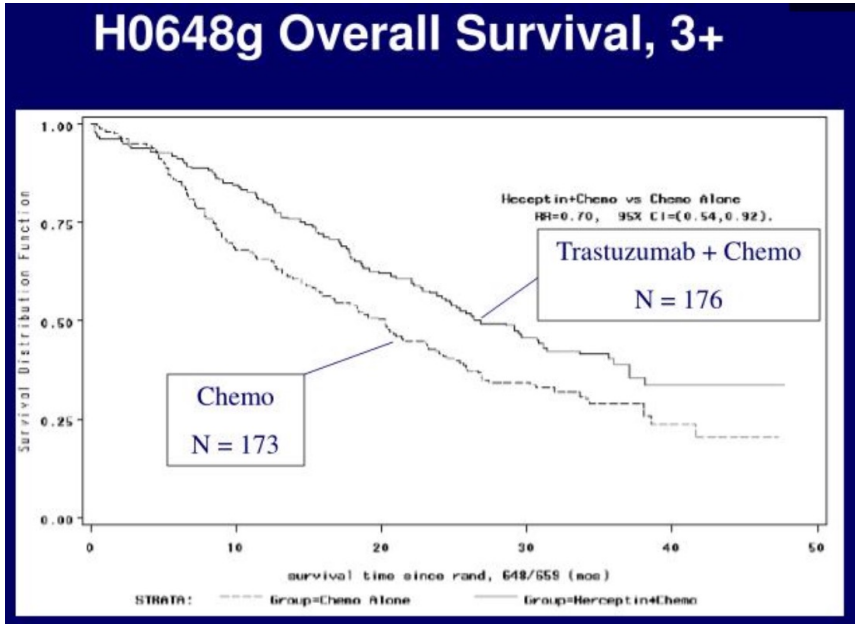
[a]The boundary for statistical significance is 0.0040.
CI, confidence interval; HR, hazard ratio; mo, month; NE, not estimable; OS, overall survival; T-DXd, fam-trastuzumab deruxtecan-nxki; TPC, treatment of physician's choice.
Krop I, et al. SABCS 2022. Oral GS2-01.

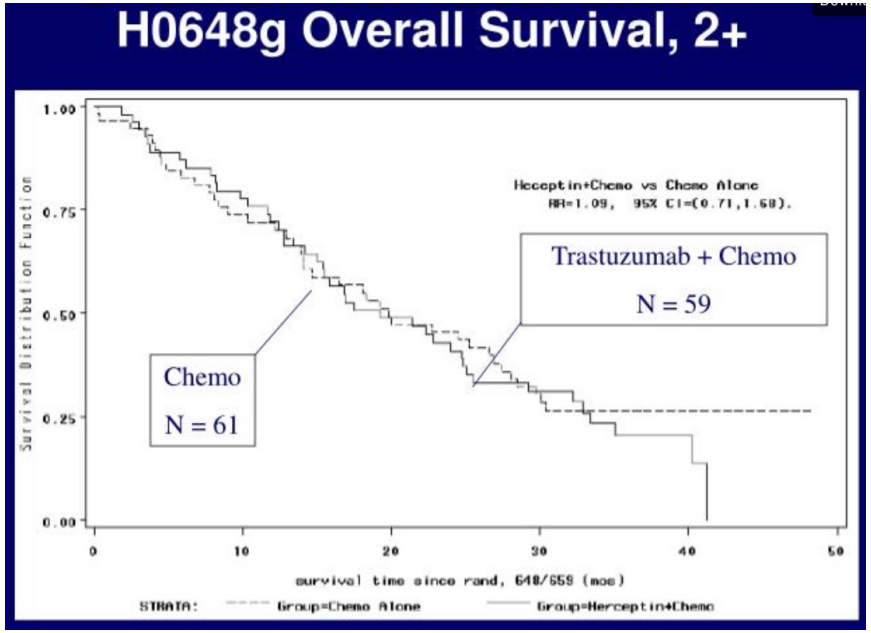
Eligibility criteria for original phase 1/2/3 trastuzumab clinical trials included HER2 IHC = 2+

H0648g Overall Survival
Trastuzumab + Chemo vs Chemo

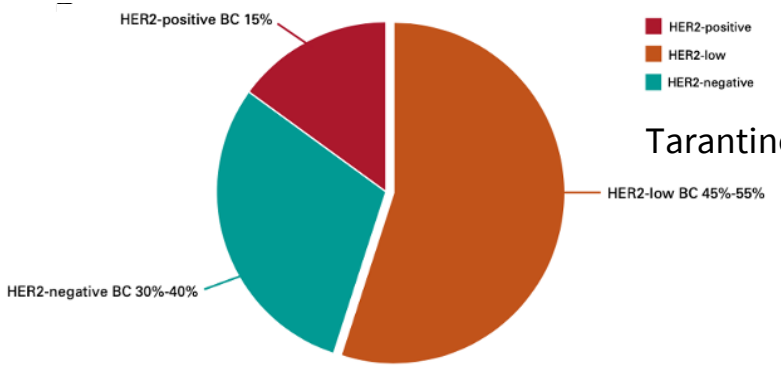
Subgroup	Relative Risk	95% CI	N
3+	0.70	0.54, 0.92	349
2+	1.09	0.71, 1.58	120
FISH (+)	0.69	0.53, 0.91	325
FISH (-)	1.07	0.70, 1.63	126

FDA Clinical Review December 5, 2001 Oncologic Drugs Advisory Committee Meeting.





DESTINY-Breast04: First Randomized Phase III of T-DXd for HER2-low Metastatic Breast Cancer



Tarantino P, et al. J Clin Oncol 38(17): 1951-62 (2020).

An open-label, multicenter study (NCT03734029)

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

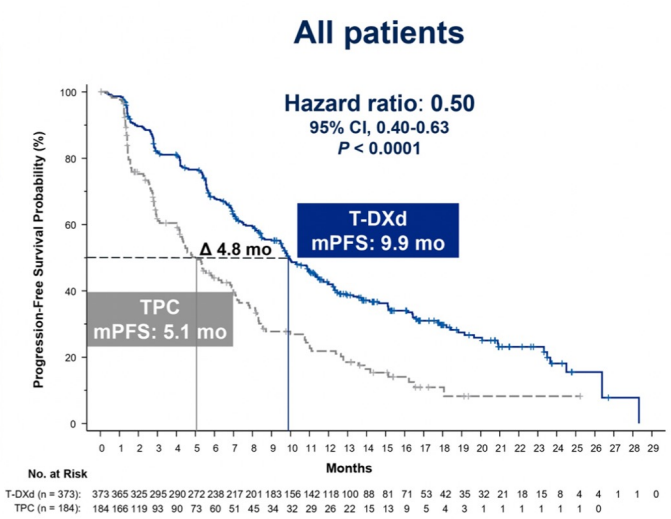
T-DXd
5.4 mg/kg Q3W
(n = 373)

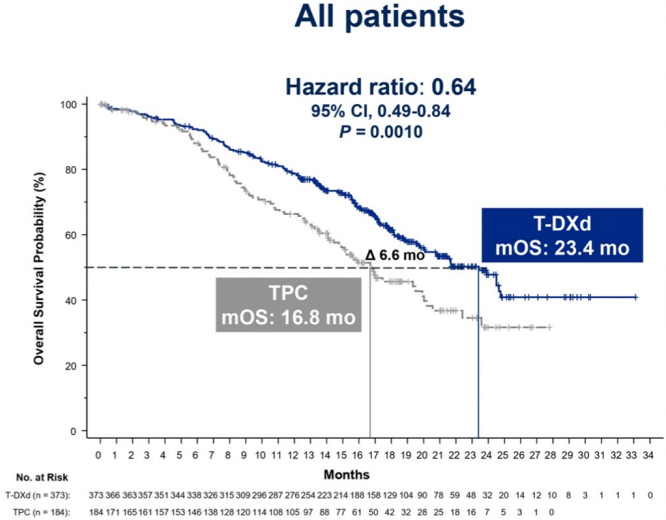
HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Stratification factors
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

DESTINY-Breast04: PFS and OS in all patients





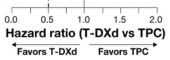
PFS by blinded independent central review.
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

The most common adverse reactions (≥20%): N/V, cytopenias, fatigue, transaminase elevation, alopecia, increased alkaline phosphatase, constipation, musculoskeletal pain, anorexia, hypokalemia, diarrhea, and respiratory infection.

I don’t always use ADCs to treat HER2-low, but when I do I prefer….

Fam-Trastuzumab Deruxtecan-nxki

Subgroup		No. of Events/ No. of Patients T-DXd	TPC	Median PFS, mo (95% CI)[a] T-DXd	TPC	Hazard Ratio (95% CI)[b]
Prior CDK4/6i use (HR+ cohort)	Yes (n = 348)	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.74)
	No (n = 143)	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
Disease burden[c]	Low (n = 235)	88/150	60/85	11.4 (9.8-16.2)	5.1 (3.1-7.3)	0.41 (0.30-0.58)
	High (n = 322)	155/223	67/99	9.5 (7.5-10.1)	4.8 (2.9-6.9)	0.58 (0.43-0.78)
Rapid progression[d]	Yes (n = 22)	9/14	6/8	8.2 (1.4-NE)	2.2 (0.6-NE)	0.38 (0.12-1.21)
	No (n = 535)	234/359	121/176	9.9 (9.0-11.3)	5.3 (4.2-6.9)	0.51 (0.41-0.64)
HER2 IHC status	IHC 1+ (n = 321)	134/214	75/107	10.0 (8.6-12.3)	4.8 (3.0-7.0)	0.48 (0.36-0.63)
	IHC 2+/ISH− (n = 236)	109/159	52/77	9.9 (8.0-11.5)	5.1 (2.9-7.1)	0.55 (0.39-0.76)
Prior lines of chemotherapy	1 (n = 321)	141/221	68/100	10.1 (8.4-12.2)	6.4 (4.3-7.8)	0.52 (0.39-0.70)
	2 (n = 234)	101/151	59/83	9.7 (8.1-11.4)	4.2 (3.0-5.4)	0.49 (0.35-0.68)
Age	<65 years (n = 426)	191/290	93/136	9.8 (8.4-11.1)	4.6 (2.9-5.9)	0.47 (0.37-0.61)
	≥65 years (n = 131)	52/83	34/48	11.4 (8.3-13.3)	6.2 (4.3-10.8)	0.57 (0.36-0.89)
Baseline CNS metastases	Yes (n = 32)	18/24	6/8	8.1 (4.0-11.3)	4.8 (0.6-11.0)	0.71 (0.28-1.80)
	No (n = 525)	225/349	121/176	10.1 (9.5-11.5)	5.1 (4.2-6.8)	0.49 (0.39-0.62)
Prior anthracycline treatment[e]	Yes (n = 342)	155/239	81/113	9.8 (8.5-11.7)	5.3 (3.0-7.9)	0.53 (0.40-0.70)
	No (n = 205)	88/134	46/71	10.0 (7.2-12.5)	4.6 (3.0-6.8)	0.46 (0.32-0.66)



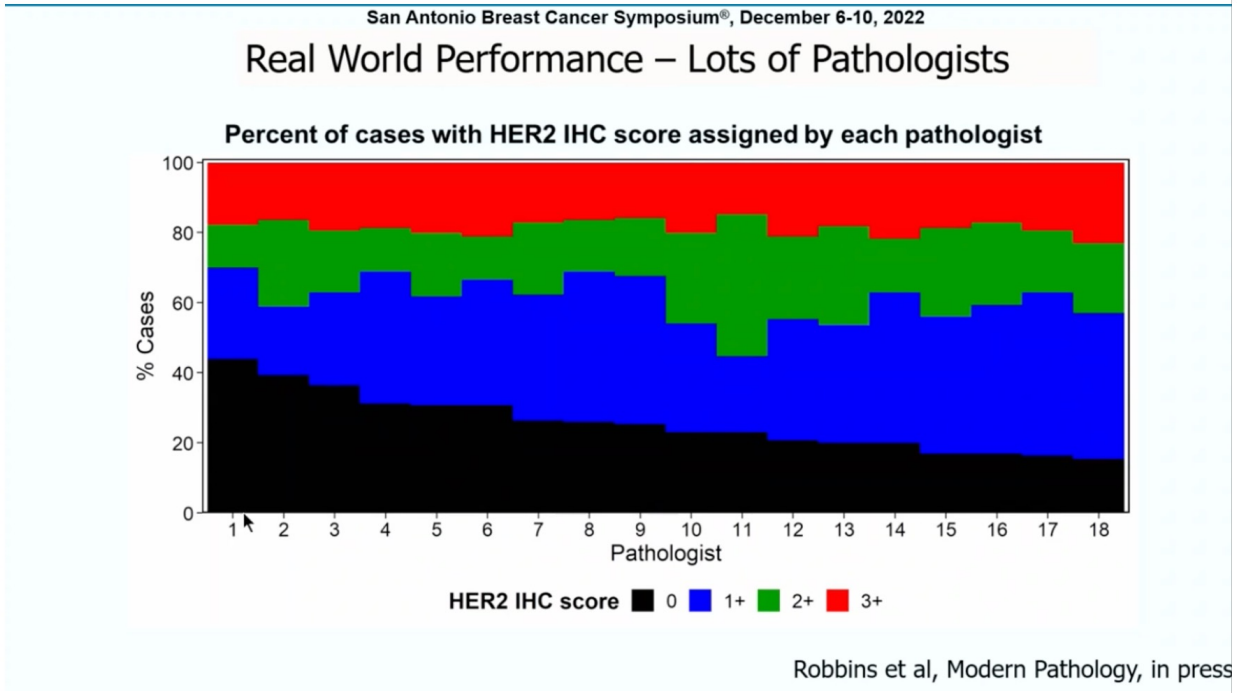
DESTINY-Breast04: PFS Subgroup Analysis

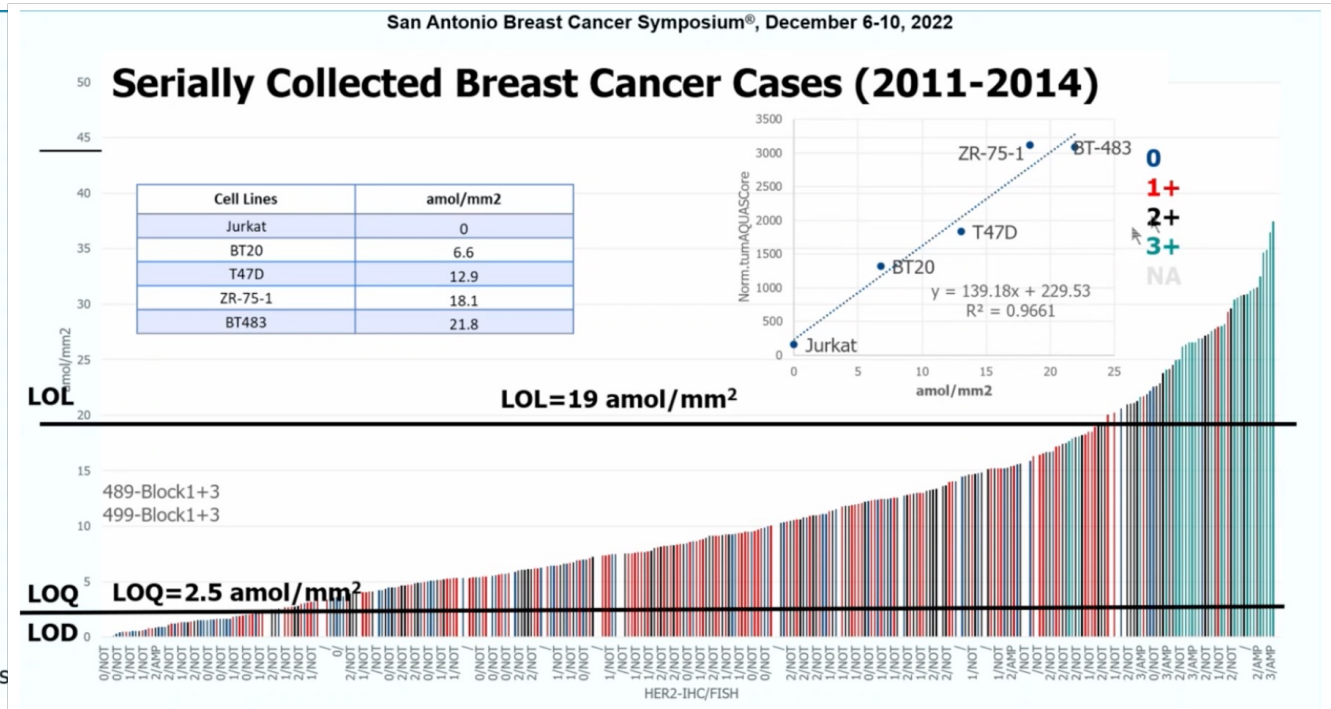
Harbeck N, et al. SABCS 2022. Poster P1-11-01.

If there is an elephant in the room… it’s because he brought one.

HER2 expression on histologic preparations using Automated Quantitative Analysis (AQUA™)

Coupled with a mass spectrometry standardized HER2 array

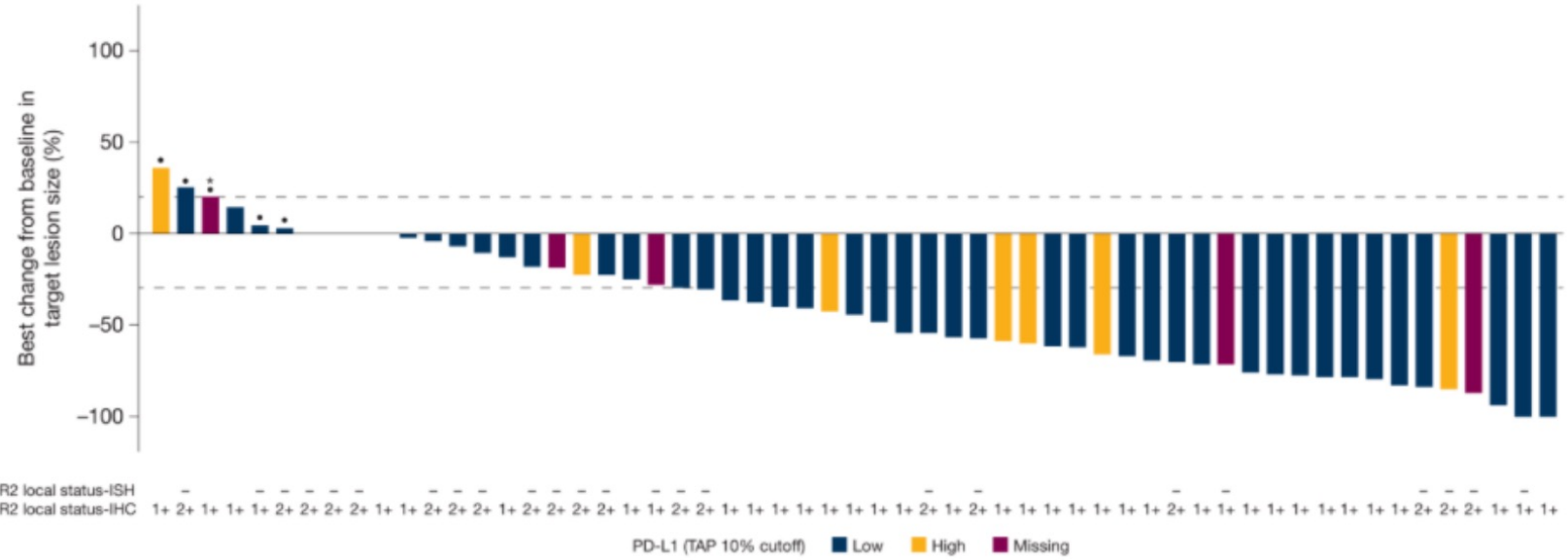




Attomole = A unit of amount of substance equal to one quintillionth of a mole (10E-18 mole). (NCI Thesaurus)

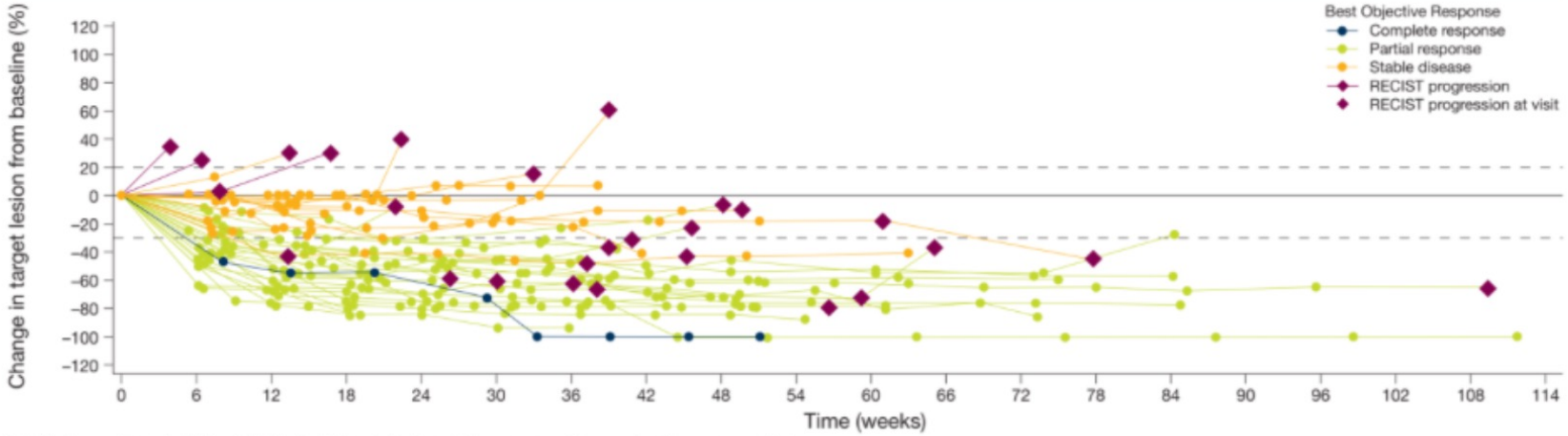
T-DXd + durvalumab as 1st line treatment for HR-/HER2-low MBC: updated BEGONIA data

Figure 1. Best change from baseline of target lesion size



Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively.
*If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. "•" Patients with progressive disease as best overall response.

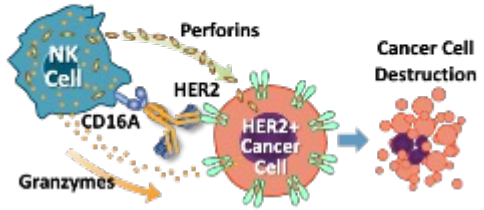
Figure 2. Change from baseline in sum of target lesions over time



Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively.

Fc-Engineered HER2-Targeted Chimeric Monoclonal Antibody Margetuximab

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

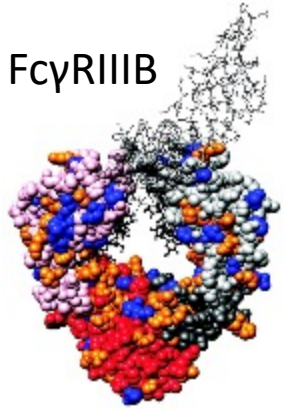


Musolino A, Gradishar WJ, Rugo HS, Nordstrom JL, Rock EP, Arnaldez F, Pegram MD.J Immunother Cancer. 2022 Jan;10(1):e003171.

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

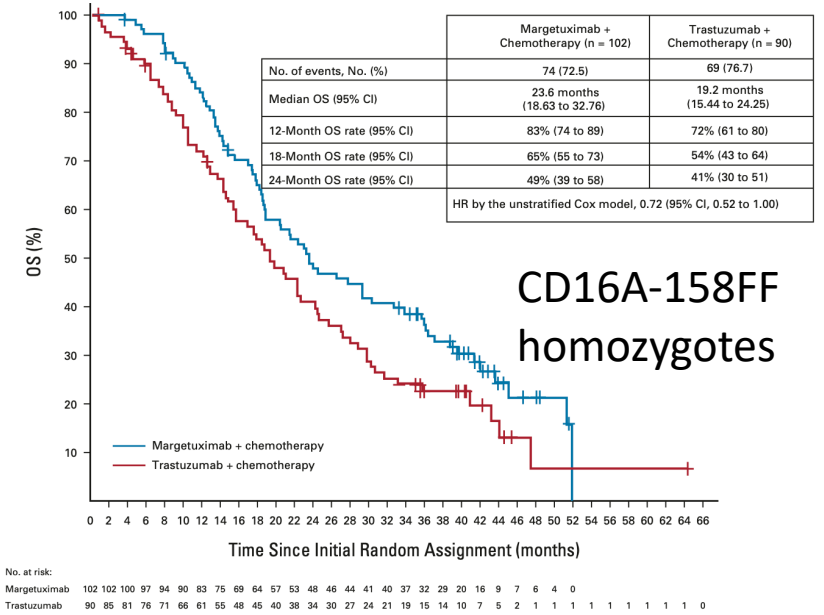
*Investigators choice of CT: capecitabine, eribulin, gemcitabine, or vinorelbine.

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%

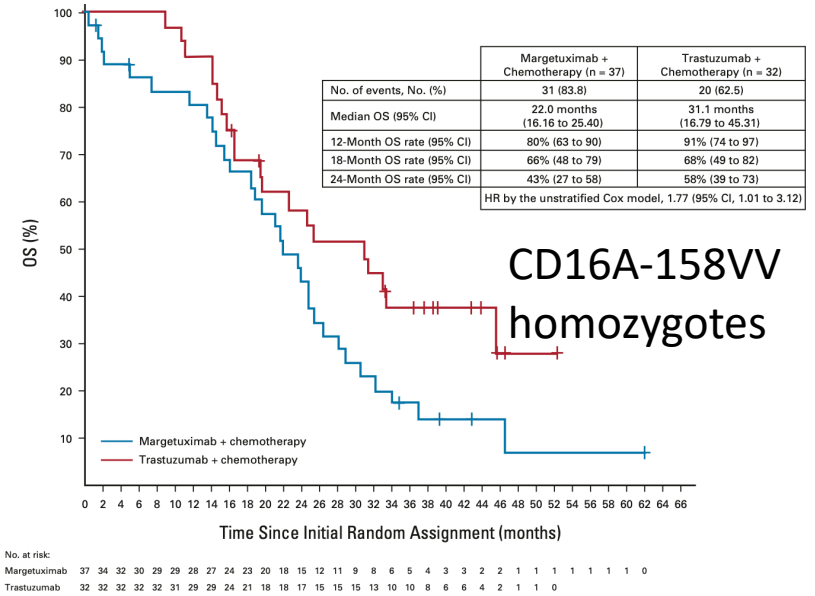
CD16A Genotype by Treatment Group

Prespecified Exploratory OS Analysis



	Margetuximab + Chemotherapy (n = 102)	Trastuzumab + Chemotherapy (n = 90)
No. of events, No. (%)	74 (72.5)	69 (76.7)
Median OS (95% CI)	23.6 months (18.63 to 32.76)	19.2 months (15.44 to 24.25)
12-Month OS rate (95% CI)	83% (74 to 89)	72% (61 to 80)
18-Month OS rate (95% CI)	65% (55 to 73)	54% (43 to 64)
24-Month OS rate (95% CI)	49% (39 to 58)	41% (30 to 51)
HR by the unstratified Cox model, 0.72 (95% CI, 0.52 to 1.00)		

CD16A-158FF homozygotes



	Margetuximab + Chemotherapy (n = 37)	Trastuzumab + Chemotherapy (n = 32)
No. of events, No. (%)	31 (83.8)	20 (62.5)
Median OS (95% CI)	22.0 months (16.16 to 25.40)	31.1 months (16.79 to 45.31)
12-Month OS rate (95% CI)	80% (63 to 90)	91% (74 to 97)
18-Month OS rate (95% CI)	66% (48 to 79)	68% (49 to 82)
24-Month OS rate (95% CI)	43% (27 to 58)	58% (39 to 73)
HR by the unstratified Cox model, 1.77 (95% CI, 1.01 to 3.12)		

CD16A-158VV homozygotes

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

Future Directions in HER2-targeted Therapy at Stanford…

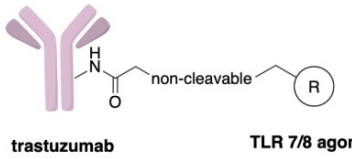
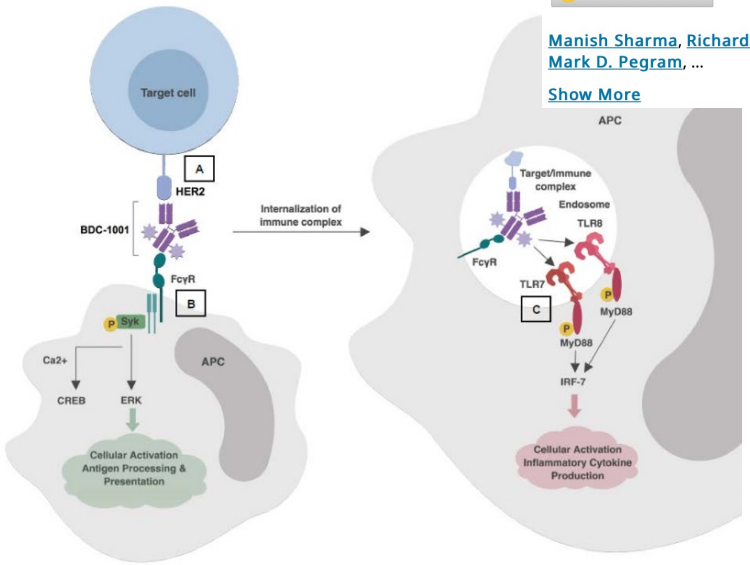


Figure 2: Proposed Mechanism of Action for BDC-1001



DEVELOPMENTAL THERAPEUTICS—IMMUNOTHERAPY

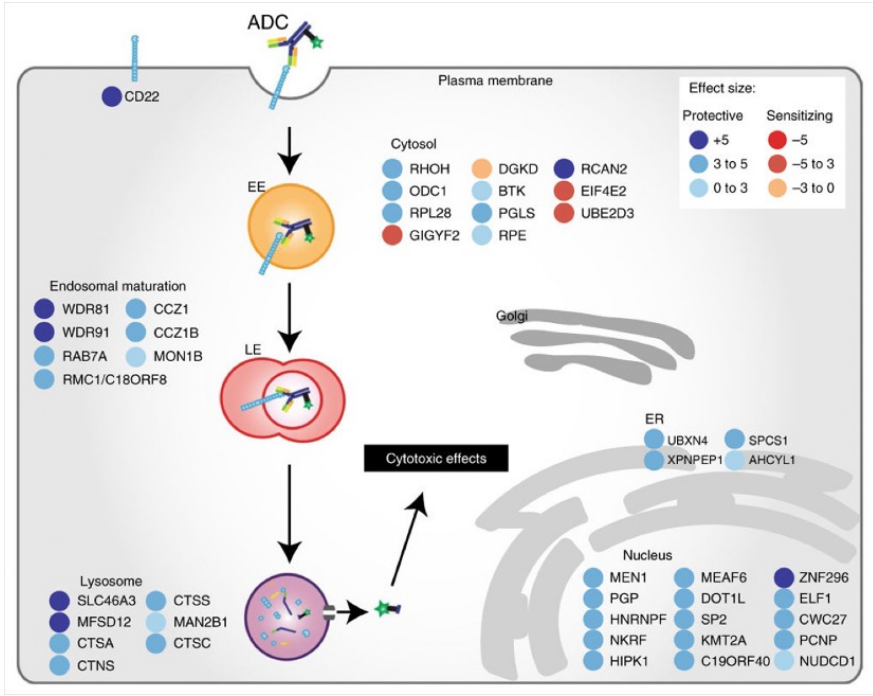
Preliminary results from a phase 1/2 study of BDC-1001, a novel HER2 targeting TLR7/8 immune-stimulating antibody conjugate (ISAC), in patients (pts) with advanced HER2-expressing solid tumors.

Check for updates

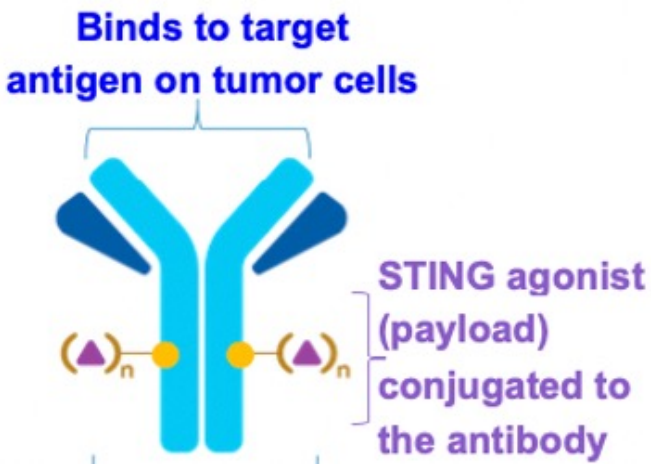
Manish Sharma, Richard D. Carvajal, Glenn J. Hanna, Bob T. Li, Kathleen N. Moore, Mark D. Pegram, …

Show More

Tsui CL, et al. Nature Chem Biol 2019 Oct; 15(10):949-958.



Endolysosomal regulators modulate ADC action

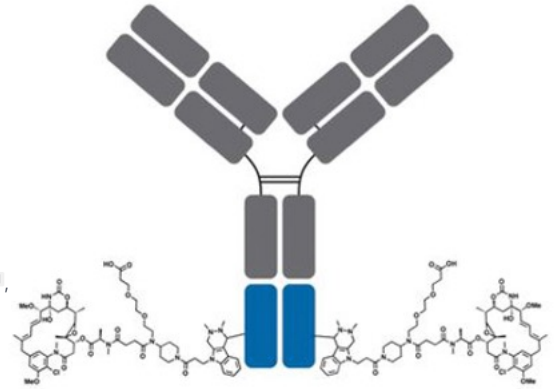


Comparative Study > Mol Cancer Ther. 2020 Sep;19(9):1866-1874.
doi: 10.1158/1535-7163.MCT-20-0190. Epub 2020 Jul 10.

A Novel HER2–targeted Antibody–drug Conjugate Offers the Possibility of Clinical Dosing at Trastuzumab–equivalent Exposure Levels

Robyn M Barfield [1], Yun Cheol Kim [1], Stepan Chuprakov [1], Fangjiu Zhang [1], Maxine Bauzon [1], Ayodele O Ogunkoya [1], Dominick Yeo [1], Colin Hickle [1], Mark D Pegram [2], David Rabuka [1], Penelope M Drake [3]

Tumor cell-targeted STING-agonist antibody-drug conjugates achieve potent anti-tumor activity. Cetinbas, et al. Proceedings AACR 2022, abstr 4873.



A schematic of the CAT-01-106 structure

Stanford University

ep·i·logue

/ˈepəˌlôg,ˈepəˌläg/

noun: epilogue; plural noun: epilogues; noun: epilog; plural noun: epilogs
-- a section or speech at the end of a book or play that serves as a comment on or a conclusion to what has happened.

- Dennis Slamon
- Richard Pietras
- Gottfried Konecny
- Angela Lopez
- Nathalie Chorn
- Richard Finn

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THANK YOU!