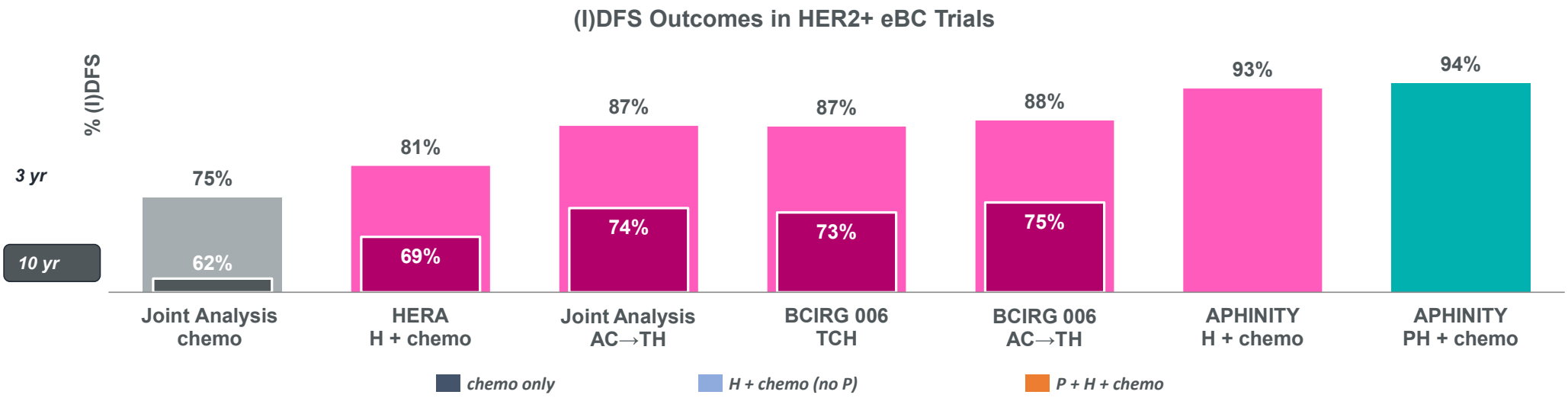
APHINITY: Key Messages



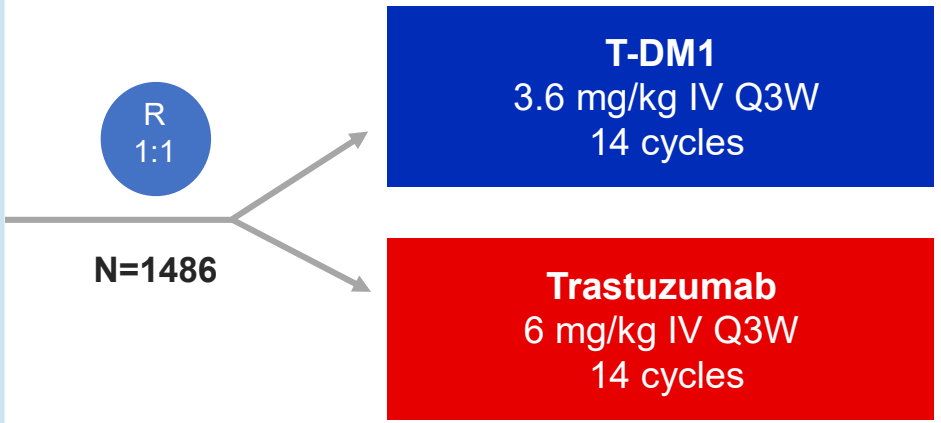
Follow-up of APHINITY is still early…

Pegram editorial comment:

“The main scientific contribution [of APHINITY] is the association between delta in pCR in NEOSPHERE translating into significant differences in long-term time-to-event analysis in the adjuvant setting”.

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



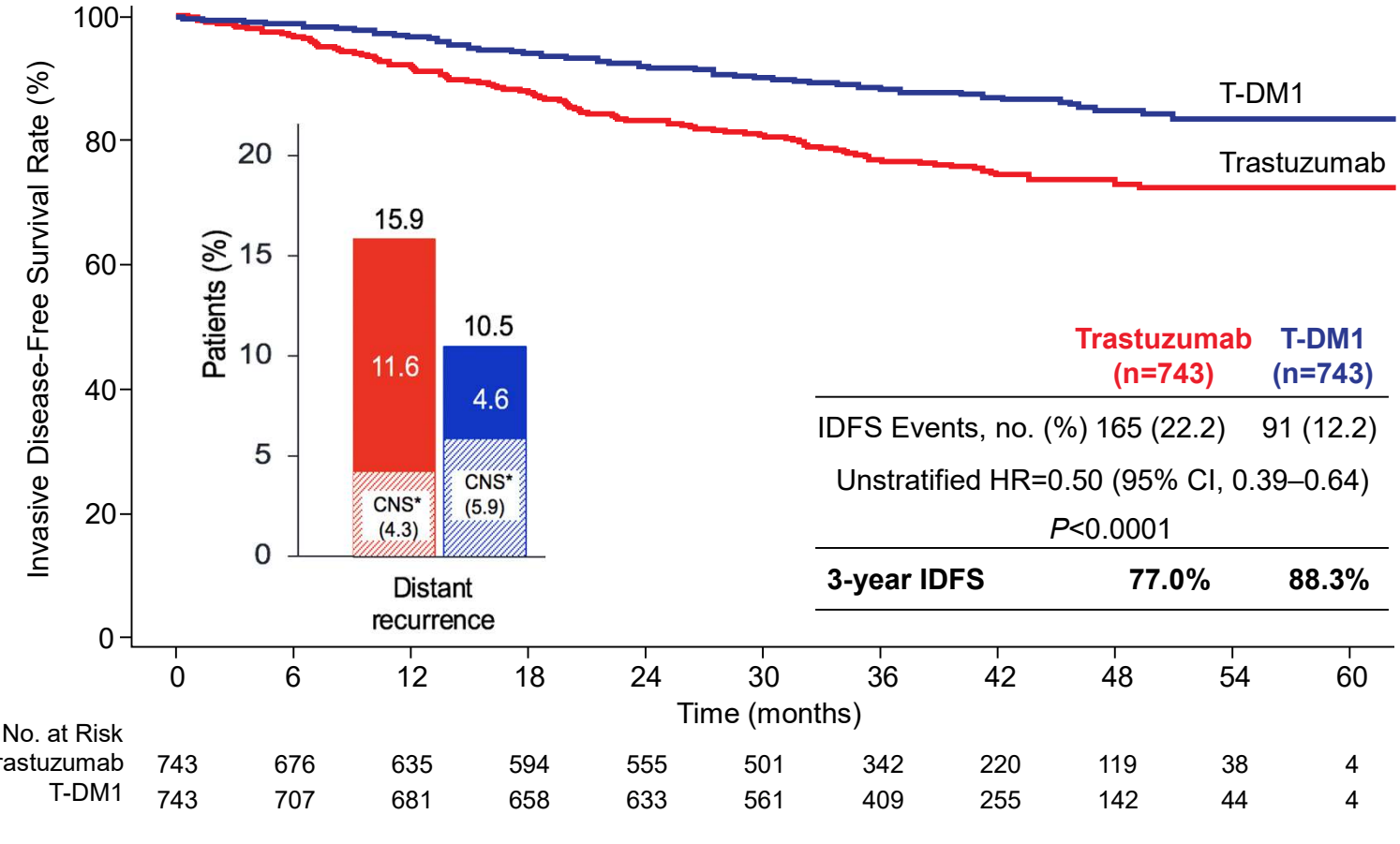
Radiation and endocrine therapy per protocol and local guidelines

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

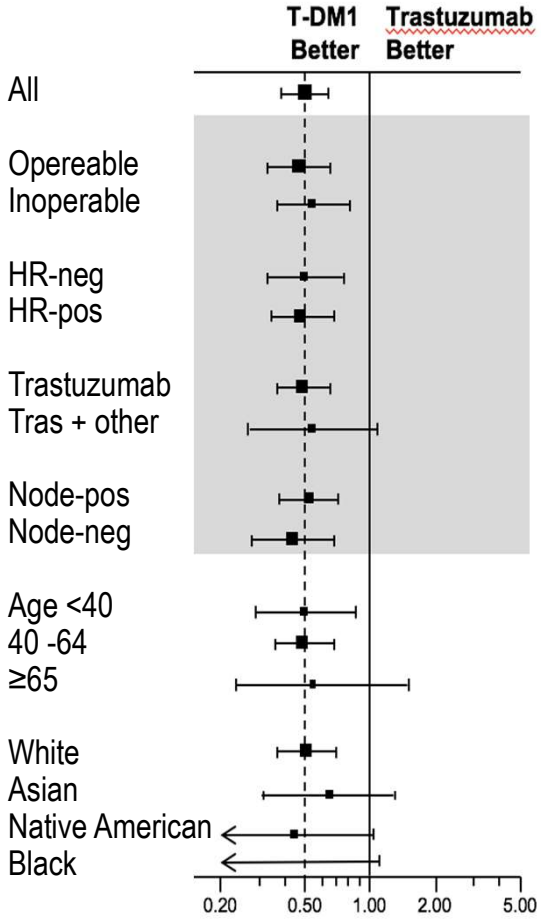
von Minckwitz G, *et* al., N Engl J Med. 2018 Dec 5. doi: 10.1056/NEJMoa1814017. [Epub ahead of print]

Invasive Disease-Free Survival



	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

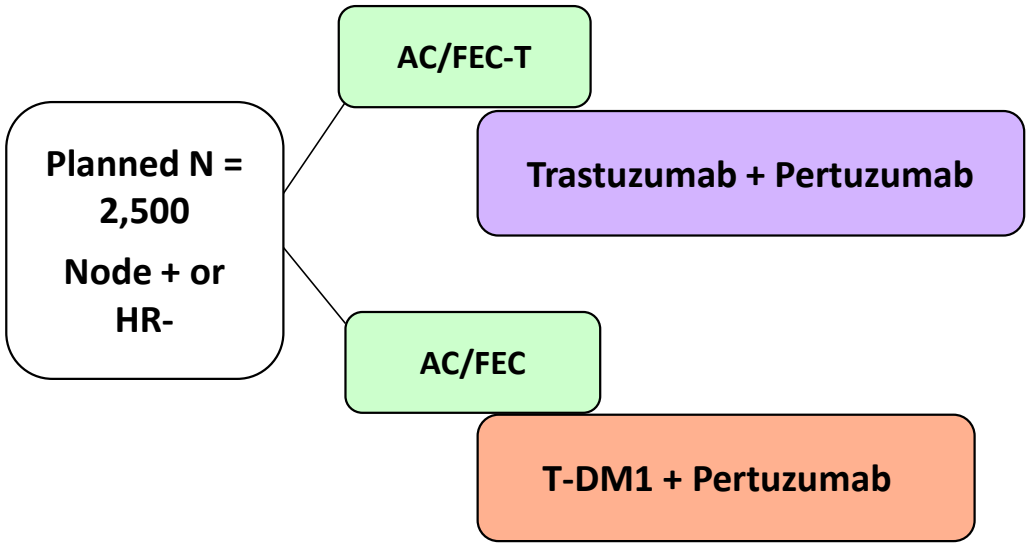


By comparison, 3 year DFS, B31/N9831 Joint Analysis: 87% vs. 75%

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]

Adjuvant T-DM1 + Pertuzumab (KAITLIN) Protocol



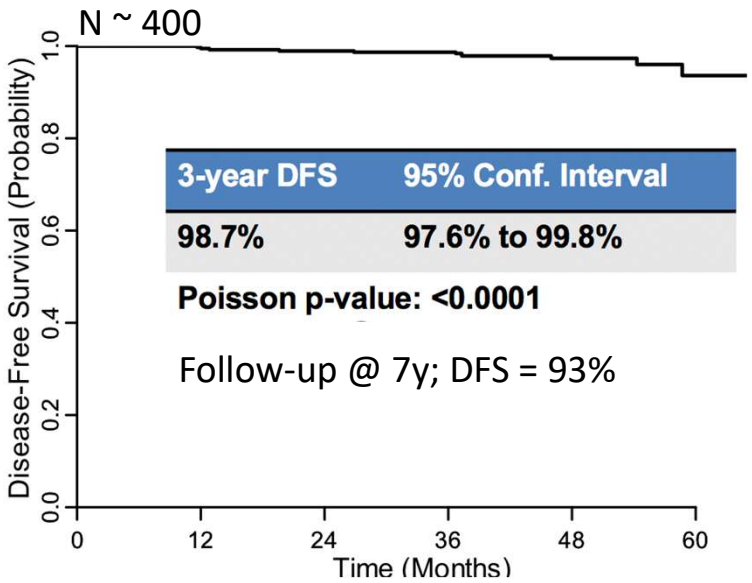
Actual N = 1,846
https://clinicaltrials.gov/ct2/show/record/NCT01966471

Primary Endpoint: DFS
Second Endpoints: OS, Safety

AC: adriamycin/cyclophosphamide; FEC: 5FU/epirubicin/cyclophosphamide; T: docetaxel Q3W or paclitaxel QW; MDD: Minimal Detectable Difference

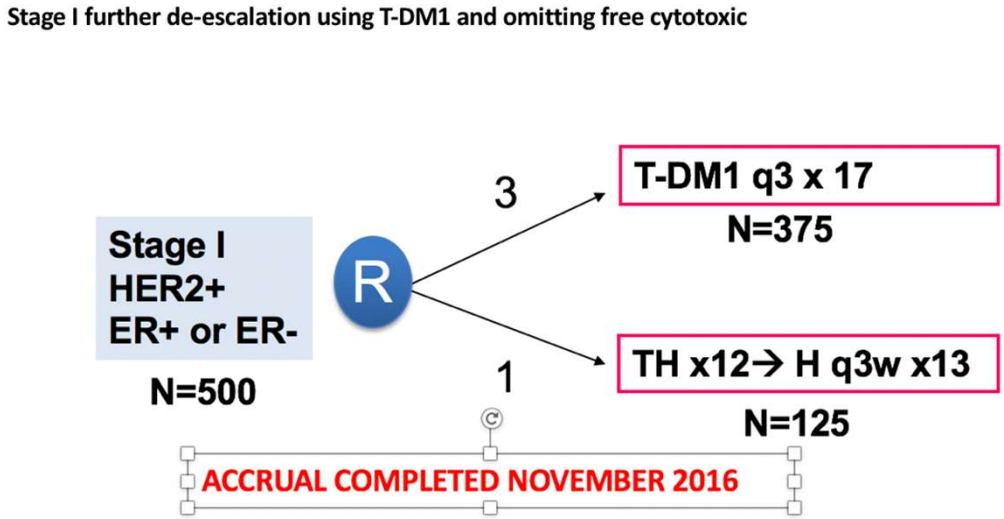
Minimalist (or no) Chemotherapy:

APT Trial (TH)



Follow-up @ 7y; DFS = 93%

ATEMPT Trial



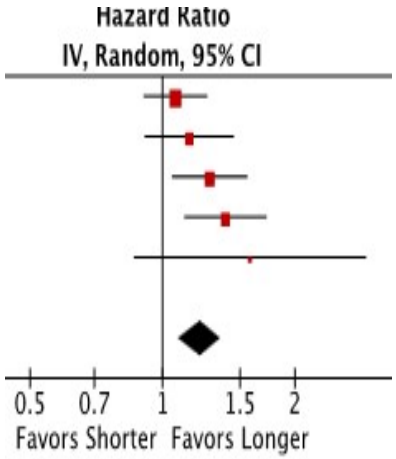
Tolaney S et al, NEJM 2015; ASCO 2017

Shorter Duration Trastuzumab: Meta-Analysis

Trial	N	Trastuzumab duration	Noninferiority DFS HR	Observed DFS HR
Persephone*	4089	6m vs 12m	< 1.29	1.05 (0.88-1.25)
Short-HER**	1253	9w vs 12m	<1.29	1.13 (0.89-1.42)
PHARE**	3384	6m vs 12m	< 1.15	1.28 (1.05-1.56)
SOLD	2176	9w vs 12m	<1.3	1.39 (1.12-1.72)
HORG**	481	6m vs 12m	< 1.53	1.57 (0.86-2.10)
Total				1.21 (1.09-1.36)
			Node-	*1.20 (0.96-1.51)*
			Node+	*1.37 (1.17-1.60)*
			ER+	*1.15 (0.98-1.34)*
			ER-	*1.33 (1.15-1.54)*

*Superiority of 12 months in pre-specified subgroups in Persephone: taxane-based chemo ($p < 0.01$), concurrent vs. sequential chemo ($p < 0.001$), and neoadj vs. adj ($p < 0.07$).

**Failed to meet non-inferiority endpoint

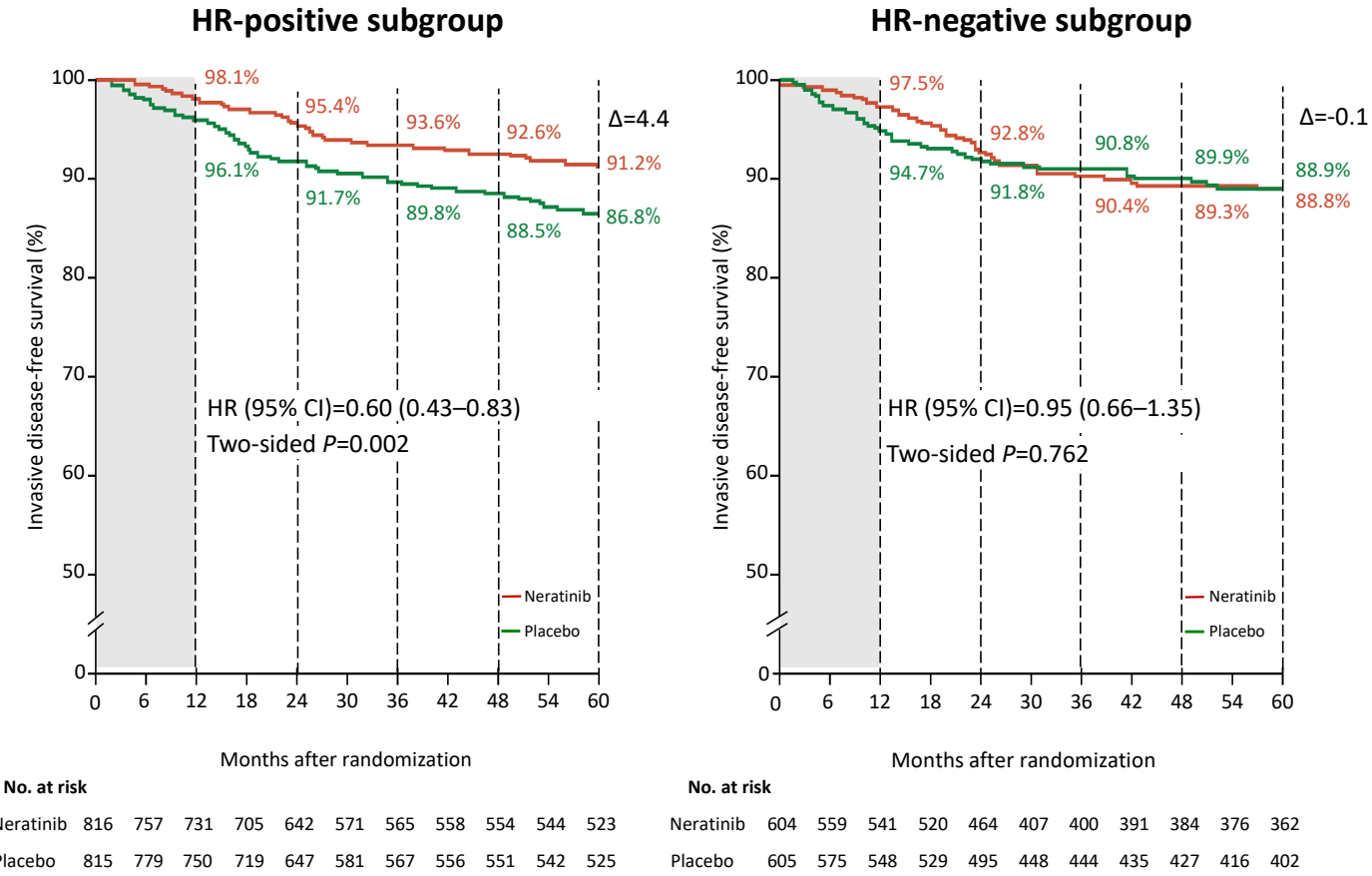


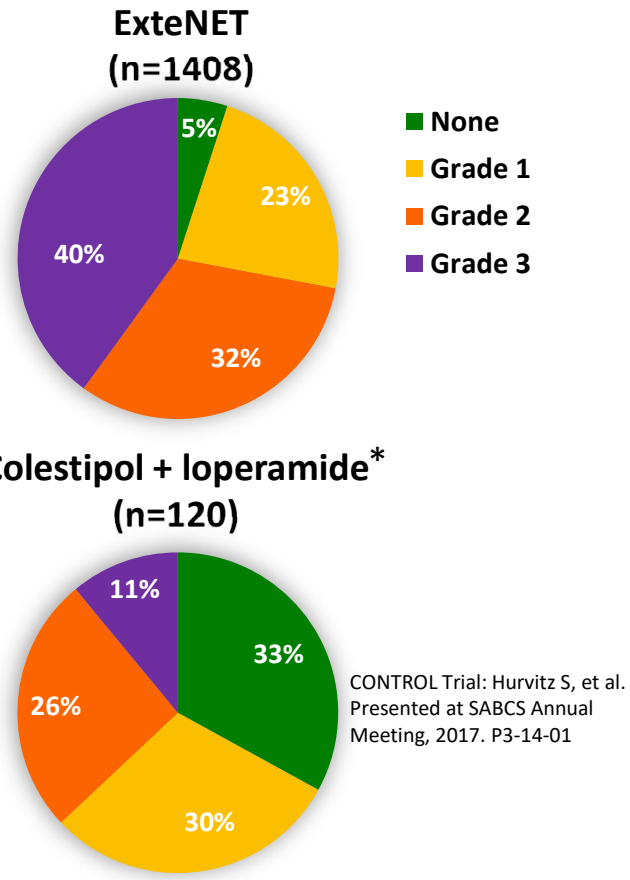
Cardiac events
longer duration
OR = 2.48 (1.94-3.17)

"If you are going to treat older ER+ patients with small lymph node negative tumors with inferior chemotherapy, and give it sequentially, then 6 months might be OK. Everyone else should receive one year". – M Pegram

Earl et al, ASCO 2018; Conte et al, Ann Oncol 2018; Pivot et al, Lancet Oncol 2013; Joensuu et al, JAMA Oncol 2018; Mavroudis et al, Ann Oncol 2015; Niraula & Gyawali, BCRT 2018

ExteNET: 5 Year iDFS by hormone receptor status (exploratory analysis) -- Martin M. et al., Lancet 2017



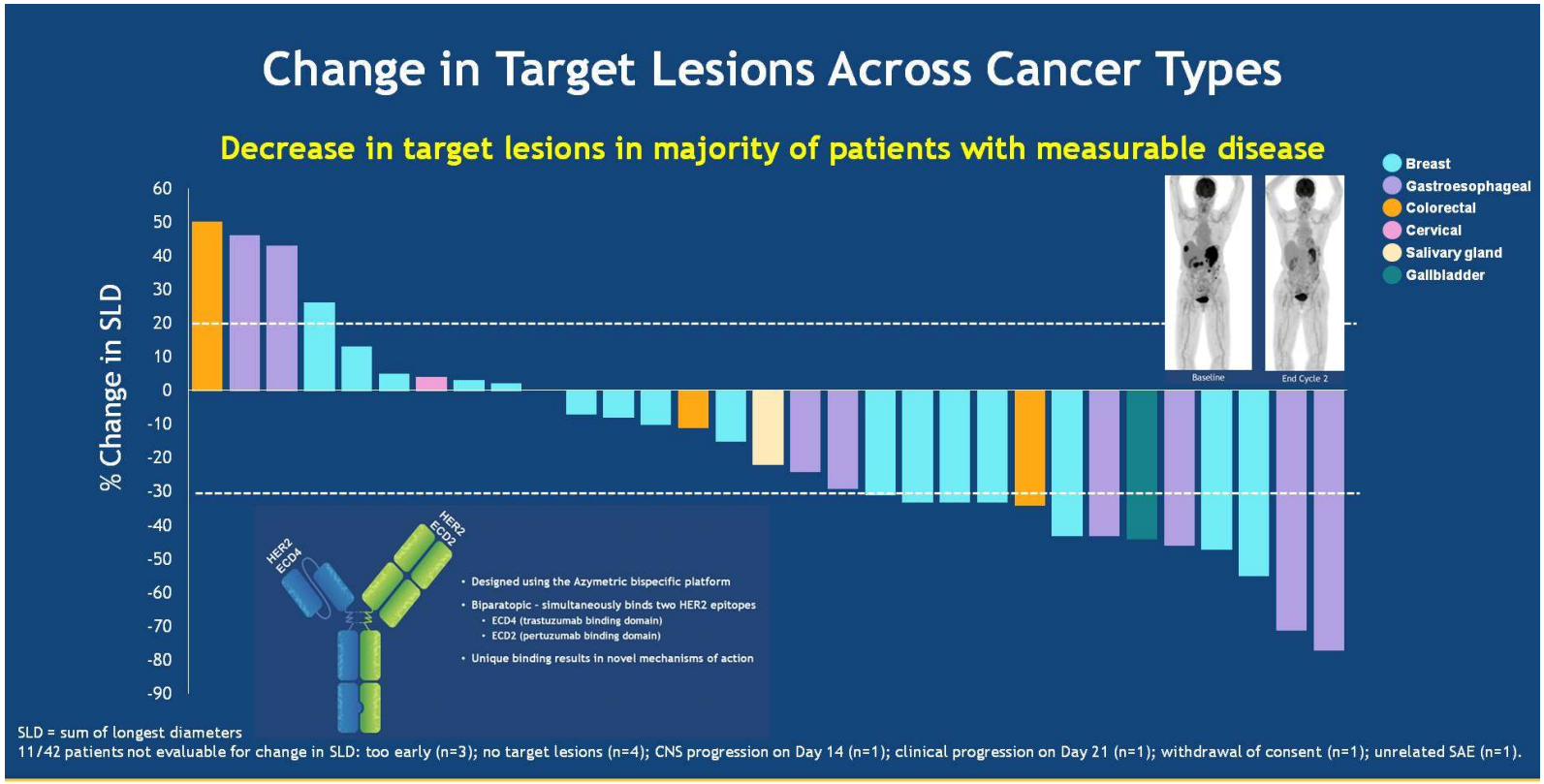


CONTROL Trial: Hurvitz S, et al. Presented at SABCS Annual Meeting, 2017. P3-14-01

Intention-to-treat population. Cut-off date: March 1, 2017

*Loperamide Prophylaxis Recommended: 12 mg on days 1-14 and 8 mg on days 15-56 (modified dosing). Loperamide Toxicities – arrythmia/sudden death, adynamic ileus, constipation, nausea, dizzyness, Stevens-Johnson syndrome, toxic epidermal necrolysis, urinary retention, sedation

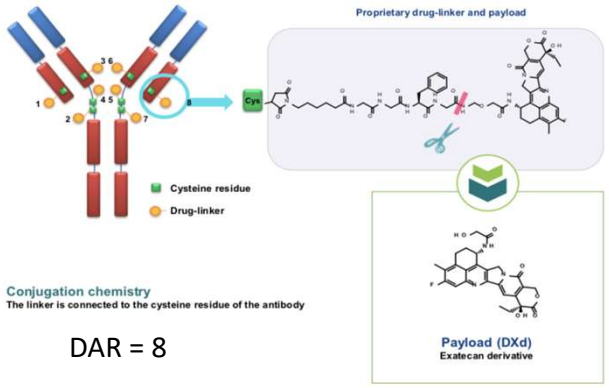
Single Agent ZW25, a HER2 Bispecific, in Heavily Pretreated HER2+ Cancers



Presented By Funda Meric-Bernstam at 2018 ASCO Annual Meeting

Trastuzumab deruxtecan (DS-8201a):

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



DAR = 8

HER2+ Data

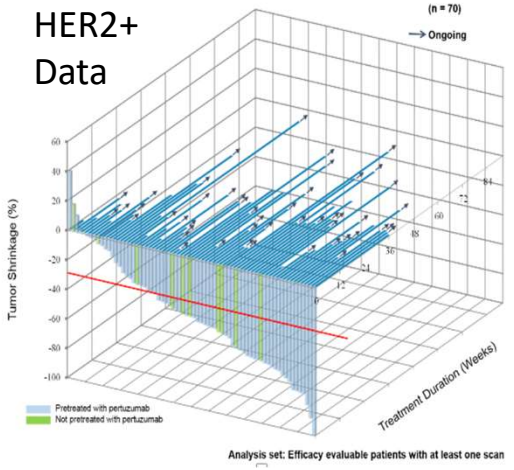
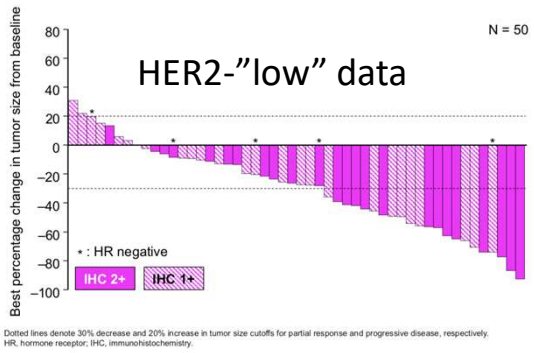
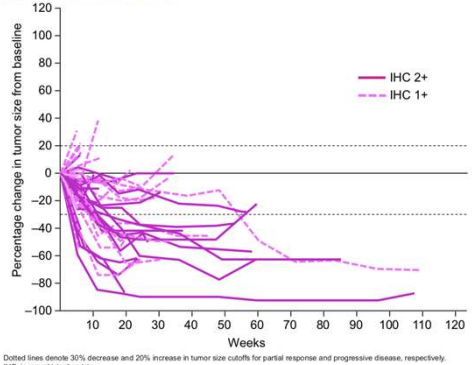


FIGURE 4. Best Percentage Change in Tumor Size from Baseline by IHC Status (October 12, 2018 Data Cutoff)



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)

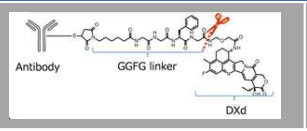
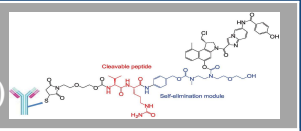


Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for partial response and progressive disease, respectively.
IHC, immunohistochemistry.

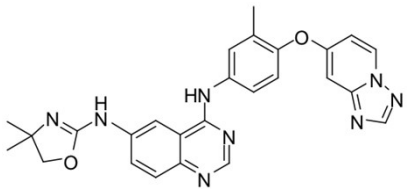
- **ILD risk significantly associated with dose, p < 0.001**
  (Cox proportional hazards)
- **ILD monitoring and management plan implemented**

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

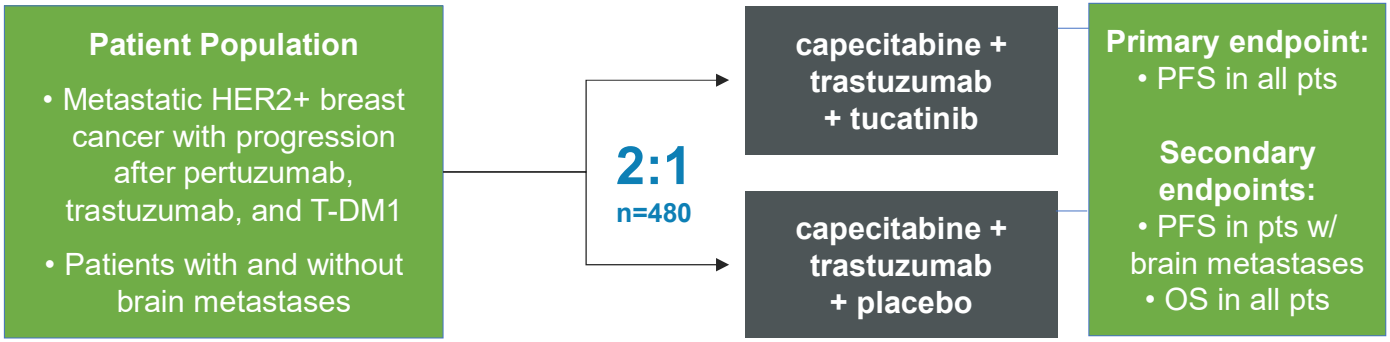
Antibody-drug conjugates (ADCs) in HER2-low MBC patients

	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%

Current 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

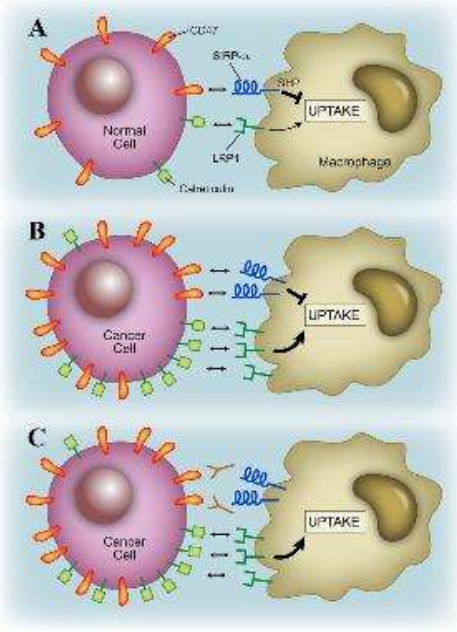


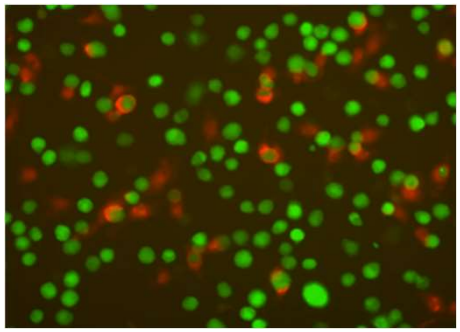
- Stratified for brain metastases, ECOG status and region of world
- Hierarchical testing of endpoints; each endpoint must be positive to enable testing of subsequent endpoint (PFS → PFS in subset of patients with brain metastases → OS)
- Goal of ≥50% improvement in PFS
  - Control arm PFS estimate = 4.5 months (historical PFS:TH3RESA control=3.3 months)
- Multi-center, multi-national

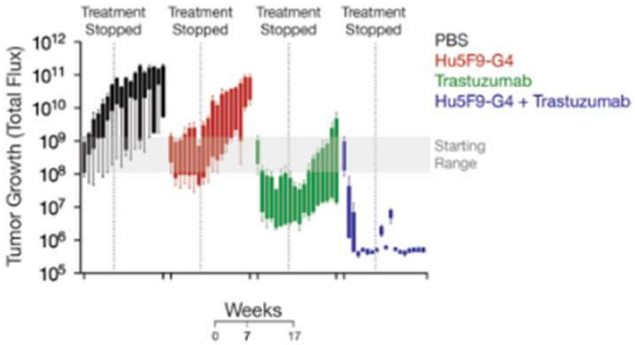
Macrophages ignore CD47+ cells as a result of negative interactions in which the CD47–SIRP-α pair promote a “don’t eat me” signal

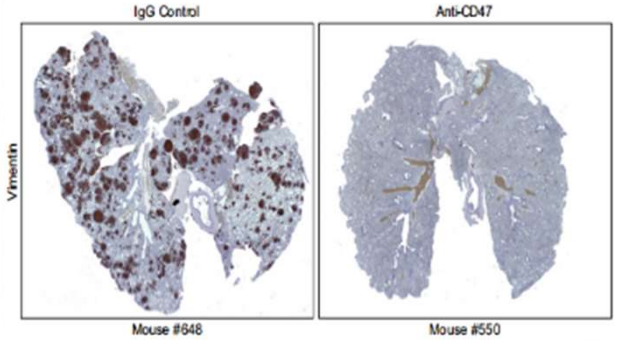
Hu5F9-G4 binds human CD47 with high affinity:

- **8-10 nM for monomeric CD47,**
- **8 pM for bivalent CD47**









Unanue E R PNAS 2013;110:10886-10887

Edris, B. et al.. PNAS 109, 6656–6661 (2012). PNAS

Irv Weissman and Ravi Majeti, personal communication (2017)


➢ Fc-engineered anti-HER2 MAb with enhanced immune effector function (ADCC)
- Margetuximab – Positive Phase III (margetux vs. tras with salvage chemo)
➢ HER2 MAb-based combinations with agonist CD137 MAb (to enhance ADCC)
- Utomilumab (PF-05082566) – Phase IB/II
➢ New HER2 ADCs with with unique linker/payloads – active even in HER2 "low"
- Phase II/III
➢ Small molecule, orally bioavailable HER2 TKIs
- Tucatinib (ONT-380) – Pivotal trial (cape/tras +/- tucatinib/placebo)
- Extended adjuvant neratinib
➢ HER2 MAb combination with anti-CD47 MAb to enhance macrophage function
- Hu5F9-G4 – Phase II
➢ Anti-HER2 strategies combined with CDK 4/6 inhibition – Phase IB/II
➢ HER2 bispecific MAbs – Phase II
James H. Clark Center
Stanford University
Stanford Bio-X Program:
Biology, Medicine, Chemistry,
Physics and Engineering