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HER2+ Breast Cancer : State of the Art

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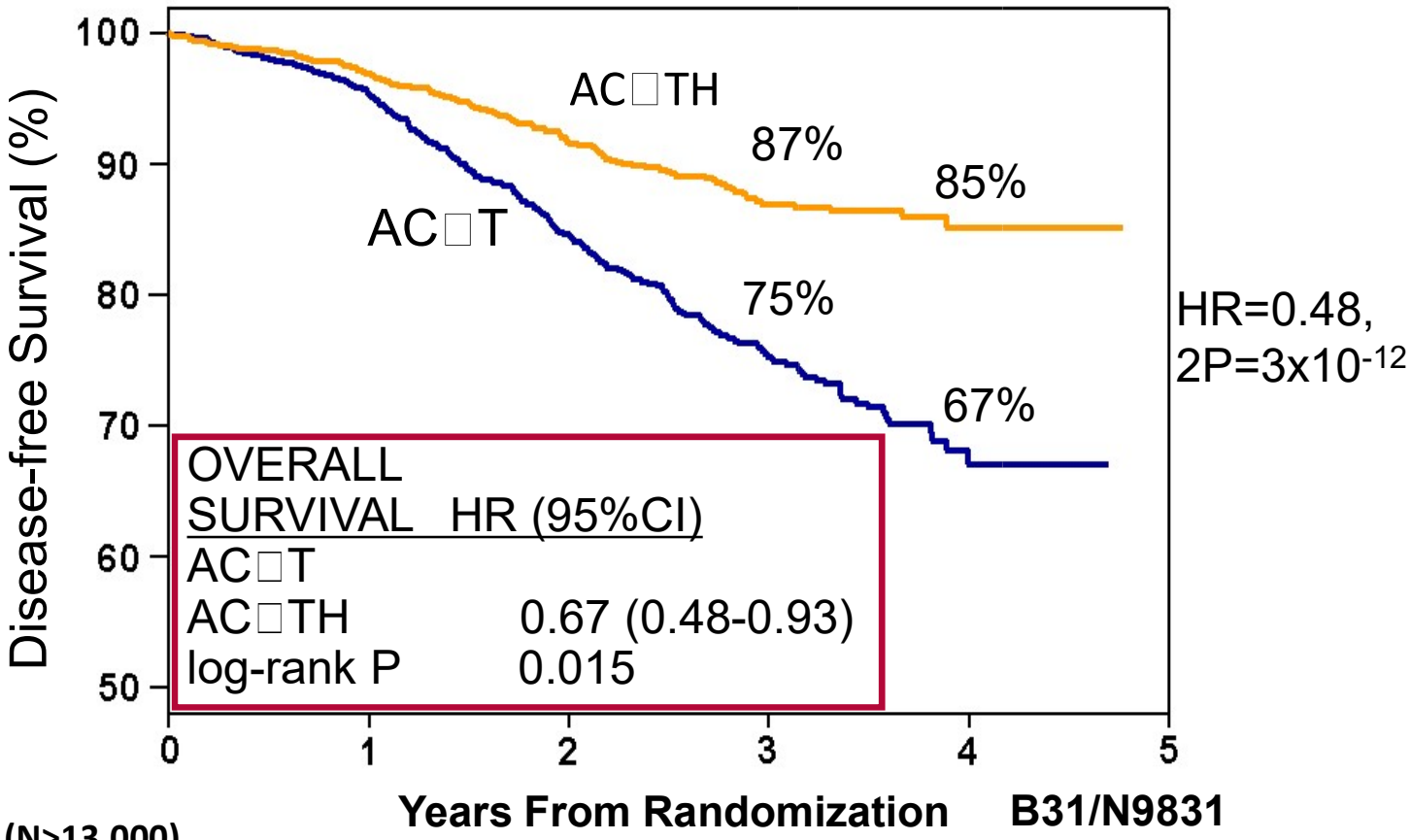
Disclosures: Genentech/Roche, AZ, Zymeworks, SeaGen, Puma

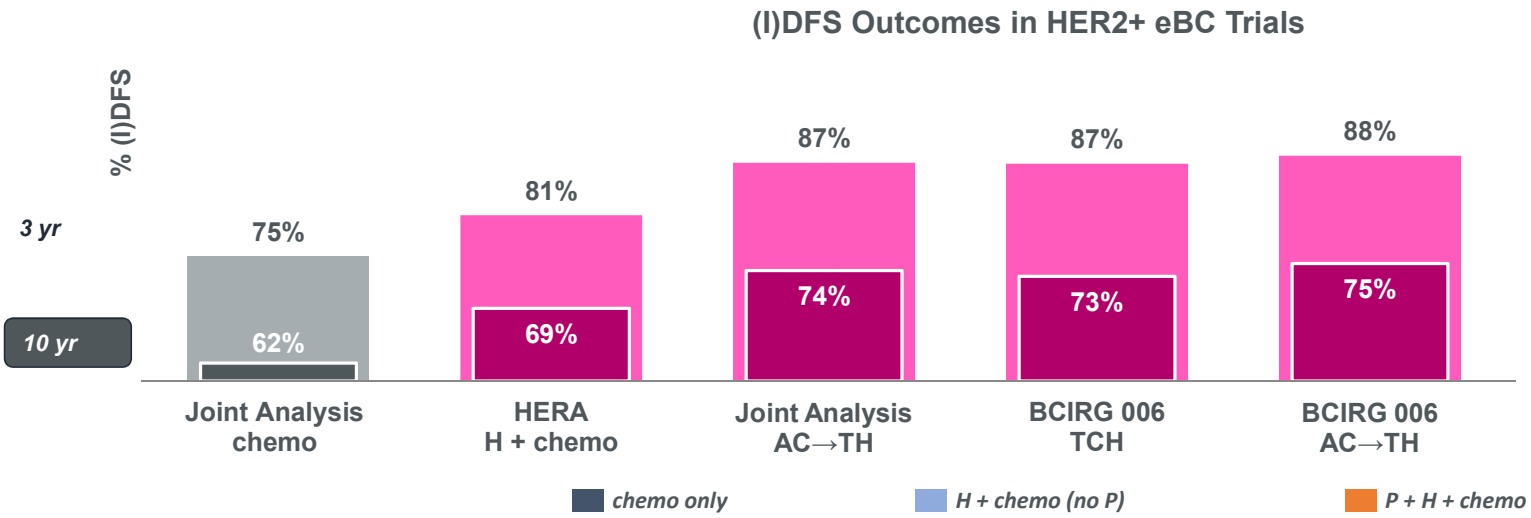
Analysis of Trastuzumab Efficacy
Joint (B31/N9831) Analysis (N = 3,351)*



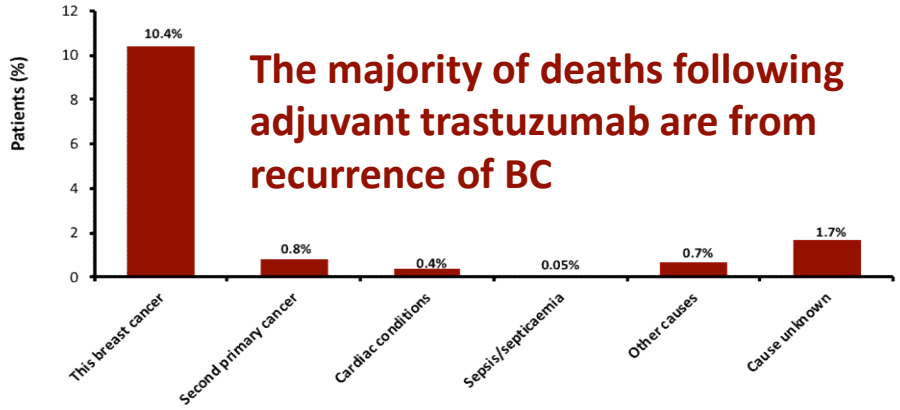
***Four pivotal trials (N>13,000) established trastuzumab as *the* standard of care for HER2-positive eBC**

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

HER2+ Breast Cancer – Remains a High Unmet Need



B-31/N9831: 10-year overall survival events and causes of death in patients treated with trastuzumab



The majority of deaths following adjuvant trastuzumab are from recurrence of BC

Chromoanasynthesis is a common mechanism that leads to ERBB2 amplifications in a cohort of early stage HER2+ breast cancer samples

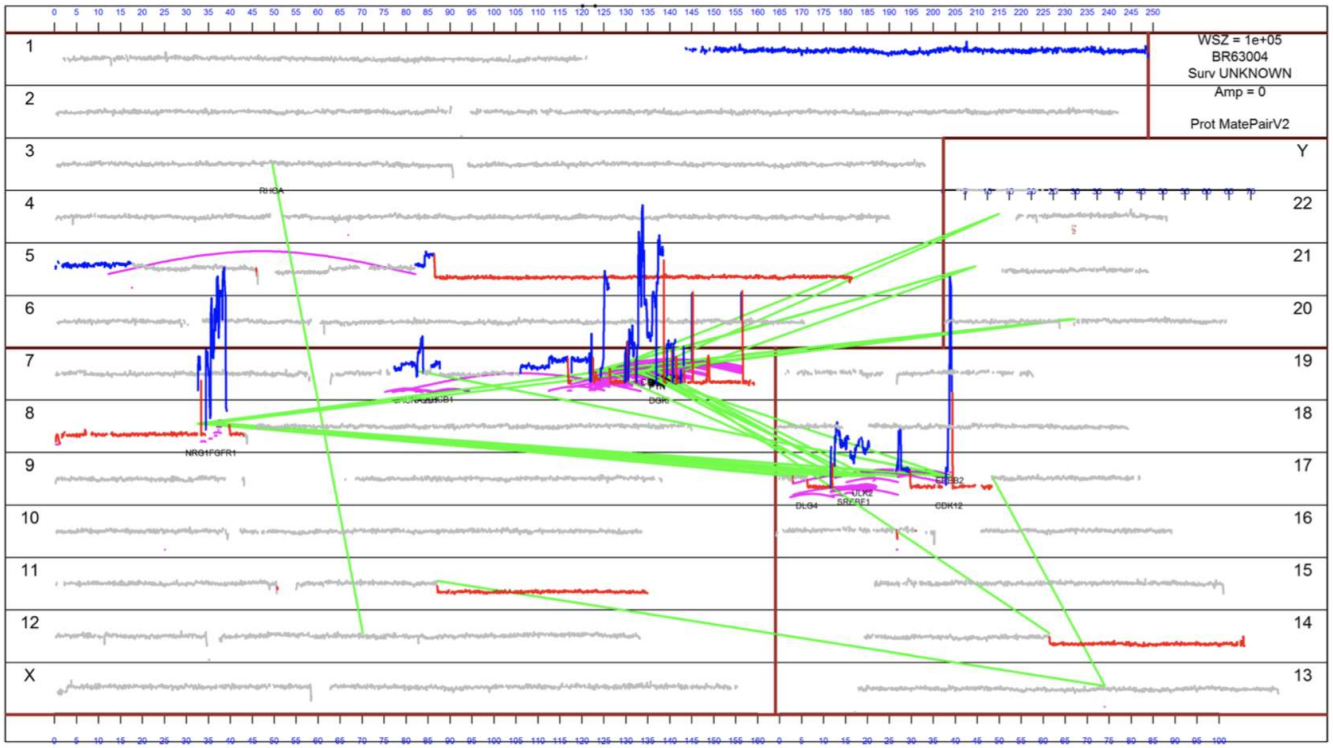
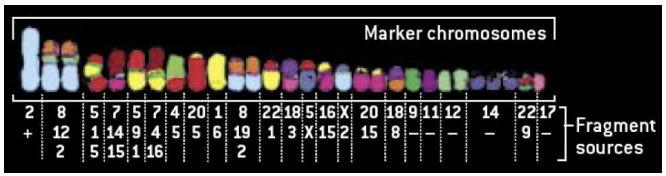


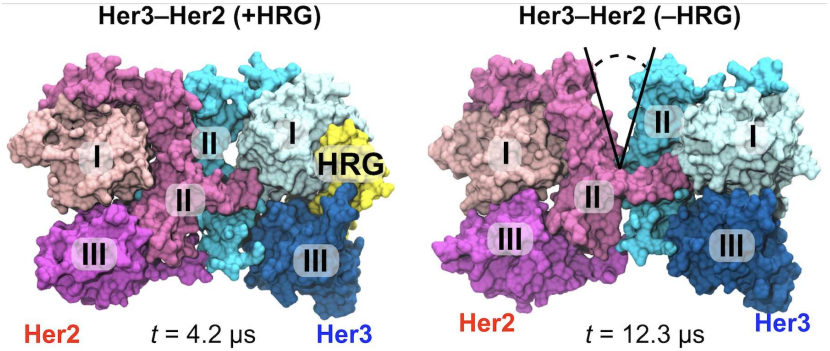
Fig. 1 Genome U-plot representation of case BRB-041. Coverage of each chromosome is presented horizontally with grey regions indicating normal diploid coverage. Red and blue chromosomal regions indicate losses and gains, respectively. Straight green lines represent translocation junctions between different chromosomes whereas magenta arcs represent junctions within chromosomes



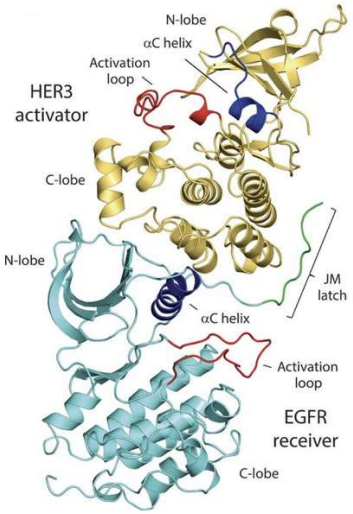
- Chromosomes 8 is commonly involved in the same chromoanasynthesis with 17
- When chromosome 8 is involved, NRG1 fusions, NRG1amplification, FGFR1 amplification and ADAM32 or ADAM5 fusions have been observed
- ERBB3 overexpression is associated with NRG1 fusions, and EGFR and ERBB3 expression are anti-correlated
- In one instance a small duplication fully encompassing the ERBB2 gene was accompanied by a pathogenic mutation

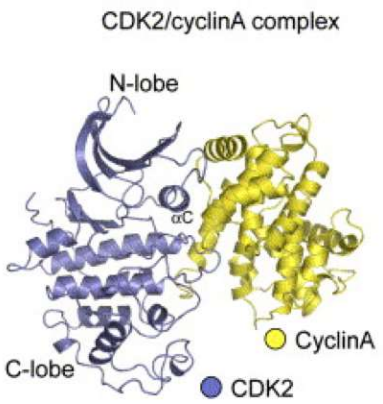
Vasmatzis et al. BMC Cancer (2018) 18:738.

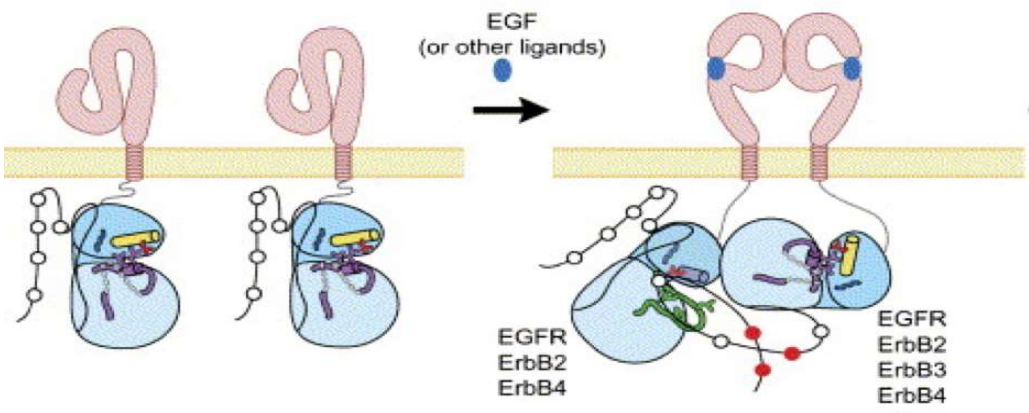
Allosteric Mechanism for Activation of EGFR-family Kinases

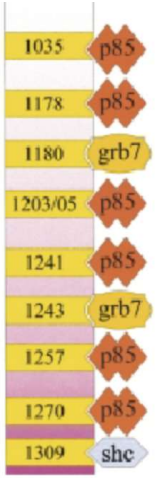


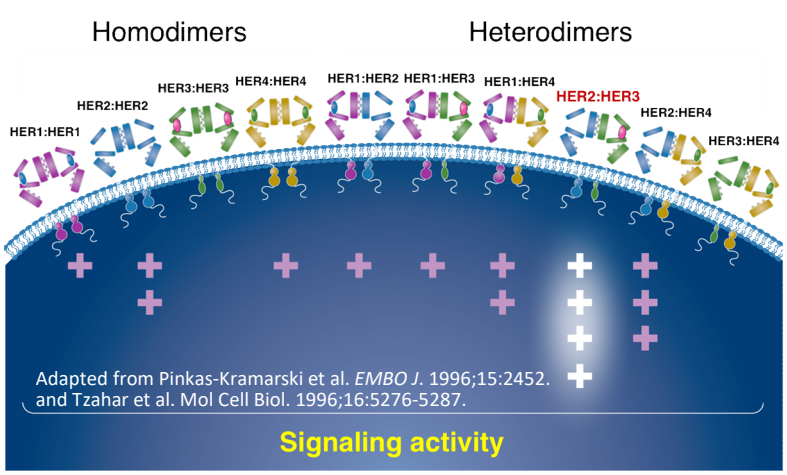
Snapshots from the simulations of the Her3–Her2 Heterodimer with (left) and without (right) HRG bound to Her3
Arkhipov, et al., eLife. 2013; 2: e00708





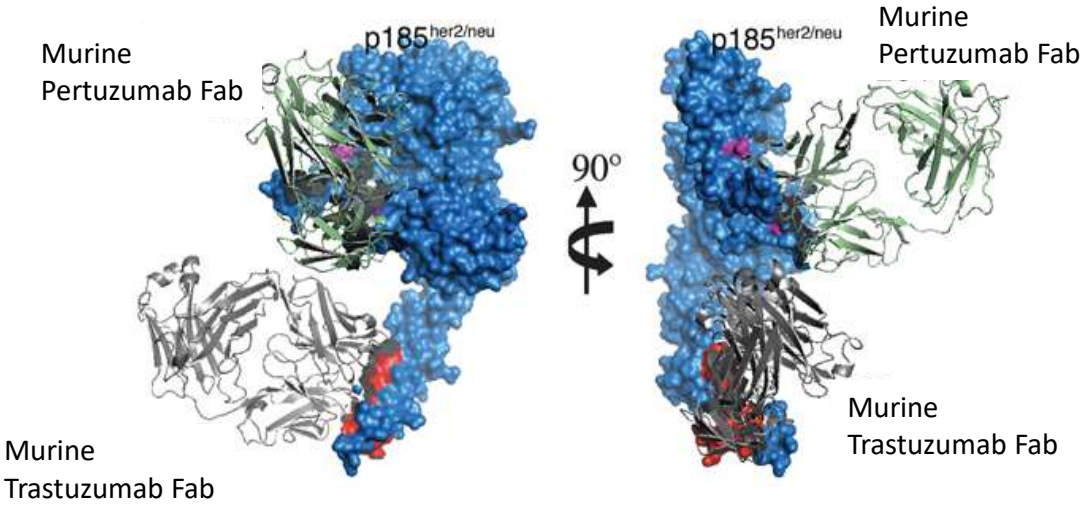




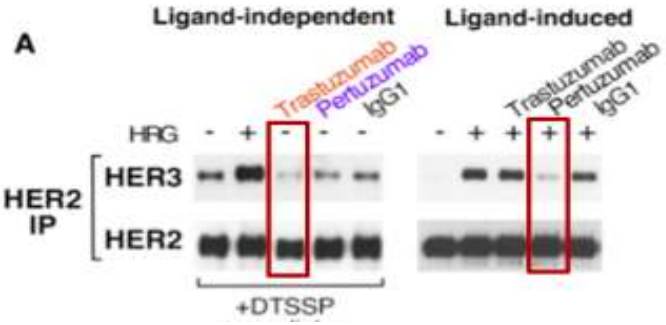


Zhang X, et al., Cell 125: 1137-49 (2006); Peter Littlefield et al., Sci. Signal. 2014;7:ra114; Olayioye, et al., EMBO Journal 19(13) 3159-67, 2000.

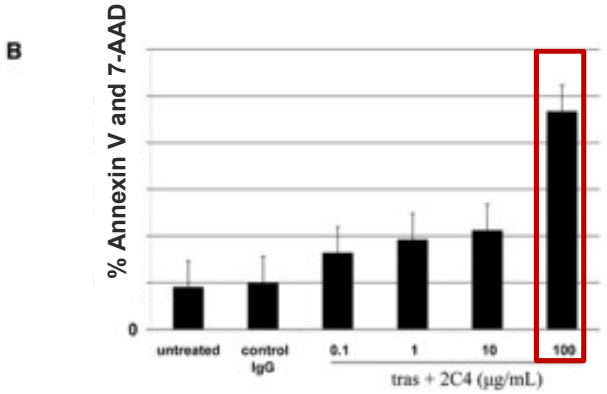
Pertuzumab Binds Subdomain II and Disrupts Ligand-Dependent HER2:HER3 Interaction; Trastuzumab + Pertuzumab Induces Apoptosis



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



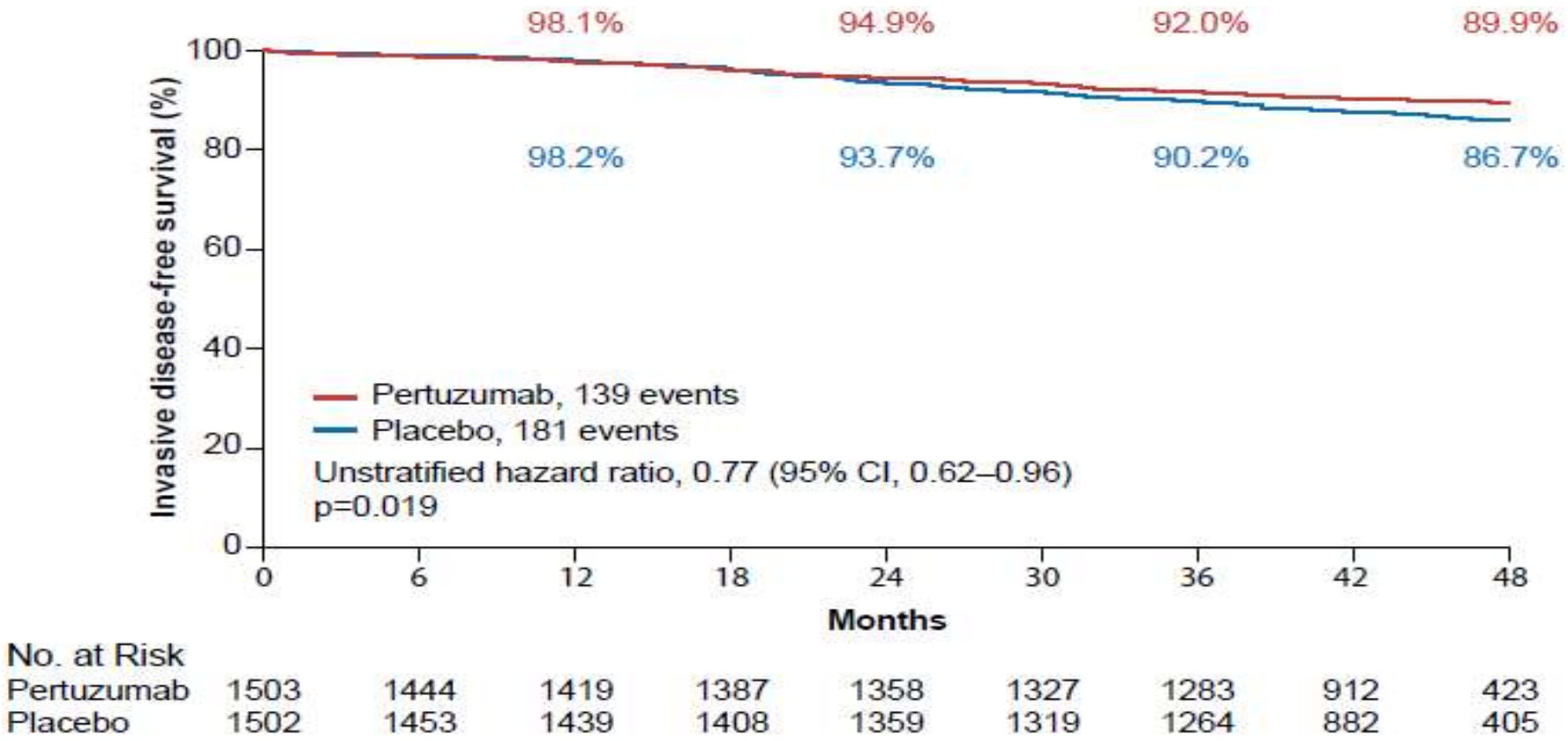
Junttila TT, et al., Cancer Cell. 2009 May 5;15(5):429-40.



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

CLEOPATRA end of study analysis: Statistically significant OS benefit at more than 8 years' follow-up (median 99 mos) = 16.3 mos (HR = 0.69), and was consistent across patient subgroups. Median PFS = 18.7 mos. [Swain SM, et al. ASCO 2019, abstract 1020].

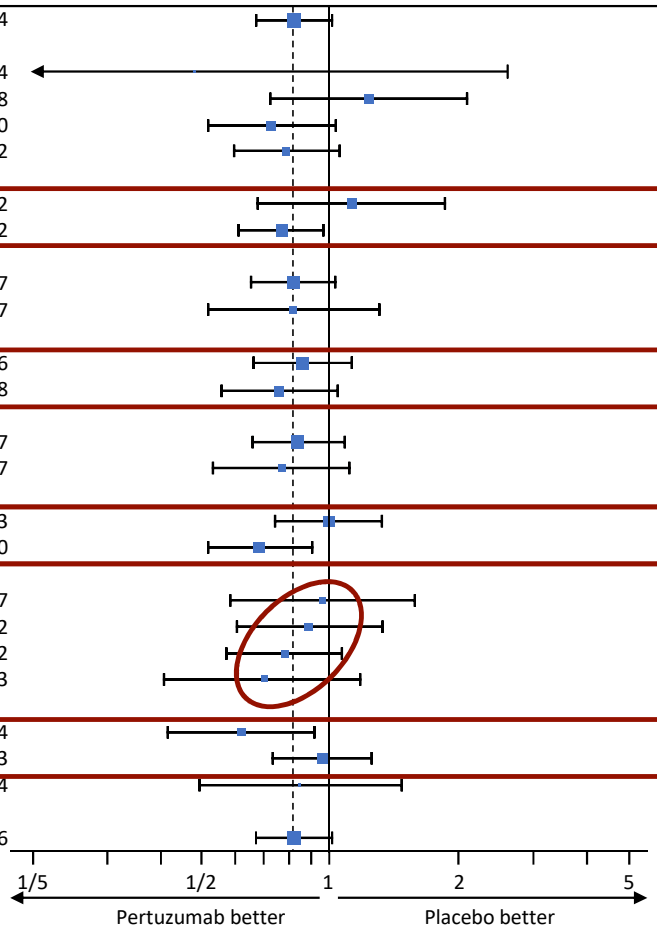
APHINITY: Node-positive Subgroup



von Minckwitz G, Procter MJ, De Azambuja E, et al: APHINITY trial (BIG 4-11): 2017 ASCO Annual Meeting. Abstract LBA500. Presented June 5, 2017.

APHINITY: IDFS Forest Plot by Subgroups

Subgroup	No. of Events / No. of Patients: Pertuzumab	No. of Events / No. of Patients: Placebo	Unstratified Hazard Ratio (95%CI)	3-year IDFS Rate, %: Pertuzumab	3-year IDFS Rate, %: 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	
40–49	48 / 708	53 / 702	0.89 (0.60–1.32)	94.5	94.3	0.781
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	
2–<5	108 / 1273	115 / 1283	0.96 (0.74–1.24)	92.5	93.0	0.203
≥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

APHINITY confirmed well known and manageable safety profile of pertuzumab|trastuzumab combination

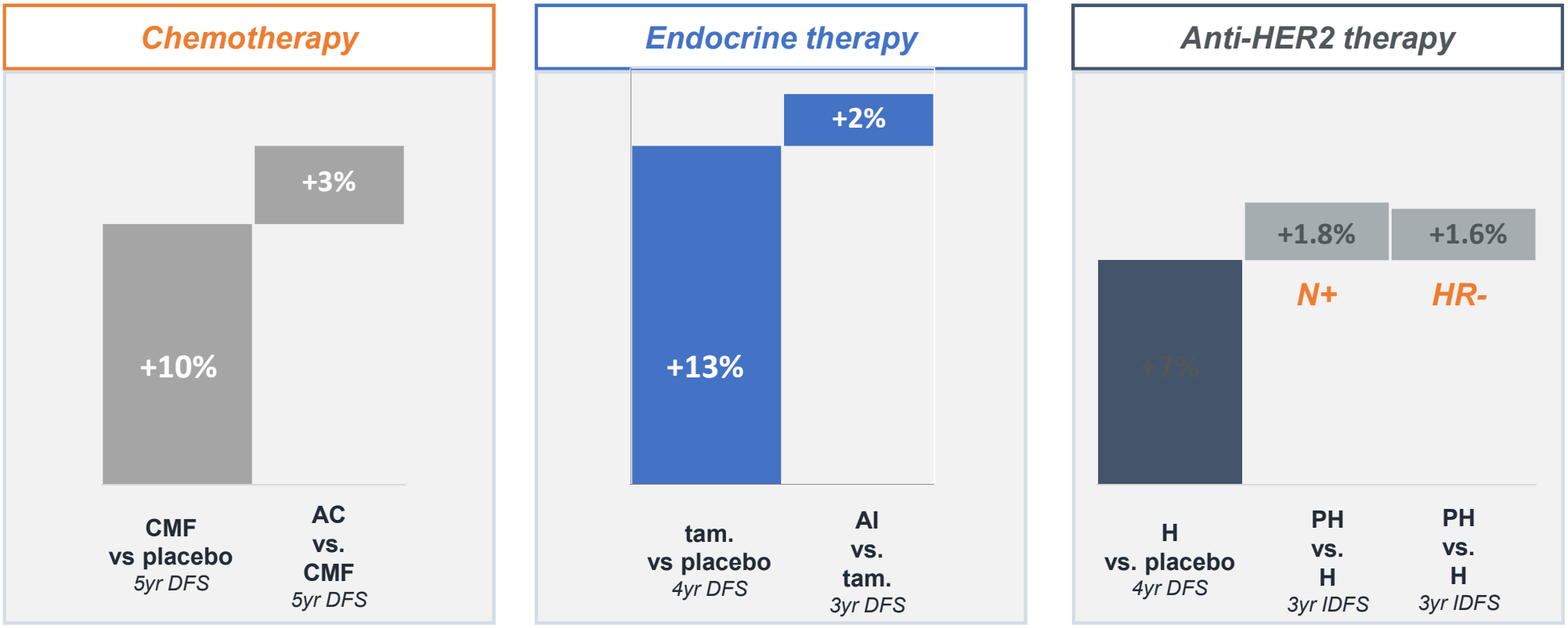
Common Grade ≥3 Adverse Events

Adverse Events	Pertuzumab, n (%) n=2364	Placebo, n (%) n=2405
Neutropenia	**385 (16.3)**	**377 (15.7)**
Febrile neutropenia	**287 (12.1)**	**266 (11.1)**
Anemia	**163 (6.9)**	**113 (4.7)**
Diarrhea	**232 (9.8)**	**90 (3.7)**
• with chemotherapy and targeted therapy	232 (9.8)	90 (3.7)
• with targeted therapy (post-chemotherapy)	12 (0.5)	4 (0.2)
• with AC→T (N=1834; 1894)	137 (7.5)	59 (3.1)
• with TCH (N=528; 510)	95 (18.0)	31 (6.1)

Less than 1% of patients in both treatment arms experienced heart failure, with the majority of patients recovering

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

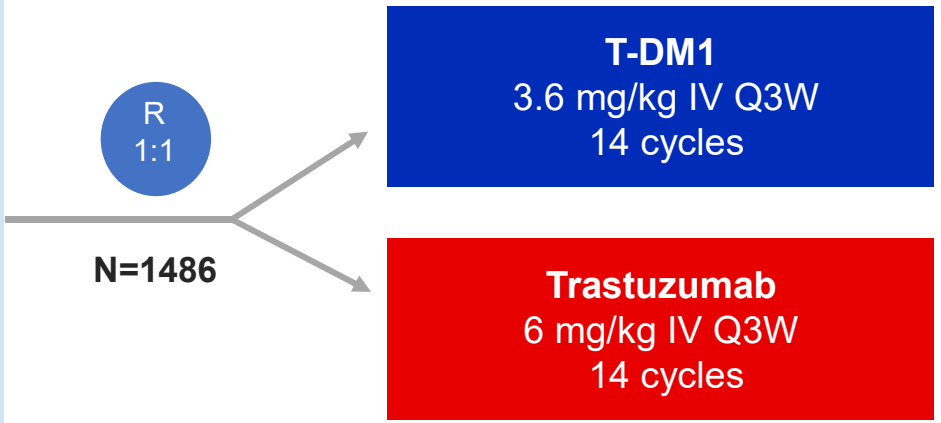
Historical Adjuvant Breast Cancer Trials



Addition of taxanes: Absolute 5-year DFS benefit of 2.9%

KATHERINE Study Design

- **cT1-4/N0-3/M0 at presentation** (cT1a-b/N0 excluded)
- **Centrally confirmed HER2-positive breast cancer**
- Neoadjuvant therapy must have consisted of
  - **Minimum of 6 cycles of chemotherapy**
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - **Minimum of 9 weeks of trastuzumab**
    - Second HER2-targeted agent allowed
- **Residual invasive tumor in breast or axillary nodes**
- Randomization within 12 weeks of surgery



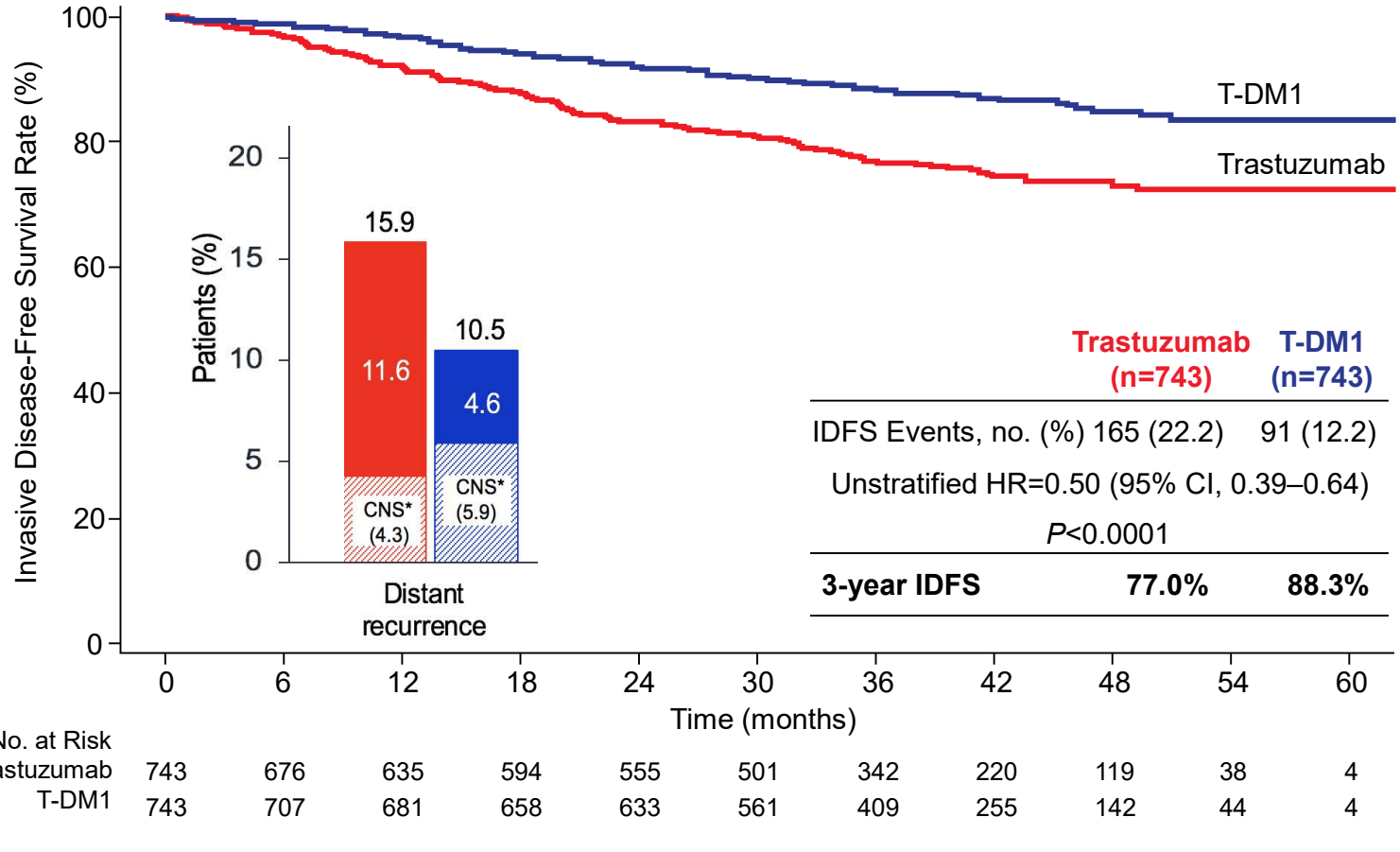
Radiation and endocrine therapy per protocol and local guidelines

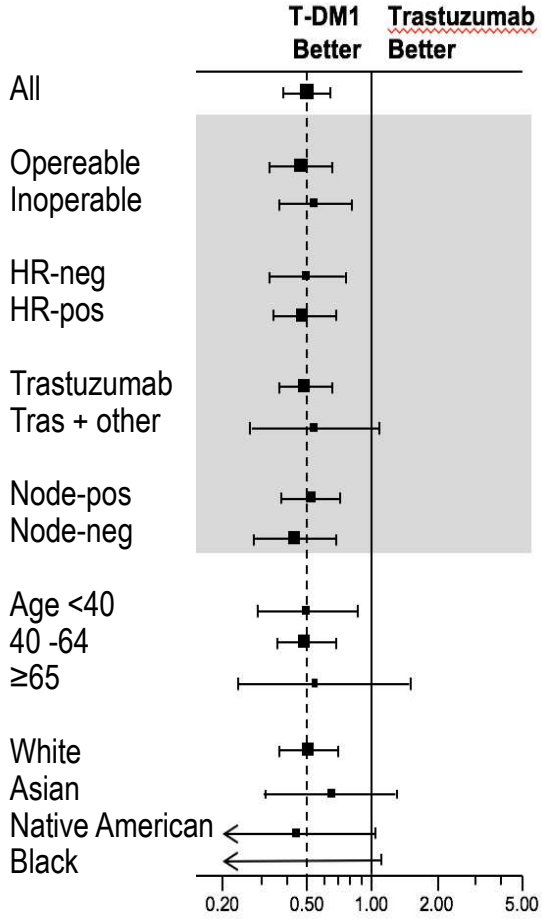
Stratification factors:

- Clinical presentation: **Inoperable (stage cT4 or cN2–3) vs operable** (stages cT1-3N0-1)
- **Hormone receptor**: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: **Trastuzumab vs trastuzumab plus other** HER2-targeted therapy
- **Pathological nodal status** after neoadjuvant therapy: Positive vs negative/not done

von Minckwitz G, *et* al., N Engl J Med. 2018 Dec 5. doi: 10.1056/NEJMoa1814017. [Epub ahead of print]

Invasive Disease-Free Survival





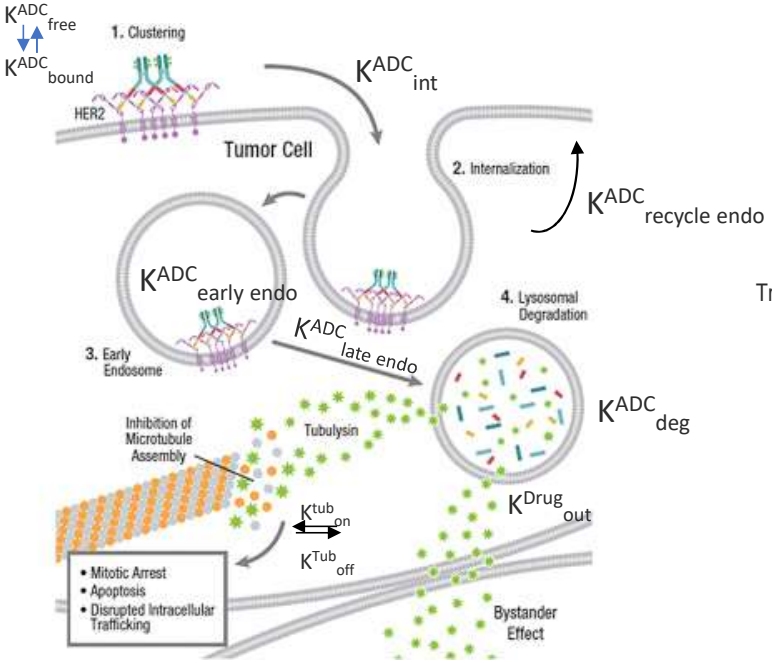
By comparison, 3 year DFS, B31/N9831 Joint Analysis: 87% vs. 75%

Echoes of "The results are simply stunning"? -- Gabriel N. Hortobagyi, N Engl J Med 2005; 353:1734-1736

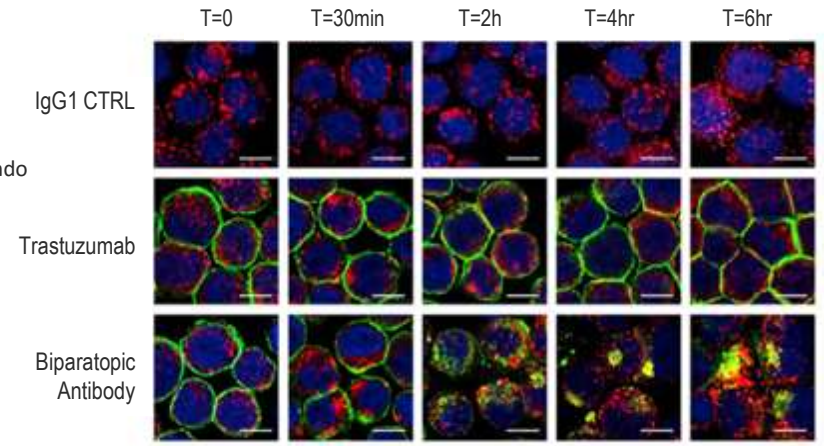
von Minckwitz G, *et* al., N Engl J Med. 2018 Dec 5. doi: 10.1056/NEJMoa1814017. [Epub ahead of print]

MEDI4276 INDUCES HER2 RECEPTOR CLUSTERING, WHICH PROMOTES ROBUST INTERNALIZATION, LYSOSOMAL TRAFFICKING, AND DEGRADATION

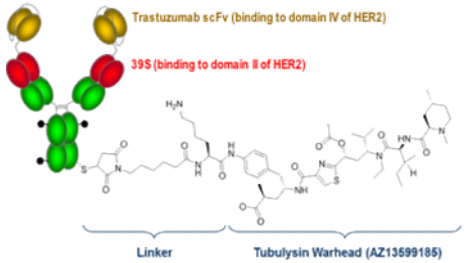
- **Proposed systems pharmacokinetic model for intracellular processing of ADCs[1]**



- **ErbB2 is an internalization-resistant receptor[2]**
- **HER2 biparatopic antibody promotes HER2 clustering and lysosomal degradation[3]**



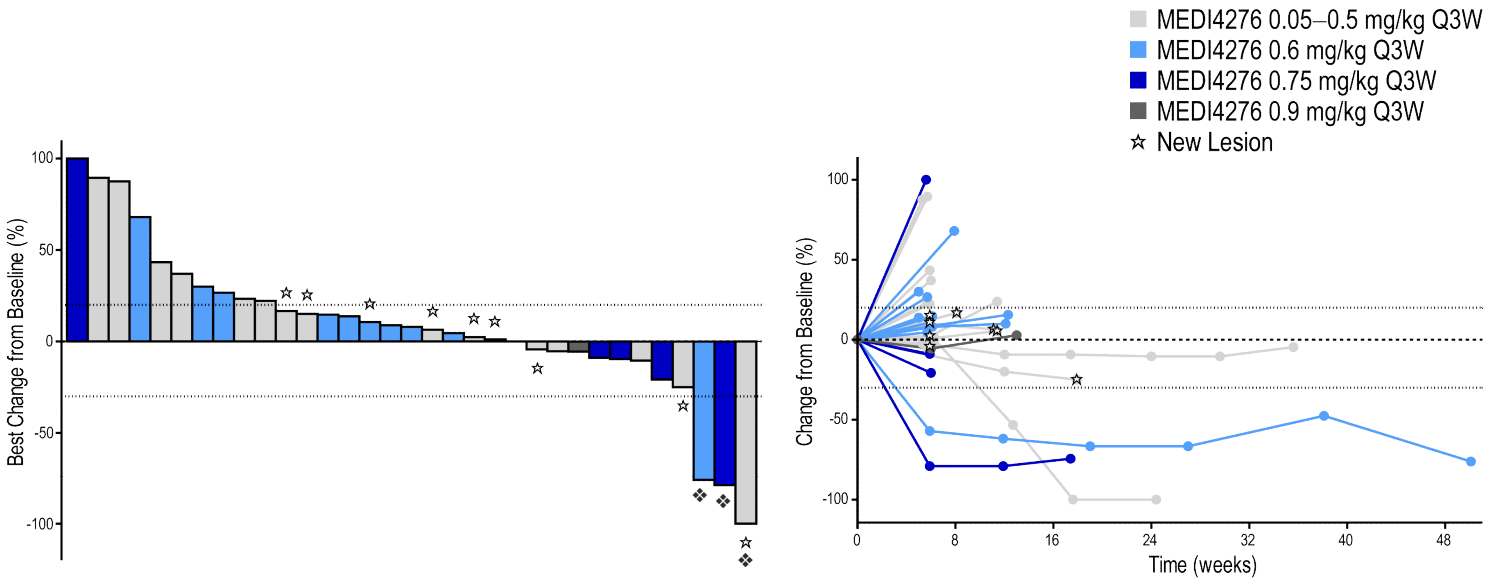
HER2+ BT474 BC cells



1. Singh, et al. *AAPS J*. 2016;18(4):861-875.
2. Hommelgaard, et al. *Mol Biol Cell.* 2004;15(4):1557-1567.
3. Li JY, et al. *Cancer Cell*. 2016;29(1):117-129.

Pegram, et al. ESMO, Targeted Anti-Cancer Therapy– Paris (2018)

CHANGE IN TUMOR SIZE FROM BASELINE: *AS TREATED POPULATION (RECIST V1.1)*

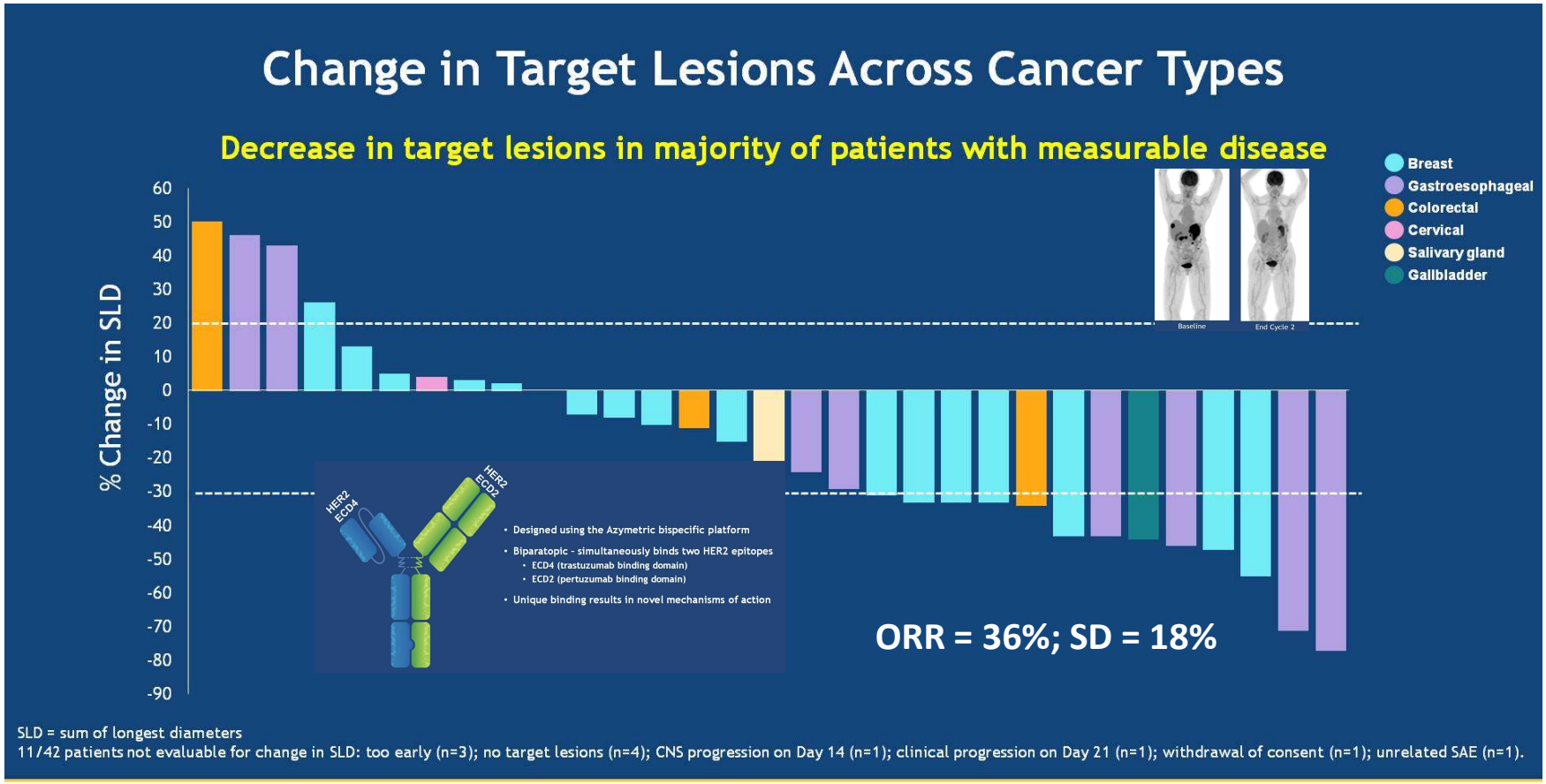


❖ **All 3 objective responders: MBC—prior trastuzumab, pertuzumab, and T-DM1**

At MTD (0.75mg/kg), 58.3% of patients experienced ≥ 1 serious and/or grade ≥ 3 severity event

Pegram, et al. ESMO, Targeted Anti-Cancer Therapy– Paris (2018)

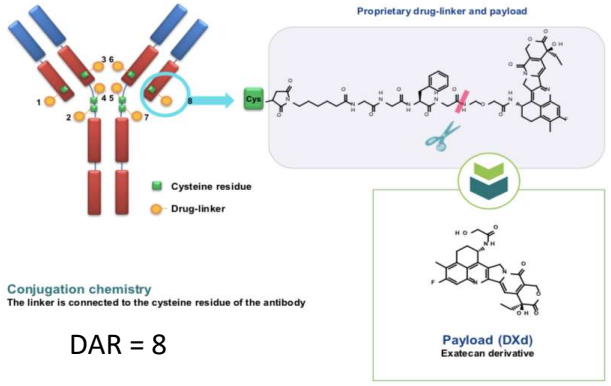
Single Agent ZW25, a HER2 Bispecific, in Heavily Pretreated HER2+ Cancers



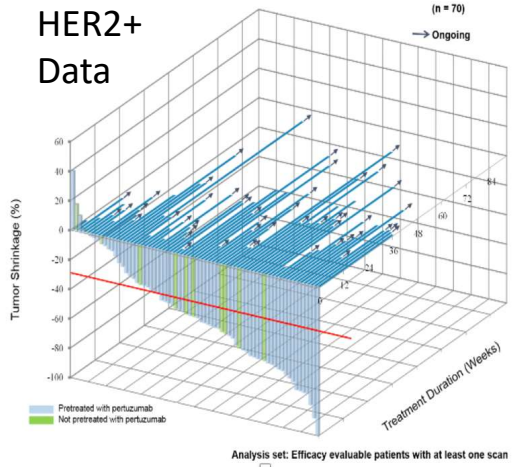
ZW49 is generated from the conjugation of a novel N-acyl sulfonamide auristatin payload to the inter-chain disulfide bond cysteines of the bispecific anti-HER2 IgG1 antibody ZW25, via a protease cleavable linker.

Trastuzumab deruxtecan (DS-8201a)

Poster # P6-17-02 – San Antonio Breast Cancer Symposium® – December 4–8, 2018.

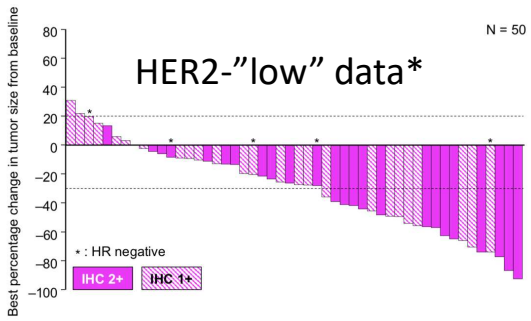


DAR = 8



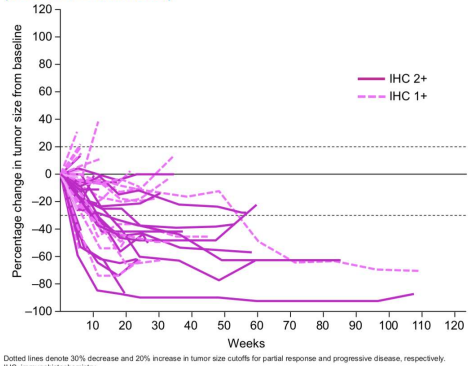
- **ILD risk significantly associated with dose, p < 0.001**
  (Cox proportional hazards)
- **ILD monitoring and management plan implemented**

FIGURE 4. Best Percentage Change in Tumor Size from Baseline by IHC Status (October 12, 2018 Data Cutoff)



Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for partial response and progressive disease, respectively.
HR, hormone receptor; IHC, immunohistochemistry.

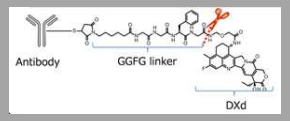
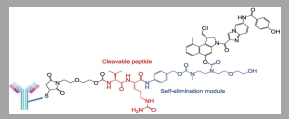
FIGURE 5. Percentage Change in Tumor Size from Baseline by IHC Status (October 12, 2018 Data Cutoff)



Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for partial response and progressive disease, respectively.
IHC, immunohistochemistry.

*Modi S, et al. A phase III, multicenter, randomized, open label trial of trastuzumab deruxtecan (DS-8201a) versus investigator's choice in HER2-low breast cancer: J Clin Oncol 37, 2019 (suppl; abstr TPS1102)

Antibody-drug conjugates (ADCs) in HER2-low MBC patients

	DS-8201a (Abstract #:2501) 	SYD985 (Abstract #:1014) 
Trial phase	Phase I	Phase I
Antibody	Trastuzumab	Trastuzumab
Payload	Deruxtecan (Topoisomerase I inhibitor)	Duocarmycin (alkylating agents)
Population	Heavily pretreated MBC	Heavily pretreated MBC
HER2 low definition	IHC 1+/2+/ISH-	IHC 1+/2+/ISH-
ORRs (95%CI)	10/26, 38.5% (20.2, 59.4)	HR+ (N=32): 27%
		HR- (N=17): 40%

Fc Receptors Modulate Antitumor Activity of Trastuzumab

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

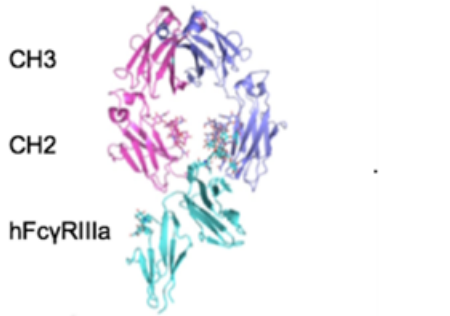
Humanization of an anti-p185^{HER2} antibody for human cancer therapy

(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

Communicated by Hilary Koprowski, January 16, 1992 (received for review February 15, 1991)

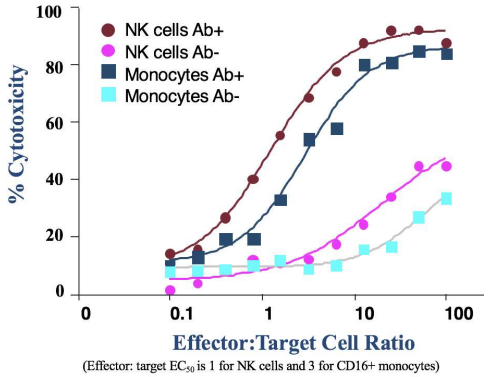


Top view of the structure of the glycosylated Fc-FcγRIIIa complex. Oligosaccharides are depicted as ball and stick representations.

Ferrara C et al. PNAS 2011;108:12669-12674 PNAS

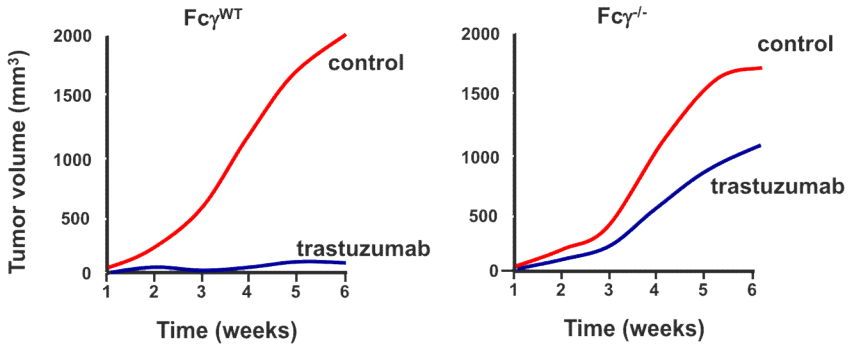
*ADCC = Antibody-Dependent Cell-mediated Cytotoxicity

The trastuzumab Fc-domain/FcgRIIIa Complex is a Potent Mediator of ADCC

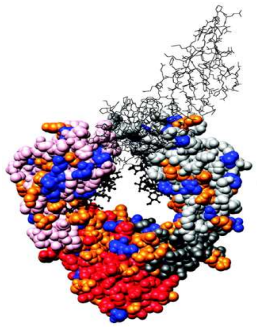


Pegram, et al., Proc Am Assoc Cancer Res 38: 602, 1997 (abstr 4044).

Breast Cancer Cell Growth Following Treatment with Trastuzumab in the Presence and Absence of Functional Fc Receptors



Adapted from Clynes et al. *Nature Med*. 2000;6:443-446

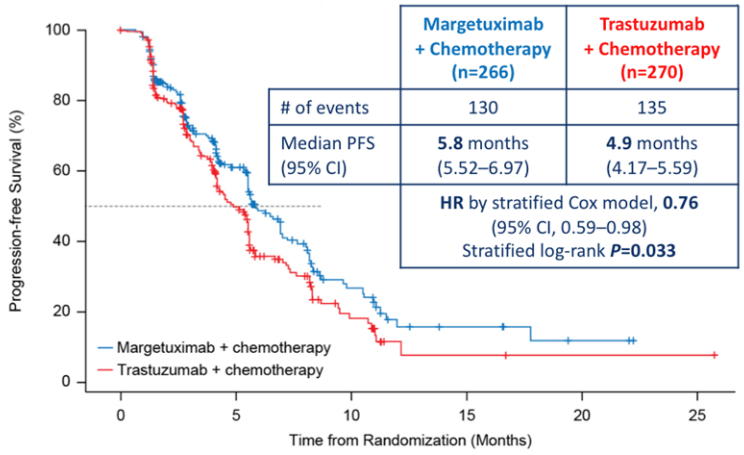


Locations of Fc mutations identified by yeast surface display identify the variant F243L/R292P/Y300L/V305I/P396L

SOPHIA: Margetuximab in Pre-Treated Patients with HER2+ mBC

PFS Analysis in the ITT Population (N=536)

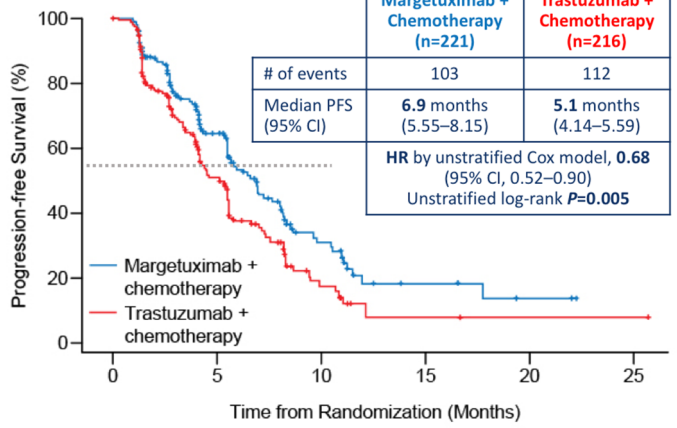
By Central Blinded Analysis (Primary Endpoint)



	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	130	135
Median PFS (95% CI)	**5.8** months (5.52–6.97)	**4.9** months (4.17–5.59)
HR by stratified Cox model, **0.76** (95% CI, 0.59–0.98) Stratified log-rank ***P*=0.033**		

Margetuximab	266	174	94	45	21	8	6	4	2	0	
Trastuzumab	270	158	74	33	13	2	2	1	1	1	1

FF or FV (n=437; 86%)



	Margetuximab + Chemotherapy (n=221)	Trastuzumab + Chemotherapy (n=216)
# of events	103	112
Median PFS (95% CI)	**6.9** months (5.55–8.15)	**5.1** months (4.14–5.59)
HR by unstratified Cox model, **0.68** (95% CI, 0.52–0.90) Unstratified log-rank ***P*=0.005**		

Margetuximab	221	157	84	42	21	8	6	4	2	0	
Trastuzumab	216	129	62	30	11	2	2	1	1	1	1

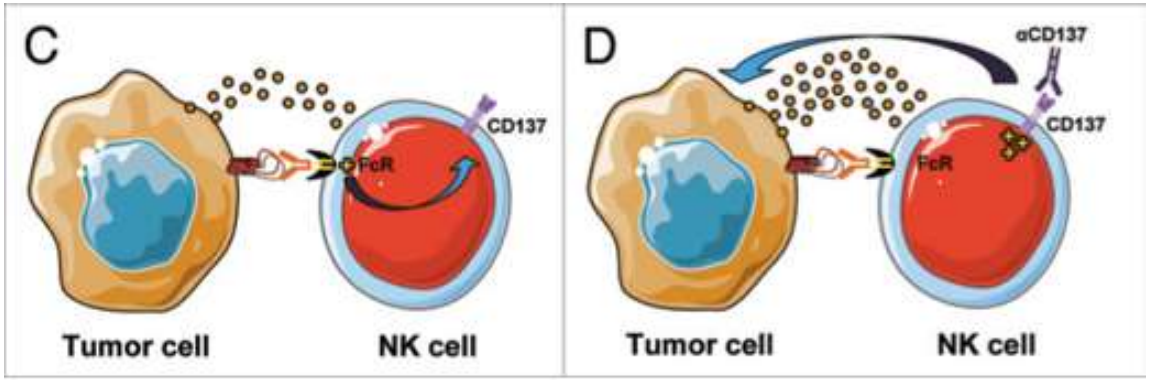
24% Risk Reduction in Hazard of Disease Progression

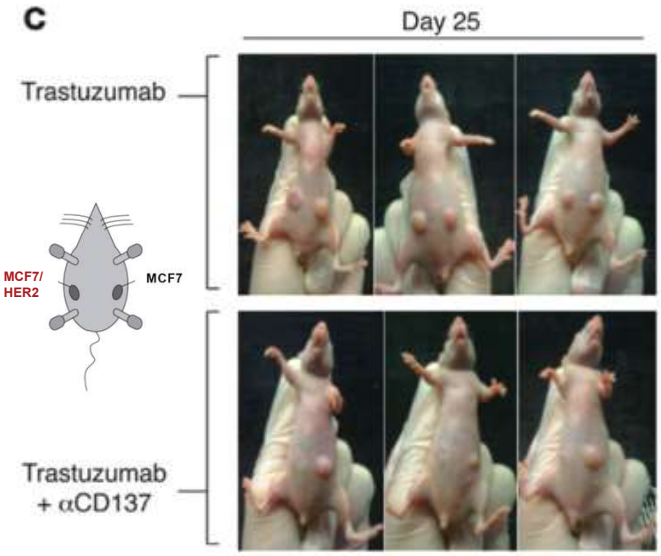
Planned Exploratory PFS Analysis by CD16A Genotype

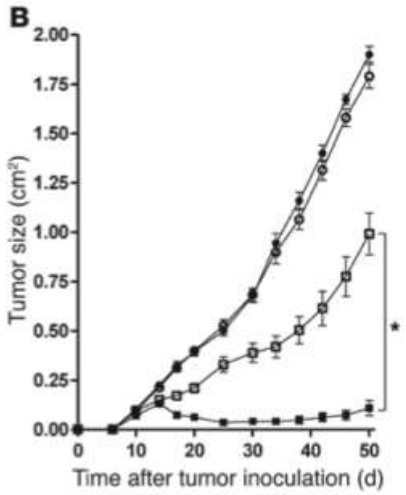
Increased Infusion Reactions on Margetuximab (14.4% vs. 3.8%), Otherwise Similar Safety; No difference in LV dysfunction (3.4 vs. 3.0%).

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

Anti-CD137 agonistic MAb enhances anti-breast cancer activity of trastuzumab in vivo







4-1BB Agonist Monoclonal Antibody Utomilumab (PF-05082566) With Trastuzumab Emtansine or Trastuzumab in Treating Patients With Advanced HER2+ Breast Cancer*

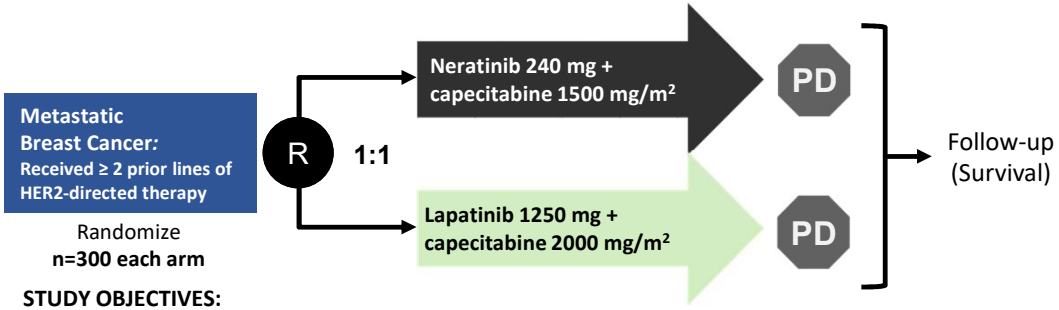
Kohrt, et al., J Clin Invest 122(5): 1066-75 (2012)
*NCT03364348

Capecitabine + Neratinib or Lapatinib as 3L+ in Patients With HER2+ mBC

NALA (ASCO 2019)

Global Phase III Registration Study Design

- **≥ 3rd-line therapy for patients with HER2+ metastatic breast cancer**
- **Prior T-DM1, pertuzumab acceptable; prior lapatinib, capecitabine not permitted**
- **Patients with asymptomatic CNS metastatic disease are eligible to enroll***
- ***TBCRC 022 – 49% CNS ORR (N+C), N=37; 29% G3 diarrhea[1]**

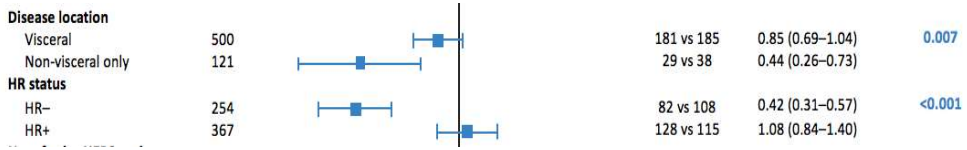


Randomize
n=300 each arm

STUDY OBJECTIVES:

Co-primary endpoints: PFS (central) and OS

Secondary endpoints: PFS (local), ORR, DoR, CBR, time to intervention for CNS metastases, safety, health outcomes



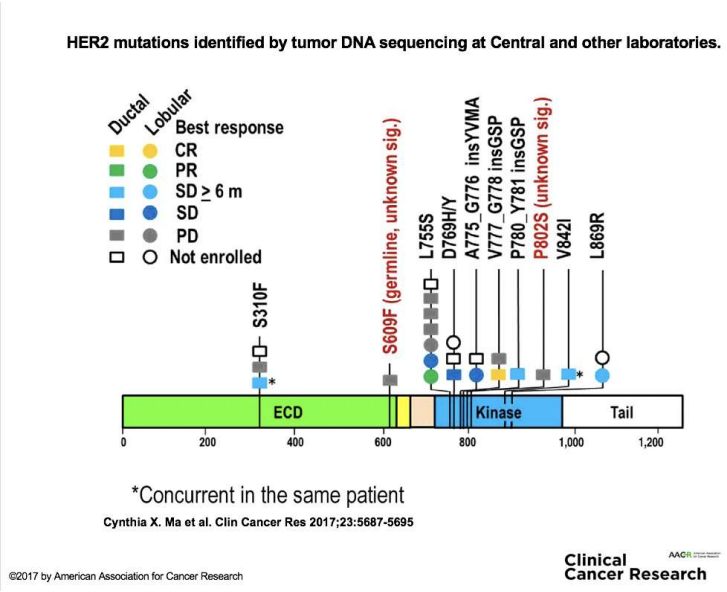
- **Time to intervention for symptomatic CNS disease longer in the N+C arm**
- **PFS HR = 0.76; 95% CI 0.63–0.93; p = 0.006 (12m PFS 28.8% vs 14.8% for N+C vs L+C, respectively)**
- **OS HR = NOT significant (0.88; 95% CI 0.72–1.07; p = 0.2086)**
- **ORR in patients with measurable disease 32.8% vs 26.7% (N+C vs L+C); p = 0.1201**
- **"Tolerability was similar between the two arms" - ??**
- **Grade 3 diarrhea increased with N+C (24.4% vs 12.5%)**

1. Freedman RA, et al. JCO (2019) 37:13, 1081-89
2. CBR is defined as Complete Response (CR) or Partial Response (PR) or Stable Disease (SD) for ≥ 24 weeks
3. Loperamide prophylaxis required in neratinib arm

CBR=clinical benefit rate; CNS=central nervous system; mBC=metastatic breast cancer; PD=progressive disease.

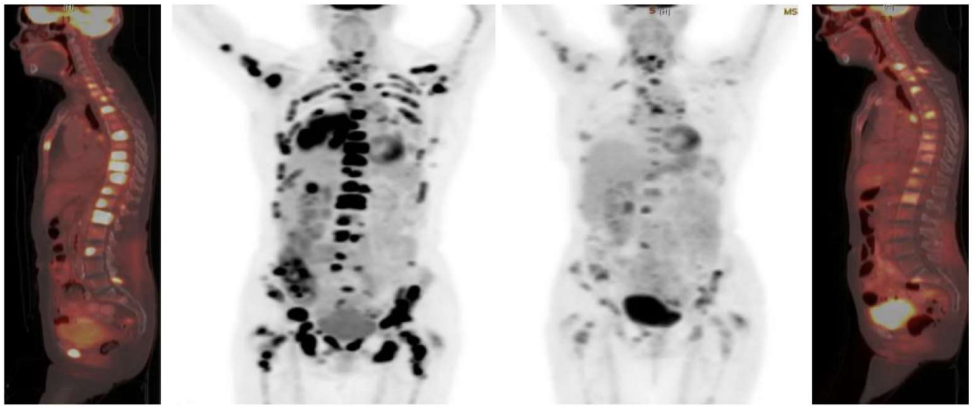
ClinicalTrials.gov Identifier: NCT01808573

Neratinib Efficacy in HER2-*mutant* Nonamplified Metastatic Breast Cancer

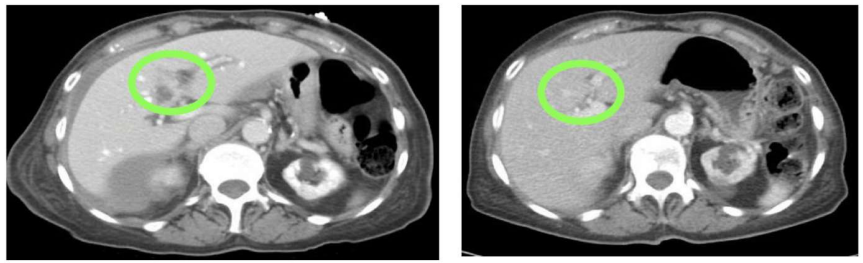


***HER2*-mutant (P780_Y781insGSP) ER+/HER2– ductal carcinoma**

Neratinib + fulvestrant treatment



Baseline



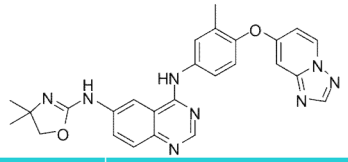
8 Weeks

PR by RECIST v1.1

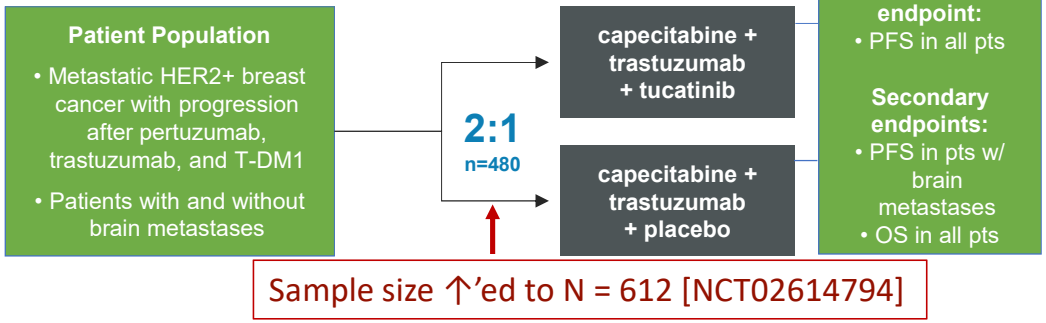
HER2 mutation frequency: 5/309 (1.6%), 4/51 (7.8%) in invasive lobular (P=0.026). At progression, emergence of several other HER2 mutations, including T798I (analogous to EGFR T790M "gatekeeper" resistance mutation). **CBR = 31%.**

Courtesy https://www.primeoncology.org/app/uploads/prime_activities/35857/1250_Baselga_St-Gallen-2017_FINAL-WEB.pdf

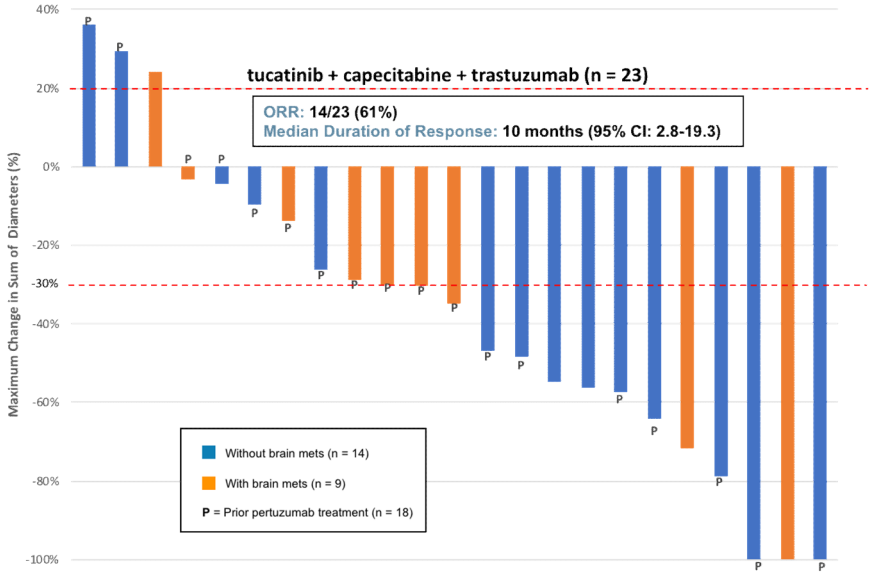
HER2CLIMB Pivotal Trial Design



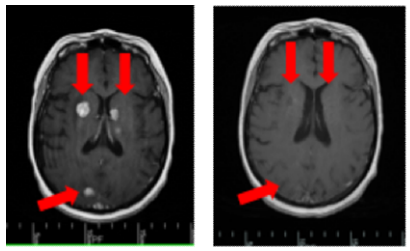
Compound	Cellular Selectivity Data	
	HER2 IC_{50} (nM)	EGFR IC_{50} (nM)
tucatinib	8	>10,000
neratinib	7	8
lapatinib	49	31



Sample size ↑'ed to N = 612 [NCT02614794]



Note: Bars represent change in measurable lesions but some patients also have nonmeasurable lesions. In addition, 4 patients in the Triplet cohort had nonmeasurable lesions only and are therefore not able to be represented on the waterfall.



(Images selected to demonstrate longest axis of lesions)

- Most (~70%) treatment-emergent adverse events were Grade 1
- No instance of CHF
- 3 patients (11%) had transient Grade 3 LFT elevations – continued therapy after dose reduction
- 3 patients (11%) had Grade 3 diarrhea seen only in capecitabine-containing cohorts -- consistent with single agent capecitabine treatment
- No deaths 2º to treatment-emergent adverse events
- 1 DLT (cerebral edema) in triplet cohort

Murthy R, et al. Lancet Oncology, VOLUME 19, ISSUE 7, P880-888, JULY 01, 2018

Chromoanasynthesis is a common mechanism leading to amplification at the ERBB2 locus (17q.12)

10 year follow-up of all the adjuvant trastuzumab trials underscores a high unmet need in HER2+ early breast cancer

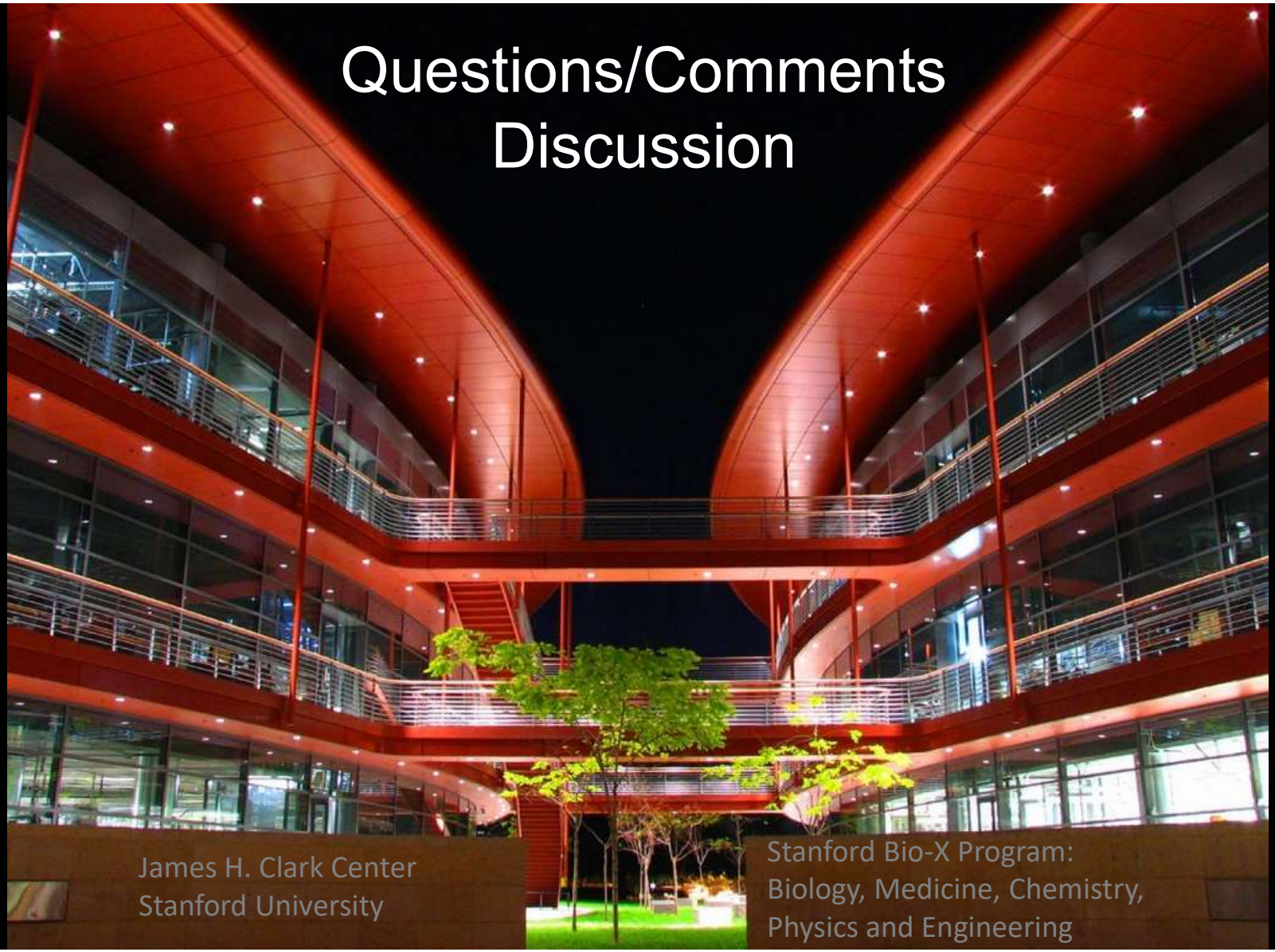
Allosteric activation of HER2|HER3 complexes is an important mitogenic stimulus – disrupted by pertuzumab

HER2/HER2 bispecific/bi-paratopic ADCs with higher internalization rates -- MEDI4276; ZW49 – tox challenges?

HER2 MAb-based combinations with agonist CD137 MAb (to enhance ADCC)
-- Utomilumab (PF-05082566) – Phase IB/II

Tucatinib, a "pure" HER2 TKI, is active in heavily pretreated HER2+ MBC (including CNS mets), and is less toxic than "dirty" HER2 TKIs

Questions/Comments
Discussion



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