STANFORD
CANCER INSTITUTE

MODULE 4: Long-Term Management of HER2+ Metastatic Breast Cancer

05 June 2017

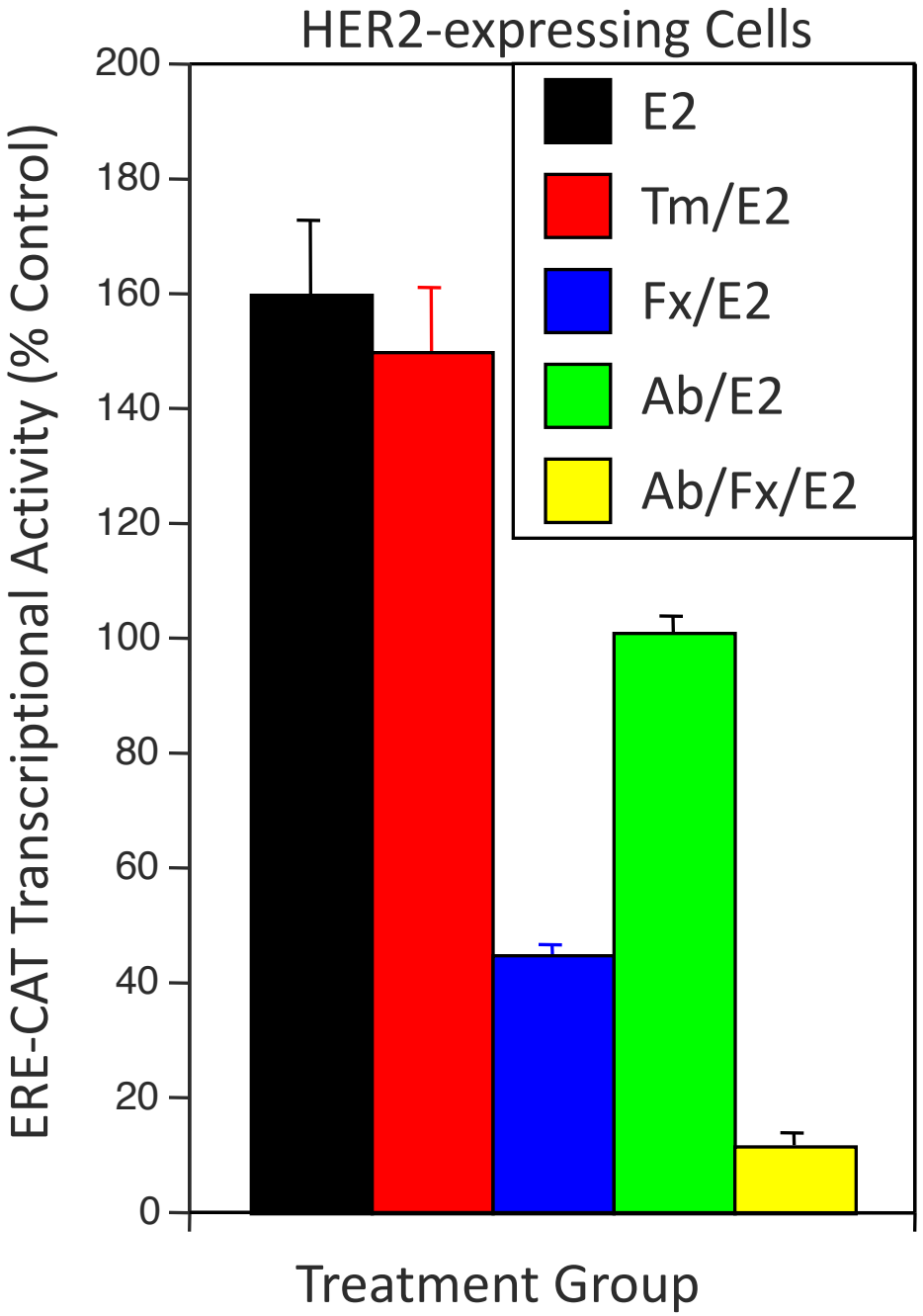
Mark Pegram, M.D.
Susy Yuan-Huey Hung Professor of Oncology
Associate Director for Clinical Research
Director, Stanford Breast Oncology Program
Associate Dean for Clinical Research Quality
Stanford University School of Medicine

Disclosures

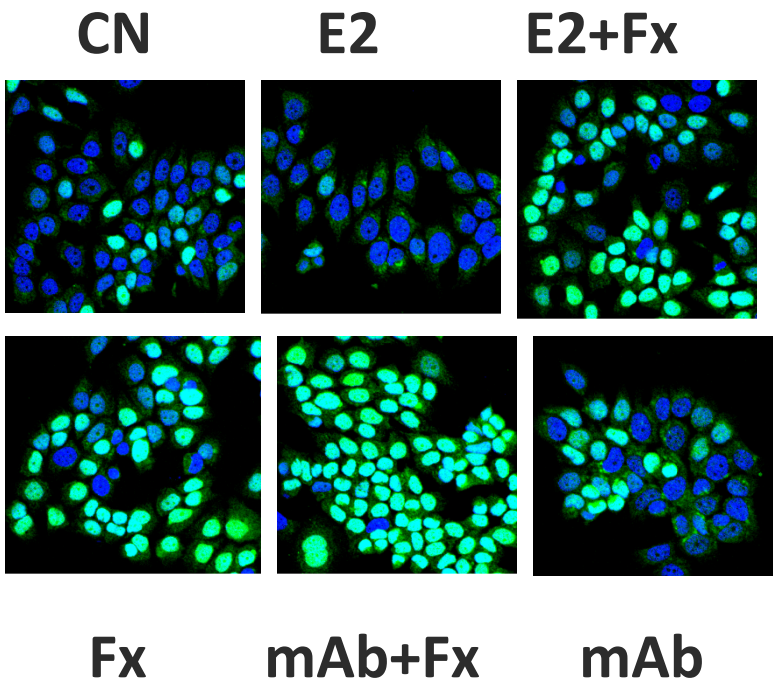
Advisory Committee and Consulting Agreements	Amgen Inc, AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Novartis, Pfizer Inc, Roche Laboratories Inc

Presentation Outline:

- Review published (and brand new) data examining the use of combined receptor blockade for patients with ER-positive, HER2+ metastatic breast cancer
- Incidence and clinical significance of HER2 mutations
- Other novel agents and strategies under development for patients with HER2-positive metastatic breast cancer



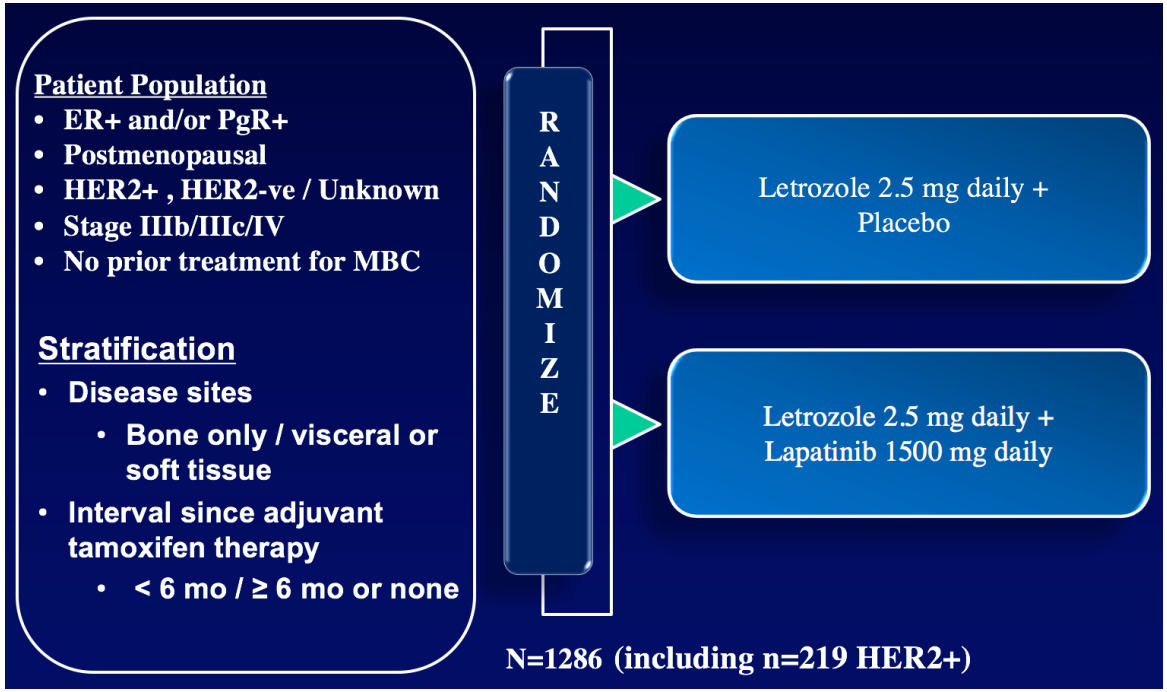
Fulvestrant (Fx) and HER2 MAb (Ab) Reduce ER-Dependent Transcriptional Activity and promote nuclear localization of p27/kip1



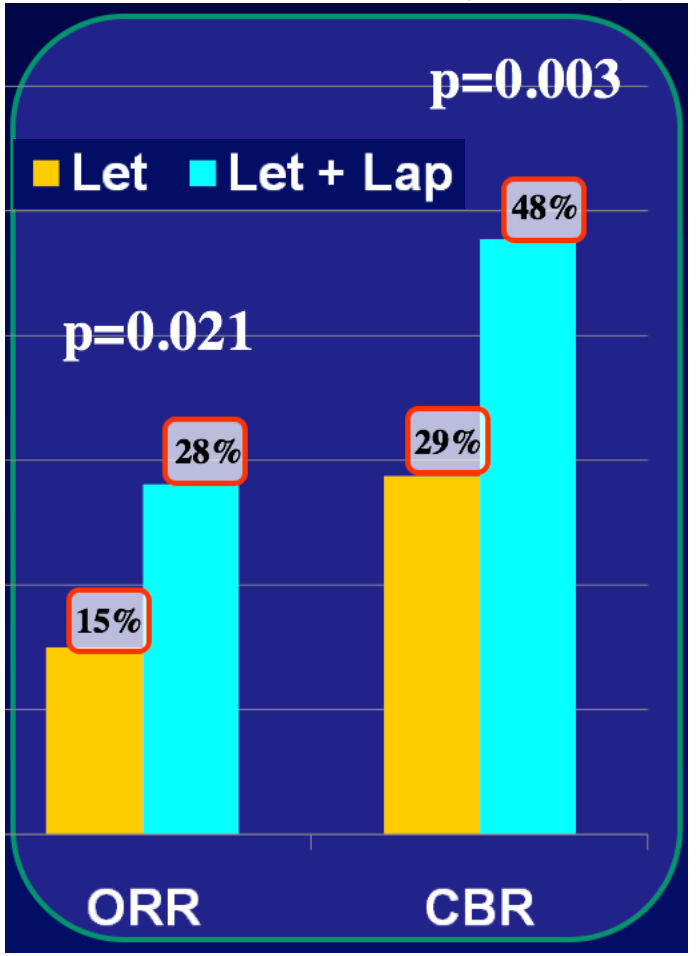
p27 = cdk inhibitor = cell cycle arrest = green

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.

Phase III, Randomized, Double-Blind Placebo-Controlled Study (EGF 30008)



HER2+ Population (N=219)



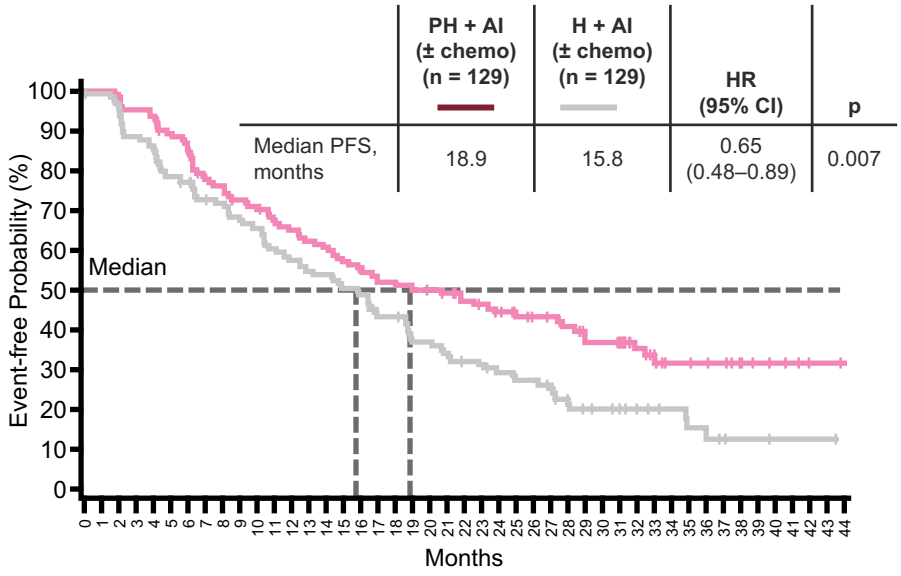
- **Median PFS ↑3.0 → 8.2 months**
- **PFS HR (95% CI) = 0.71 (0.53-0.96); P=0.019**
- **Accelerated FDA approval, Jan 2010**

Response rates were compared using stratified Fisher's exact test.

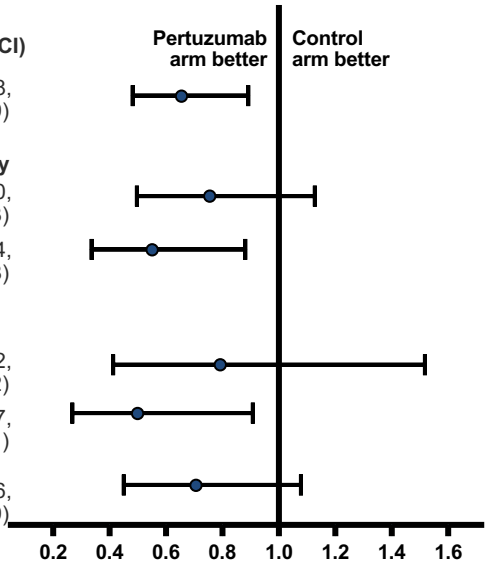
Johnston S, Pippen J Jr, Pivot X, Lichinitser M, Sadeghi S, Dieras V, Gomez HL, Romieu G, Manikhas A, Kennedy MJ, Press MF, Maltzman J, Florance A, O'Rourke L, Oliva C, Stein S, Pegram M. J Clin Oncol. 2009 Nov 20;27(33):5538-46.

PERTAIN: Efficacy and safety of pertuzumab (P) and trastuzumab (H) plus aromatase inhibitor in 1L HER2- and HR-positive mBC

Primary PFS analysis (median follow-up: 31 months)



Subgroup	n	Events	HR*	(95% CI)
ITT population	258	166	**0.66**	(0.48, 0.89)
Chosen to receive induction chemotherapy				
Yes	148	94	**0.75**	(0.50, 1.13)
No	110	72	**0.55**	(0.34, 0.88)
Time since adjuvant hormone therapy				
<12 months	48	37	**0.79**	(0.42, 1.52)
≥12 months	84	45	**0.50**	(0.27, 0.91)
No prior hormone therapy	126	84	**0.71**	(0.46, 1.09)



- The combination of PH and AI was superior to trastuzumab and AI
- The most common AEs (≥20% either arm) were: diarrhea, alopecia, nausea, asthenia and arthralgia

* HR for pertuzumab arm vs. control arm (control arm, reference category) from an unstratified Cox model.

M Rimawi, et al. Oral presentation, Abstract S3-04 (presented by Grazia Arpino)

ALTERNATIVE: Study Design

- Global study conducted across 112 sites, 29 countries; Data cutoff: March 11, 2016
- **Primary endpoint → changed from OS to PFS**

N=355

- Postmenopausal women with confirmed ER+ and/or PgR+, HER2+ MBC; **Prior Rx with Tras and CT in (neo)adjuvant or 1st line MBC settings.**

R
1:1:1

- **LAP (1000 mg/day)+TRAS[a]+AI[b] (n=120)**
- **TRAS[a]+AI[b] (n=117)**
- **LAP (1500 mg/day)+AI[b] (n=118)**

Therapy until disease progression, unacceptable toxicity or death, withdrawal of consent or investigator discretion

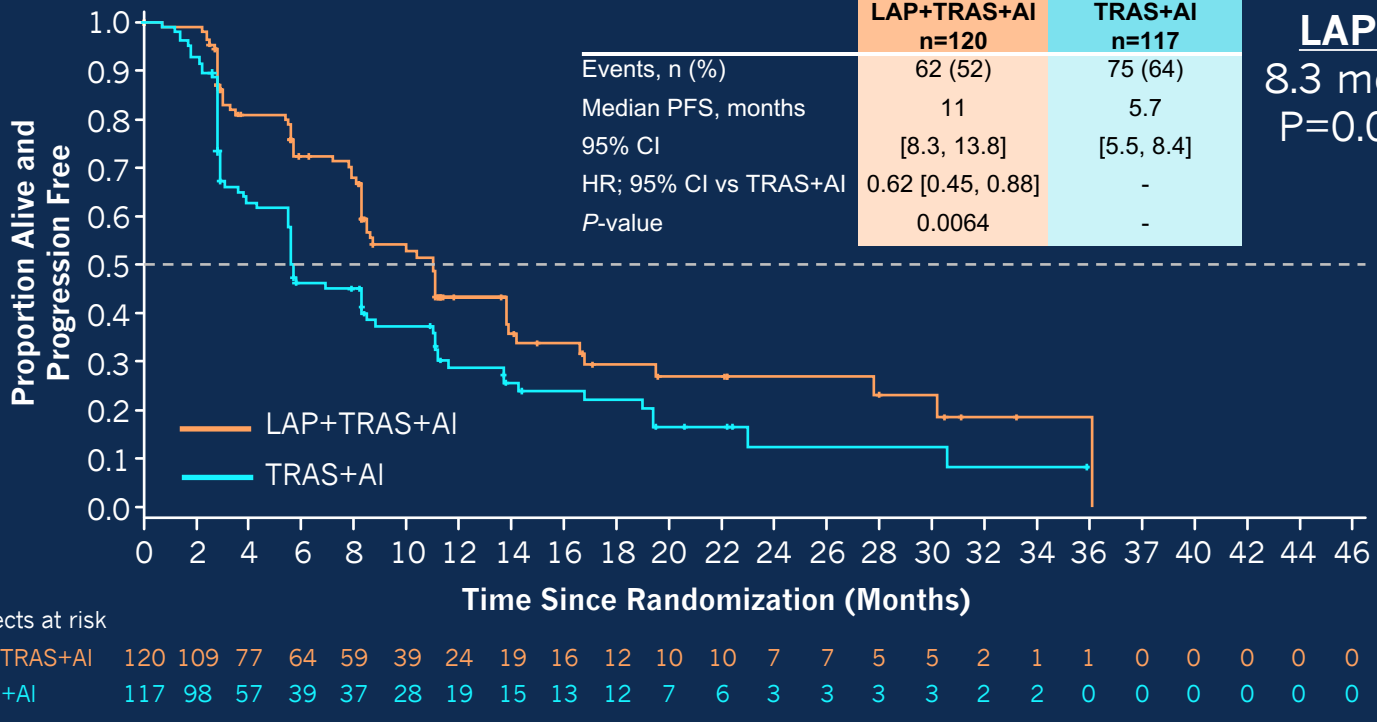
Stratification factors:

- Prior TRAS in neo/adjuvant or metastatic setting
- Investigator's choice of AI (steroidal/nonsteroidal)

~35% non-visceral disease, ~1/2 bone mets, ~1/2 lung mets, ~30% liver mets
~30% prior tras in MBC setting

[a]TRAS 8 mg/kg IV loading dose followed by 6 mg/kg IV q3weeks; [b]Investigator's choice of AI included LET (2.5 mg/day), ANA (1 mg/day) or EXE (25 mg/day).
AI, aromatase inhibitor; ER+, estrogen receptor-positive; HER2+, human epidermal growth factor receptor 2-positive; LAP, lapatinib; MBC, metastatic breast cancer; PgR+, progesterone receptor-positive; TRAS, trastuzumab.

ALTERNATIVE: Primary Endpoint
PFS With LAP+TRAS+AI vs TRAS+AI (ITT Population)



	LAP+TRAS+AI n=120	TRAS+AI n=117
Events, n (%)	62 (52)	75 (64)
Median PFS, months	11	5.7
95% CI	[8.3, 13.8]	[5.5, 8.4]
HR; 95% CI vs TRAS+AI	0.62 [0.45, 0.88]	-
P-value	0.0064	-

LAP+AI
8.3 months
P=0.0361

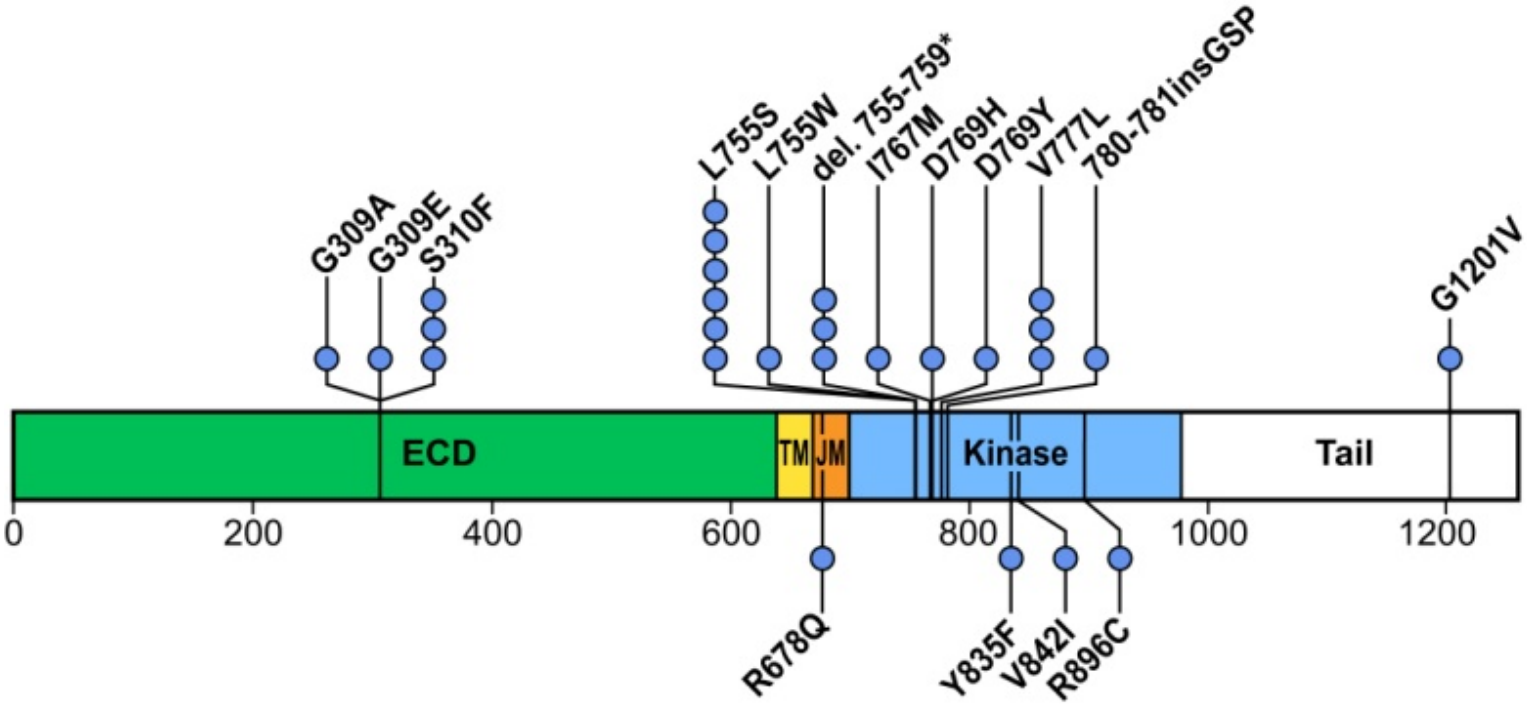
Subjects at risk

LAP+TRAS+AI	120	109	77	64	59	39	24	19	16	12	10	10	7	7	5	5	2	1	1	0	0	0	0	0
TRAS+AI	117	98	57	39	37	28	19	15	13	12	7	6	3	3	3	3	2	2	0	0	0	0	0	0

AI, aromatase inhibitor; HR, hazard ratio; ITT, intent-to-treat; LAP, lapatinib; PFS, progression-free survival; TRAS, trastuzumab;

Non-significant trend in OS favoring LAP+TRAS+AI; P=0.07 for TRAS+AI comparison.
Rash, diarrhea, paronychia, nausea – higher in the 3-drug combination arm.
No difference in SAEs between arms, and Rx discontinuation 2° AEs less common in LAP+TRAS+AI arm

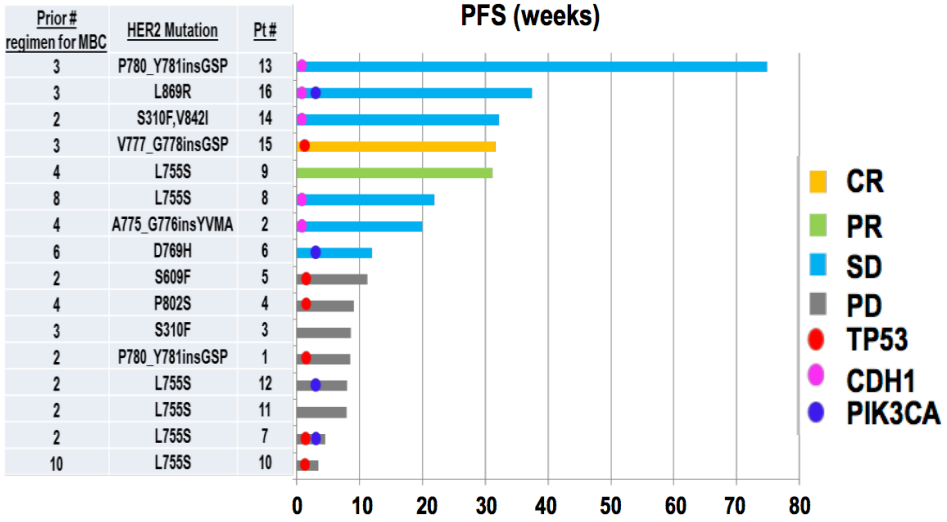
25 Patients with HER2 Somatic Mutations

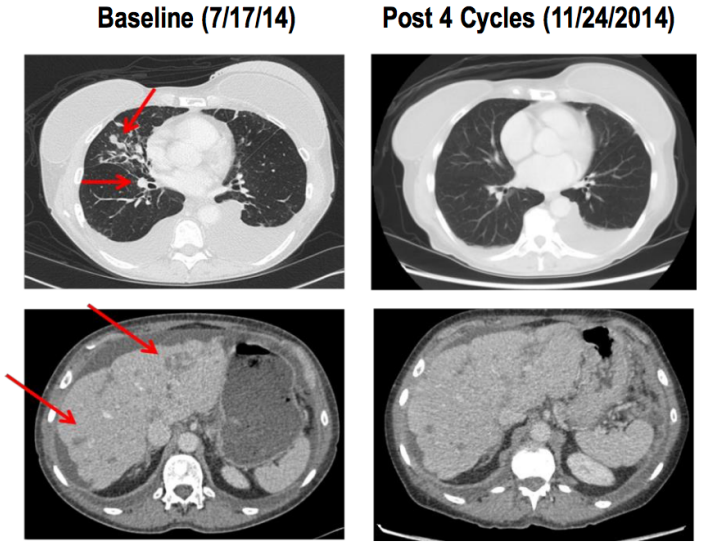


- Each blue circle represents a patient.
- From 8 publications with a total of 1,499 patients.
- 20% of patients have mutations at amino acids 309 or 310.
- 68% of patients have mutations at amino acids 755-781.

Neratinib Efficacy and Circulating Tumor DNA Detection of *HER2* Mutations* in *HER2* Non-amplified Metastatic Breast Cancer

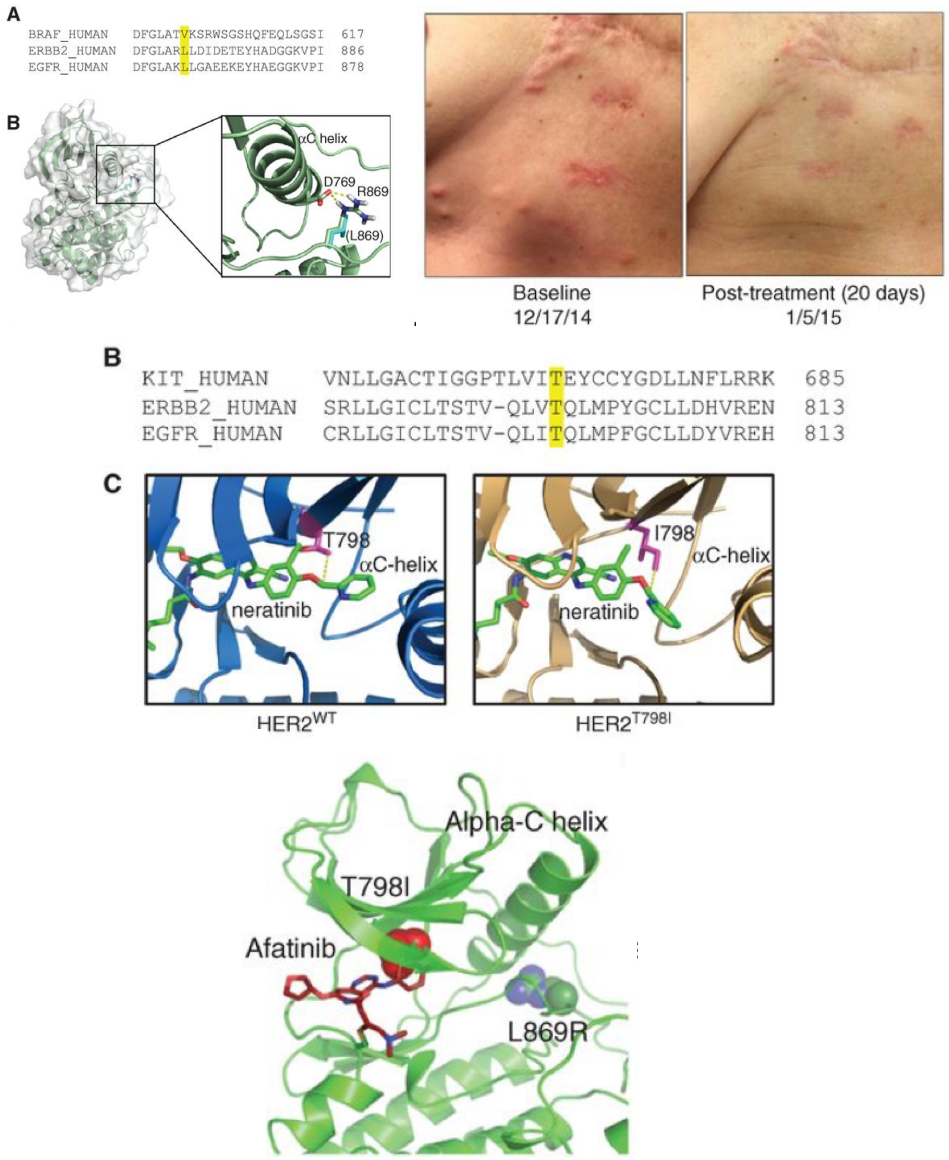
**HER2* mutations detected in 5/309 invasive ductal cancers (1.6%); and in 4/51 (7.8%) Invasive lobulars (P=0.026)





Ma, *et al., Clin Cancer Res (2017), In Press.*

HER2L869R exhibits a gain-of-function phenotype that is blocked by neratinib. “Second site” T798I mutation leads to neratinib resistance – responds to Afatinib.



Ariella B. Hanker et al. Cancer Discov 2017;7:575-585 CANCER DISCOVERY

2017 Renaissance in HER2-targeted Therapies

- Afucosylated anti-HER2 MAb with enhanced immune effector function (ADCC)
  - Margetuximab – Phase III
- HER2/HER2 bispecific/bi-paratopic ADCs with higher internalization rates
  - MEDI4276; ZW33 – Phase I/pre-clinical
- Small molecule, orally bioavailable “pure” HER2 TKIs
  - Tucatinib (ONT-380) – Phase III
- HER2 MAb-based combinations with agonist CD137 MAb (to enhance ADCC)
  - Utomilumab (PF-05082566) – Phase IB/II
- HER2 MAb/ADC combinations with checkpoint-inhibitor MAbs – Phase IB/II
- HER2 MAb combination with anti-CD47 MAb to enhance macrophage function
  - Hu5F9-G4 – Pre-clinical/Phase I
- Anti-HER2 strategies combined with CDK 4/6 inhibition – Phase IB/II

The Biosimilars Are Coming!

P. Revere, *et al*., Midnight Ride, April 18, 1775.

MESSAGES:

- **Combined receptor blockade targeting HER2 and ER is synergistic, efficacious, well-tolerated, FDA-approved and under-utilized in "triple-positive" MBC**
- **HER2 kinase domain mutations, while uncommon, respond to neratinib. "Second-site" resistance mutation story parallels the EGFR kinase inhibition story in NSCLCA**
- **In 2017 we are enjoying a renaissance in HER2-targeted therapeutic strategies, so stay tuned -- the HER2 story is just getting started**

James H. Clark Center
Stanford University

Stanford Bio-X Program:
Biology, Medicine, Chemistry,
Physics and Engineering