Review of Breast Cancer ASCO abstracts (neo-adjuvant and metastatic) GASCO annual meeting August 27th 2011, Atlanta, GA

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Louisa and Rand Glenn Family Chair in Breast Cancer Research

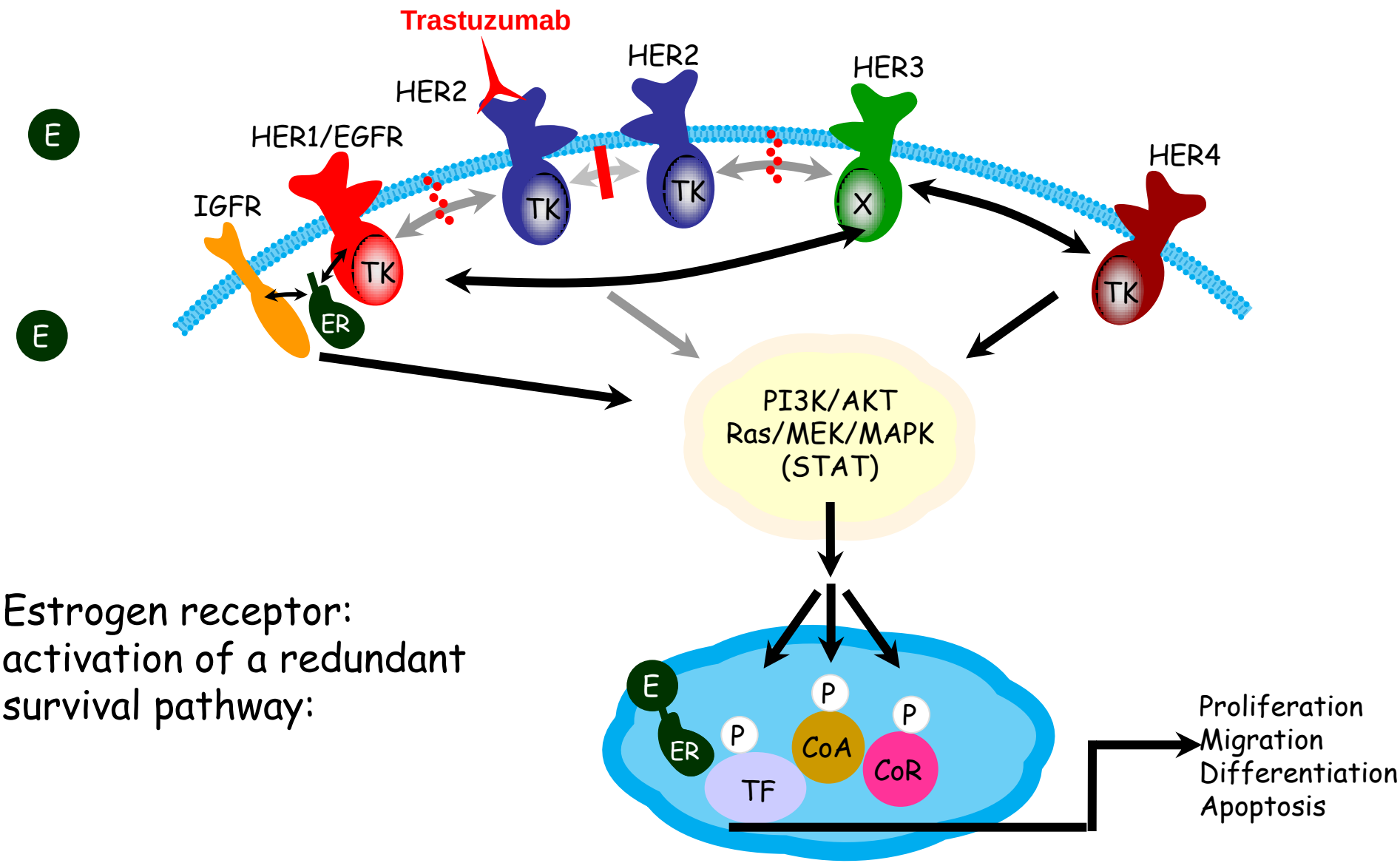
TBCRC 006: A multicenter phase II study of neoadjuvant lapatinib and trastuzumab without chemotherapy in patients with HER2 overexpressing breast cancer

Jenny C. Chang, I. A. Mayer, A. Forero-Torres, R. Nanda, M. P. Goetz, A. A. Rodriguez, A.C. Pavlick, T. Wang, S. G. Hilsenbeck, C. Gutierrez, R. Schiff, C. K. Osborne, M. F. Rimawi

Abstract 505

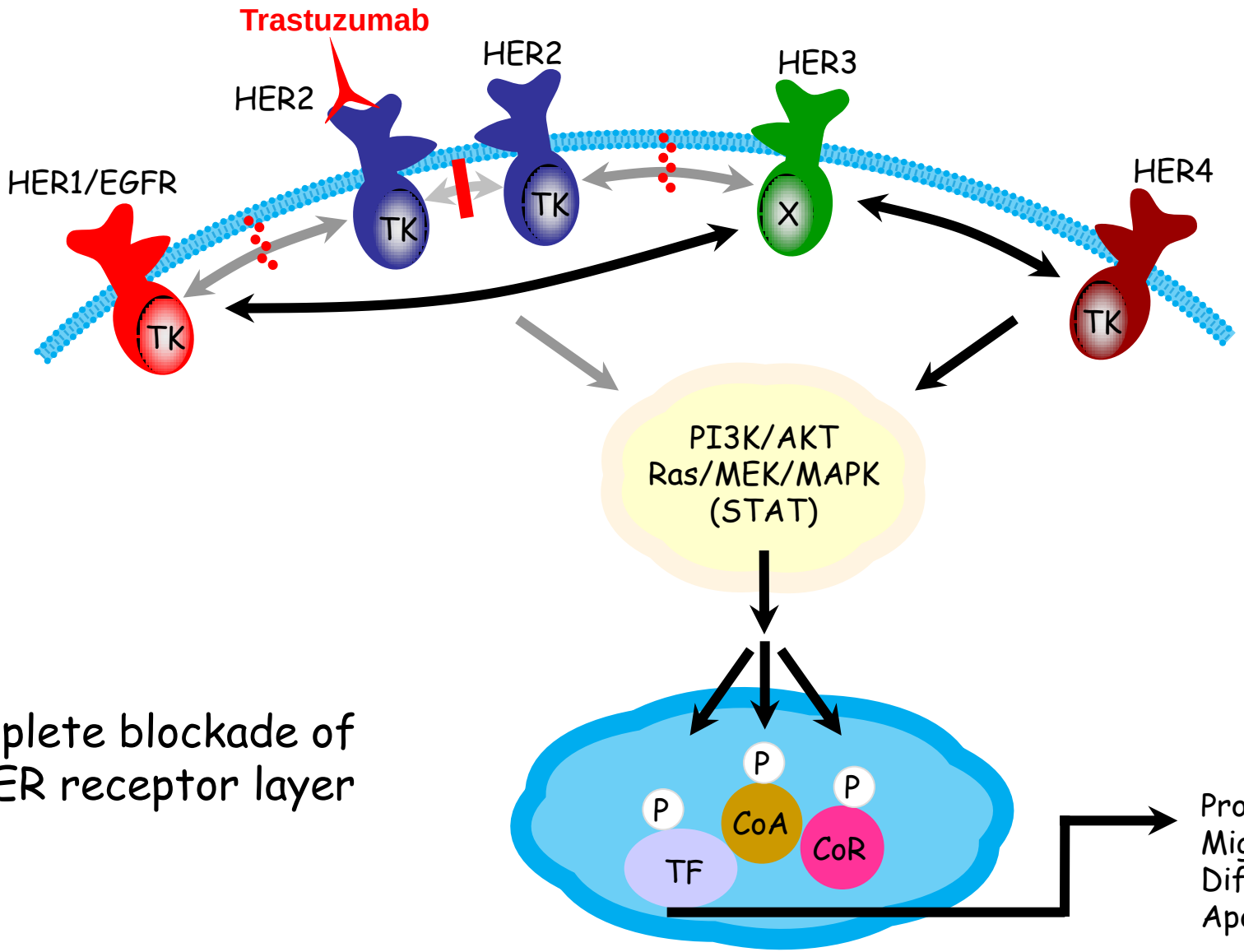
tbcrc Translational Breast Cancer Research Consortium

Mechanisms of Resistance to HER Targeted Therapy



Estrogen receptor: activation of a redundant survival pathway:

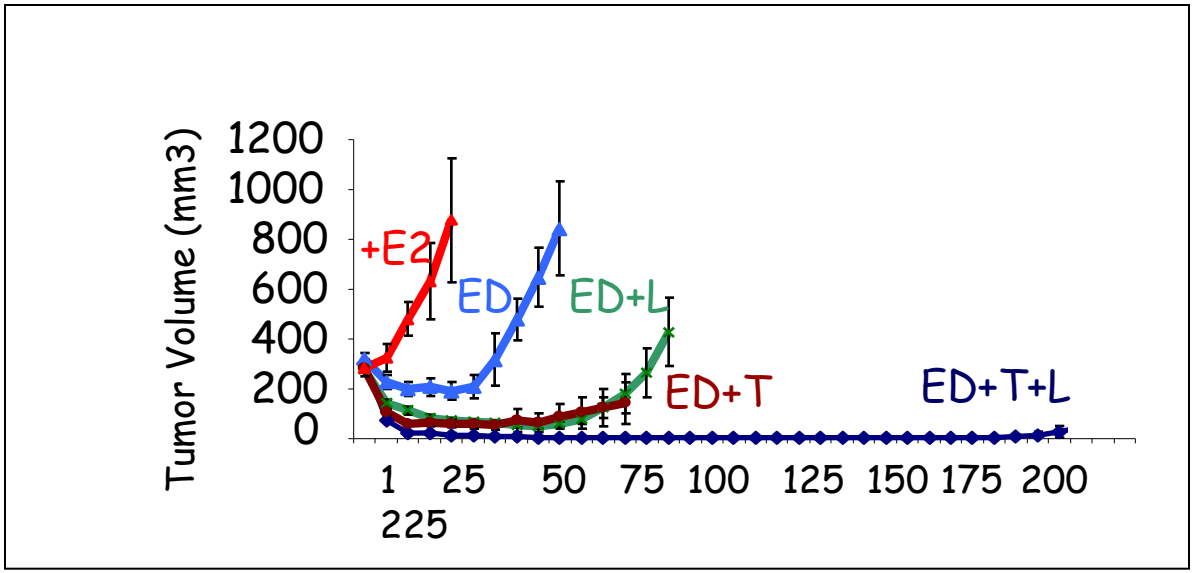
Mechanisms of Resistance to HER Targeted Therapy



Incomplete blockade of the HER receptor layer

Superiority of Dual Blockade In Xenograft Models

Estrogen Deprivation (ED)



T – Trastuzumab
L – lapatinib
L+T – Trast + Lap

M Rimawi. CCR 2011;17(6):1351-61

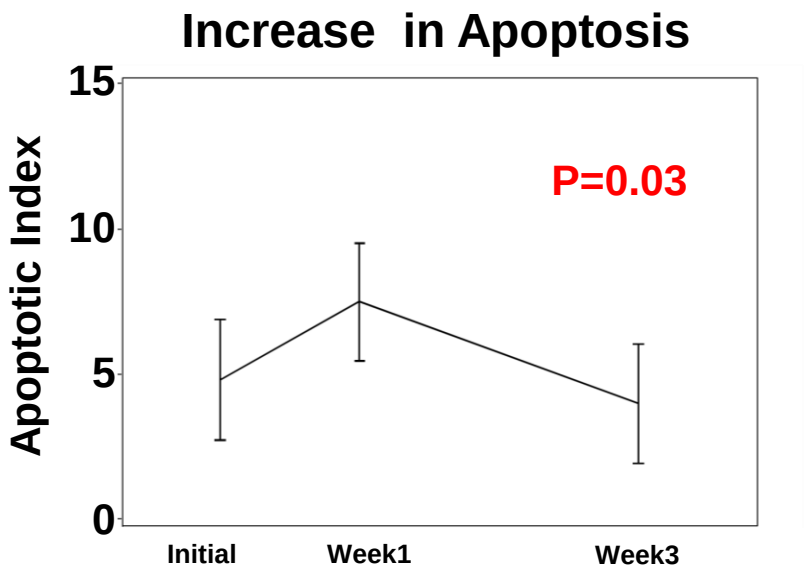
Neoadjuvant HER2 Targeted Therapy

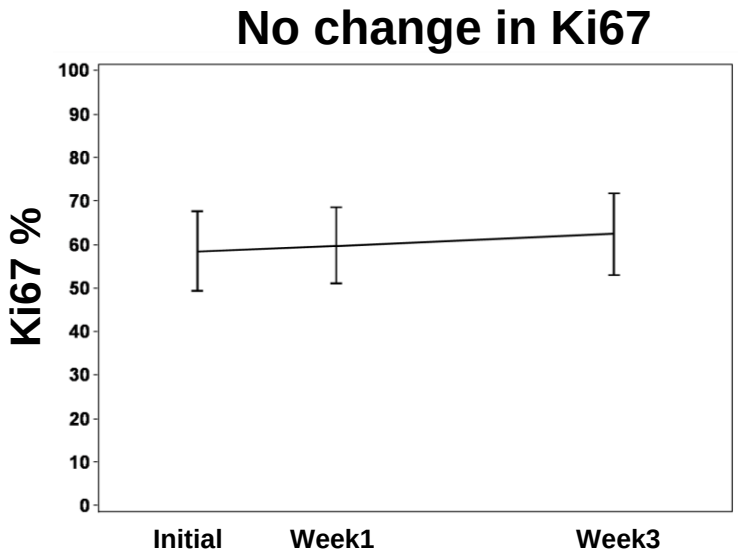
- Two sequential neoadjuvant trials
  - Trastuzumab: from 2000 to 2005
  - Lapatinib: from 2005 to 2008
- IHC 3+/ FISH amplified
- Locally advanced breast cancers (Med = 10 and 6 cm)
- Primary cancers amenable to serial biopsies
- Adequate cardiac function
- ECOG PS 0, 1

S Mohsin …J Chang (2005). JCO; 23:2460-2468
B Dave B…J Chang (2011). JCO; 29 : 166-173

Mechanism of Action: T vs. L

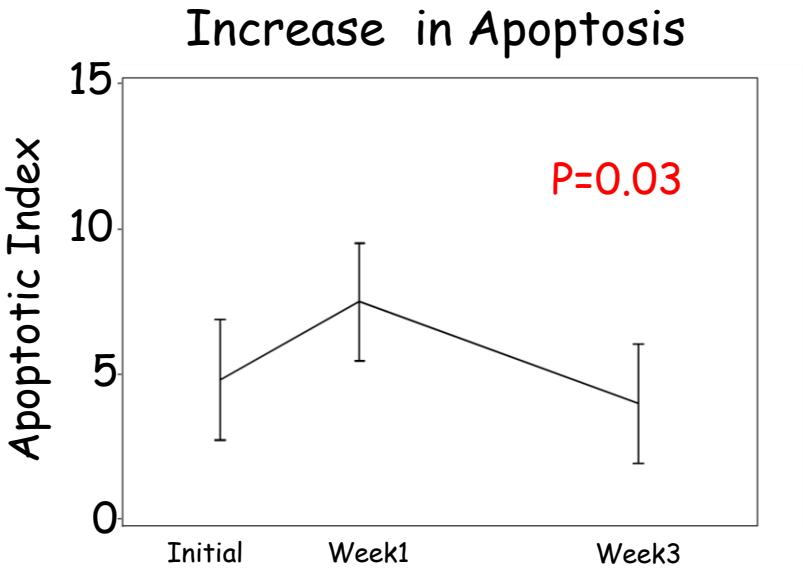
Trastuzumab:

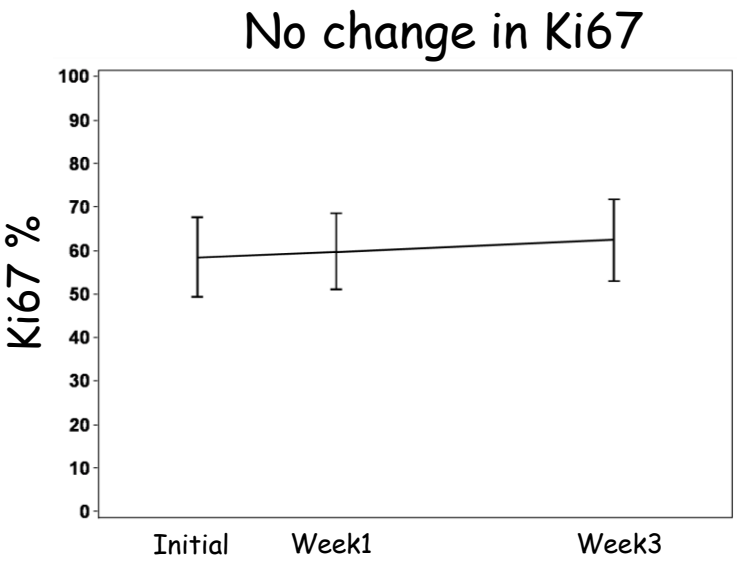




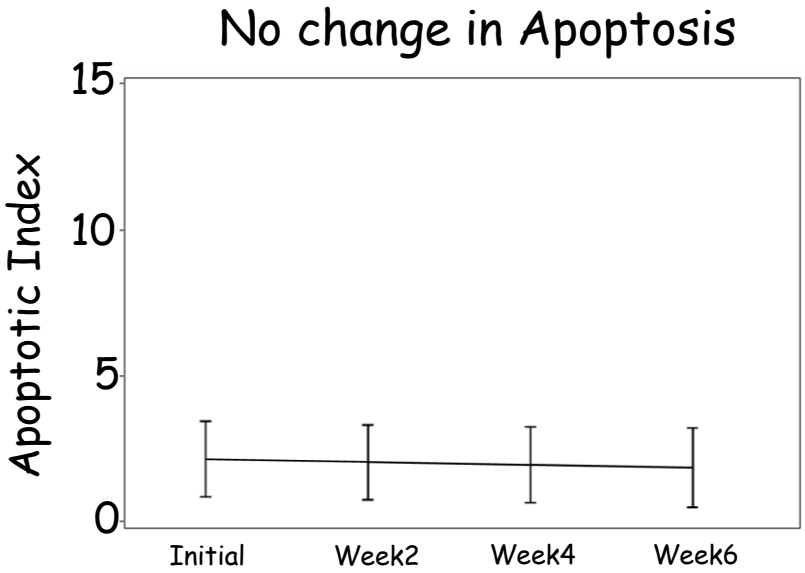
Mechanism of Action: T vs. L

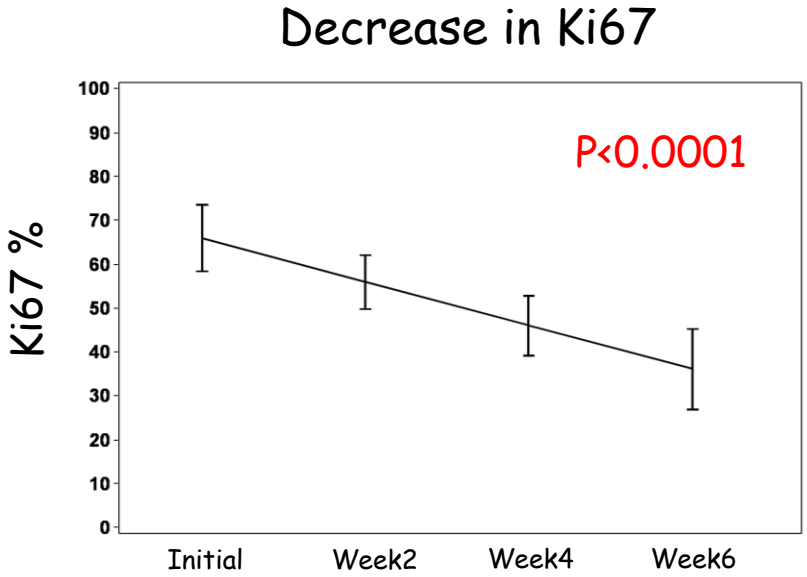
Trastuzumab:



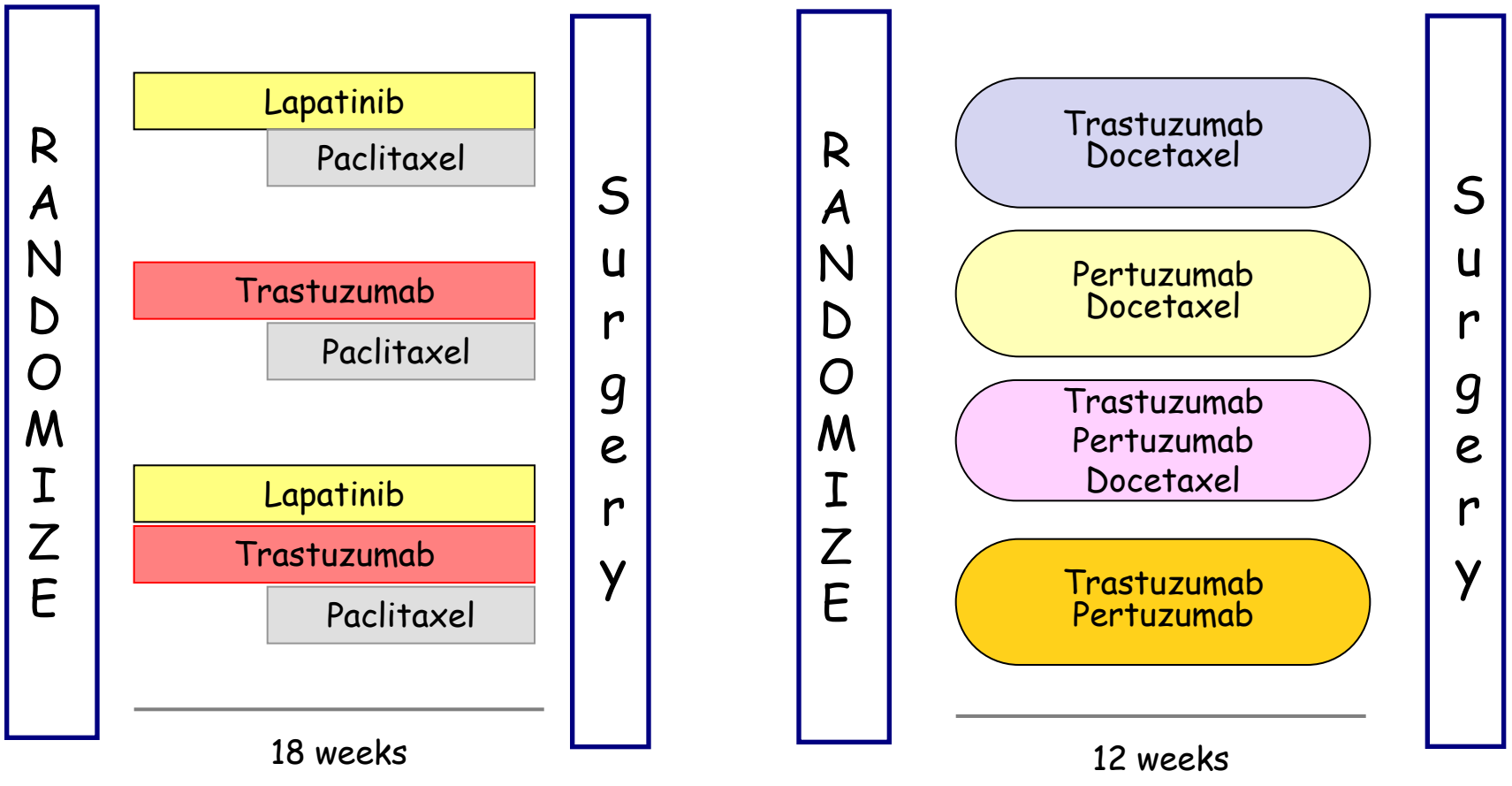


Lapatinib:





Dual Blockade with Taxanes: NeoAltto and NeoSphere: Study Design

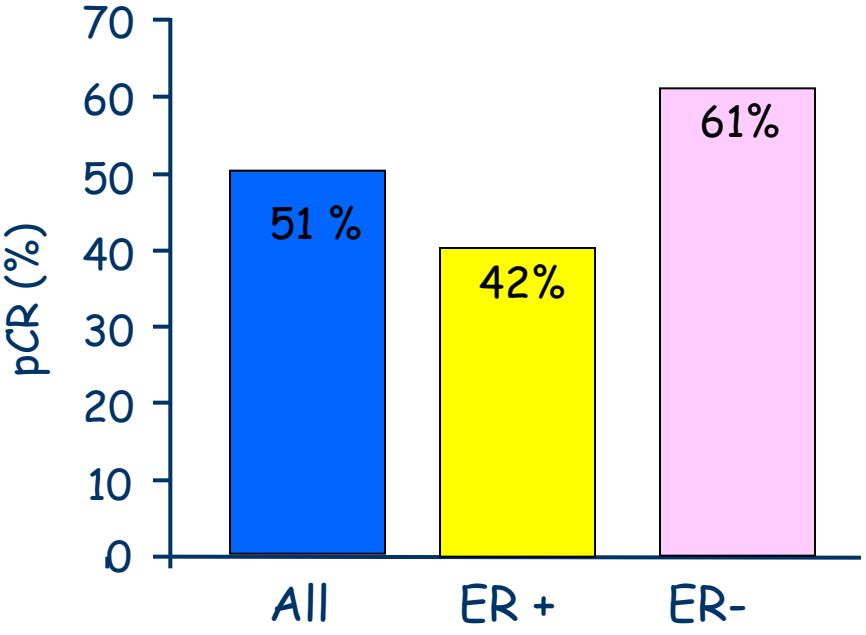


Neo-Altto

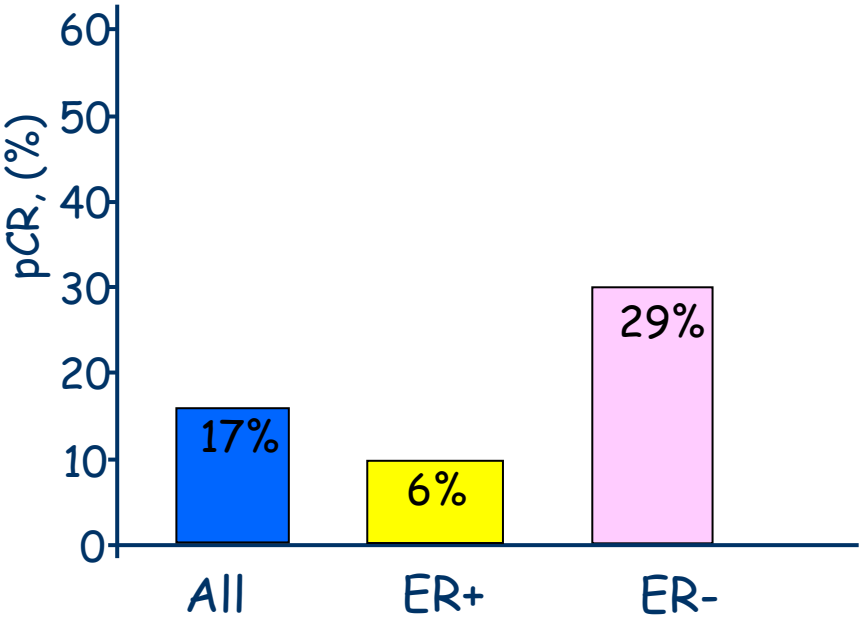
Neo-Sphere

Neo-Altto and Neo-Sphere: path CR rates

Neo-Altto (L+T+paclitaxel)



Neo-Sphere (T+P)



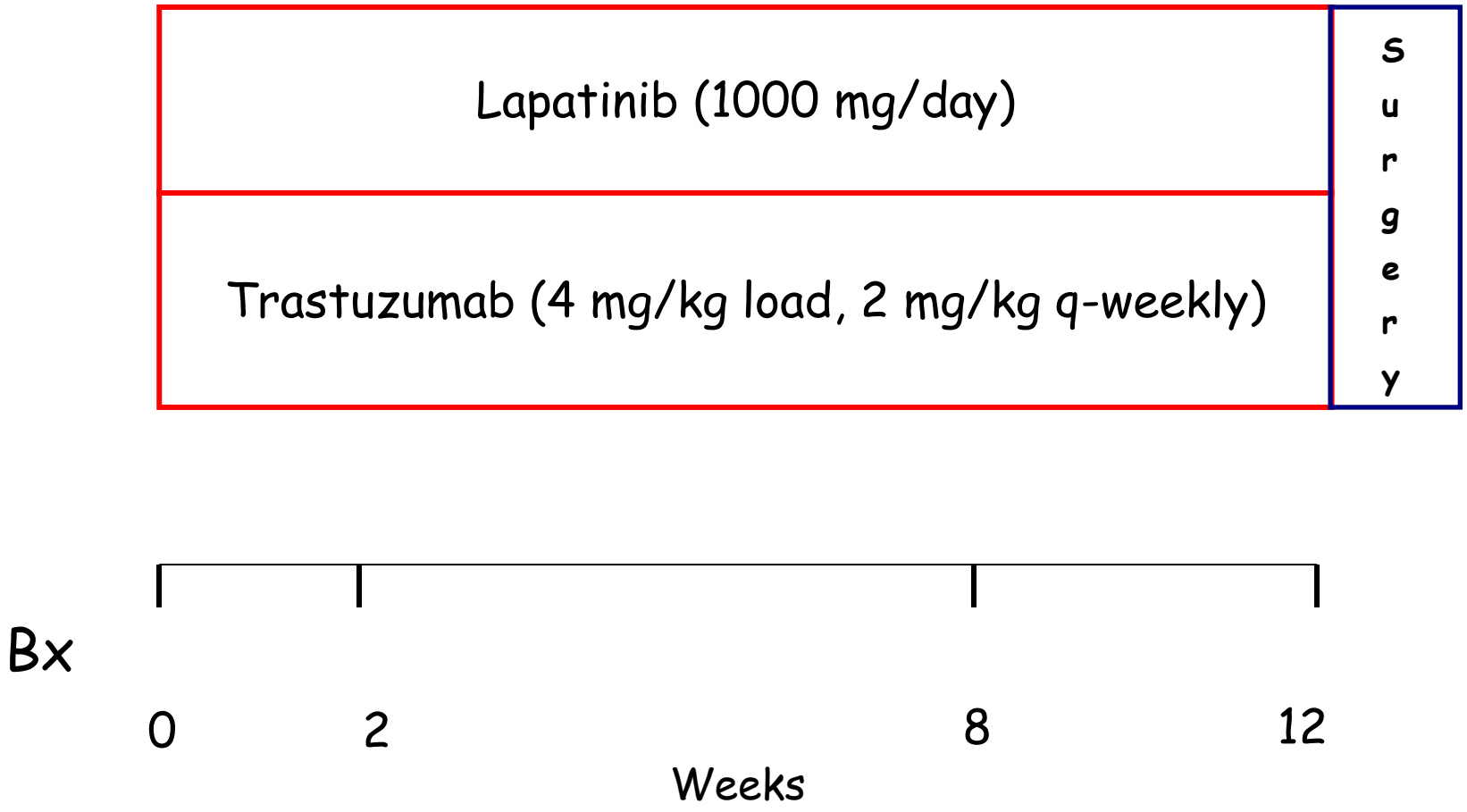
Regimen

- Neoadjuvant 12-week regimen
- Weekly T (load 4 mg/kg i.v, then 2mg/kg) + Daily L 1000 mg p.o
- ER+ patients also received letrozole (plus goserelin, if premenopausal)
- Biopsies:
  - Baseline, week 2, 8, 12 (surgery)

Eligibility Criteria

- HER2 +: IHC 3+/ FISH amplified
- T>3cm, or >2cm with palpable lymph nodes
- Adequate cardiac function
- ECOG PS 0, 1

Neoadjuvant Lapatinib & Trastuzumab Without Chemotherapy : Study Schema



Lap (L) + Tras (T) + Endocrine Rx if ER+

Pathologic Response

- Evaluated after completion of neoadjuvant therapy
- Definition:
  - pCR (path complete response):

    Absence of invasive cancer in breast

  - npCR (near path complete response):
    Residual disease (<1 cm) in breast

Patients Demographics (N=66)

- BCM, Alabama, Vanderbilt, Chicago, Mayo
- Median age: 50 years
- Median Size: 6 cm (1.5, 30cm)

  T>5 cm: 39 (62%)
- Menopausal: Pre: 36 (54%)
  Post: 30 (46%)

Patients Demographics (N=66)

- Estrogen Receptor: ER+: 41 (62%)
  ER-: 25 (38%)

- Progesterone Receptor: PR+: 29 (44%)
  PR-: 31 (47%)
  NK: 6 (9%)

- ER+/PR+: 29 (48%)
- ER+/PR-: 10 (17%)
- ER-/PR+: 0 (0%)
- ER-/PR-: 21 (32%)

Adverse Events (N=65)

- Discontinued therapy: 5 (8%)

- Grade 1-2:
  - Gastrointestinal
    - Diarrhea: 43 (66%)
    - Nausea: 20 (31%)
  - Skin
    - Acneiform rash: 30 (46%)
  - Abnormal LFTs: 16 (25%)

- Grade 3-4
  - Abnormal LFTs: 3 (<5%)

Clinical Response (N=64)

- Overall RR: 48/64 (75%)
  - Partial Response: 28/64 (44%)
  - Complete Response: 20/64 (31%)

- ER pos: 32/39 (82%)
  - Partial Response: 17/39 (44%)
  - Complete Response: 15/39 (38%)

- ER neg: 16/25 (64%)
  - Partial Response: 1125 (28%)
  - Complete Response: 5/25 (20%)

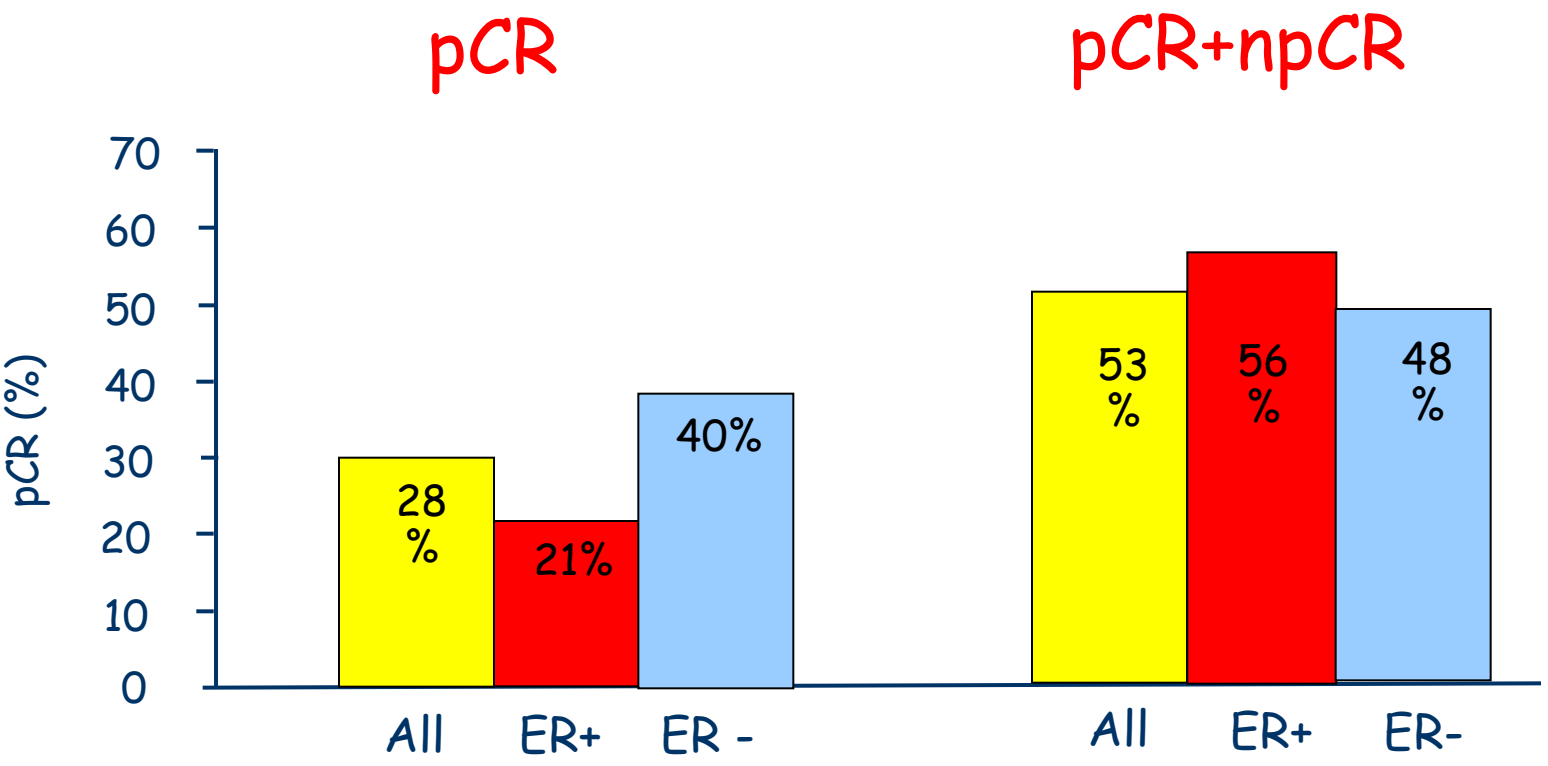
Pathologic Response (N=64)

- pCR rates: 18/64 (28%)
  - ER pos: 8/39 (21%)
  - ER neg: 10/25 (40%)

Pathologic Response (N=64)

- pCR+npCR rates: 34/64 (53%)
  - ER pos: 22/39 (56%)
  - ER neg: 12/25 (48%)

Pathologic Response



Conclusions

- Well tolerated regimen, targeted therapy alone without chemotherapy
- High clinical response rate
- High pCR rates
  - 28% pCR rate, 40% in ER neg
  - ER pos, 56% had residual disease <1cm
- HER2 blockade with lapatinb and trastuzumab with estrogen deprivation associated with high pathologic responses

Correlation of Molecular Effects and Pathologic Complete Response to Preoperative Lapatinib and Trastuzumab, Separately and Combined Prior to Neoadjuvant Breast Cancer Chemotherapy

Frankie Ann Holmes, MD

VA Espina, LA Liotta, YM Nagarwala, M Danso, K McIntyre, D Osborne, T Anderson, A Florance, J Mahoney, JA O'Shaughnessy

US Oncology Research
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Presented at the 2011 ASCO Annual Meeting. Presented data is the property of the author.

ASCO Annual '11 Meeting

Rationale

- 15% relapse despite adjuvant HER2-based therapy
- Preoperative therapy allows tumor molecular interrogation
- The mechanism of lapatinib HER2 inhibition differs from trastuzumab

Aim

- Prospectively define molecular features seen in breast tumors with pathologic complete response (pCR) or resistance (NO-pCR) to preoperative HER2-directed therapy

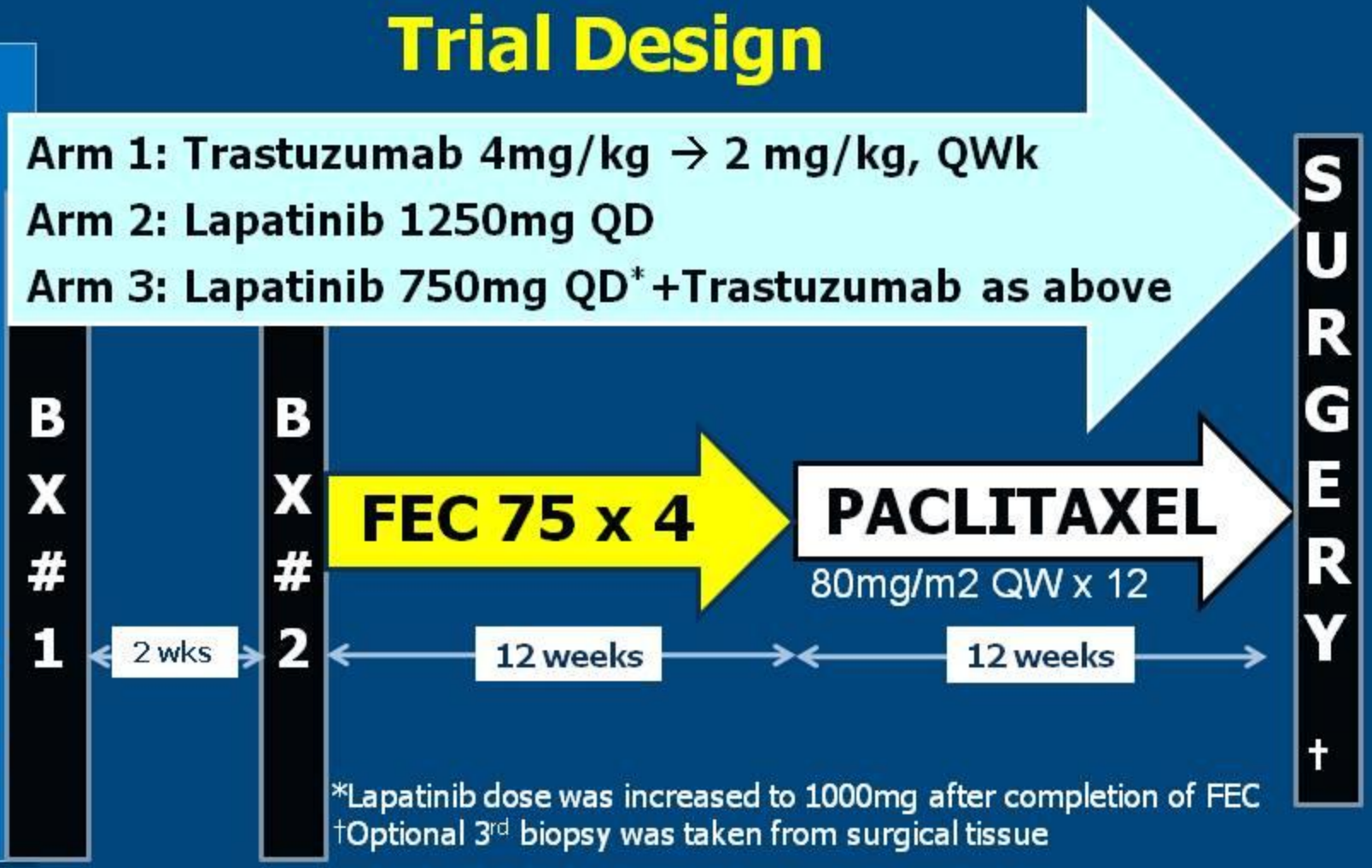
Romond EH et al. *N Engl J Med.* 2005;353(16):1673-1684
Slamon DJ et al. *Proc San Antonio Breast Cancer Symp* 2009; Abs 62

PRESENTED AT: ASCO Annual '11 Meeting

Trial Design

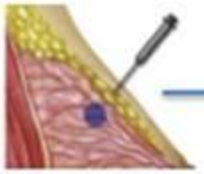
Eligibility

- Stage II, III biopsy-proven invasive, HER2 positive
- Adequate organ reserve, performance status 0-1
- Written Inf Consent



Analysis: Intention to Treat–Evaluable (ITT-E): ITT patients with evaluable tumor responses. Evaluable: ≥75% compliant to chemotherapy; had surgery

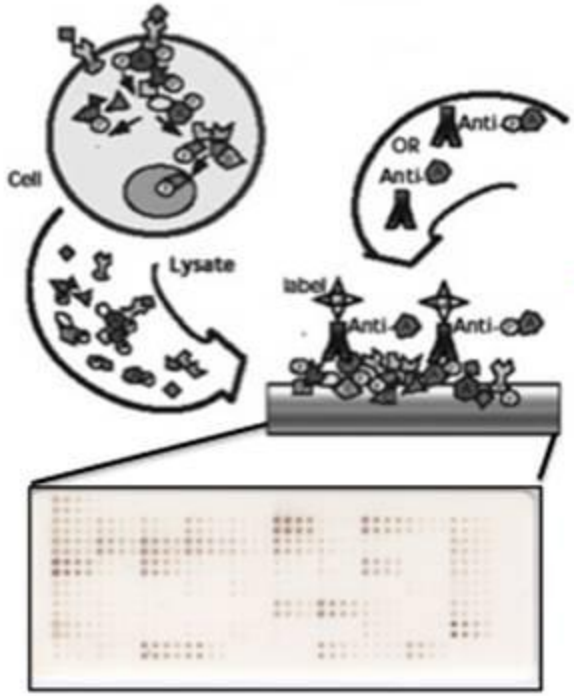
Tumor Tissue Processing



Biopsy

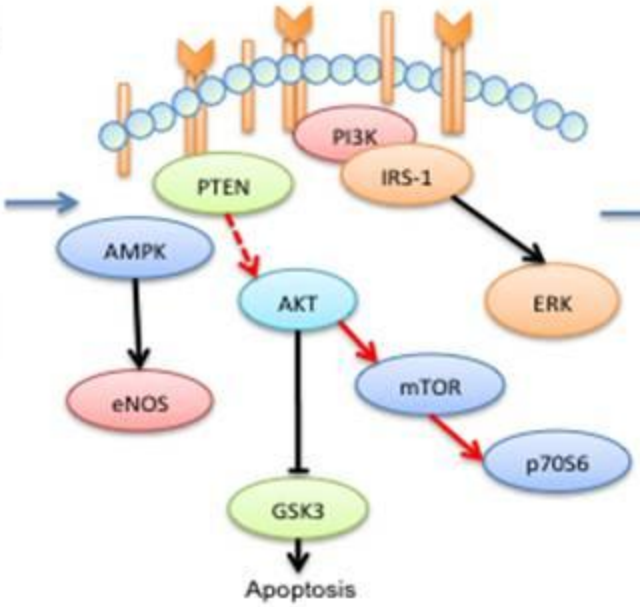
Stabilize phosphoproteins

Laser capture microdissection



Reverse phase protein microarray

More sensitive than IHC



Signal pathway map

49 evaluable pre/post biopsy pairs in 3 treatment arms:

- **Trastuzumab n=20**
- **Lapatinib n=17**
- **T + L n=12**

Patient and Tumor Characteristics: Intention to Treat (ITT)*

	T (n=33)	L (n=34)	T + L (n=33)	Total (N=100)
Median age, years	54.0	52.0	50.0	51.5
Base ECOG 0	94	88	97	93
T2/T3, %	67/24	35/32	67/18	56/25
N0/N1, %	55/36	32/47	39/42	42/42
ER+/PR+, %	45/30	41/26	58/48	48/35
IHC 3+/FISH+, %	67/82	76/71	79/70	74/74

T=trastuzumab; L=lapatinib.

*All patients randomized regardless of actual treatment.

100 pts Randomized 8/07 – 2/10
Core Needle Biopsy PRE & POST HER2-RX

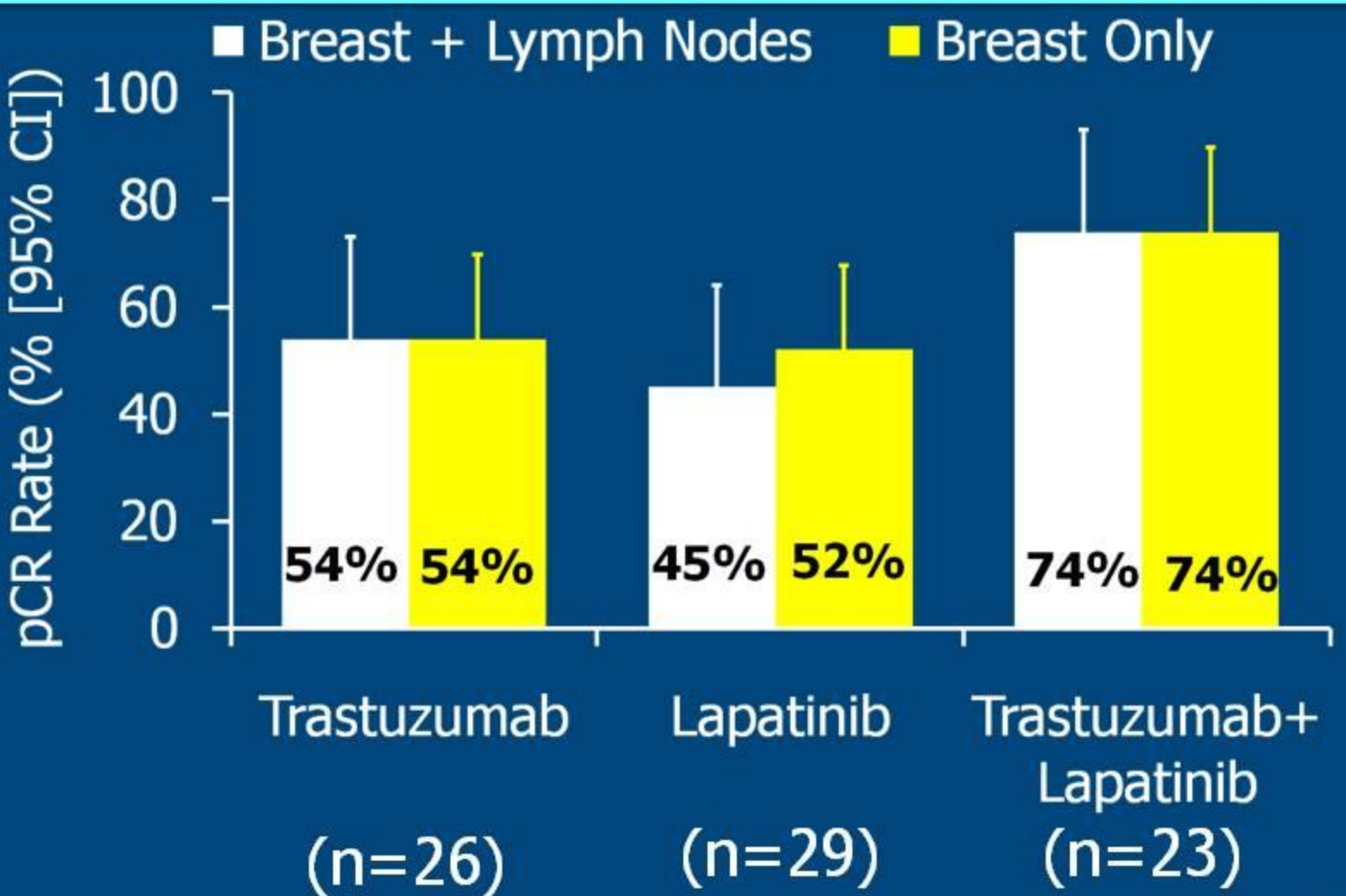
Trastuzumab	Lapatinib	T+L
n=33 (26) ♀	n=34 (29) ♀	n=33 (23) ♀
T not evaluable* n=7	L not evaluable* n=5	T+L not eval.* n=10
T not paired pre/post tx n=6	L not paired pre/post tx n=12	T+L not paired pre/post tx n=11
T pairs for analysis† n=20	L pairs for analysis n=17	T+L pairs for analysis n=12

*Inevaluable tumor responses ♀ Had Surg, >75% Rx

†Patients with paired biopsies were analyzed

PRESENTED AT: ASCO Annual '11 Meeting

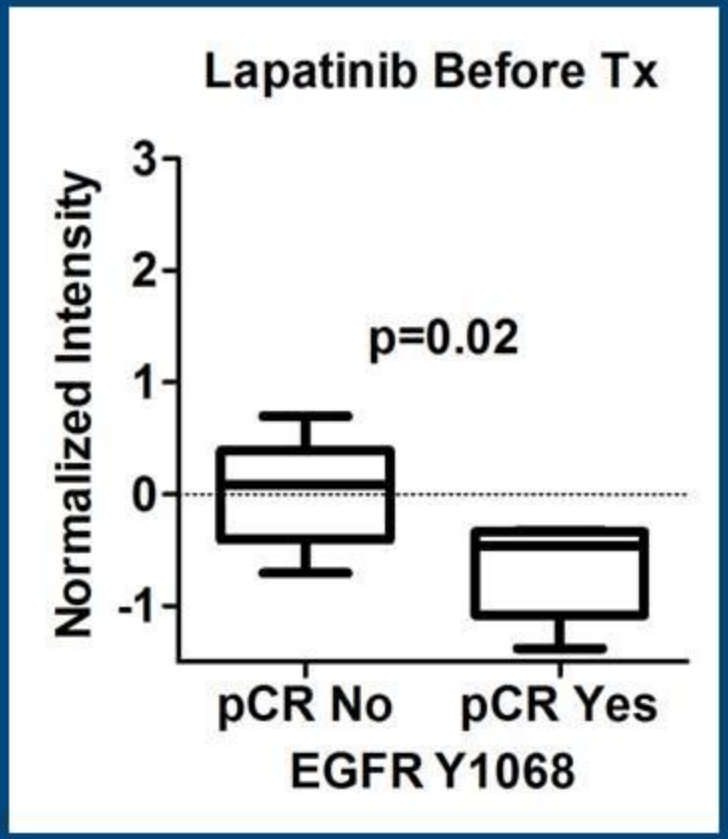
pCR in ITT-E in Breast + Lymph Nodes and Breast Only Correlated Closely



Molecular Correlations from Baseline Biopsies* with Tumor Response

- p-EGFR Tyr1068
- FOXO1A/3A-Thr 24/32
- (STAT5 – day 14*)
- Autophagy
- Tumor "social" network

Baseline EGFR-Tyr1068 Phosphorylation: Lapatinib NO-pCR



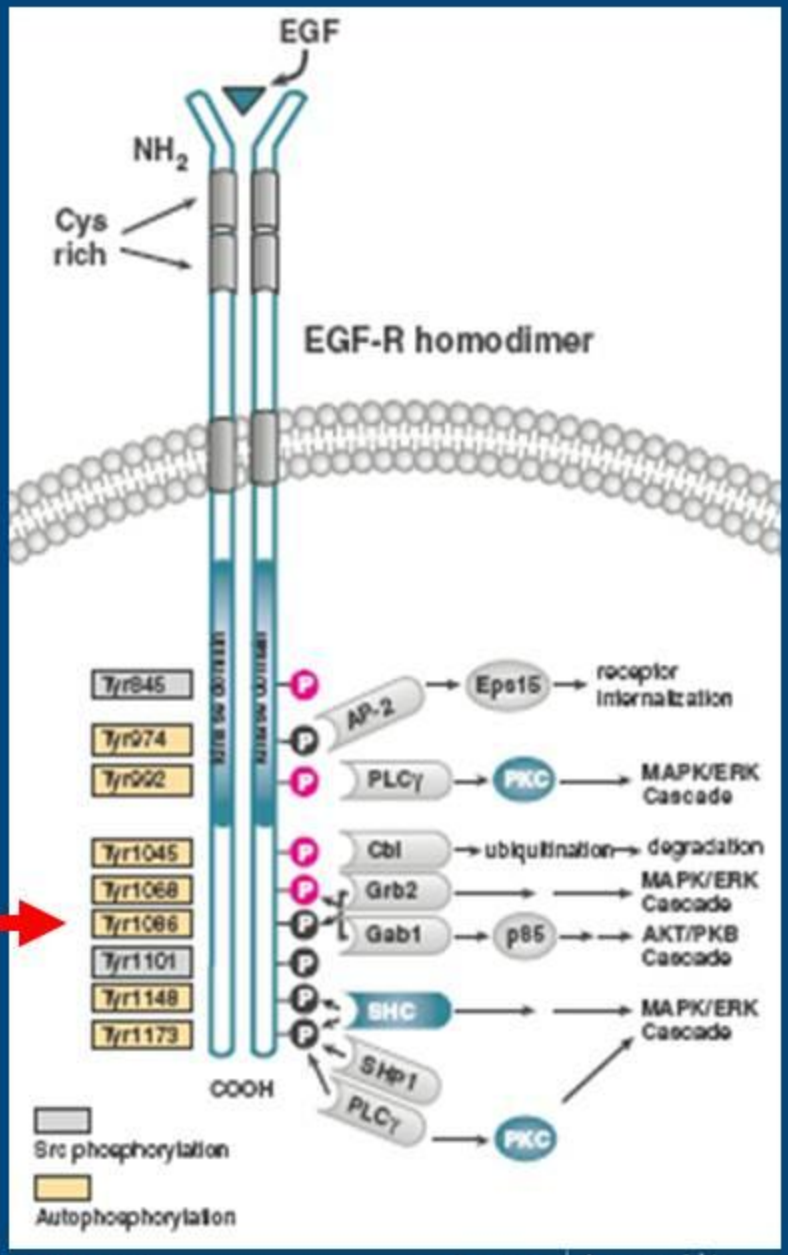
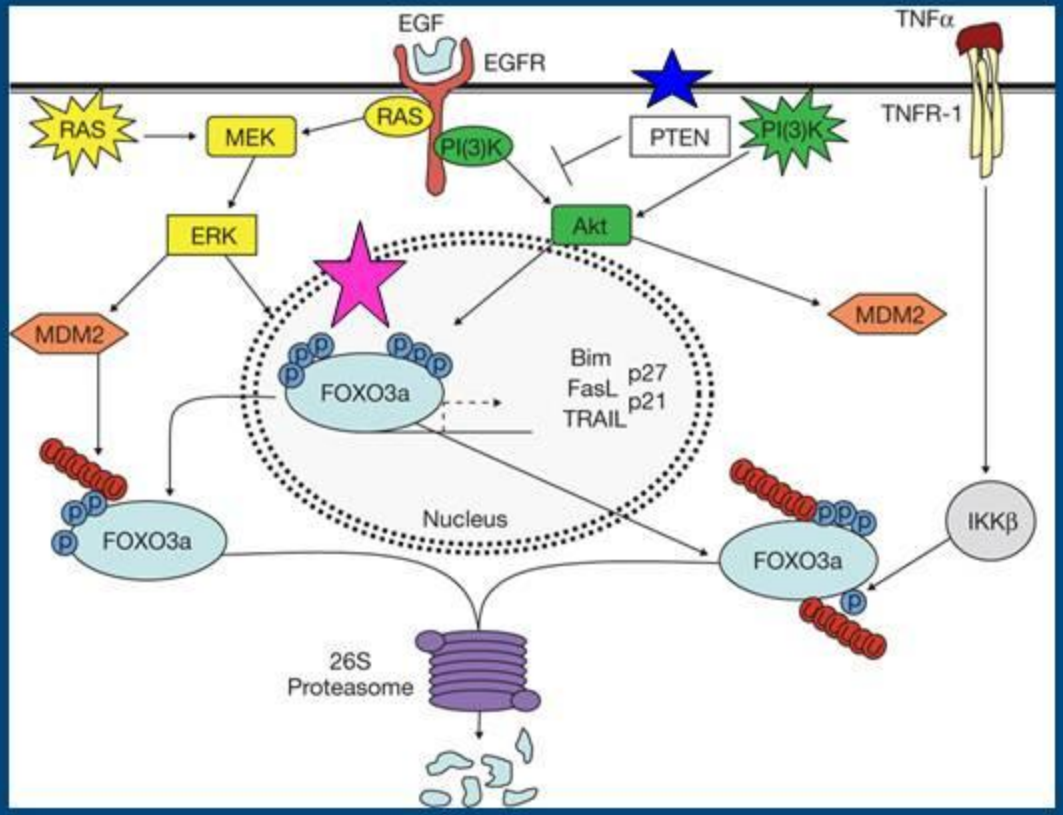


Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

FOX01/03a: Forkhead Box 03 Transcription Factor



- Triggers cell cycle arrest & apoptosis
- Must be in nucleus to do this
- Phosph'n inhibits
- →exit nucleus → no transcript'n control
- IGFR1 AKT/PI3K → p→suppress death

Krol J et al. *Mol Cancer Ther* 2007; 6(12 Pt 1):3169

Wu Y et al. *Cancer Res* 2010; 70:5475

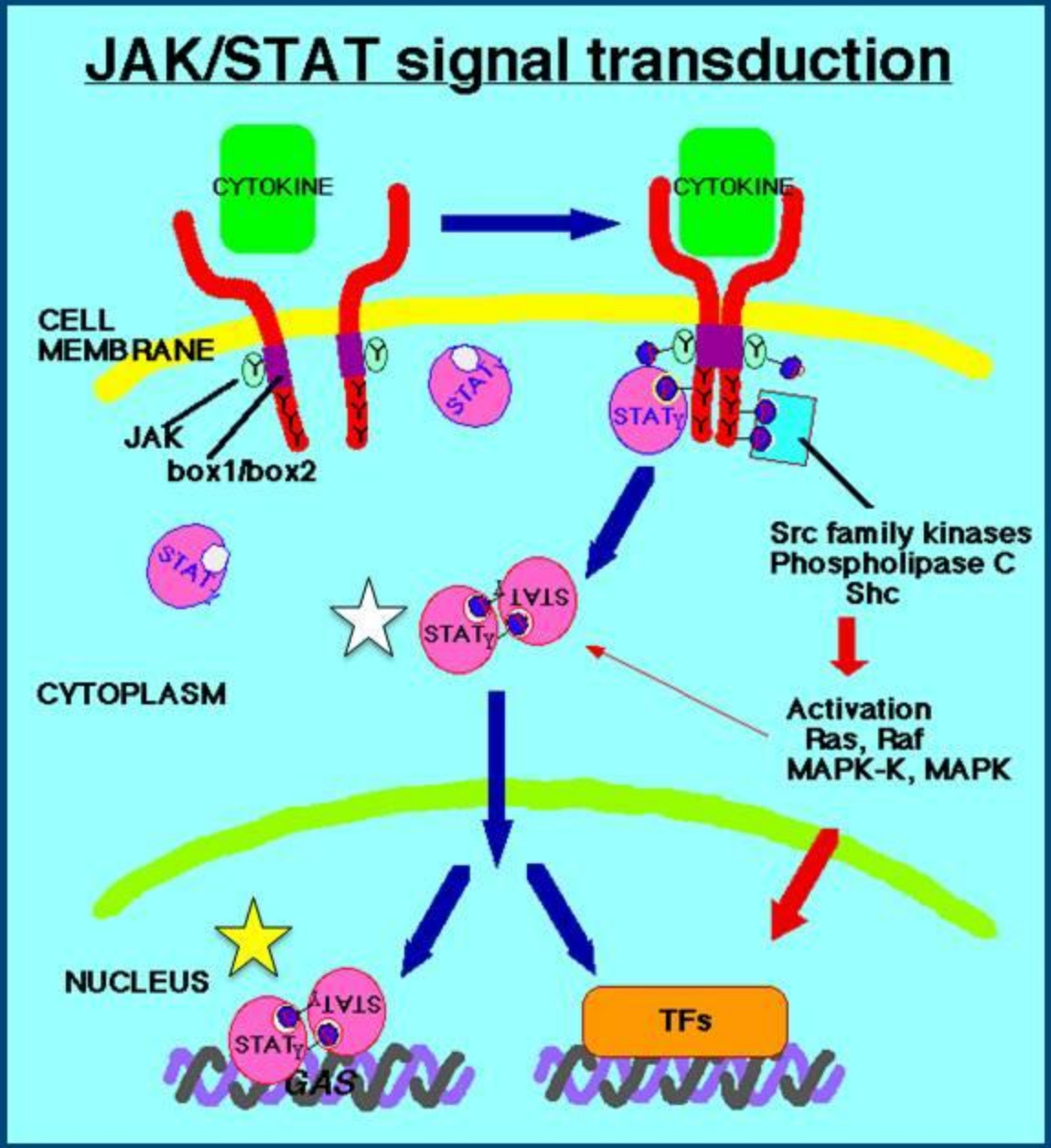
Protein Ratios in Baseline Biopsy Predictive for Subsequent pCR in ALL arms

PhosphoPTEN to phosphoFOXO (p=0.01)

- NO-pCR mean ratio= 0.04 (n=22) ★
- pCR mean ratio= 2.79 (n=27) ★

PI3 Kinase to phosphoFOXO (p=0.039)

- NO-pCR mean ratio= –0.2 (n=22)
- pCR mean ratio= 3.23 (n=27)

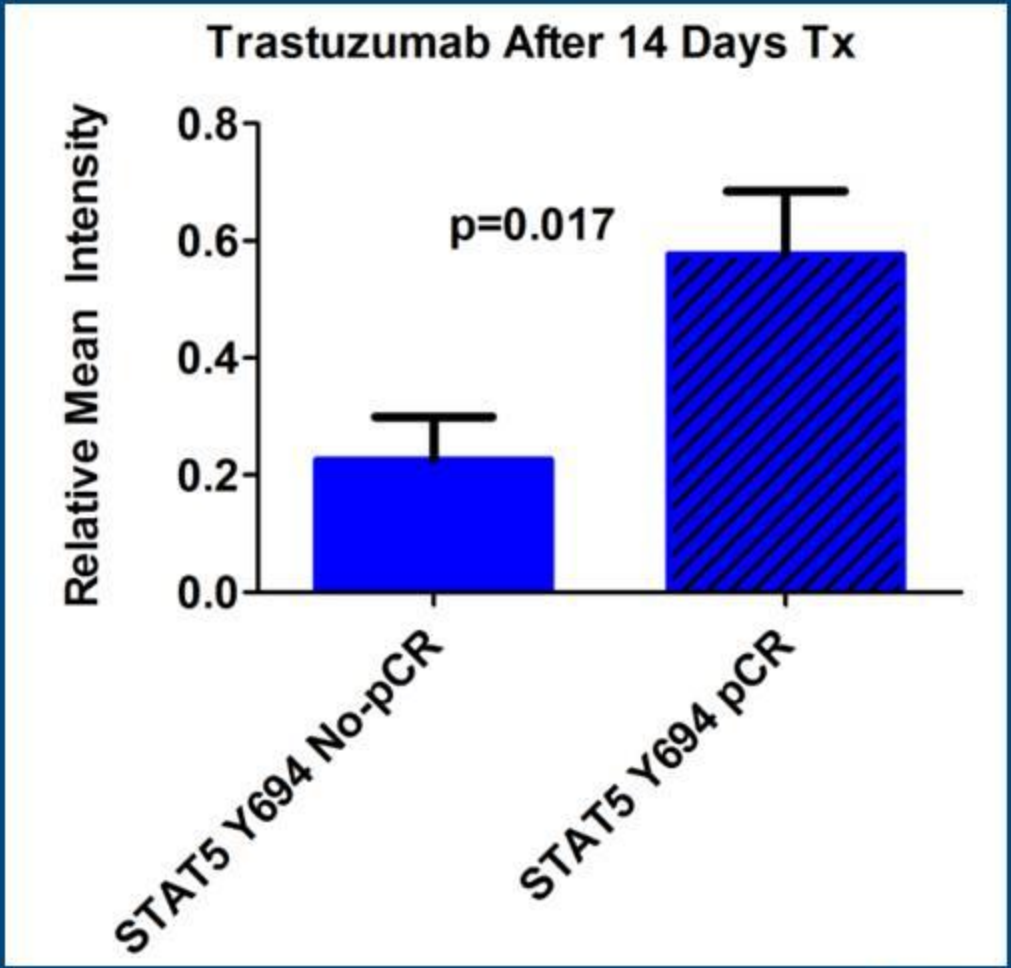


STAT5

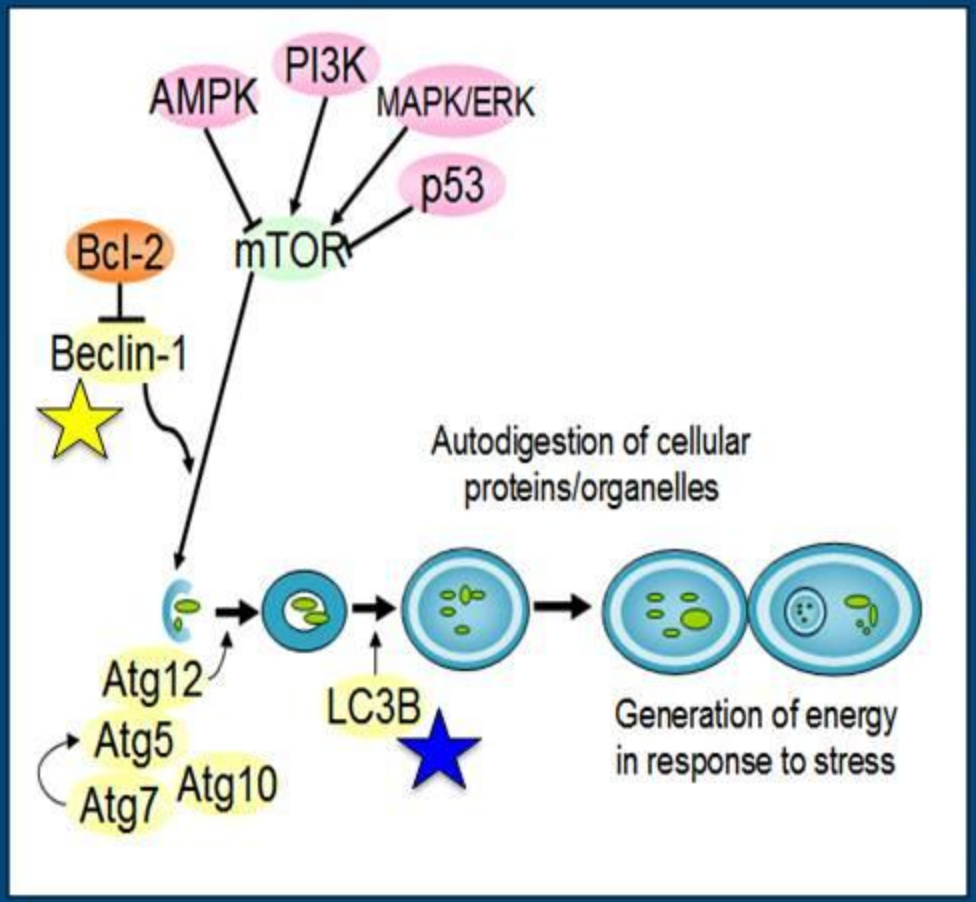
- Transcript'n factor
- downstream from EGFR, HER2
- Phosphorylat'n → activat'n, nucleus translocation
- E-cadherin
- Phosphorylation → ↓ invasion, better prognosis

Sultan Oncogene 2005; Peck JCO '11

Trastuzumab – Day 14 Proteins by pCR
Adaptive Response: pSTAT5 Increased in pCR



Autophagy Pathway Protects Cells during Starvation, Hypoxia, Stress



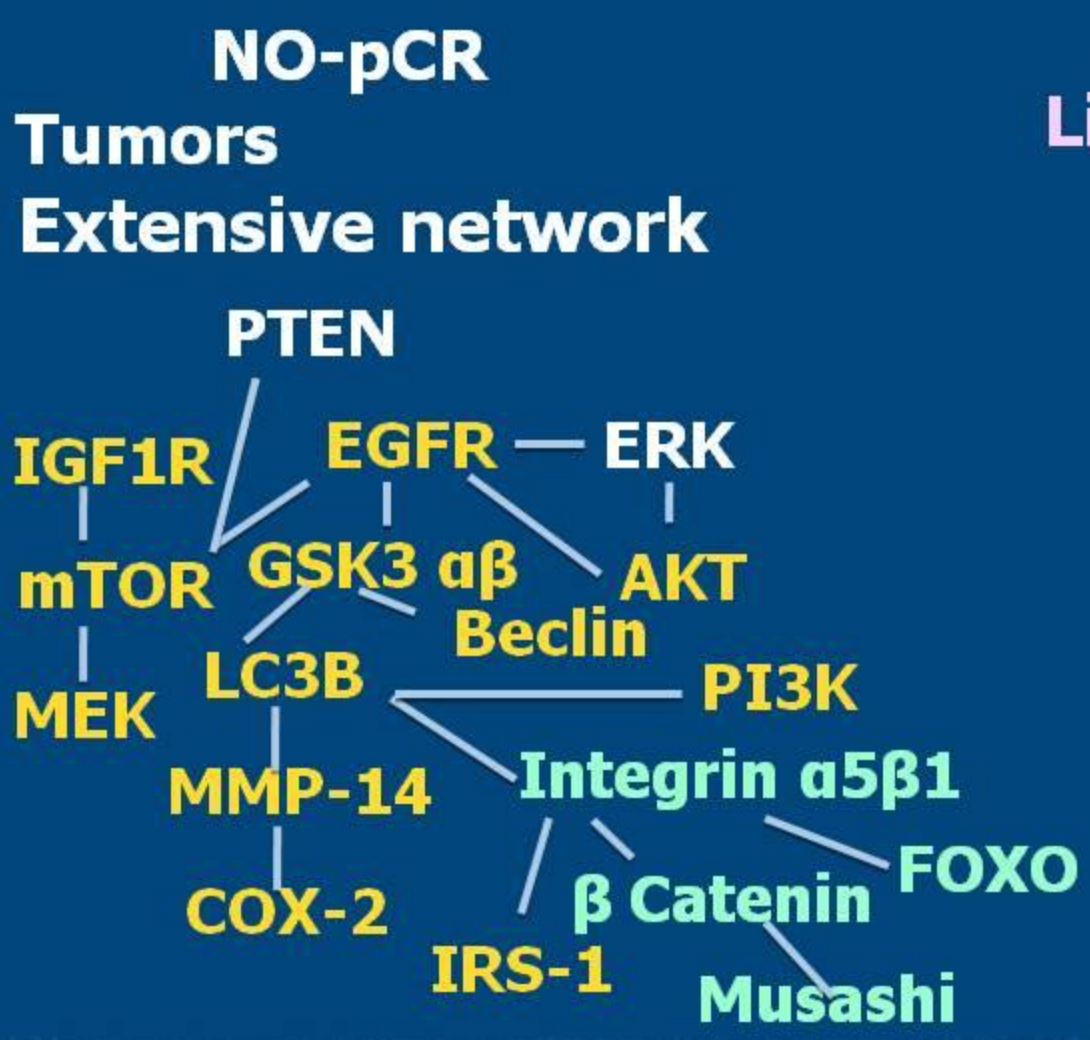
- Survival pathway in metabolic, hypoxic, chemo stress
- Active @ hypoxic tumor regions
- mTOR regulates
- Prevent cell injury from "toxic wastes" from damaged protein & organelle by digest & recycle

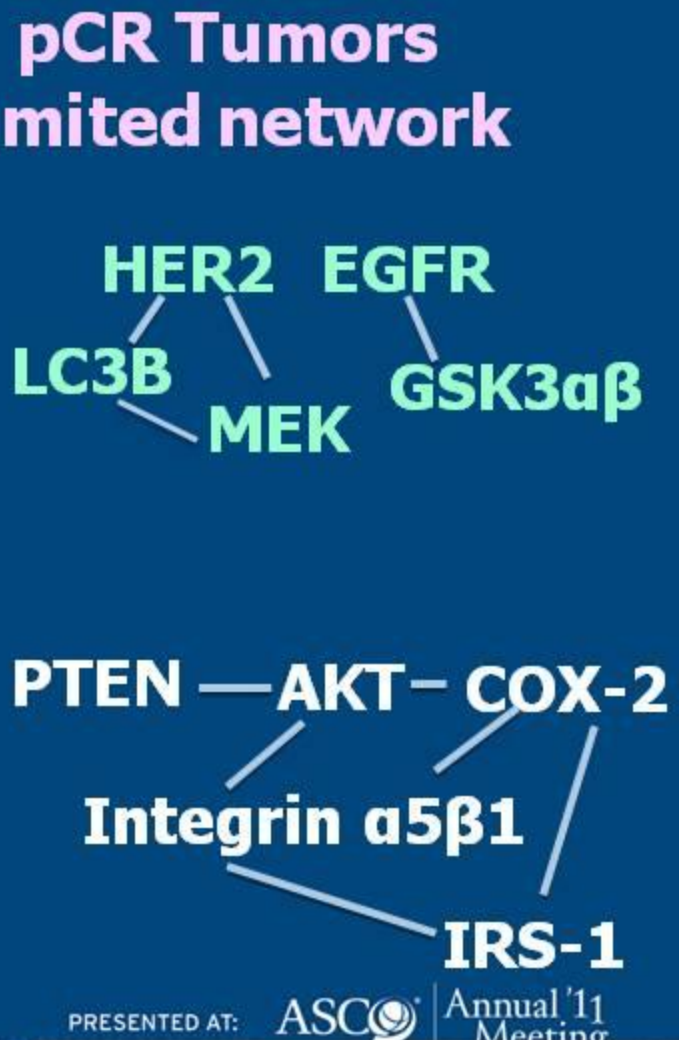
- LC3B: is marker, Beclin-1 required

Autophagy Pathway at Baseline: Activated→NO-pCR; Not Active→pCR

NO-pCR: LC3B Baseline linkage with analyte	SR (p<0.001)
• Beclin 1	0.88
• MMP14	0.83
pCR: LC3B Baseline linkage with analyte:	SR (p<0.001)
• HER2	0.88
• Stat5 Y694 w LC3B	0.86

Protein Signal Pathway Interconnections in Baseline Biopsies





Summary and Conclusions

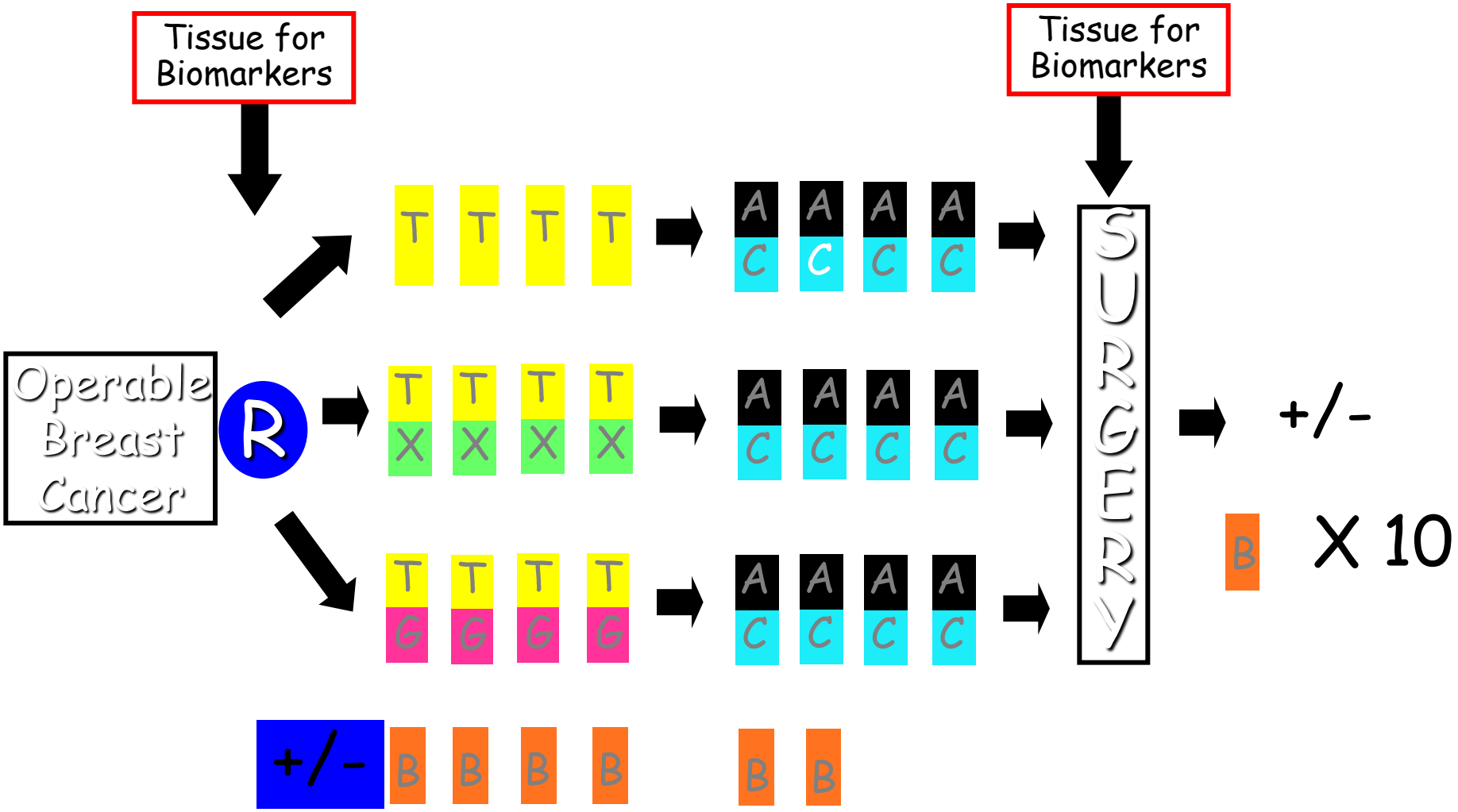
- **This exploratory study identified phenotypes of pCR/NO-pCR** from phosphorylation profiles at baseline and after a 2-week run-in of a HER2-directed agent
  - **pEGFR Tyr1068 baseline**: Lapatinib NO-pCR;
  - **Baseline ratios of pFOXO** to PTEN, PI3K correlated with response
  - **pSTAT5** after trastuzumab correlated with pCR
  - Activation of autophagy at baseline correlated with NO-pCR to ALL therapies
  - **NO pCR tumors** are **highly networked**
- The **pathway to accelerating the cure of breast cancer** is in **every oncologist's office** if networked to high quality, tissue-based research trials.

NSABP Protocol B-40
The Effect on pCR of Bevacizumab and/or Antimetabolites Added to Standard Neoadjuvant Chemotherapy

Harry D. Bear, Gong Tang, Priya Rastogi, Charles E. Geyer, Jr., André Robidoux, James N. Atkins, Luis Baez-Diaz, Adam Brufsky, Rita S. Mehta, Louis Fehrenbacher, Eduardo R. Pajon, Francis M. Senecal, Rakesh Gaur, Richard G. Margolese, Paul T. Adams, Howard M. Gross, Joseph P. Costantino, Sandra M. Swain, Elfetherios P. Mamounas, Norman Wolmark

NSABP®

NSABP B-40



Endpoints: pCR, cCR, DFS, gene expression patterns

NSABP B-40
Primary Aims

- To determine whether adding capecitabine or gemcitabine to docetaxel followed by AC will increase the pathologic complete response (pCR) rates in the breast
  - pCR = no invasive cancer in breast; may have DCIS

- To determine whether the addition of bevacizumab to docetaxel/anthracycline-based regimens will increase pCR rates in the breast

NSABP B-40
Selected Patient Eligibility Criteria

- Palpable tumor; diameter ≥ 2.0 cm
- Invasive adenocarcinoma by *core needle biopsy*
- HER-2 negative
- T2 or T3 tumor
- cN0, cN1 or cN2a
- Normal LVEF

NSABP B-40 Stratification Factors

- Clinical Tumor Size (2.0 - 4.0 cm, > 4.0 cm)
- Clinical Nodal Status (negative, positive)
- Hormone Receptor Status (ER-positive and/or PgR-positive, ER- and PgR-negative)
- Age (< 50, ≥ 50)

NSABP B-40 Accrual

- Accrued 1,206 patients over 42 months
  (1/5/2007 – 6/30/2010)

NSABP B-40
Patient Characteristics

- Age
  - ≤ 49 52%
  - 50 - 59 32%
  - ≥ 60 16%
- Race
  - White 83%
  - Black 13%
  - Other/Unk 3%

- Tumor size
  - 2-4 cm 46%
  - > 4 cm 54%
- Clinical Nodal Status
  - Pos. 47%
  - Neg. 53%

NSABP B-40
Patient Characteristics

- Tumor Grade*
  - Well 7%
  - Moderate 36%
  - Poor 56%
  - Unknown 1%

- HR status*
  - «Pos. 59%
  - «Neg. 41%

* Based on institutional assessments

NSABP B-40
Primary Aims

- To determine whether adding capecitabine or gemcitabine to docetaxel followed by AC will increase the pathologic complete response (pCR) rates in the breast

- To determine whether the addition of bevacizumab to docetaxel/anthracycline-based regimens will increase pCR rates in the breast

NSABP B-40
Overall Maximum Toxicity* (%)

GRADE	T → AC (396)	TX → AC (399)	TG→AC (396)
0-2	45	31	27
3	48	55	61
4	7	14	12
5	<1	<1	0

* Toxicity information available from 1191 patients.

3-31-11

NSABP B-40
Neutropenia* (%)

GRADE	T → AC (396)	TX → AC (399)	TG→AC (396)
0-2	85	79	65
3	10	13	26
4	5	7	9
5	0	0	0

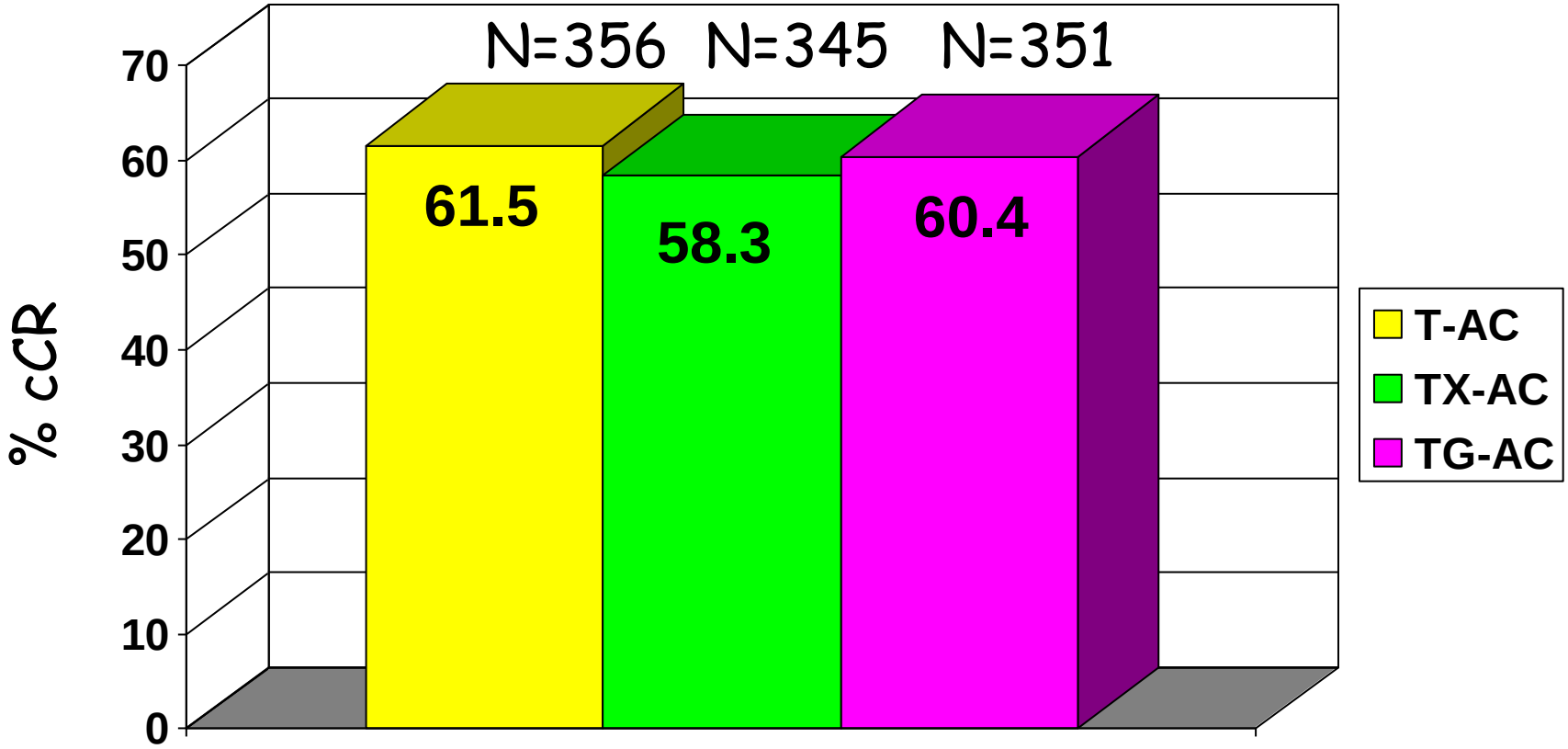
* Toxicity information available from 1191 patients.

NSABP B-40
Hand-Foot Syndrome* (%)

GRADE	T → AC (396)	TX → AC (399)	TG→AC (396)
0-2	97	77	99
3	3	23	1

* Toxicity information available from 1191 patients.

NSABP B-40
Clinical Complete Responses After All Neoadjuvant Therapy by Chemotherapy Regimen



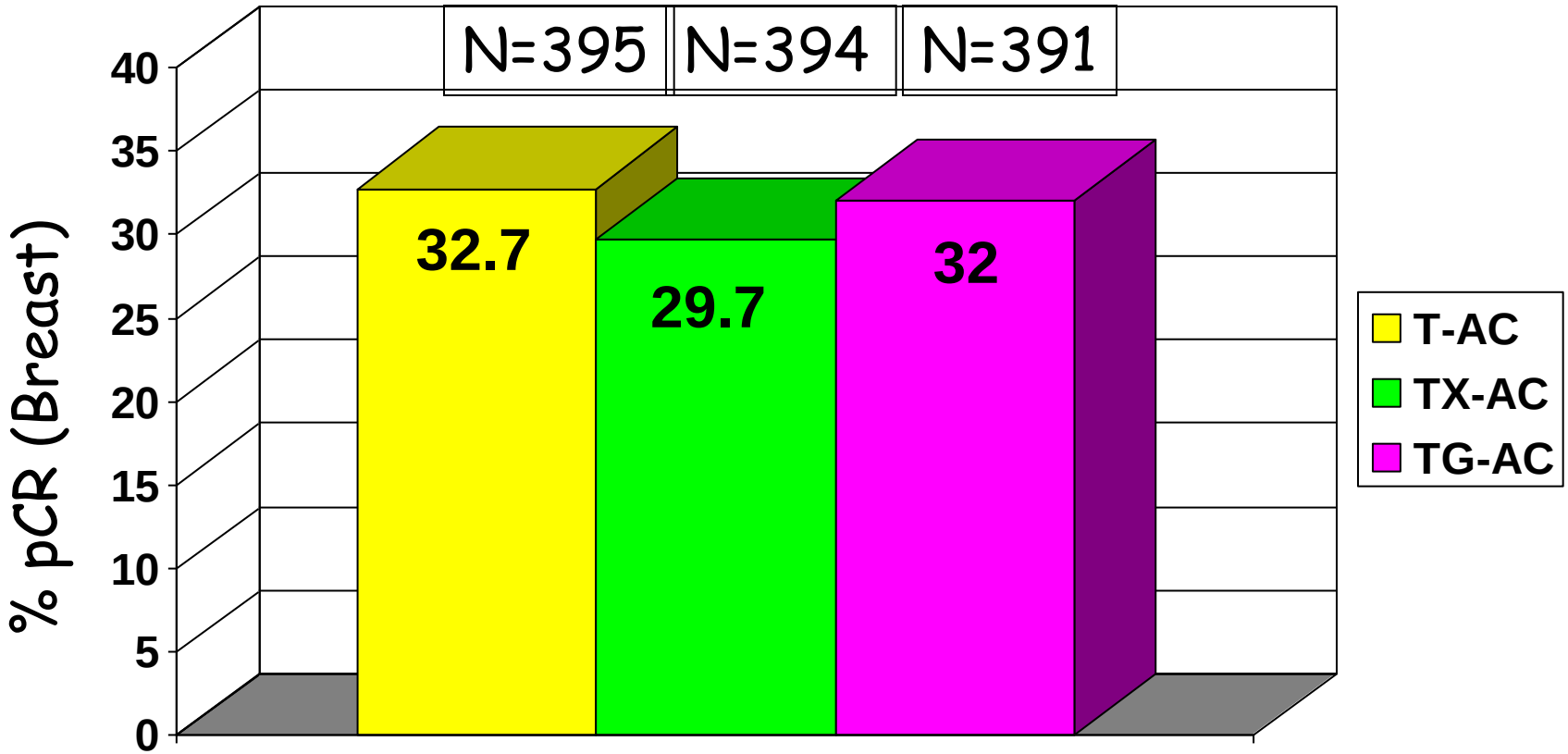
Chi-square test for cCR: T→AC vs. TX→AC (p=0.422)
T→AC vs. TG→AC (p=0.82)

# of missing clinical response status=154

NSABP B-40
Surgery Type

	T→AC	TX→AC	TG→AC
No surgery	2 (<1)	7 (2)	5 (1)
Lumpectomy	179 (45)	171 (43)	196 (50)
Mastectomy	213 (54)	221 (55)	194 (49)
Total	394	399	395

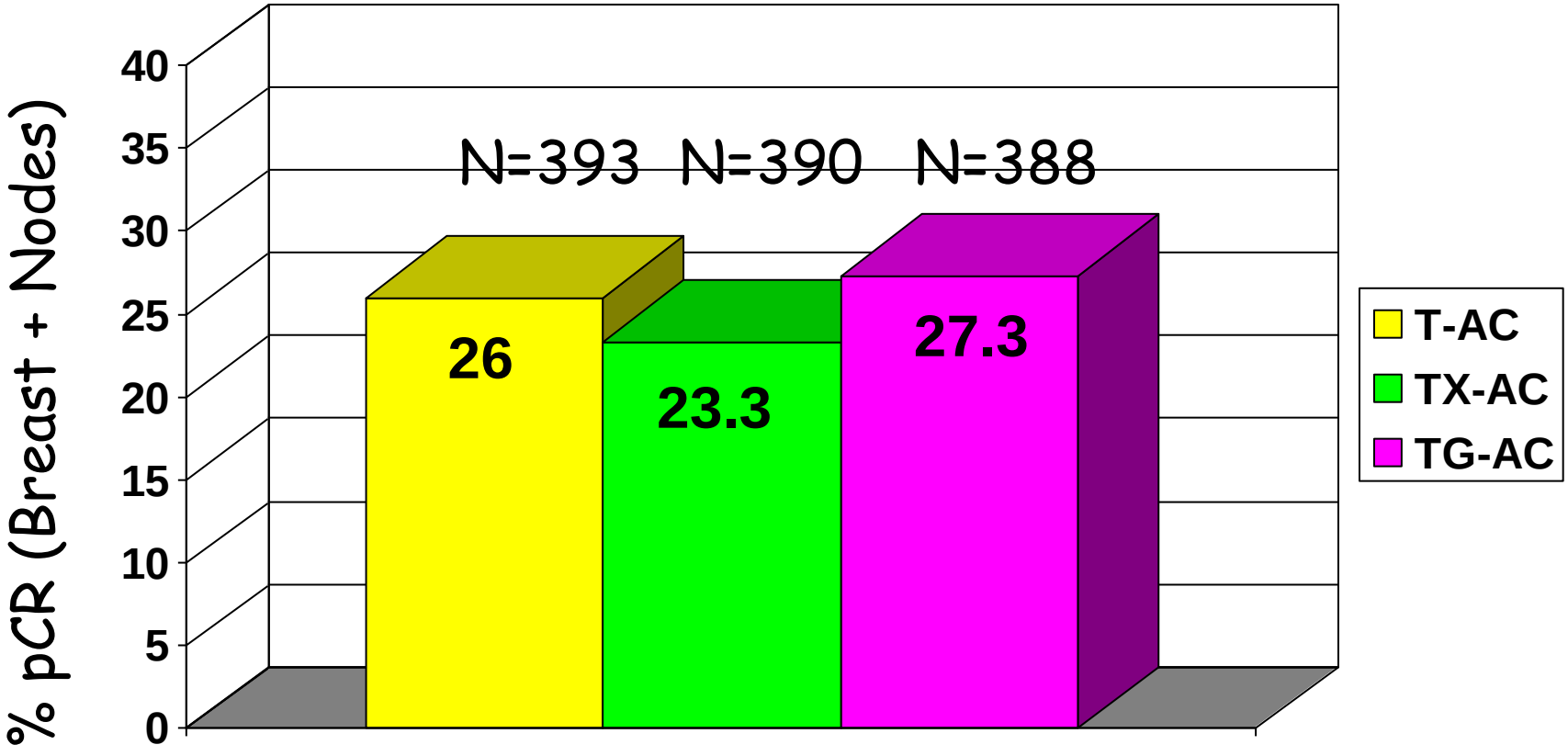
NSABP B-40
Pathologic Complete Response (Breast)



Chi-square test: T→AC vs TC→AC (p=0.411)
T→AC vs.TG→AC (p=0.896)

NSABP B-40

Pathologic Complete Response (Breast and Nodes)



Chi-square test: T→AC vs. TC→AC (p=0.443)
T→AC vs. TG→AC (p=0.726)

NSABP B-40
Primary Aims

- To determine whether adding capecitabine or gemcitabine to docetaxel followed by AC will increase the pathologic complete response (pCR) rates in the breast

- To determine whether the addition of bevacizumab to docetaxel/anthracycline-based regimens will increase pCR rates in the breast

NSABP B-40
Overall Maximum Toxicity* (%)

GRADE	w/o BEV (596)	BEV (595)
0-2	41	27
3	49	61
4	9	12
5	<1	<1

* Toxicity information available from 1191 patients.

NSABP B-40
Hypertension* (%)

GRADE	w/o BEV (596)	BEV (595)
2	1	13
3	<1	10
4	0	<1
5	0	0

* Toxicity information available from 1191 patients.

NSABP B-40
Hand-Foot Syndrome* (%)

GRADE	w/o BEV (596)	BEV (595)
2	11	15
3	8	11

* Toxicity information available from 1191 patients.

NSABP B-40
Mucositis* (%)

GRADE	w/o BEV (596)	BEV (595)
2	10	20
3	3	5
4	0	0
5	0	0

* Functional/Symptomatic

Toxicity information available from 1191 patients.

NSABP B-40
Left Ventricular Systolic Dysfunction* (%)

GRADE	w/o BEV (596)	BEV (595)
0-2	100	99
3	<1	1
4	<1	<1
5	0	0

* Toxicity information available from 1191 patients.

NSABP B-40

Completion/Discontinuation of Neoadjuvant Treatment in Arms *Without* BEV

	N=580
Completed neoadjuvant per protocol	488 (84%)
Discontinued early	92 (16%)
- AE from docetaxel	16 (3%)
- AE from AC	11 (2%)
- AE from multiple therapies	6 (1%)
- New lesion/progression	27 (5%)
- Alternative therapy	8 (1%)
- Death	1 (<1%)
- Other	23 (4%)

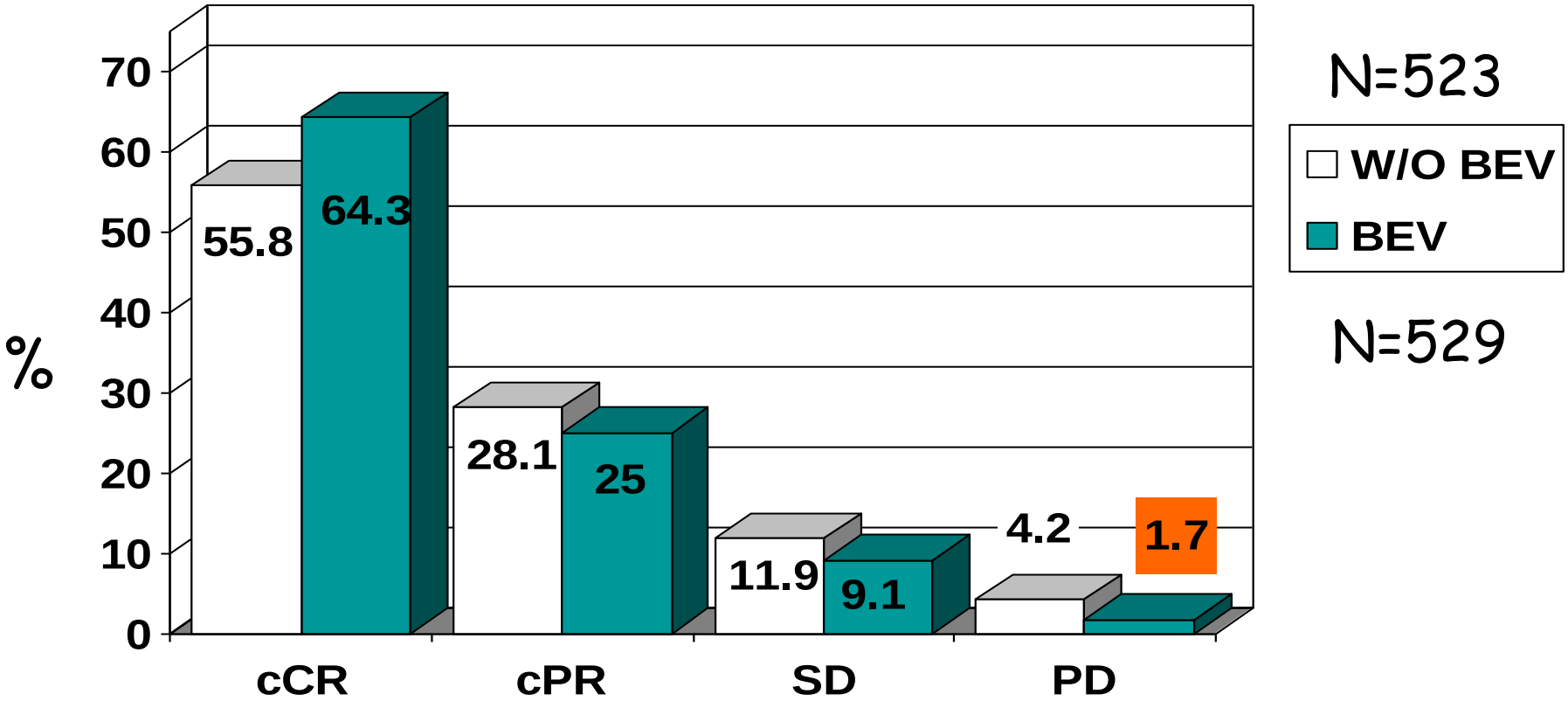
NSABP B-40

Completion/Discontinuation of Neoadjuvant Treatment in Arms *With* BEV

	N=576
Completed neoadjuvant per protocol	460 (80%)
Discontinued	116 (20%)
- AE from docetaxel	12 (2%)
- AE from AC	10 (2%)
- AE from Bev	30 (5%)
- AE from multiple therapies	25 (4%)
- New lesion/progression	10 (2%)
- Alternative therapy	2 (<1%)
- Death	0 (0%)
- Other	27 (5%)

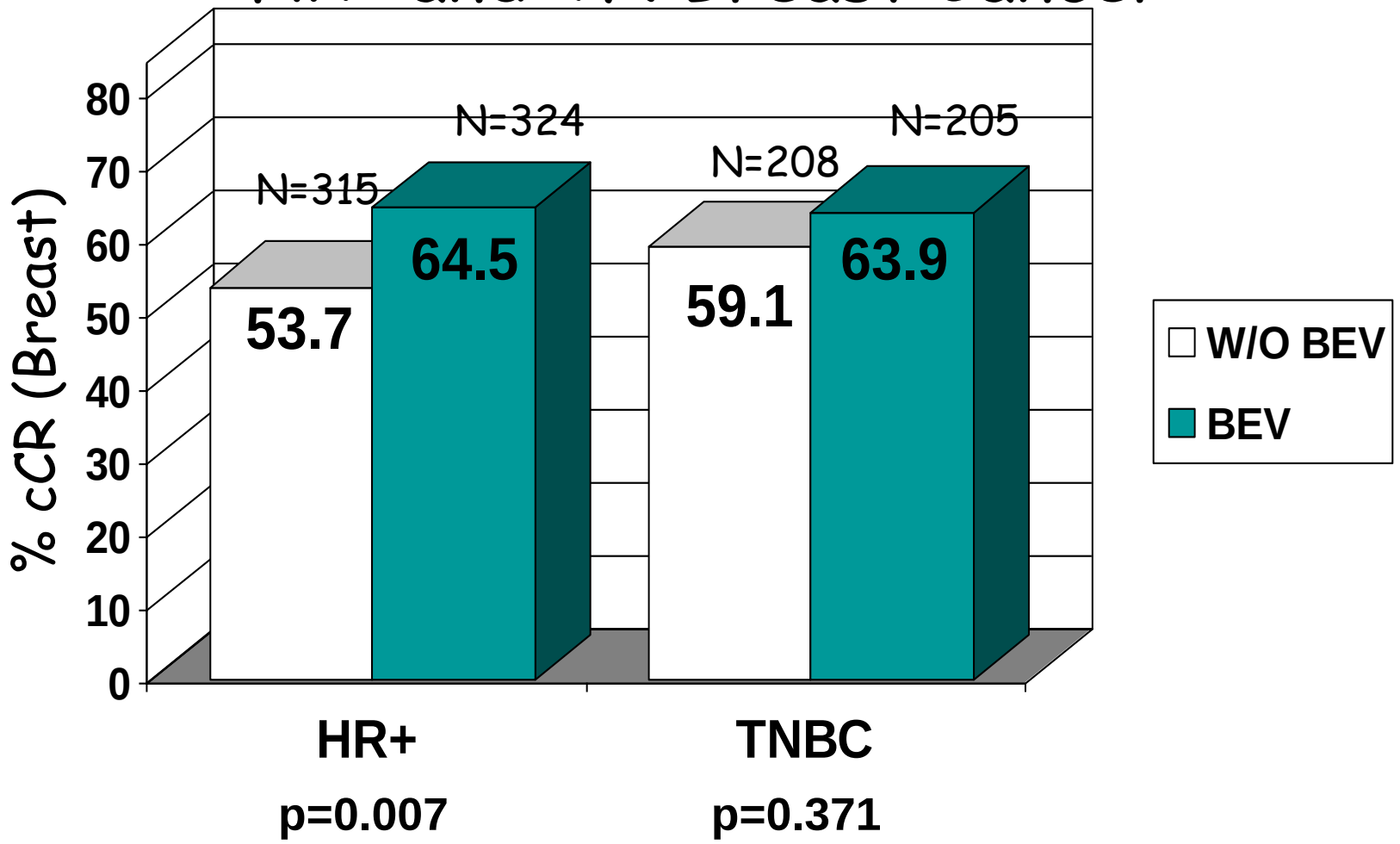
NSABP B-40

Clinical Responses After All Neoadjuvant Therapy Based on Bevacizumab Administration



Chi-square test for cCR: p=0.006

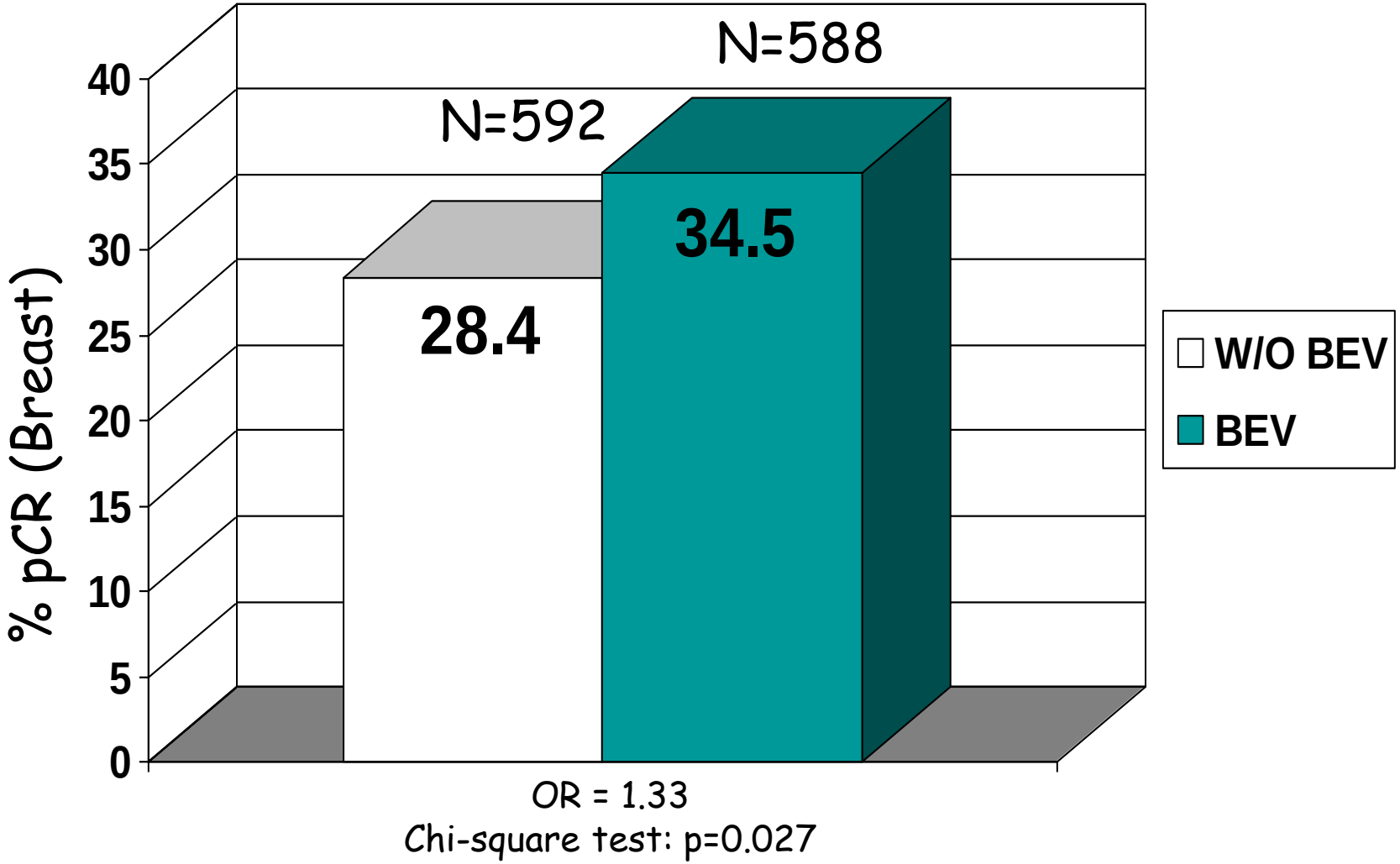
NSABP B-40
Clinical Complete Responses for HR+ and TN Breast Cancer



NSABP B-40
Surgery Type

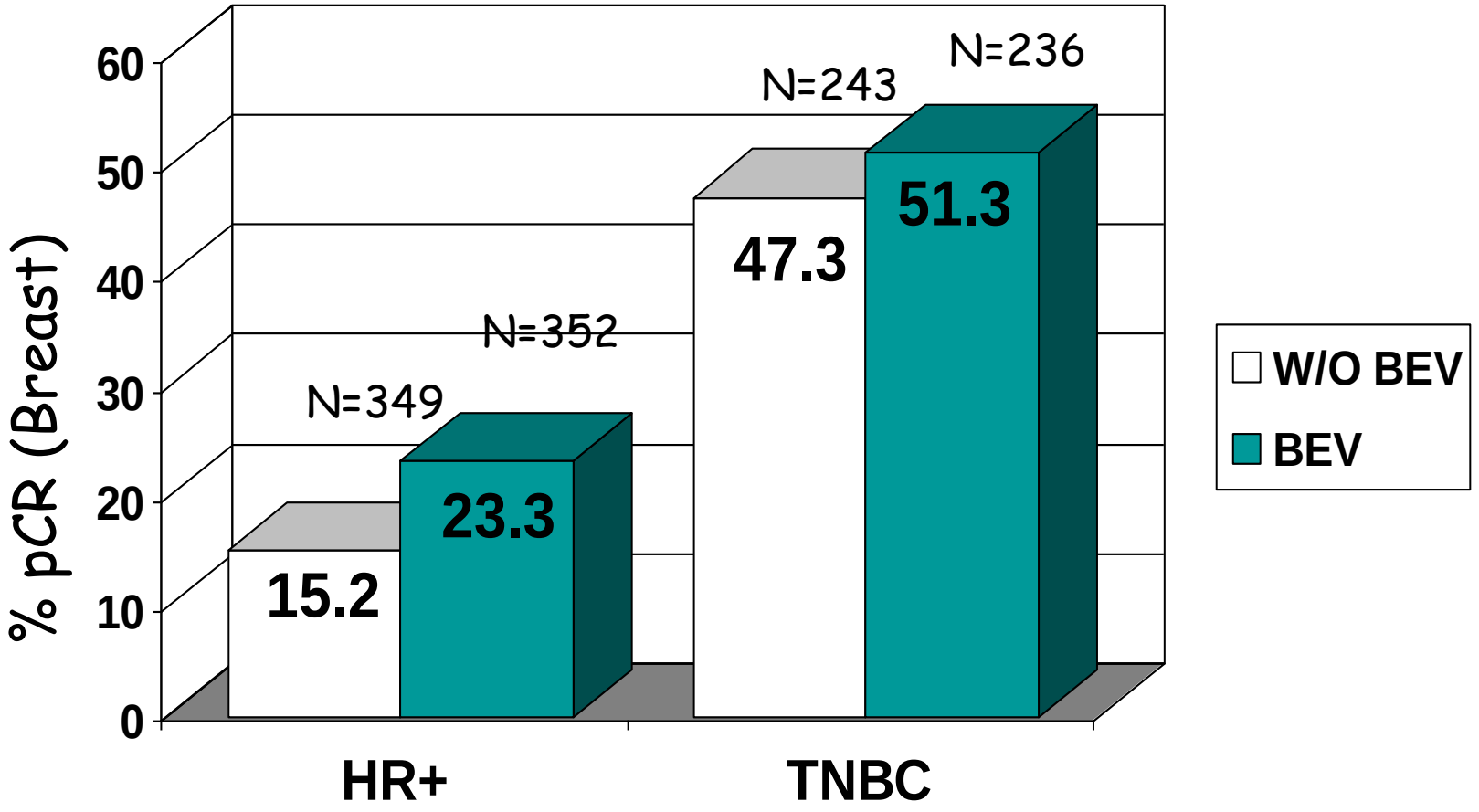
	w/o BEV	BEV
No surgery	5 (<1)	9 (1)
Lumpectomy	267 (45)	279 (47)
Mastectomy	321 (54)	307 (52)
Total	593	595

NSABP B-40
Pathologic Complete Response (Breast)



NSABP B-40

Pathologic Complete Responses (Breast) for HR+ and TN Breast Cancer



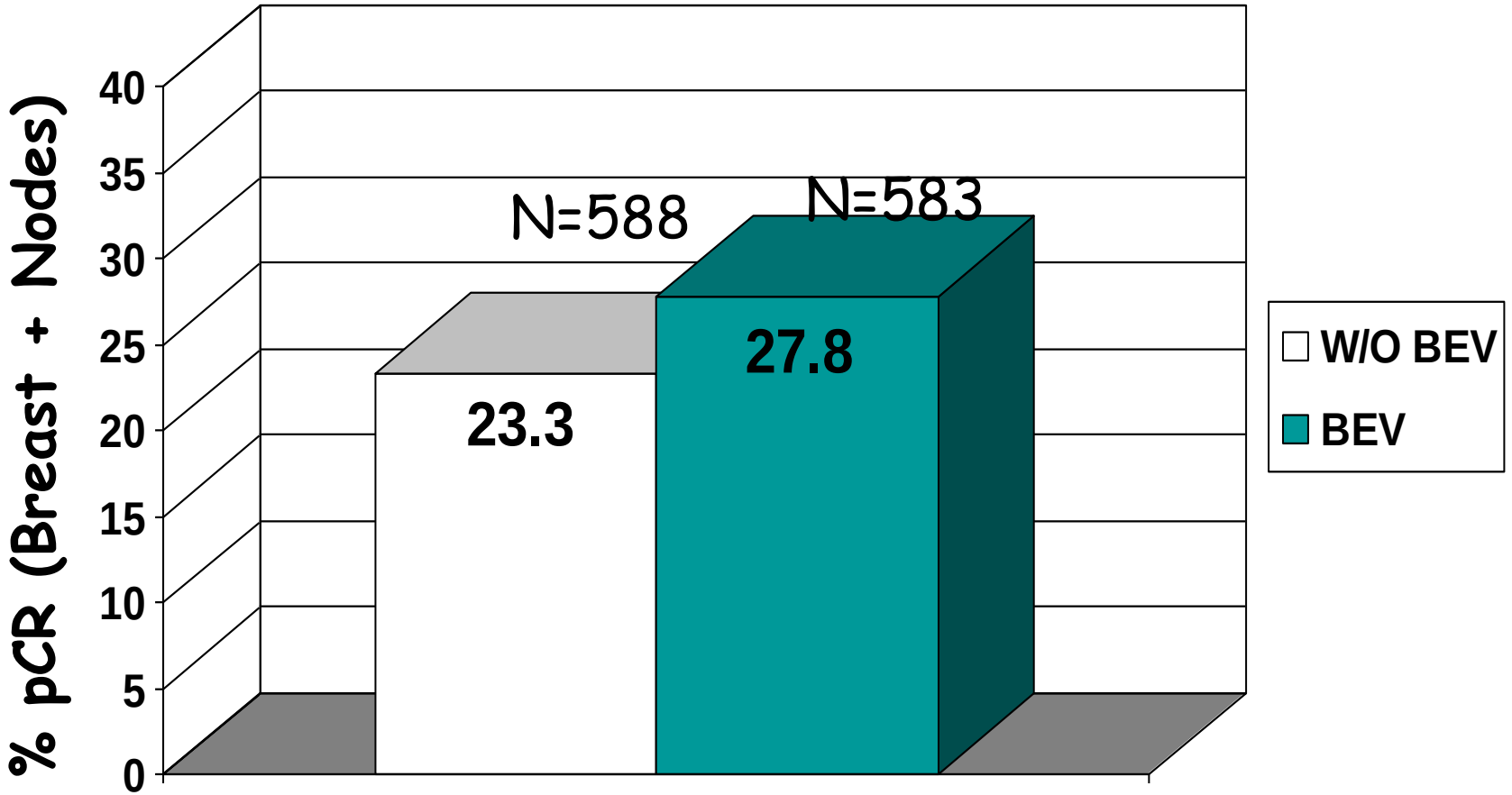
OR = 1.70
p=0.008

OR = 1.17
p=0.44

Interaction p value = 0.166

NSABP B-40

Pathologic Complete Response (Breast and Nodes)

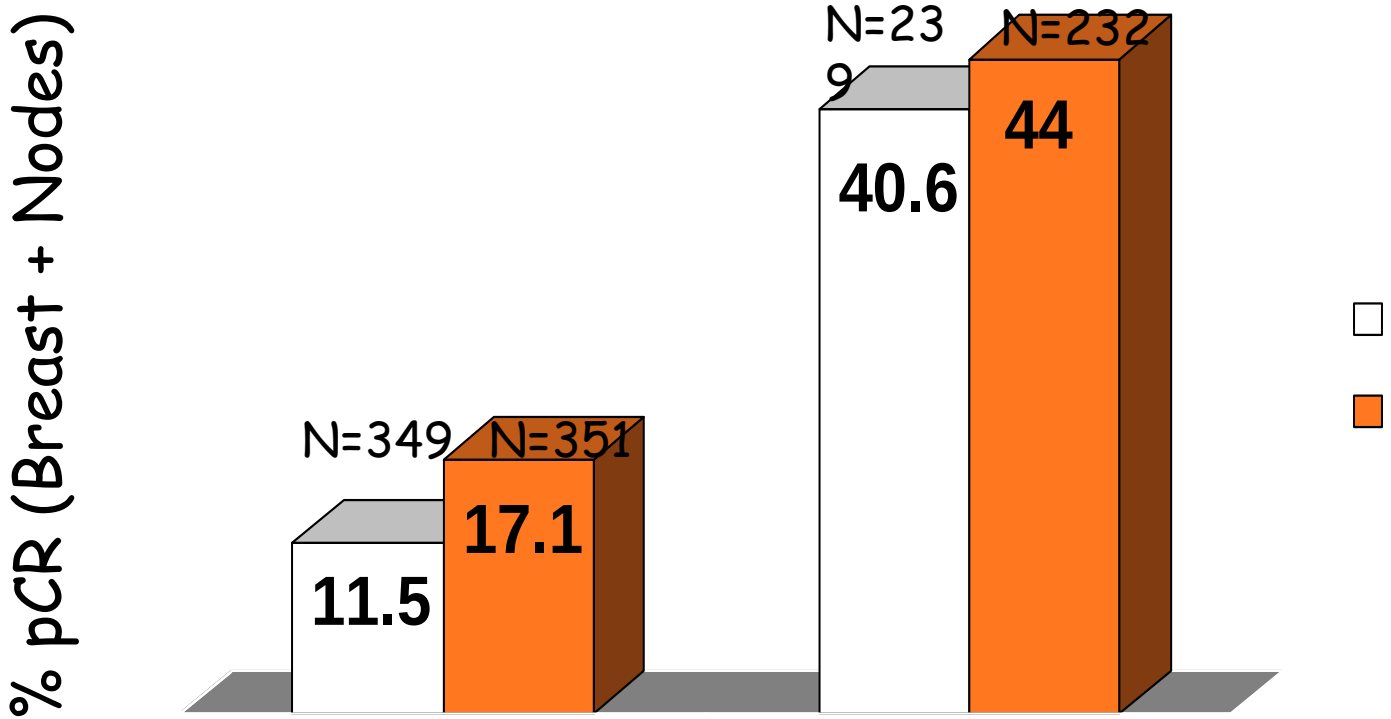


OR = 1.27

Chi-square test: p=0.09

NSABP B-40

Pathologic Complete Response (Breast and Nodes) for HR+ and TN Breast Cancer



OR = 1.59
p=0.033

OR = 1.15
p=0.458

Interaction p value = 0.256

NSABP B-40
Conclusions to Date

- Neither Capecitabine nor Gemcitabine added to Docetaxel increased clinical or pathologic response rates

- Adding Cape or Gem DID increase toxicity

NSABP B-40 Conclusions to Date

- Bevacizumab added to regimens based on T followed by AC significantly increased clinical and pathologic complete response rates
  - Most apparent in HR+ subset
    - However, p values for interaction were <u>not</u> significant
  - Bev did not change surgical options

NSABP B-40 Questions Remaining

- Impact of Bev on OS and DFS
  - Long-term follow-up of B-40 and other trials recently completed or in progress (e.g., BETH, BEATRICE, GeparQuinto, E5103, B-46)
- Biologic correlates/predictors of response to chemotherapy and/or specific agents
- Validate Residual Cancer Burden (RCB) as predictor of outcome
- Effect of pre-op and post-op Bev on wound healing

A Randomized Phase III Study of Iniparib (BSI-201) in Combination with Gemcitabine and Carboplatin in Metastatic Triple Negative Breast Cancer (mTNBC)

Joyce O'Shaughnessy,[1,2,3] Lee Schwartzberg[4,5] Michael A. Danso,[3,6] Hope Rugo,[7] Kathy Miller,[8] Denise Yardley,[9,10] Robert W. Carlson,[11] Richard Finn,[12] Eric Charpentier,[13] Sunil Gupta,[13] Monica Freese,[13] Anne Blackwood-Chirchir,[14] and Eric P. Winer[15]

[1]Baylor Sammons Cancer Center, [2]Texas Oncology; [3]US Oncology, Dallas, TX; [4]Accelerated Community Oncology Research Network, Memphis, TN; [5]The West Clinic, Memphis, TN [6]Virginia Oncology Associates, Norfolk, VA; [7]University of California, San Francisco, CA; [8]Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; [9]Sarah Cannon Research Institute, Nashville, TN; [10]Tenessee Oncology, PLLC, Nashville, TN; [11]Stanford Comprehensive Cancer Center, Palo Alto, CA; [12]University of California Los Angeles School of Medicine, Los Angeles, CA; [13] Sanofi, Paris, France; [14]BiPar Sciences, Inc. South San Francisco, CA, and [15]Dana Farber Cancer Institute, Boston,

Iniparib (BSI-201)

A novel, investigational, anti-cancer agent

- In triple negative breast cancer cell lines[1-4]:
  - Induces cell cycle arrest in the G2/M phase
  - Induces double strand DNA damage g-H2AX foci but does not inhibit PARP 1 and 2 at physiologic drug concentrations
  - Potentiates cell-cycle arrest induced by DNA damaging agents, including platinum and gemcitabine
- Physiologic targets of iniparib and its metabolites are under investigation

Clinical Data:

- In a randomized phase 2 study, addition of iniparib to gemcitabine/carboplatin improved CBR, ORR, PFS and OS in patients with mTNBC[5]
- No potentiation of chemotherapy-related toxicities when iniparib is combined with gemcitabine/carboplatin

Iniparib is the United States Adopted Name (USAN) for the investigational agent BSI-201.

1. Ossovskaya V, *et al. SABCS* 2010, San Antonio, TX. Poster P5-06-09; 2. Ossovskaya V, *et al. AACR* 2009, Denver, CO. Abstract 5552;
3. Ossovskaya V, *et al. AACR* 2011, Orlando, FL. Abstract LB-401; 4. Ji et al. AACR 2011, Orlando, FL. Abstract 4527; 5. O'Shaughnessy J, *et al. N Engl J Med* 2011; 364:205–214.

Schema

Study Design: Multi-center, randomized open-label Phase III Trial

Study Population:

- Stage IV TNBC
- ECOG PS 0–1
- Stable CNS metastases allowed
- 0-2 prior chemotherapies for mTNBC

- Randomization stratified by prior chemo in the metastatic setting:
  - 1st-line (no prior therapy)
  - 2nd/3rd-line (1-2 prior therapies)

R

Gem/Carbo (GC)
(N= 258)

Gemcitabine 1000 mg/m^2 IV d 1, 8
Carboplatin AUC2 IV d 1, 8

21-day cycles

Gem/Carbo + Iniparib (GCI)
(N= 261)

Gemcitabine - 1000 mg/m2 IV d 1, 8
Carboplatin - AUC2 IV d 1, 8
Iniparib - 5.6 mg/kg IV d 1,4,8,11

21-day cycles

Crossover allowed to GCI following Disease Progression*
(central review)

96% (n=152) of progressing patients crossed over to GCI at time of primary analysis

NCT00938652

Study Objectives

Primary:

- Co-primary endpoints:
  - Overall survival (OS)
  - Progression-free survival (PFS)
  - Study considered positive if either endpoint met

Secondary:

- Objective response rate (ORR)
- Safety, tolerability, and Pharmacokinetics of GCI

Statistical Considerations

Type-I error adjustment for co-primary endpoints

Total alpha level = 0.05 split: 0.04 for OS and 0.01 for PFS

Planned sample size and hypothesis:

Total number of planned patients: 420

OS: HR = 0.66, power = 90%, alpha = 0.04 (2-sided)

Total 260 deaths

PFS: HR = 0.65, power = 90%, alpha = 0.01 (2-sided)

Total 322 PFS events

Efficacy analyses:

ITT- population based on treatment group assigned at randomization

N = 519 (over enrolled due to very rapid enrollment 7/09 – 3/10)

Safety population:

All patients who received at least 1 dose of any study drug

Baseline Characteristics

	GC (N=258)	GCI (N=261)
Age, years, median	54	53
ECOG PS, %		
0 / 1	53 / 45	57/ 42
No. metastatic sites, %		
1	14	8
2	26	34
≥3	60	58
Metastatic site, %		
Lung	43	38
Liver	61	62
CNS/Brain	8	8
Bone	30	33
Skin/Soft Tissue	23	25
Lymph nodes	72	76
Breast	19	18

Baseline Characteristics

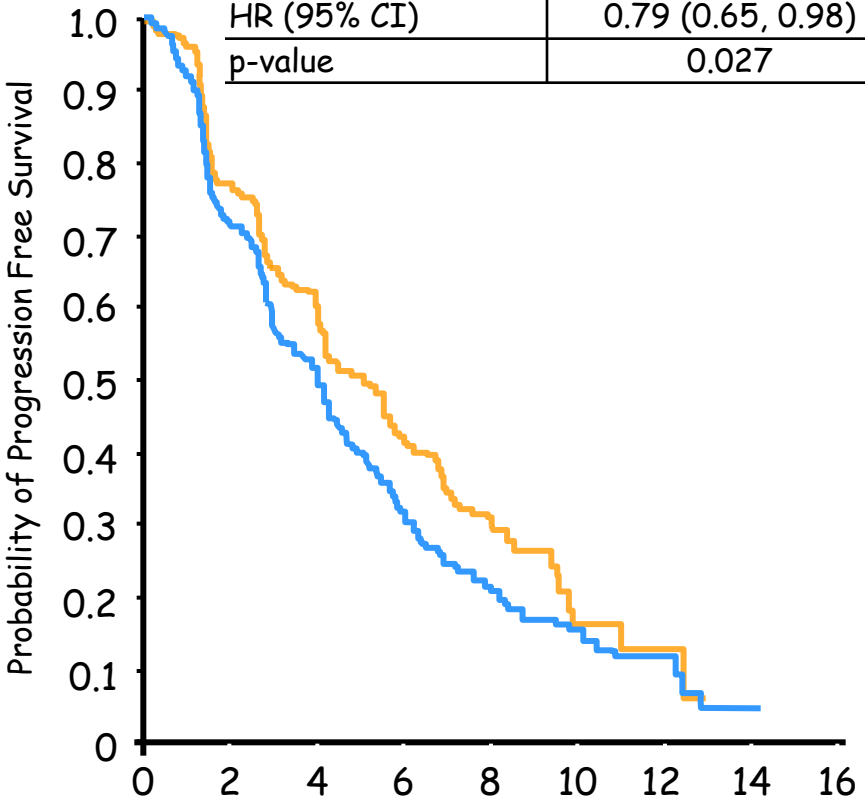
	GC N=258	GCI N=261
Patients with prior chemotherapies n, %	232 (90)	231 (89)
Prior neoadjuvant or adjuvant	204 (79)	201 (77)
Prior metastatic		
0	148* (57)	147* (56)
≥1	110* (43)	114* (44)
Prior Anthracycline	74	70
Prior Taxane	85	83
Prior Bevacizumab**	32	28
Disease Free Interval (DFI)†		
Median	15 months	12 months
≤ 12 months	44%	51%
> 12 months	56%	49%
DFI - 1st line	(n=149)	(n=148)
Median	15.9 months	9.5 months
DFI - 2nd/3rd line	(n=109)	(n =113)
Median	13.8 months	15.7 months

Treatment Emergent Adverse Events Safety Population

	GC N= 244		GCI N = 255	
AE	**All Grades %**	**Grade 3/4 %**	**All Grades %**	**Grade 3/4 %**
Neutropenia	**65**	**53**	**71**	**61**
Febrile Neutropenia	**2**	**2**	**2**	**2**
Anemia	**62**	**22**	**64**	**18**
Thrombocytopenia	**54**	**24**	**54**	**28**
Fatigue	**64**	**6**	**71**	**8**
Alanine aminotransferase increased	**19**	**6**	**28**	**6**
Dyspnea	**27**	**4**	**29**	**6**
Deaths within 30 days of last dose*, n (%)	**8 (3.3)**		**16 (6.3)**	
Adverse Event	2 (0.8)		4 (1.6)	

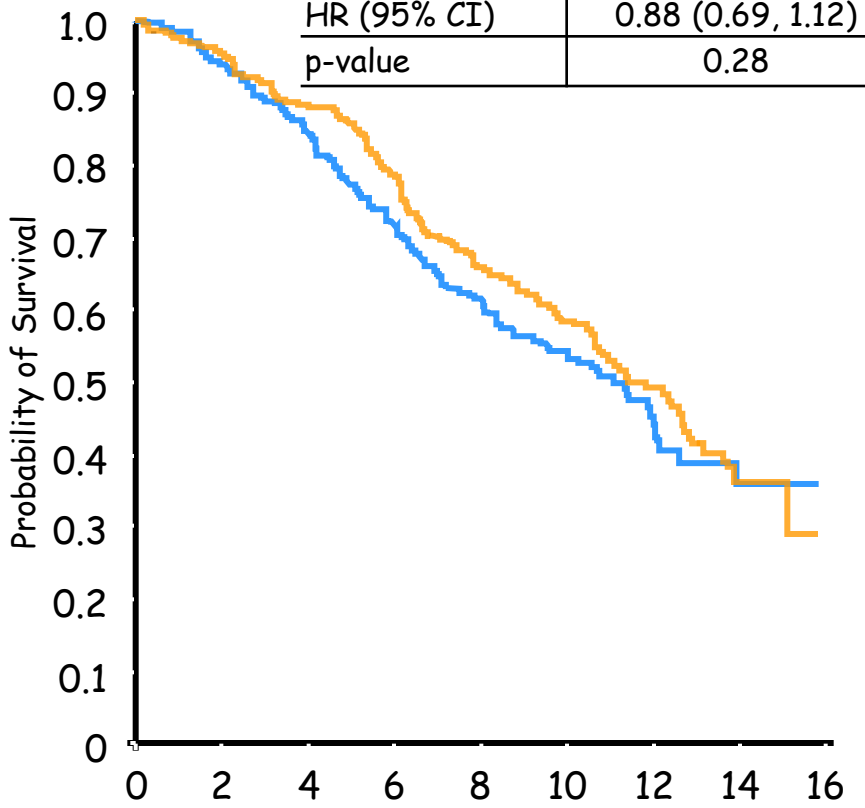
Efficacy Endpoints – ITT population

PFS	GC (N=258)	GCI (N=261)
Median PFS, mos (95% CI)	4.1 (3.1, 4.6)	5.1 (4.2, 5.8)
HR (95% CI)	0.79 (0.65, 0.98)	
p-value	0.027	



No. at risk									
GC	258	171	116	63	38	18	6	1	0
GCI	261	187	138	83	53	11	2	0	0

OS	GC (N=258)	GCI (N=261)
Median OS, mos (95% CI)	11.1 (9.2, 12.1)	11.8 (10.6, 12.9)
HR (95% CI)	0.88 (0.69, 1.12)	
p-value	0.28	

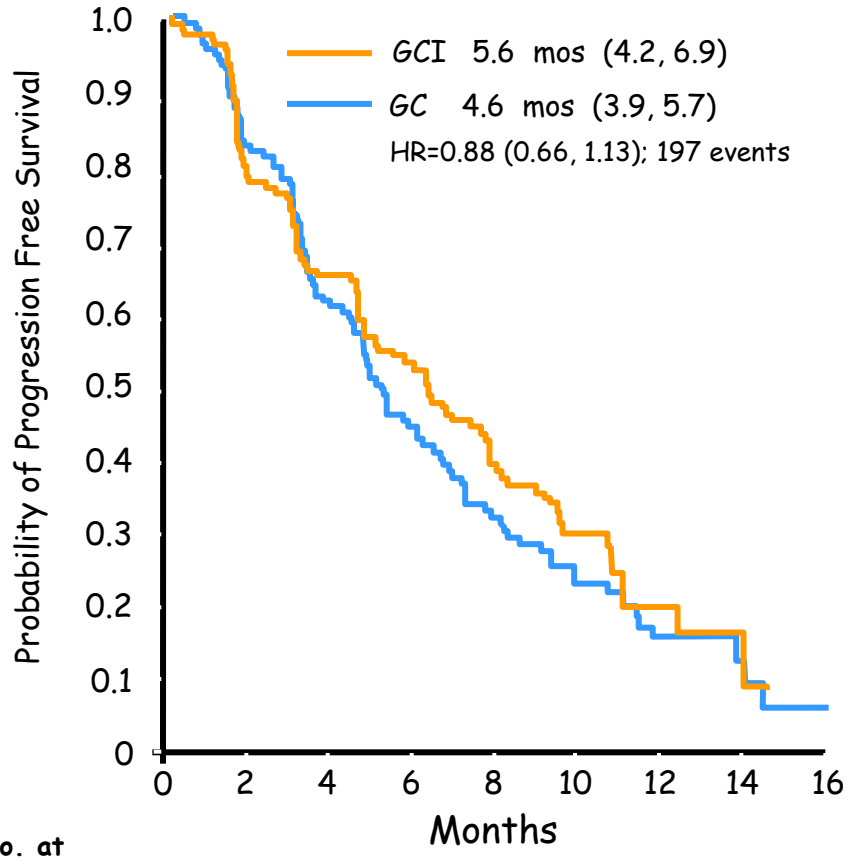


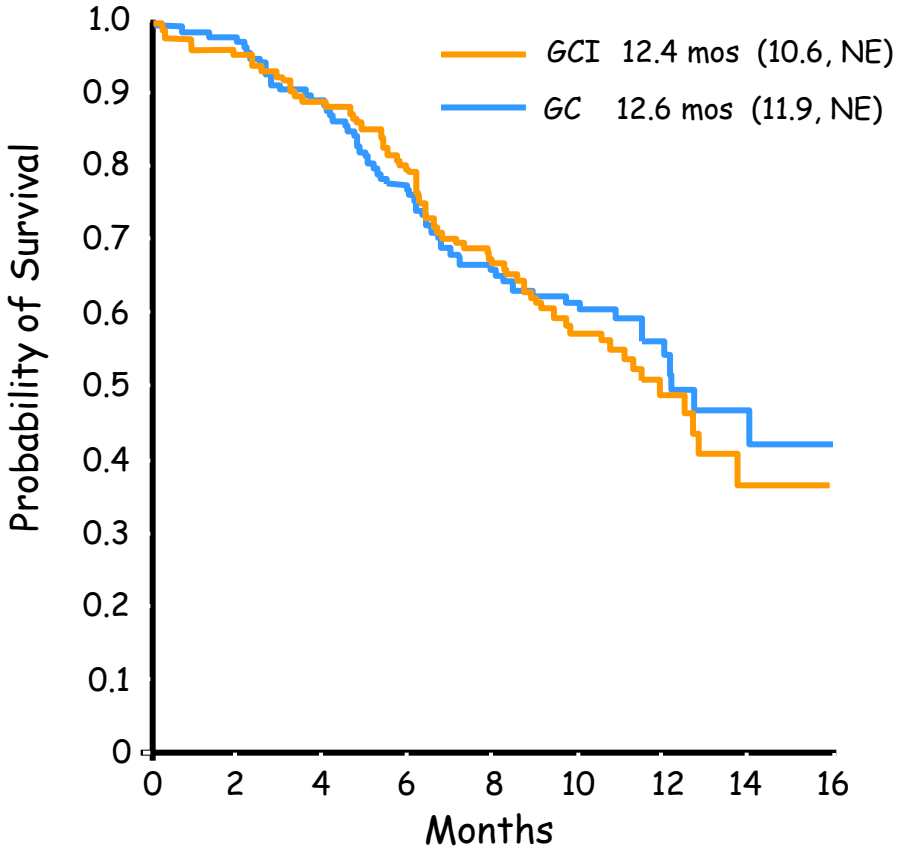
No. at risk									
GC	258	239	214	181	151	99	38	11	0
GCI	261	248	230	204	169	111	52	15	0

Overall Response Rate* – ITT Population

Response, n (%)	*GC* N = 258	*GCI* N = 261
Complete response	4 (1.6)	5 (1.9)
Partial response	74(29)	83 (32)
Stable disease	89 (35)	99 (38)
Progressive disease	62 (24)	62 (24)
Inevaluable	29 (11)	12 (4.6)
SD > 6 months	14 (5.4)	19 (7.3)
ORR, n (%) (95% CI)	78 (30) (25–36%)	88 (34) (28–40%)
Clinical Benefit Rate, n (%) [CR +PR +SD(> 6 mos)]	92 (36)	107 (41)

Exploratory Analysis 1st -line ITT Population



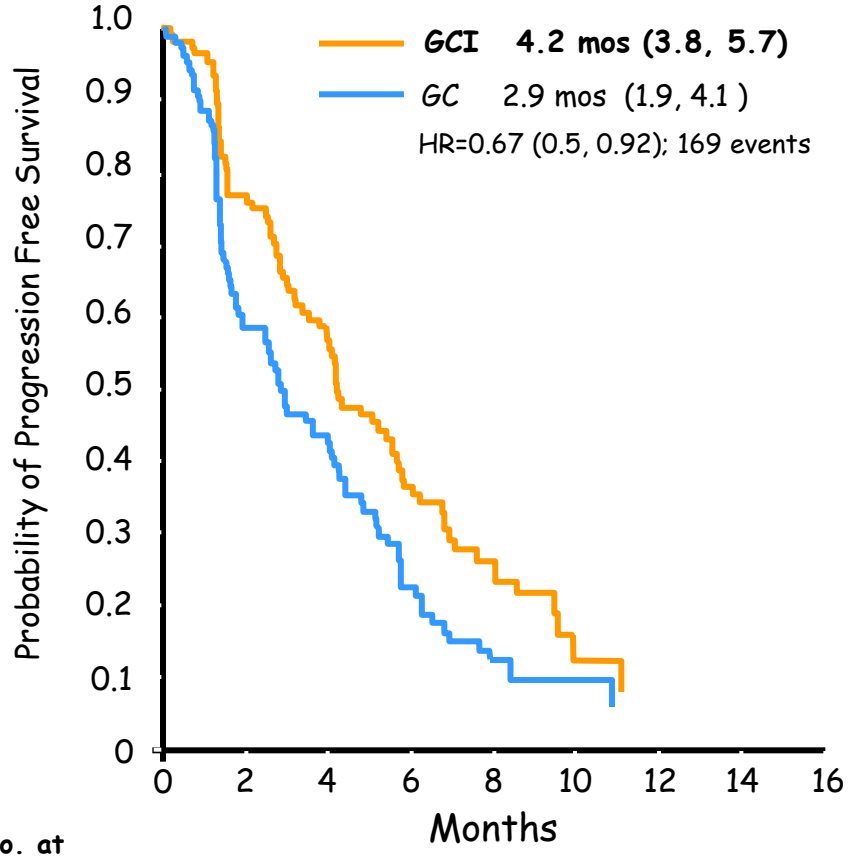


No. at risk									
GC	149	110	74	44	29	13	5	1	0
GCI	148	106	79	51	35	7	2	0	0

149	143	130	113	97	70	27	9	0
148	141	132	118	99	64	28	6	0

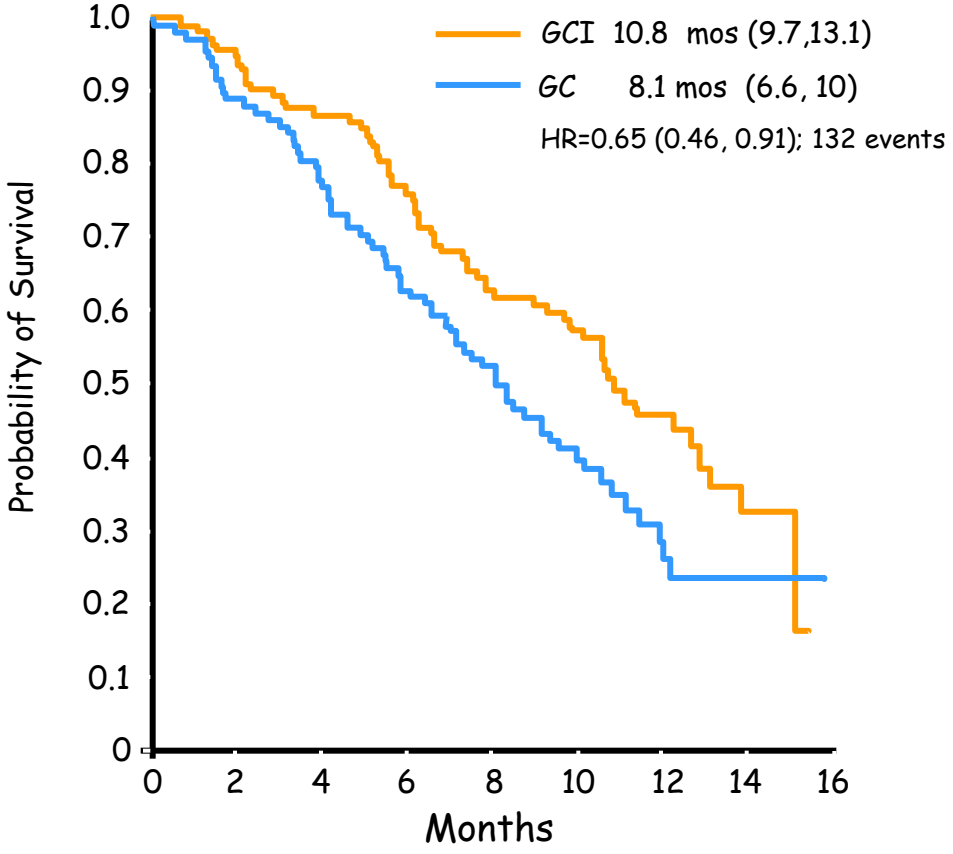
Exploratory Analysis 2nd /3rd-line ITT Population

PFS



No. at risk									
GC	109	61	42	19	9	5	1	0	0
GCI	113	81	59	32	18	4	0	0	0

OS



	109	96	84	68	54	29	11	2	0
	113	107	98	86	70	47	24	9	0

Multivariate Analysis - OS

Evaluate impact of imbalances in specific baseline characteristics on OS per multivariate analyses as specified in the statistical analysis plan (SAP)

Analyses based on :

- Pre-specified baseline factors: age, disease burden, ECOG PS, line of therapy, race, time since diagnosis of mTNBC, visceral disease, and elevated alkaline phosphatase
- Pre-specified baseline factors above - but replace time since diagnosis of mTNBC with Disease Free Interval from primary BC surgery to onset of metastatic disease

Treatment Estimates for OS determined using Multivariate Cox Model

	ITT Population		1st-line		2nd/3rd-line	
	HR	p	HR	p	HR	p
Unadjusted	0.88	0.28	1.1	0.56	0.65	0.012
Using pre-specified baseline factors	0.81	0.08*	0.91	0.62*	0.72	0.07*
Using pre-specified baseline factors with DFI replacement	0.78	0.05*	0.83	0.32*	0.71	0.05*

Multivariate Analysis - PFS

Evaluate impact of imbalances in specific baseline characteristics on PFS

Analyses as described

Treatment Estimates for PFS determined using Multivariate Cox Model

	ITT Population		1st-line		2nd/3rd-line	
	HR	p	HR	p	HR	p
Unadjusted	0.79	0.027	0.88	0.37	0.67	0.011
Using pre-specified baseline factors	0.75	0.006*	0.81	0.15*	0.72	0.033*
Using pre-specified baseline factors with DFI replacement	0.74	0.004*	0.80	0.117*	0.71	0.031*

Conclusions

The addition of iniparib to GC did not improve PFS or OS according to the pre-specified criteria for these co-primary endpoints

- 96% of GC patients eligible for crossover at time of analysis crossed over to GCI and received median of 2 cycles of therapy

Exploratory analyses of PFS and OS by prior therapy suggests:

- Potential efficacy benefit among 2nd/3rd line patients
- Confirmatory study needed

GCI safety profile confirmed; toxicity comparable to GC arm

mTNBC population is highly heterogeneous on intrinsic subtyping

Biomarker analyses underway to evaluate patient populations that may benefit from iniparib

LANDSCAPE: a FNCLCC phase II study with lapatinib and capecitabine in patients with brain metastases from HER2-positive metastatic breast cancer before whole brain radiotherapy

Thomas BACHELOT, Gilles ROMIEU, Mario CAMPONE, Véronique DIERAS, Claire CROPET, Florence DALENC, Marta JIMENEZ, Emilie LE RHUN, Jean-Yves PIERGA, Anthony GONCALVES, Marianne LEHEURTEUR, Julien DOMONT, Maya GUTIERREZ, Hervé CURE, Jean-Marc FERRERO, **Catherine LABBE- DEVILLIERS**

Brain metastases are an important issue in the management of HER2+ metastatic breast cancer patients

- Incidence up to 30 to 40 %
- Strong contribution to morbidity and mortality
- Few therapeutic options beside whole brain radiation therapy (WBR) when multiple localizations

Lapatinib and capecitabine

- Have been approved for trastuzumab resistant HER2+ MBC
  - Objective response rate: 23% (95% CI: 16-29)
  - Median time to progression: 6.2 months

- Have shown notable activity in patients with progressive BM after WBR
  - CNS volumetric response rate: 20% (95% CI: 3-33.7)
  - Median time to progression: 3.65 months (95% CI: 2.4-4.4)

LANDSCAPE PROTOCOL

Objective :

- To assess the clinical benefit of lapatinib plus capecitabine in combination for BM in HER2+ MBC patients not previously treated with WBR

Upfront systemic treatment of patients with BM allows:

- *Concomitant treatment of extra CNS disease*
- *Delay WBR and associated toxicities*

LANDSCAPE PROTOCOL

- Key Inclusion Criteria
  - HER2+ MBC
  - Newly diagnosed brain metastases, at least 1 cm in diameter (T1 gado. MRI)
  - Not candidate for brain surgery
  - Any previous treatment except WBR, lapatinib or capecitabine
  - ECOG PS status 0-2

- Treatment: L: 1,250 mg/d, PO, continuous
  C: 2,000 mg/m^2/d, PO, d1–14 q3weeks

- Clinical assessment (including NSS) every 3 weeks
- Cerebral and systemic imaging every 6 weeks

LANDSCAPE PROTOCOL

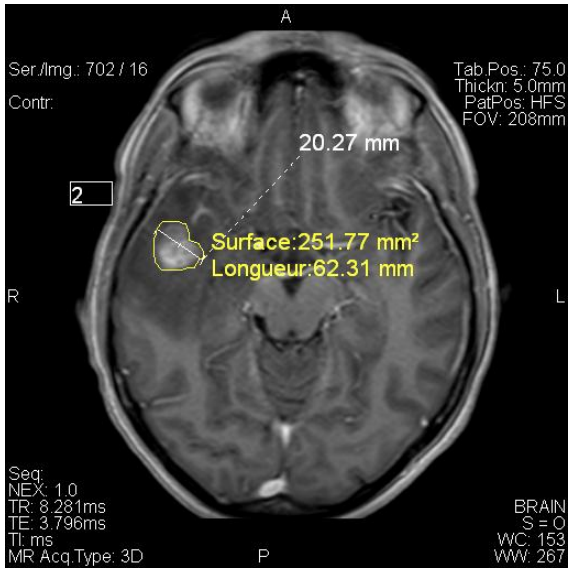
- Primary endpoint
  - Centrally assessed CNS objective response (CNS-OR) defined as a ≥50% volumetric reduction of CNS lesions[1]
  - ➢ in the absence of: increasing steroid use
    progressive neurologic symptoms
    progressive extra-CNS disease
- Secondary endpoints
  - Time to progression (CNS and extra-CNS)
  - Safety
  - Time to WBR
  - Prognostic and predictive value of circulating tumor cells (CTC) at baseline and day 21 (CellSearch® system)

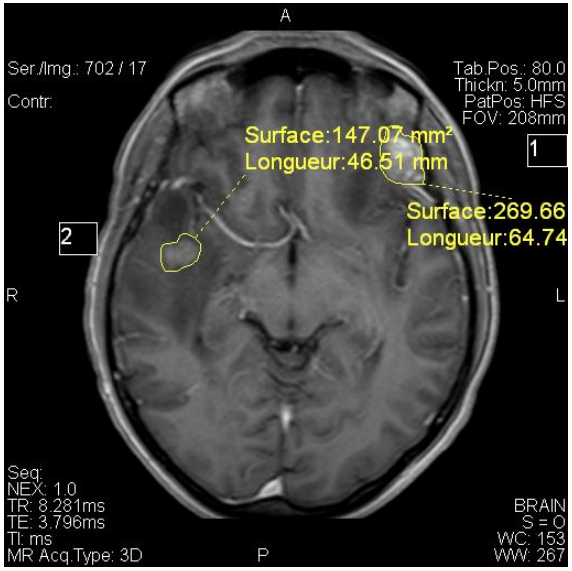
1. Lin et al. Clin Cancer Res 2009; 15: 1452-59

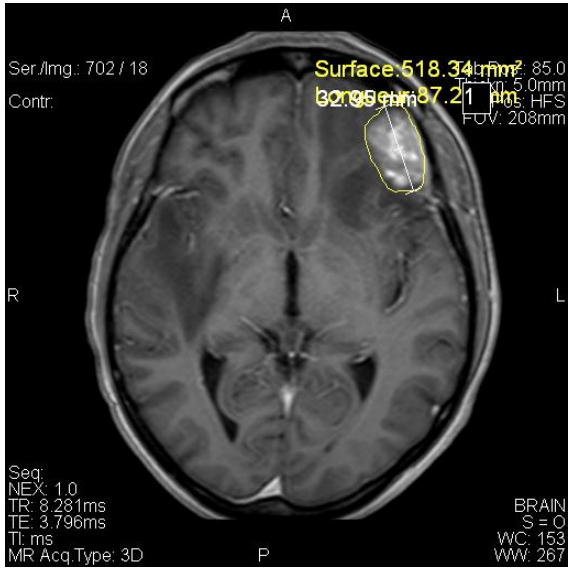
Efficacy assessment

Centrally and blinded volumetric assessment of CNS lesions

- Whole brain, T1 Gado.; axial view, 5mm thickness
- All target lesions contoured across all slices,
- Tumor volume = ∑(outlined surfaces * slice thickness)







- Lin et al. Clin Cancer Res 2009; 15:

Patient Characteristics (n=45)

Median age, years (range) < 60 years, n (%)	56 (35-79) 26 (57.8)
ECOG PS, n (%)* 0 1 2	 17 (38.6) 25 (56.8) 2 (4.5)
Hormone receptor status, n (%)* ER + and/or PR+ ER- and PR-	 22 (50) 22 (50)
Breast cancer GPA index[1], n(%)* 1 2 3 4	 0 0 22 (50) 22 (50)

*1 missing value

Patient Characteristics (n=45)

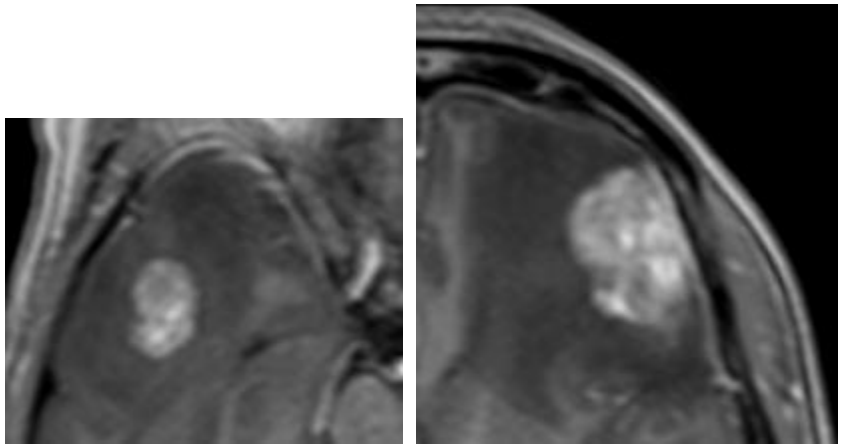
Median disease free interval, mo. (range)	34.2 (0-205)
Median time from metastatic relapse to inclusion, mo. (range)	9.7 (0-114)
Disease extension, CNS Median number of CNS lesions (range) 1 CNS lesion, n (%) Patients with NSS at inclusion, n (%)	 3 (1- >25) 6 (13.3) 25 (55.6)
Disease extension, extra-CNS, n (%) No extra-CNS Liver Lung 3 or more	 7 (15.6) 22 (48.9) 16 (35.6) 14 (31.1)
Previous trastuzumab treatment, n (%) No trastuzumab Adjuvant only Metastatic +/- adjuvant	 3 (6.7) 11 (25) 31 (68.9)

Primary Endpoint: CNS volumetric response

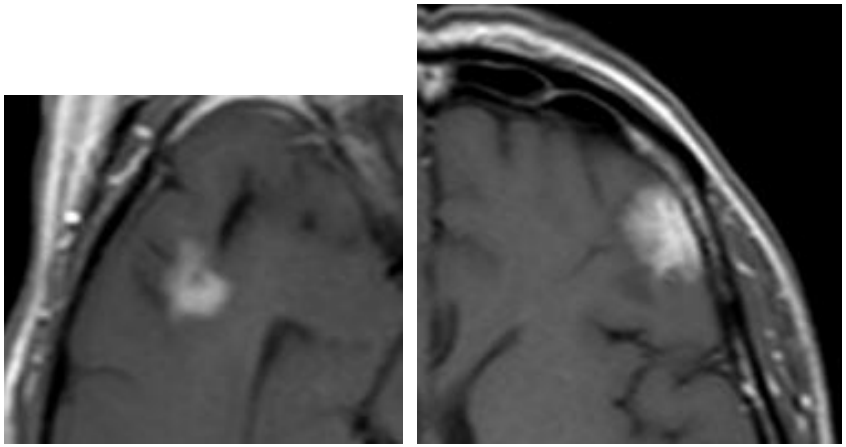
CNS Volumetric change	n = 43 (%)	
≥ 80% Reduction	9	(20.9)
50- <80% Reduction	20	(46.5)
20- <50% Reduction	6	(14)
> 0- <20% Reduction	2	(4.7)
Progression*	6	(14)

NSS improvement : 14/24 = 58.3% (95% CI: 36.6-77.9)

Bone and pulmonary mets: trastuzumab + paclitaxel
Progression and multiple brain mets: October 2009



October 23, 2009



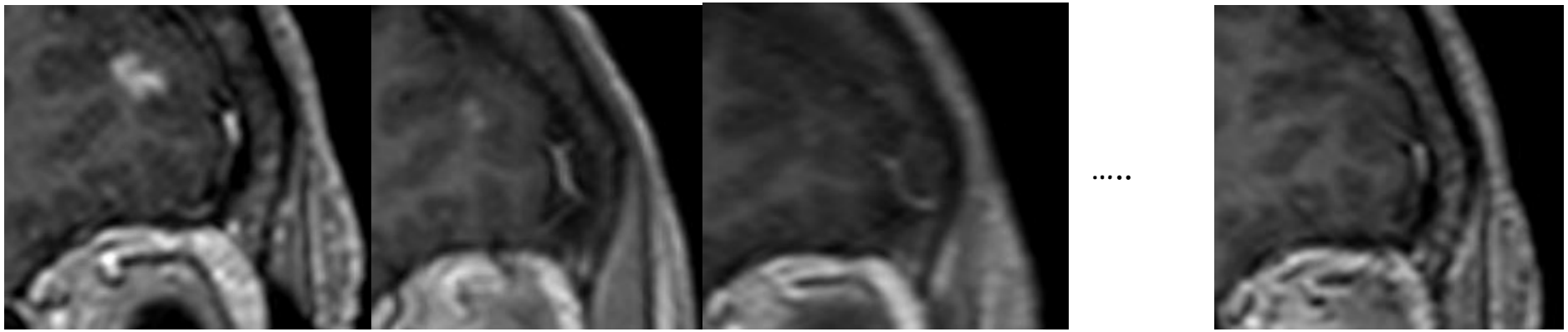
January 27, 2010

Volumetric reduction: 70%

CNS 1progression : June 4, 2010

WBR : July 8, 2010

43-year-old patient, left breast cancer pT1pN1: June 2006
Bone, liver, pulmonary mets: March 2009, trastu. + paclitaxel
Symptomatic multiple brain mets (25): June 2009



July 6, 2009 August 20, 2009 Oct. 1, 2009 July 23, 2010

Volumetric reduction: 98%

Still on treatment after 13 months (1 dose reduction)

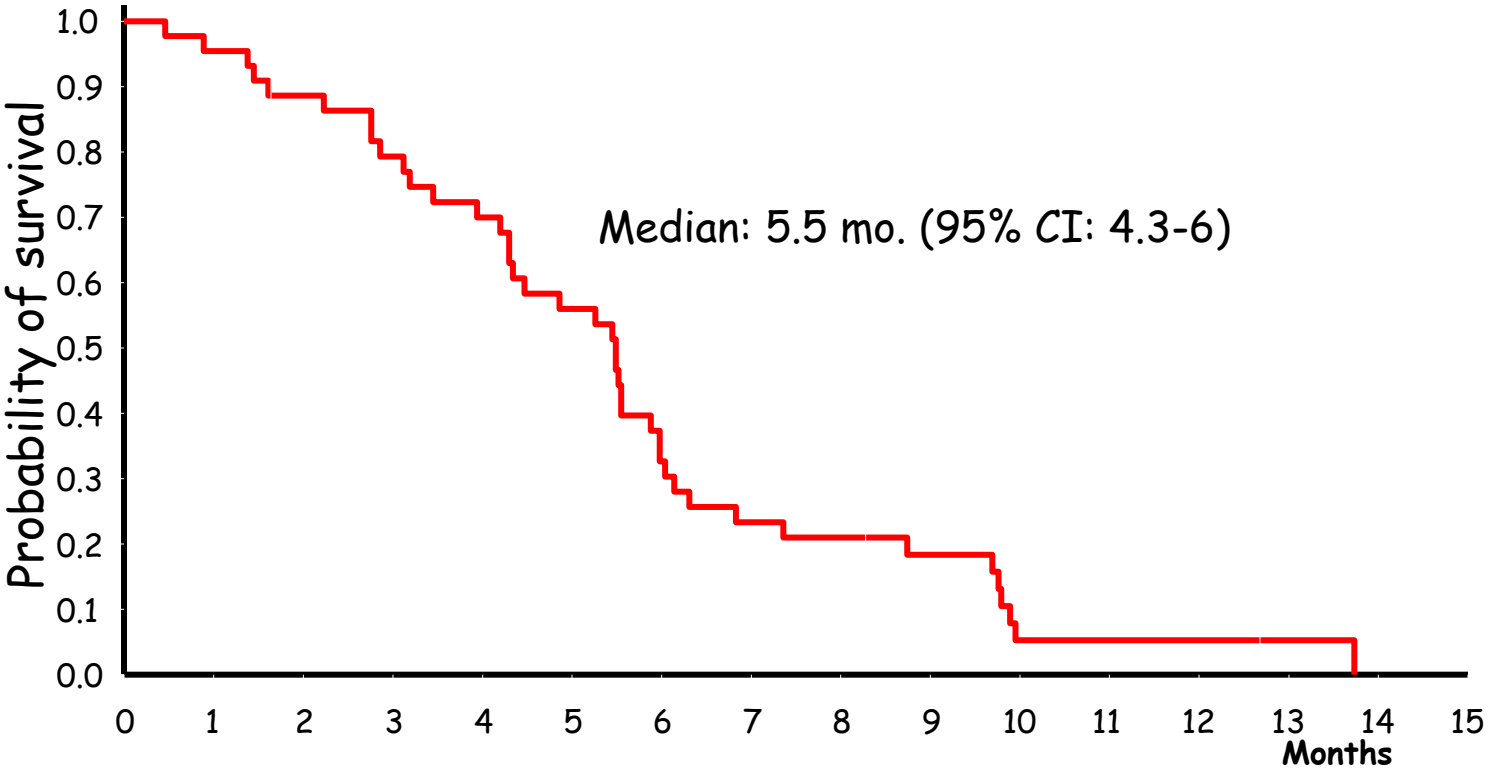
Extra-CNS RECIST response

Extra-CNS-OR : 15/35 = 42.9% (95% CI: 26-61)

Extra-CNS RECIST evaluation	n = 35 (%)	
Complete response	1	(2.9)
Partial response	14	(40)
Stable disease	16	(45.7)
Progression	4	(11.4)

- **7 patients had no extra-CNS disease**
- **2 patients had no RECIST evaluable lesions**

Time to progression



Patients at risk:	44	42	38	34	30	24	14	10	9	7	2	2	2	1

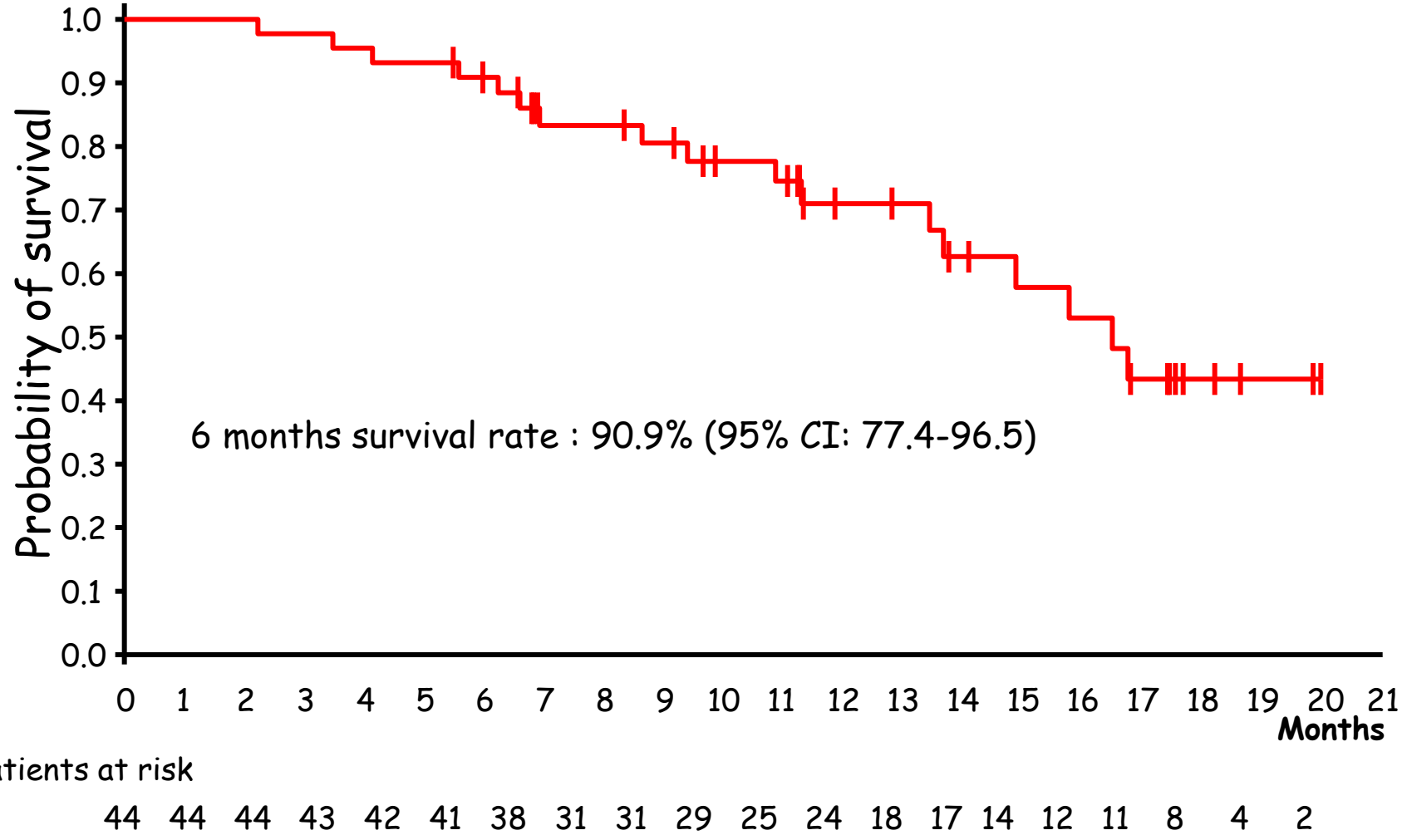
Site of first progression	n = 43 (%)	
CNS	32	(73.4)
Extra CNS	3	(7)
Concomitant CNS & extra CNS	5	(11.6)

Time to WBR

- Data were available for 43 patients
- At time of analysis, 32 (74.4%) had received WBR

➢ Median time to WBR is 7.8 mo. (95% CI: 5.4-9.1)

Overall Survival



Adverse Events

Incidence, n (%)	n = 45	
Grade	Any	3/4
Patients with at least one SAE	14 (31.1)	
Most Common Adverse Events		
Diarrhea	38 (84.4)	9 (20)
Hand foot syndrome	34 (75.5)	9 (20)
Fatigue	22 (48.9)	6 (13.3)
Rash	11 (24.4)	2 (4.4)
Nausea	23 (51.1)	1 (2.2)
Bilirubin increase	21 (46.6)	1 (2.2)
Vomiting	16 (35.5)	1 (2.2)
Stomatitis	13 (28.9)	1 (2.2)
Dose reduction due to AE	Lapatinib	17 (37.8)
	Capecitabine	26 (57.8)
Treatment discontinuation due to AE	3 (6.7)	

No toxic death

CNS volumetric response
Selected subgroup **analysis**

CNS-OR, n (%)	n=43
ALL	29/43 (67.4)
GPA index = 3 GPA index = 4	14 / 20 (70) 14 / 22 (63.6)
1 or 2 CNS lesions ≥ 3 CNS lesions	13 / 20 (65) 16 / 22 (72.7)
Patients with NSS at inclusion Patients without NSS at inclusion	16 / 23 (69.6) 13 / 20 (65)
Previous metastatic trastuzumab No previous metastatic trastuzumab	20 / 29 (69) 9 / 14 (64.3)

Conclusions

L+C for newly diagnosed BM in HER2+ MBC:

- L+C is highly active for untreated BM
  - CNS volumetric response rate was 67% (95% CI: 51-81)
  - Median TTP was 5.5 months
- This combination warrants further evaluation
  - Phase III trial
  - Multimodal therapy with surgery/SRS
  - Prevention strategy