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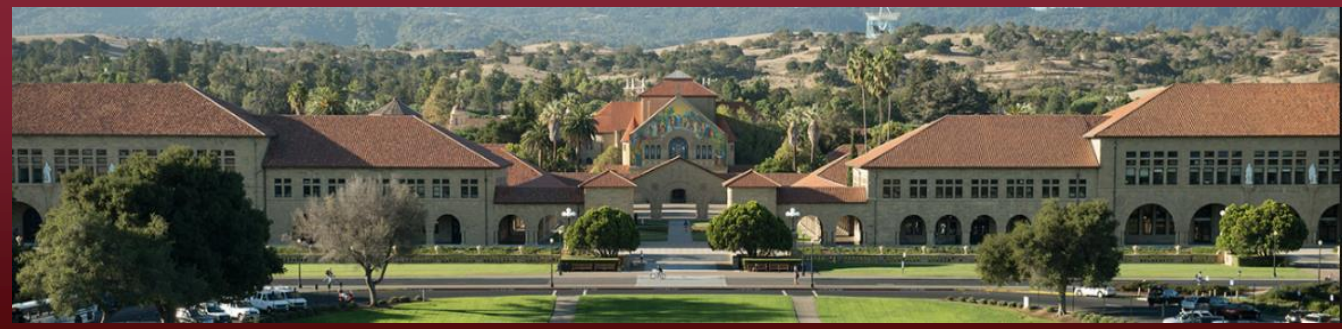
New and Evolving Directions in the Treatment of HER2 Positive Breast Cancer



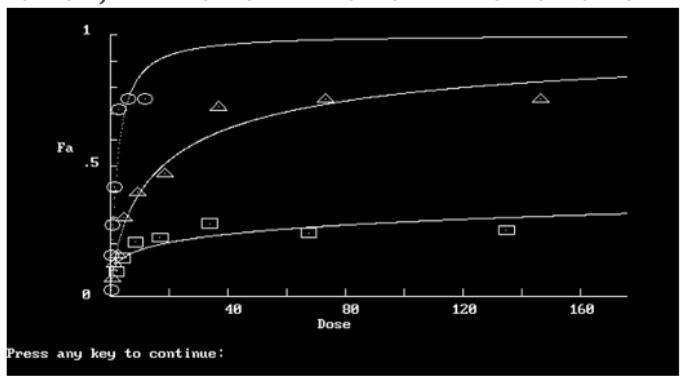
January 2025

Mark Pegram, M.D.
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

Trastuzumab MOA -- Synergy with Chemotherapy

Combination Index Isobologram Analysis

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



Docetaxel, trastuzumab, combination

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

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

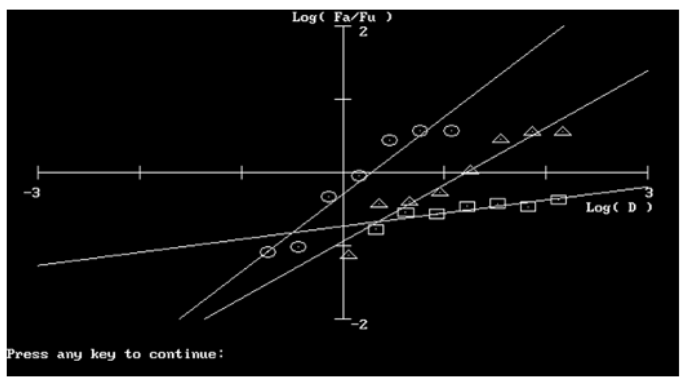
Table 2 Mean combination index values for chemotherapeutic drug/rhuMAb HER2 combinations *in vitro*

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

P values indicate level of significance compared to CI = 1.0

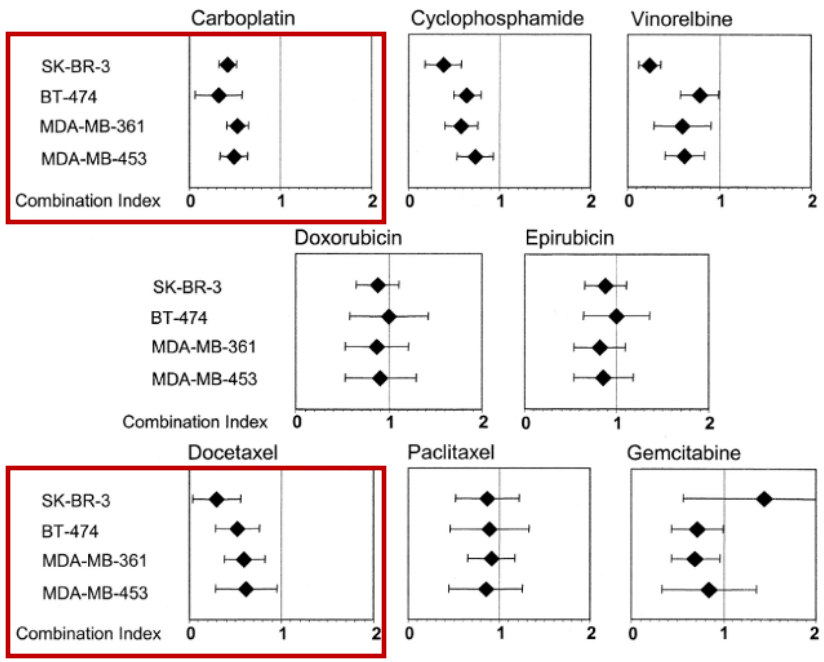
$$\text{Dose}_1 = \text{Dose IC}_{50}[(1 - f)/f]^{1/m} \longleftarrow \text{Median Effects Principle}$$

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



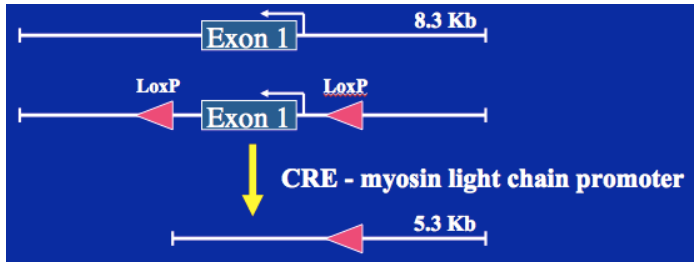
Median Effects Plot: docetaxel, trastuzumab, combination

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

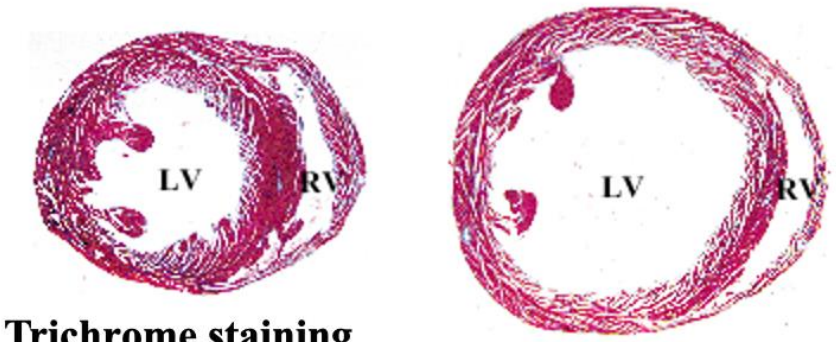


Pegram, MD, Konecny GE,... Slamon DJ, et al. JNCI 96 (10):2004, 739–49.

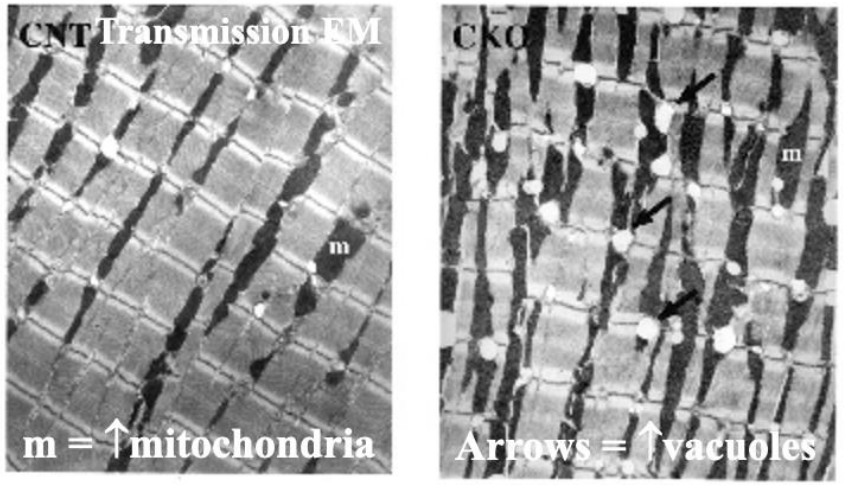
Phenotypic Analysis of erbB2 Conditional Knock-out Mouse Myocardium



erbB2-floxed **erbB2-CKO**



Trichrome staining

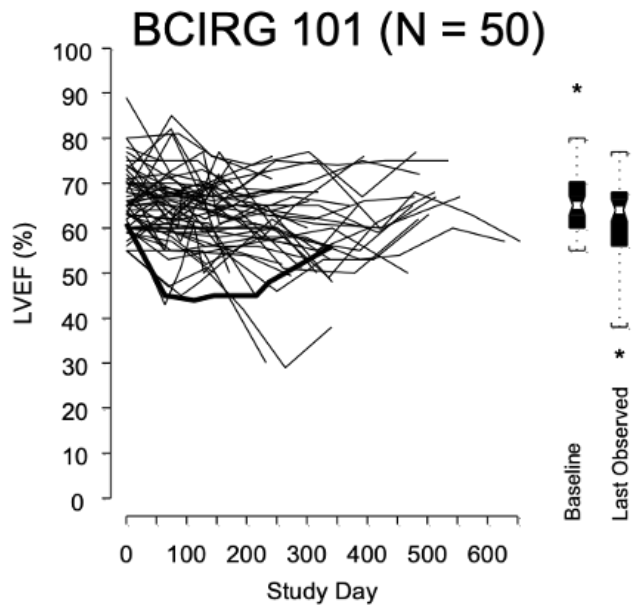


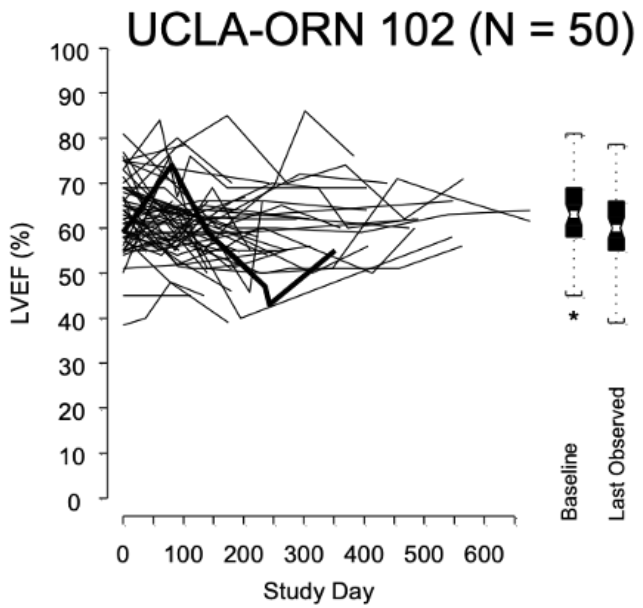
Crone SA, et al., Nature Medicine 8: 459-465 (2002).

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*]

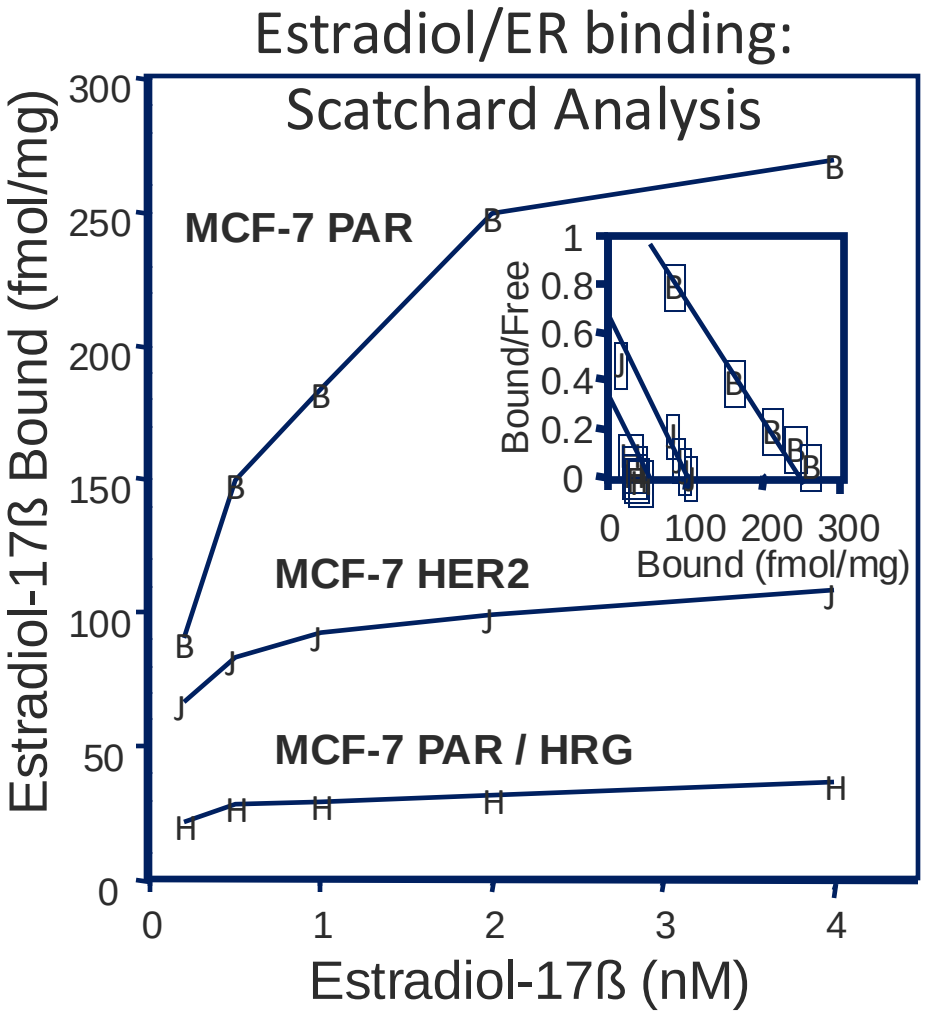
NE* = Not Estimable



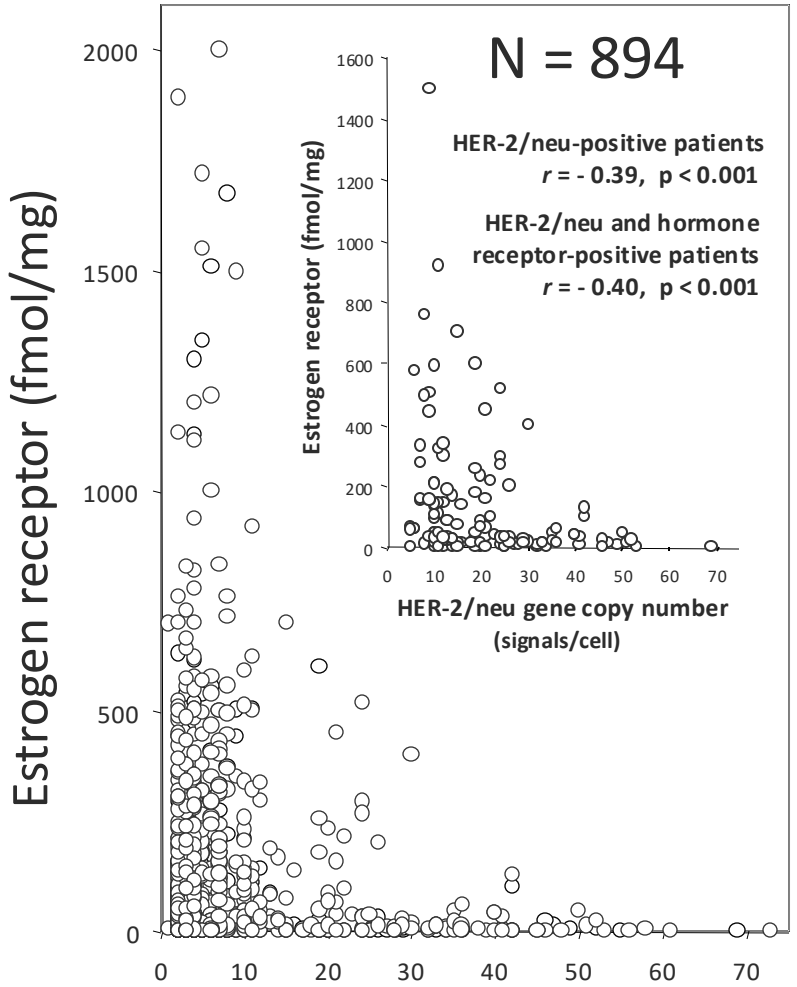


Pegram, et al., J Natl Cancer Inst. 96:759-69 (2004).

Downregulation of ER Expression by HER2



Pietras,…Pegram, *et al.*, Oncogene 10: 2435-2446, (1995)



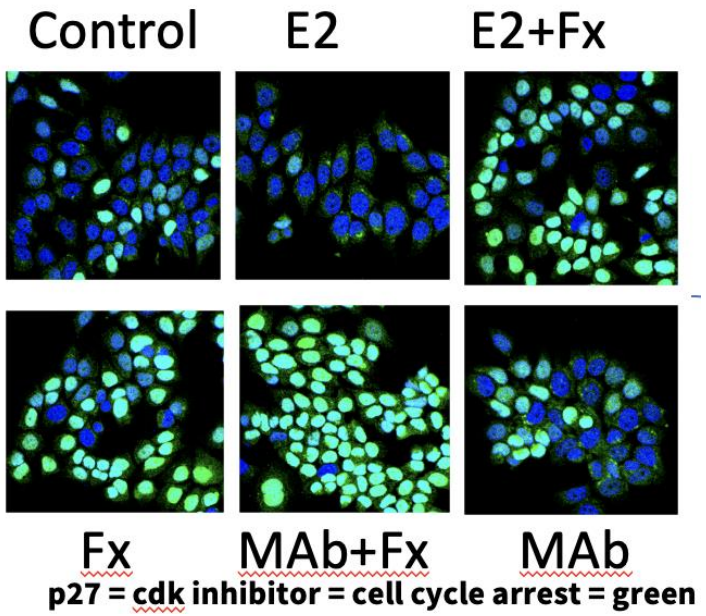
Konecny, Pauletti, Pegram, *et al.*, JNCI 2003

Combined Receptor Blockade Targeting HER2 and ER

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

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

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

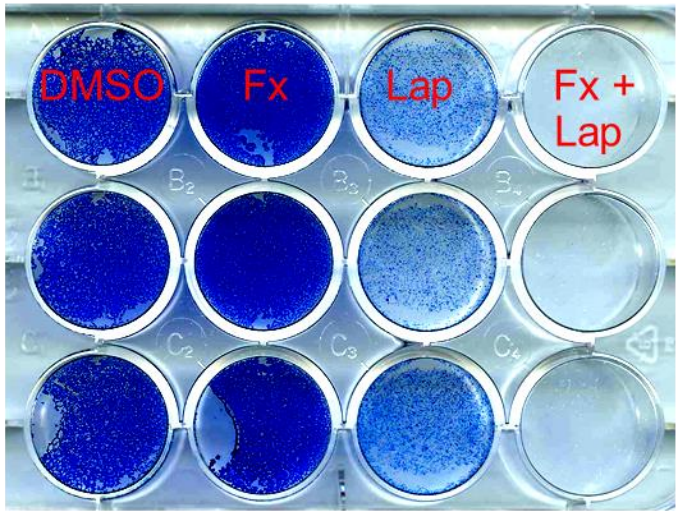


p27 = cdk inhibitor = cell cycle arrest = green

Xia W, et al. PNAS. 2006;103(20):7795-800.

(Neal Spector's lab, Duke)

Cell proliferation with fulvestrant + lapatinib, compared to either alone[2]



Fx + lap markedly inhibited the outgrowth of HER2++/ER+ breast cancer cells.

Simultaneous inhibition of HER2 and ER signaling prevents the development of acquired resistance to lapatinib in HER2-overexpressing/ER+ breast cancer cells

DMSO = dimethyl sulfoxide; E2 = estradiol; Fx = fulvestrant; Lap = lapatinib; MAb = anti-HER2 monoclonal antibody.

VOLUME 27 · NUMBER 33 · NOVEMBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY

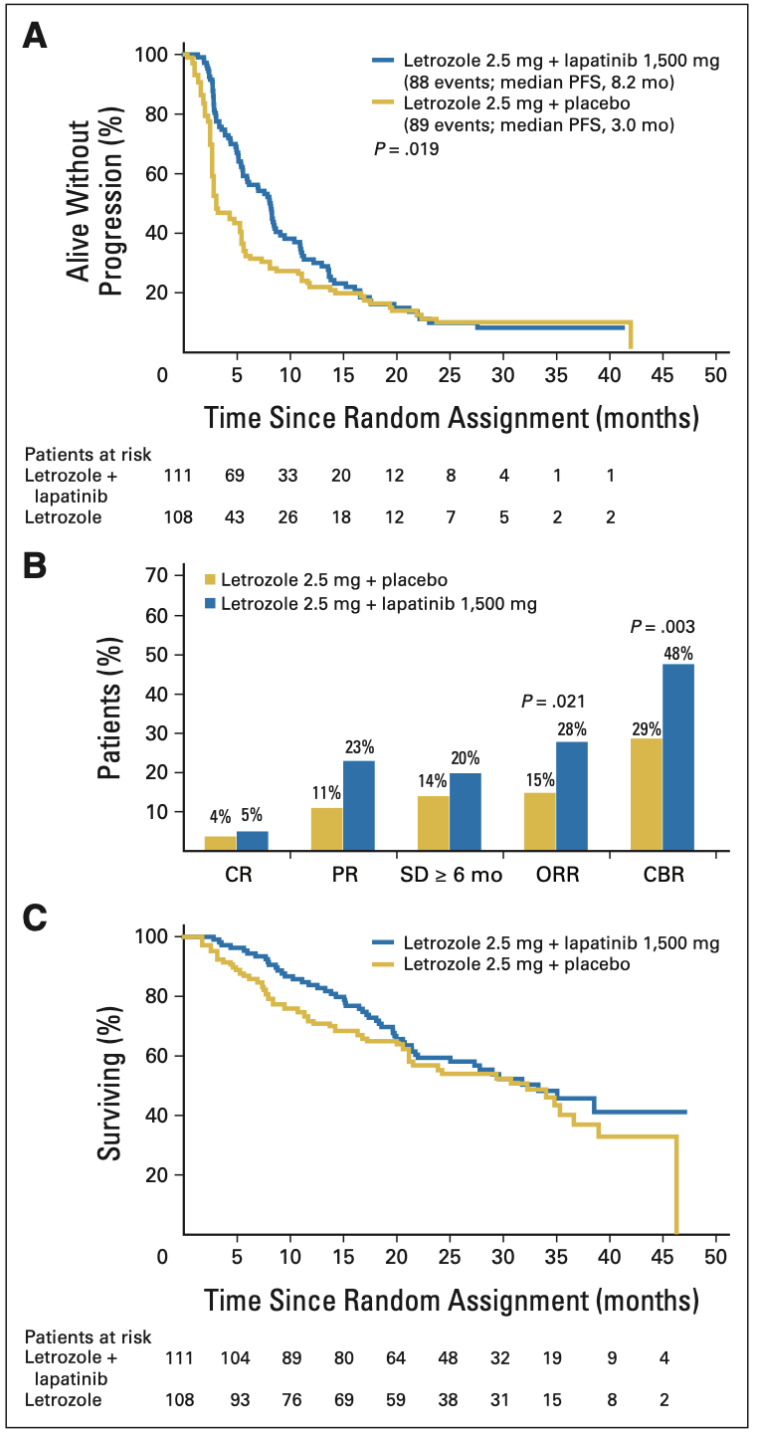
ORIGINAL REPORT

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

From the Royal Marsden Hospital, London; GlaxoSmithKline, Middlesex, United Kingdom; Sammons Cancer Center, Dallas, TX; David Geffen School of Medicine; University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA; GlaxoSmithKline, Collegeville, PA; GlaxoSmithKline, Durham, NC; University of Miami Sylvester Comprehensive

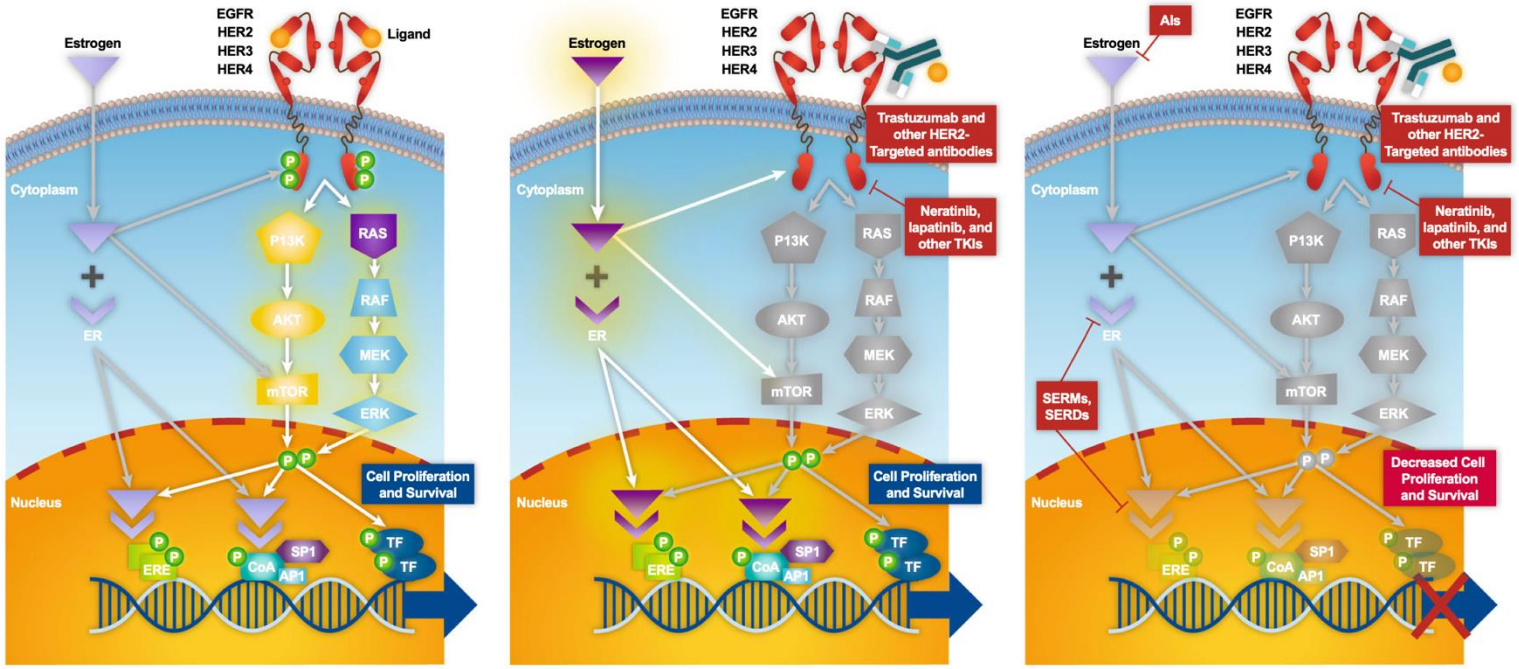
Stephen Johnston, John Pippen Jr, Xavier Pivot, Mikhail Lichinitser, Saeed Sadeghi, Veronique Dieras, Henry Leonidas Gomez, Gilles Romieu, Alexey Manikhas, M. John Kennedy, Michael F. Press, Julie Maltzman, Allison Florance, Lisa O'Rourke, Cristina Oliva, Steven Stein, and Mark Pegram

See accompanying editorial on page 5492 and article on page 5529



Estrogen/HER2 receptor crosstalk in breast cancer: combination therapies to improve outcomes for patients with hormone receptor-positive/HER2-positive breast cancer

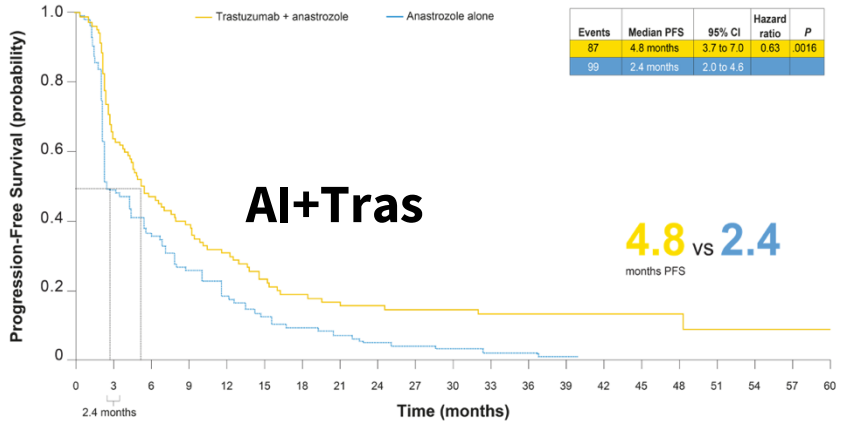
Pegram M, Jackisch C, Johnston S. NPJ Breast Cancer (2023)9:45.



Dual targeting of HER2 and HR confirmed to have significant PFS benefit for MBC patients

1L anti-HER2 Tx

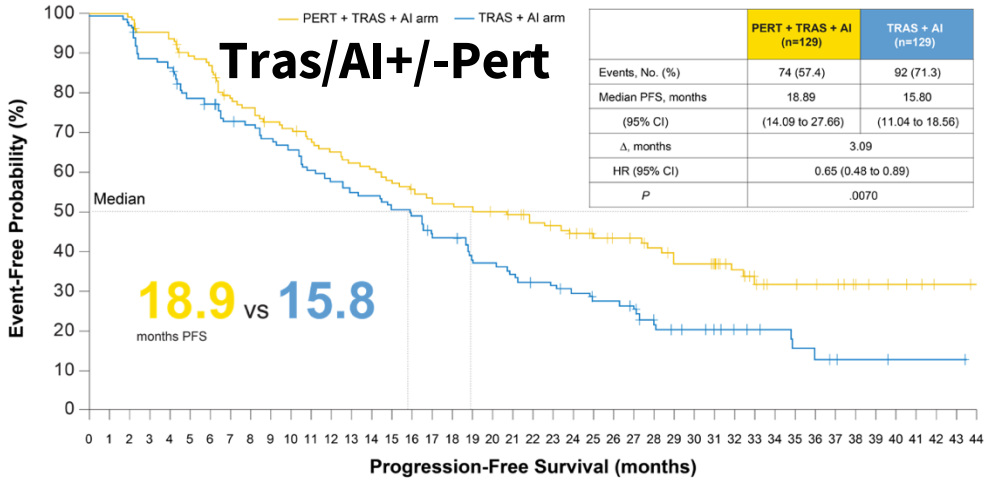
TAnDEM trial:
AI ± TRAS in postmenopausal HER2+ / HR+ MBC patients[1]



Patients in the TRAS + AI arm experienced significantly improved PFS vs AI alone

1L anti-HER2 + AI

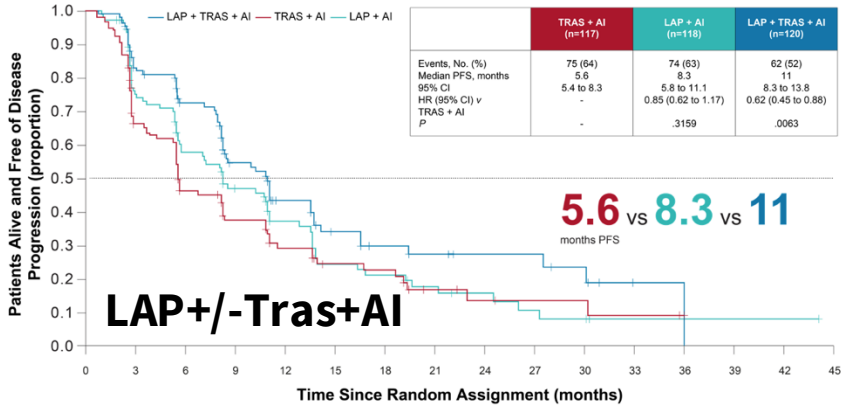
PERTAIN trial:
PERT ± TRAS + AI in 1L HER2+/HR+ MBC/LABC patients[1]



PERT + TRAS + AI is effective for the treatment of HER2+ MBC/LABC

2L anti-HER2 Tx

ALTERNATIVE trial:
LAP ± TRAS + AI in HER2+ / HR+ MBC patients[1]



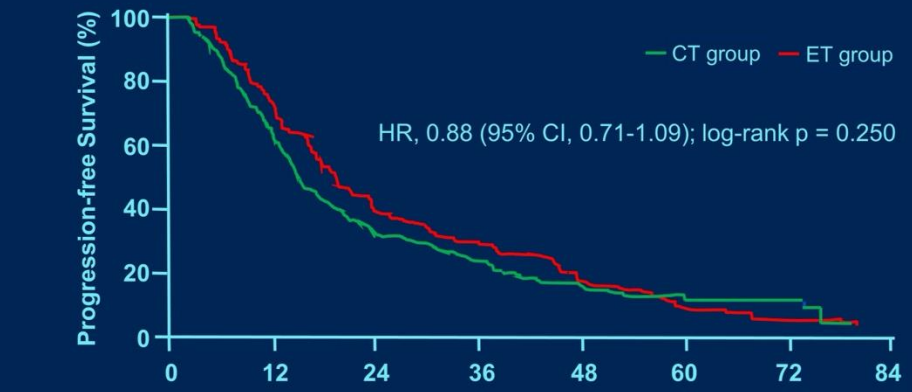
LAP + TRAS + AI showed superior PFS benefit vs TRAS + AI

AI, aromatase inhibitor; HER2, Human Epidermal Growth Factor Receptor 2; HR, hormone receptor; LABC, locally advanced breast cancer; LAP, lapatinib; MBC, metastatic breast cancer; PERT, pertuzumab; PFS, progression-free survival; TRAS, trastuzumab. MBC, metastatic breast cancer; PFS, progression-free survival.

1. Kaufman, et al. J Clin Oncol. 2009;27(33):5529-37. 2. Johnston SRD, et al. J Clin Oncol. 2021;39(1):79-89. 3. Rimawi M, et al. J Clin Oncol. 2018;36:2826-35.

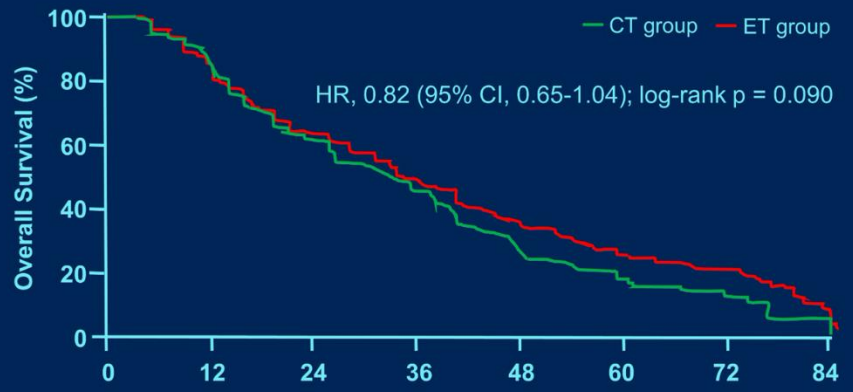
Trastuzumab plus endocrine therapy or chemotherapy as first-line treatment for HER2+/ER+ metastatic breast cancer: SYSUCC-002 randomized clinical trial

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

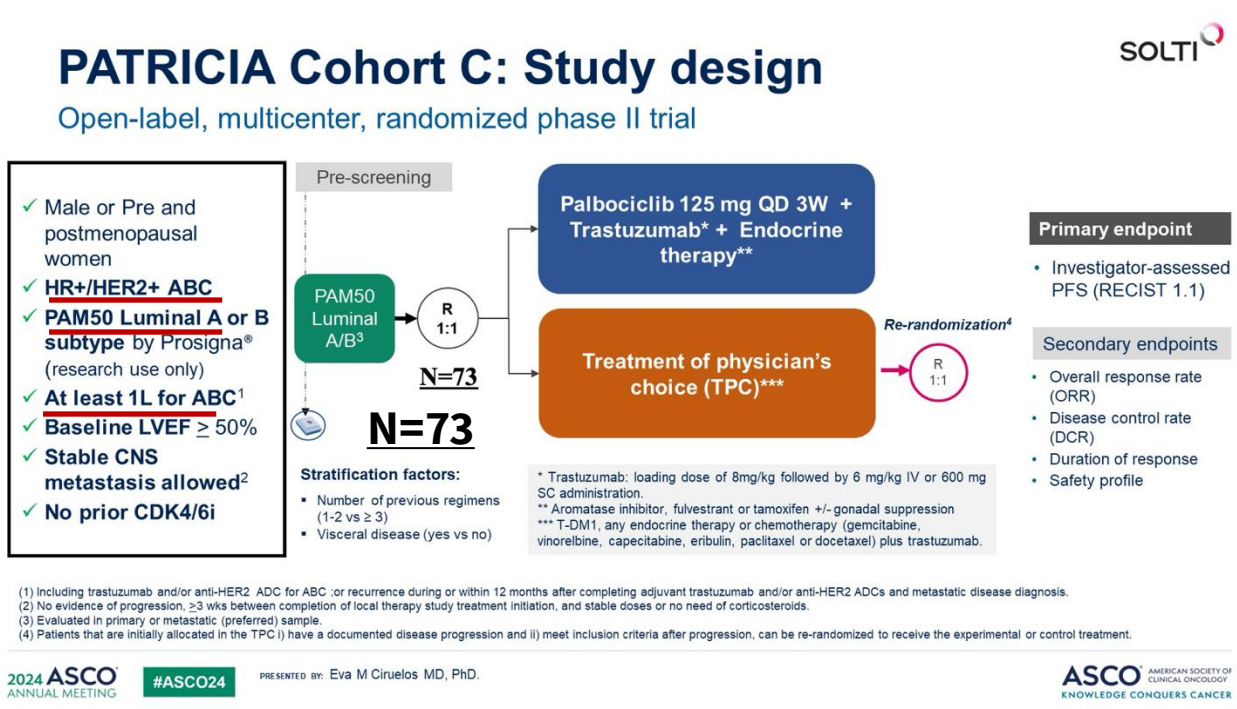
Subgroup	ET group (events/ n)	CT group (events/ n)	Hazard Ratio (95% CI)	p value
Age, years				0.146
≤ 40	29/31	30/42	1.14 (0.67, 1.91)	
> 40	151/165	135/154	0.80 (0.63, 1.00)	
Receptor status				0.099
ER and PR positive	143/157	128/157	0.90 (0.71, 1.15)	
ER or PR positive	37/39	37/39	0.76 (0.48, 1.20)	
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)	

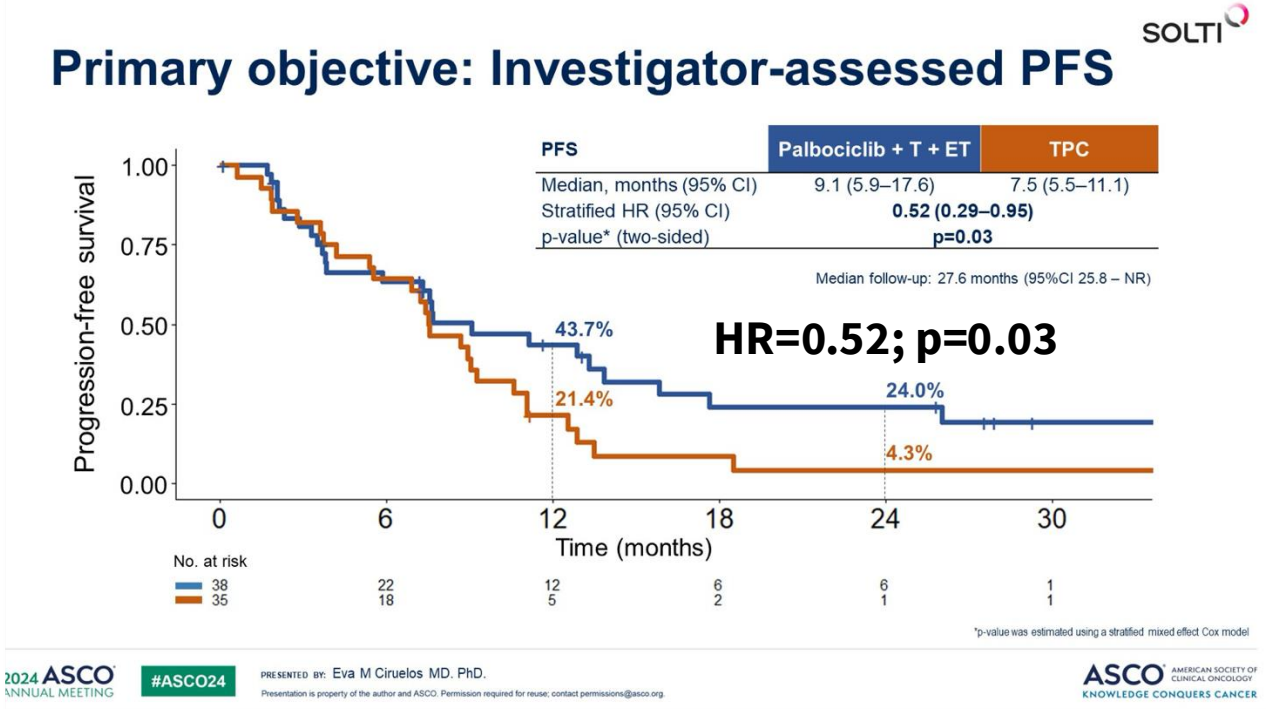
- **Trastuzumab plus endocrine therapy was non-inferior to, and had fewer toxicities than trastuzumab plus chemotherapy in patients with HR+/HER2+ MBC**
- **Exploratory subset analysis suggests endocrine therapy plus trastuzumab was likely more beneficial for patients with DFI >24 months**
- **Question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

Hua X, et al. Clin Cancer Res. 2021 Nov 22;28(4):637–645.

CDK 4/6 inhibition + endocrine therapy + Tras <u>Versus</u> TPC (T-DM1, or Endocrine Rx + Tras, or Chemo* + Tras) (PALBO)

*GEM, NAV, CAPE, PAC, DOC or Eribulin





<u>?Will this foreshadow PATINA</u>

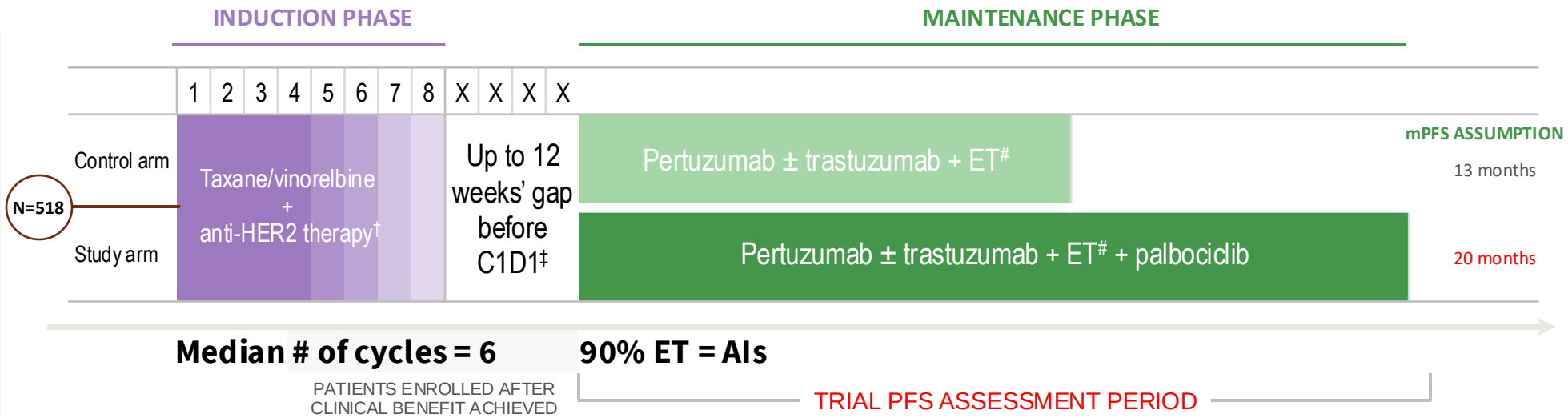
F/U to Shom Goel – Overcoming Therapeutic Resistance in HER2-Positive Breast Cancers With CDK4/6 Inhibitors. Cancer Cell. 2016 Mar 14;29(3):255-269.

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

The PATINA trial is a randomized Phase III pivotal registration trial designed to demonstrate that the combination of palbociclib with anti-HER2 therapy + endocrine therapy is superior to anti-HER2-based therapy + endocrine therapy alone in improving the outcomes of subjects with HR+/HER2+ mBC

Key Eligibility Criteria

- Histologically confirmed
  - HR+/HER2+ mBC
- Anti-HER2-based induction CT Tx prior to randomization*
- No prior Tx in advanced setting beyond induction Tx
- No prior Tx with a CDK4/6 inhibitor
- No evidence of disease progression after induction Tx



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

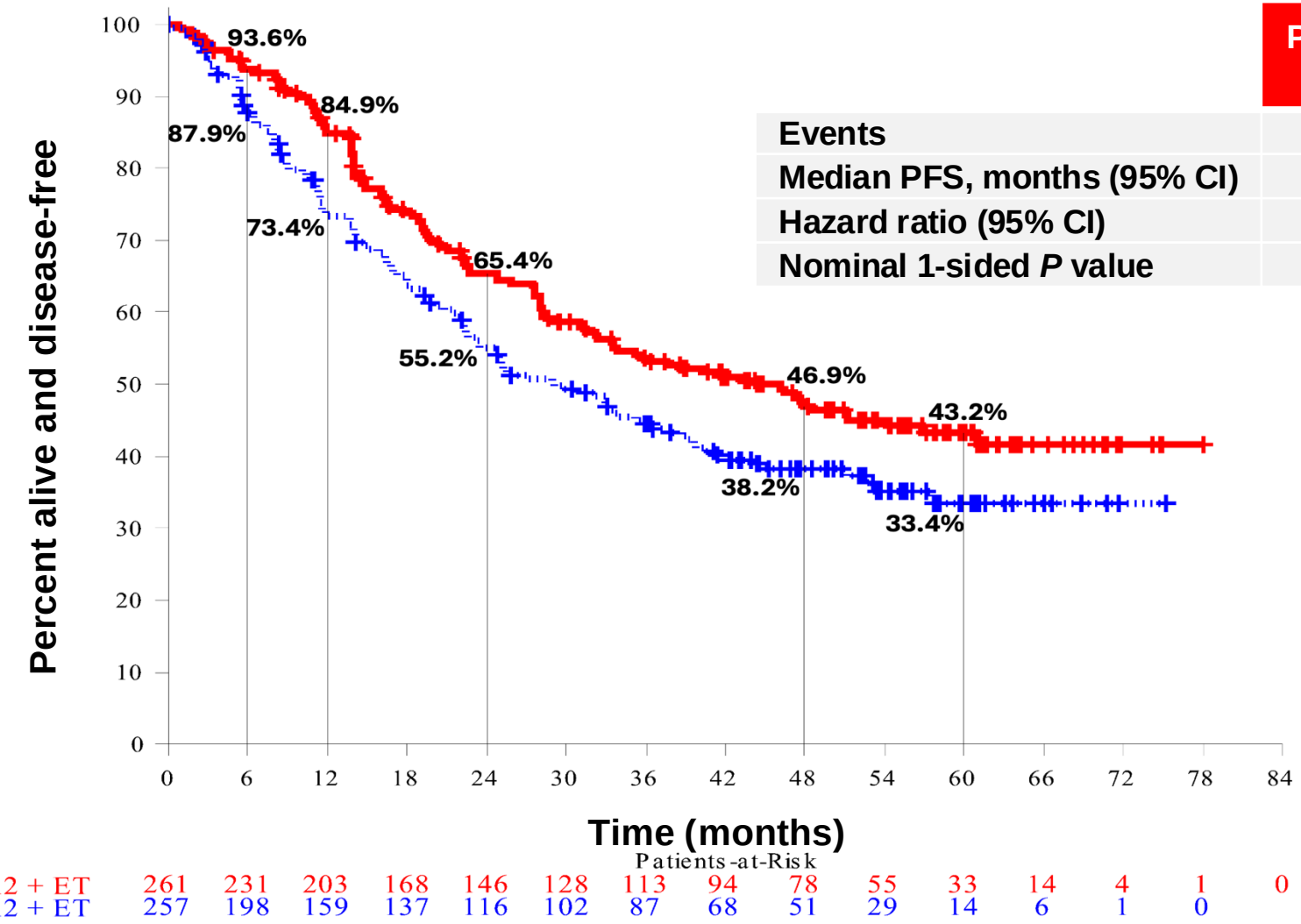
*Patients received induction therapy for 4–8 cycles depending on tolerability. †Anti-HER2+ Therapy – Anti-HER2 treatment options are trastuzumab + pertuzumab or trastuzumab only (limited to 20% of study patients). The same anti-HER2-regimen should be used pre- and post- randomization. ‡Patients randomized immediately following completion of their induction therapy, or for those who have already completed induction, a gap of 12 weeks between their last infusion/dose of induction therapy and the C1D1 visit was permitted. Patients were eligible provided they were without evidence of disease progression by local assessment (i.e. CR, PR or SD). #Endocrine therapy options are either an aromatase Inhibitor or fulvestrant. Pre-menopausal women must receive ovarian suppression with a LHRH agonist if the patients have not documented ovarian ablation or bilateral oophorectomy before randomization or during the conduct of the study

C1D1 = cycle 1 day 1; CBR = clinical benefit rate; CDK = cyclin-dependent kinase; CR = complete response; CT = chemotherapy; DoR = duration of response; ET = endocrine therapy; HER2(+) = human epidermal growth factor receptor 2 (-positive);
HR+ = hormone receptor-positive; LHRH = luteinizing hormone-releasing hormone; mBC = metastatic breast cancer; mPFS = median progression-free survival; ORR = objective response rate; OS = overall survival; PFS = progression-free survival;
PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PK = pharmacokinetic; PR = partial response; PRO = patient-reported outcome; SD = stable disease; Tx = treatment.

1. ClinicalTrials.gov NCT02947685. https://www.clinicaltrials.gov/ct2/show/NCT02947685. 2. PATINA (ClinicalTrials.gov NCT02947685) Trial Protocol (data on file).

Primary Endpoint: PFS (Investigator-Assessed)

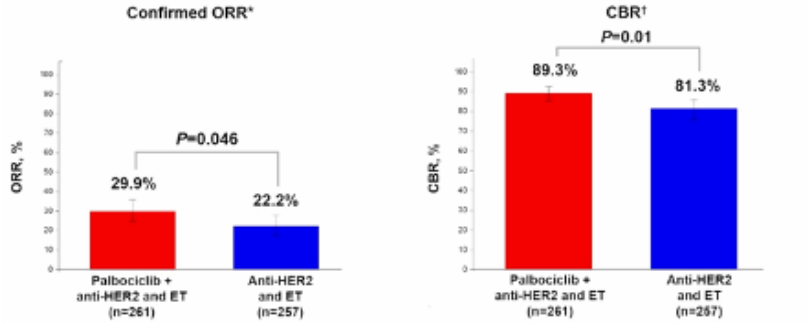
OS analysis remains immature, with only 119 of 247 planned events observed to date; median OS (control arm) = 77 mos.



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

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

Secondary Endpoints: ORR and CBR (Investigator-Assessed)



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

Otto Metzger, et al. SABCS 2024.

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

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

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

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

Otto Metzger, et al. SABCS 2024.

Implications to Clinical Practice

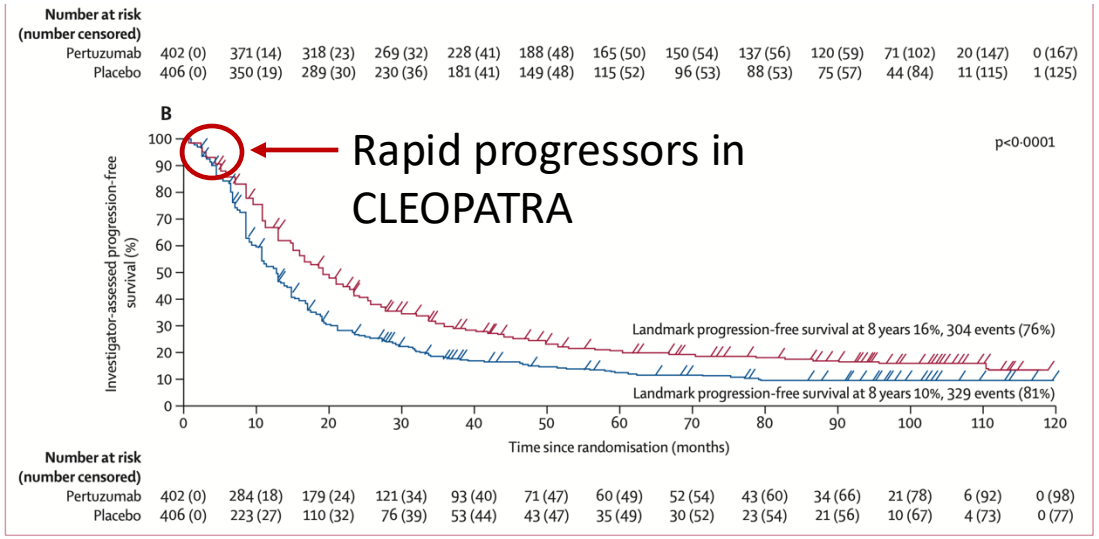
- The AFT-38 PATINA phase III study demonstrates a **clinically meaningful** improvement in PFS among patients diagnosed with HR+,HER2+ breast cancer
  - Median PFS increased from 29.1 to 44.3 months (Δ15.2 months)
  - Manageable toxicity

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

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

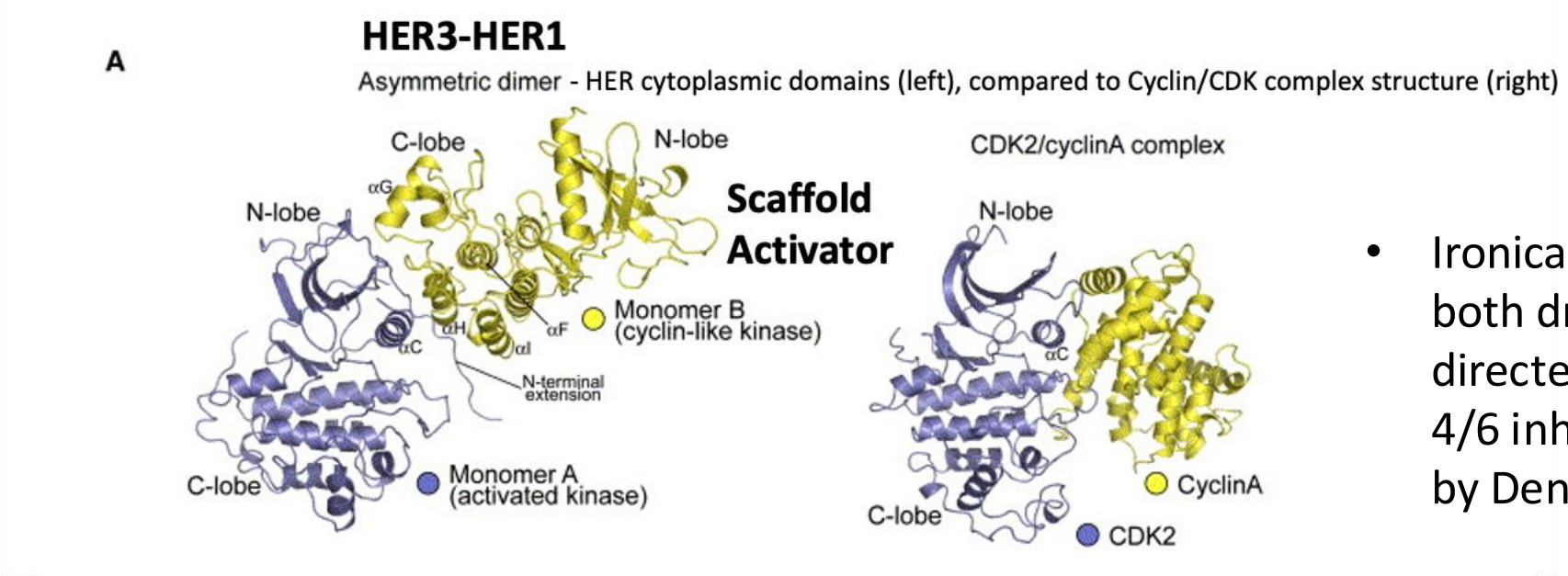
Caveats:

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

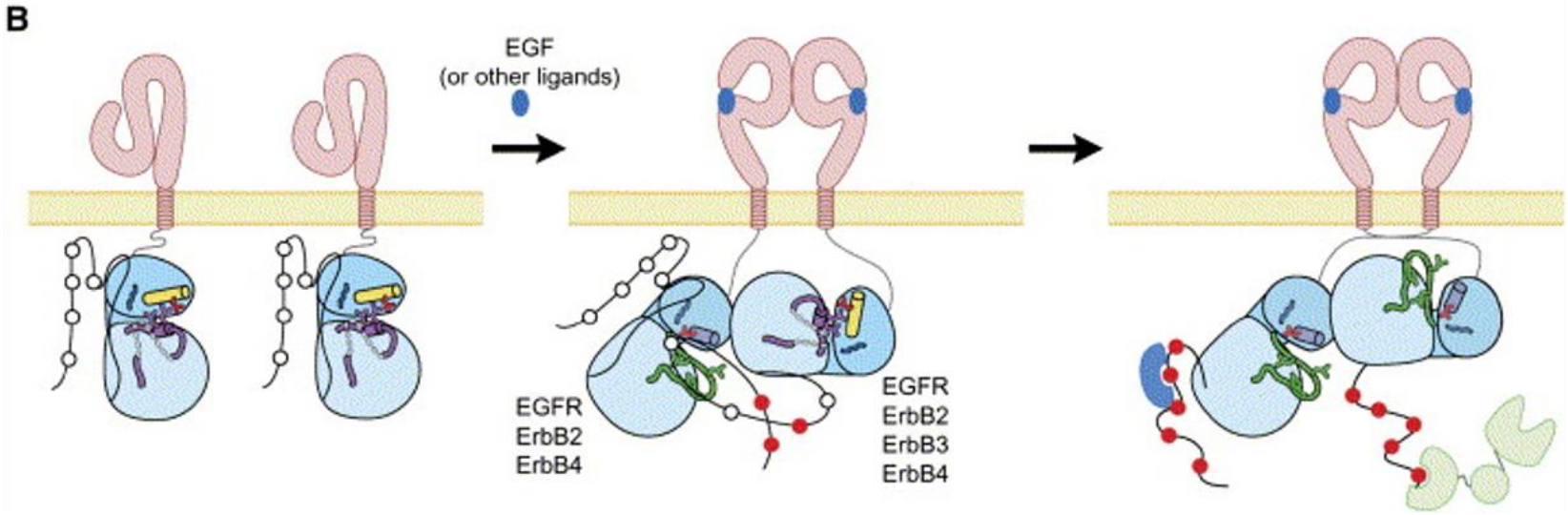


2. These data pre-date the anticipated results from DB-09, which has no real "maintenance" phase.
3. Febrile neutropenia not reported, ILD apparently not increased.
4. Will need FDA or guideline(s) nod for insurance authorization.

General Model for Activation of the EGFR Family



- Ironically, brings together both drug classes (HER2-directed therapies and CDK 4/6 inhibitors) championed by Dennis Slamon.



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

KEY TAKEAWAYS:

1. **A wealth of preclinical evidence highlights the role of ER and HER2 crosstalk in the development of resistance to both endocrine and anti-HER2 therapies, thus supporting the rationale for combined receptor blockade targeting the ER and HER2 as a treatment approach in breast cancer [Pegram M, et al. NPJ Breast Cancer. 2023 May 31;9(1):45].**

2. **PATINA validates HER2/ER preclinical synergy data published by Richard Pietras at UCLA almost 30 years ago, and Shom Goel's elegant experiments targeting CDK 4/6 in HER2+ models, published in Cancer Cell 2016. Brings together both drug classes (HER2-directed and CDK 4/6 inhibition) championed by Dennis Slamon.**

3. **In a nonrandomized "real-world" analysis of National Cancer Database patients with HR+/HER2+ mBC who were treated between 2010 and 2015, among 6234 patients analyzed, 3770 (60.5%) of whom received ET and 2464 (39.5%) of whom received chemotherapy, multivariate analysis suggested that patients receiving ET plus anti-HER2 experienced improved OS compared with those receiving chemotherapy plus anti-HER2 (hazard ratio, 0.74; p = 0.004).**

4. **Taken together, these studies suggest the potential utility of combined receptor blockade targeting HER2 and ER as a chemotherapy-free option in selected patients with HR+/HER2+ tumors.**

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Questions/Comments
Debate/Discussion
Criticism

The Many Thousands of Patients and Their Families

ACKNOWLEDGEMENTS: Some Unsung Heroes (from my POV)

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

Mark Sliwkowski – GNE (head, protein chemistry)
Rob Akita – GNE (preclinical)
Teemu Juntilla – GNE (scientist)
Hank Fuchs – GNE (clinical)
Melody Cobleigh – Rush (single agent trastuzumab trial)
Chuck Vogel – (first-line single agent trastuzumab trial)
Jose Baselga – MSKCC (paclitaxel + trastuzumab work)
Larry Norton – MSKCC (trastuzumab phase 3 study design)
Michael Sela – (anti-EGFR + platinum work)
Michael Untch (professor, Berlin)
Judith Hurley (Univ Miami, neoadjuvant TCH)
Kenneth Chien – (Harvard, HER2 cardiotoxicity)
Jim Mortimer – (Sanofi-Aventis, BCIRG, CCO)
Vinay Jain – (support for grad student in the lab)
Susy Yuan-Huey Hung Family – (endowed professorship)
Jill and John Freidenrich – (endowed professorship)
Carl Tras – GNE (regulatory)

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THANK YOU!