Triple negative breast cancer
2014 GASCO Annual meeting
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EMORY

WINSHIP CANCER INSTITUTE

NCI–Designated

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Case History

- 40-year old female presents with right palpable breast mass
- Imaging demonstrates suspicious mass measuring 35mm and an enlarged right axillary node
- Biopsy demonstrates infiltrating ductal cancer, grade 3, ER 0%, PR 0%, HER2 1+
- FNA of axillary node is positive for cancer
- BRCA testing negative

Incidence of pCR by Breast Cancer Subtype

- 107 patients treated with neoadjuvant AC and hormone therapy if HR+.

Response Type	All Patients N=107 (%)	Basal Like N=34 (%)	HER2 N=11 (%)	Luminal B N=26 (%)	Luminal A N=36 (%)
CR	14	29	10	8	6
PR	47	56	60	50	33
SD	38	15	30	42	58
PD	1	0	0	0	3
pCR	16	27	36	15	0

Carey et al; Clin Cancer Res 2007; 13(8)

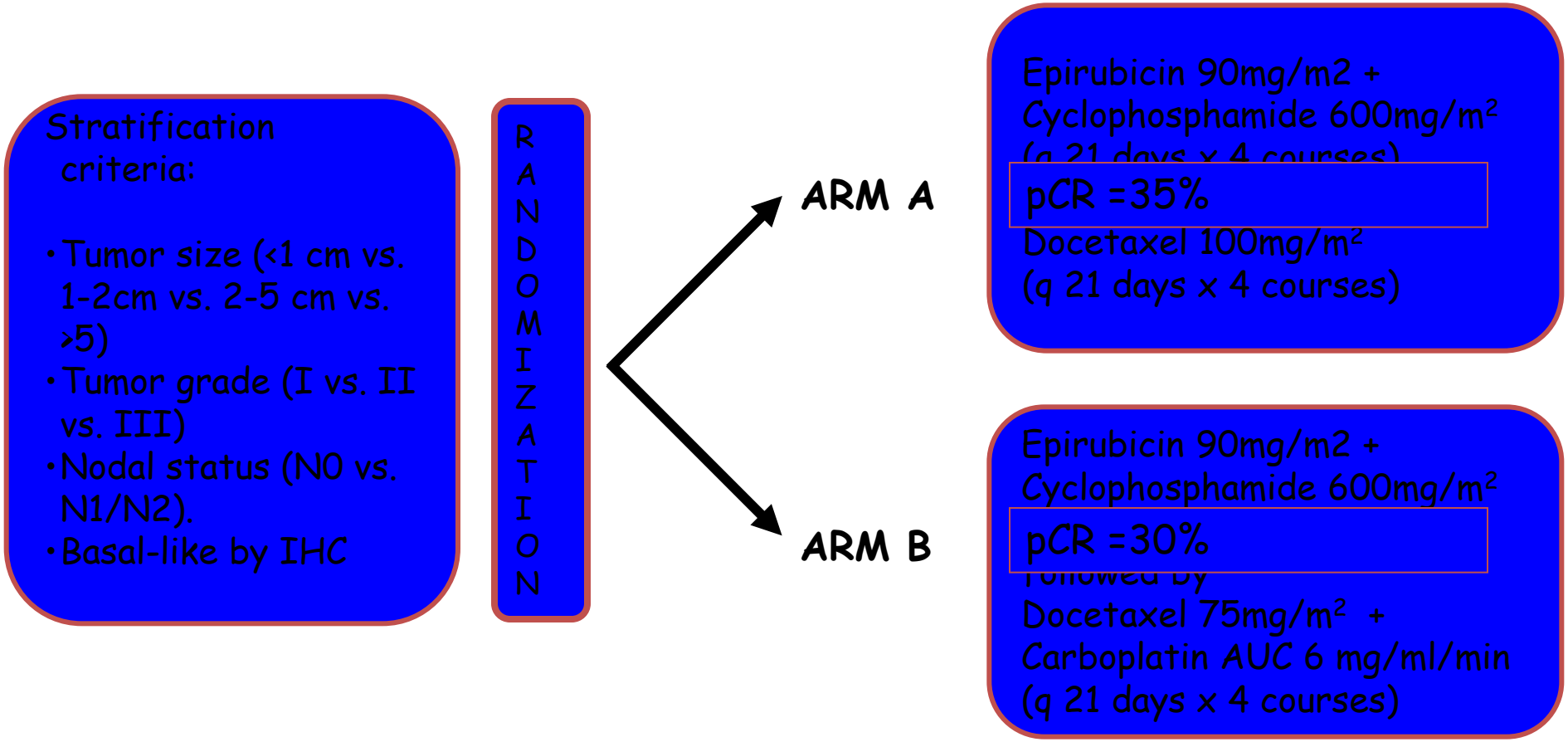
Neoadjuvant Cisplatin in BRCA1-deficient and Triple Negative Breast Cancer

Patient Population	Stage	Regimen	Pathological Complete Response, n (%)
BRCA1 mutation (n = 25)	I – III*	Cisplatin 75 mg/m^2 q3w X4	18 (72%)
Triple negative (n = 28)	II - III	Cisplatin 75 mg/m^2 q3w X4	6 (22%)**
Triple negative (n = 51)	II - III	Cisplatin 75 mg/m^2 q3w X4 + bevacizumab 15 mg/kg q3w X3	8 (16%)
Triple negative (n = 78)	II - III	Multiple cisplatin - based***	NA (32%)

Bottom line: Activity of platinums in TNBC appears similar to other agents but appear particularly active in cancers with mutations of BRCA (and maybe in cancers with other defects in DNA repair)

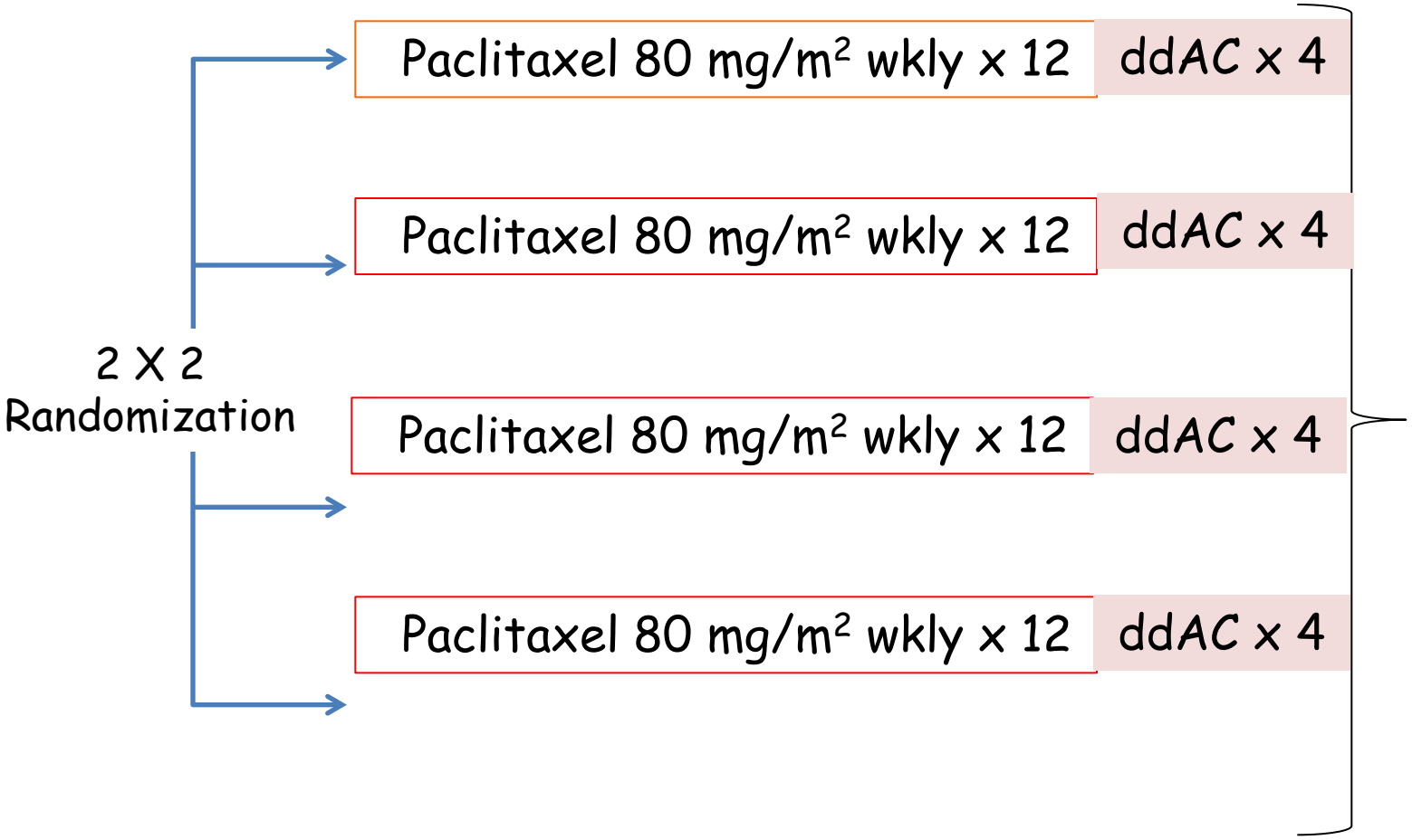
Gronwald et al. J Clin Oncol 2009
Ryan et al. J Clin Oncol 2009
Garber et al. Breast Cancer Res Treat 2006
Leone et al. J Clin Oncol 2009

GEICAM Phase II Study

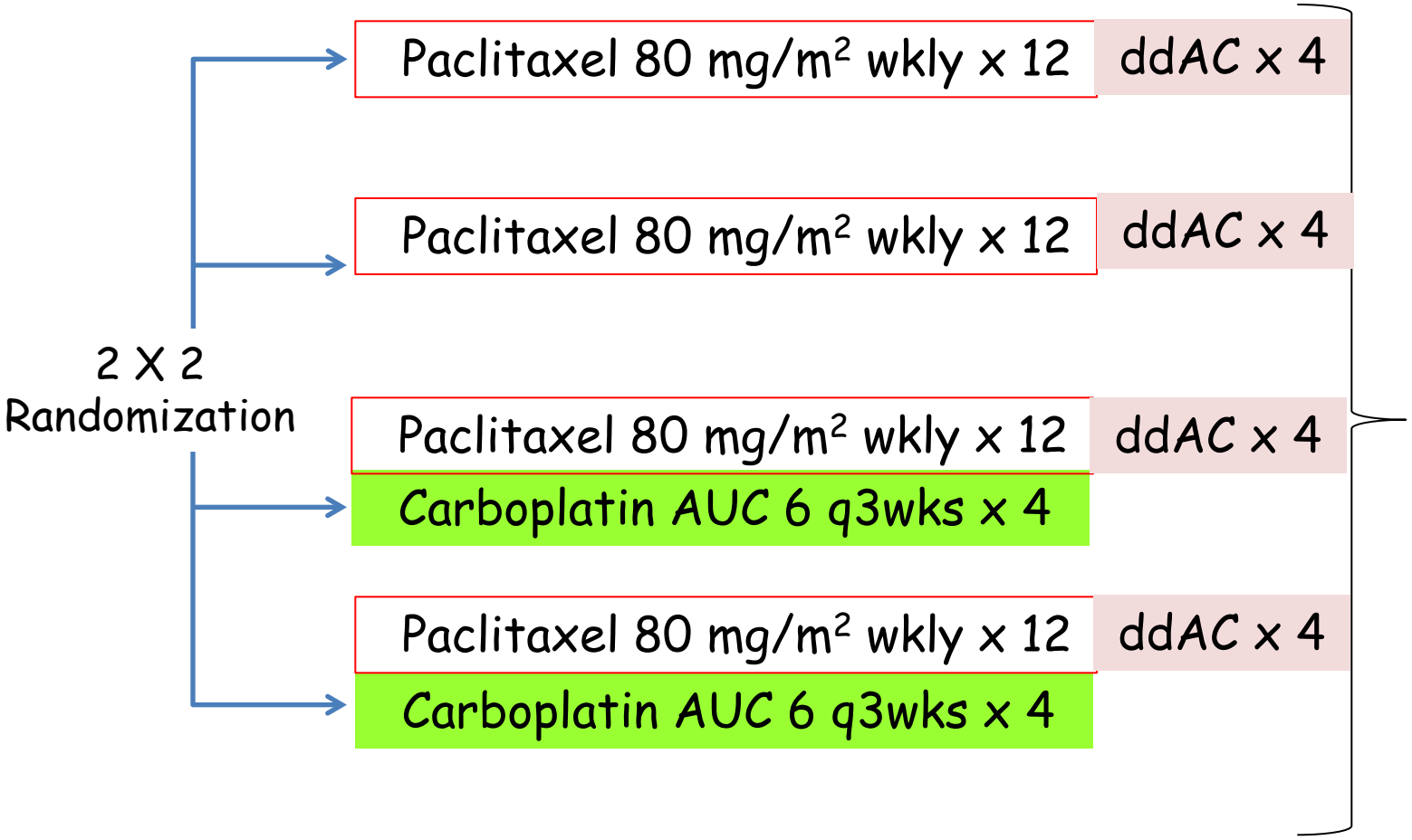


Alba E, et al. Abstract 74933, ASCO 2011

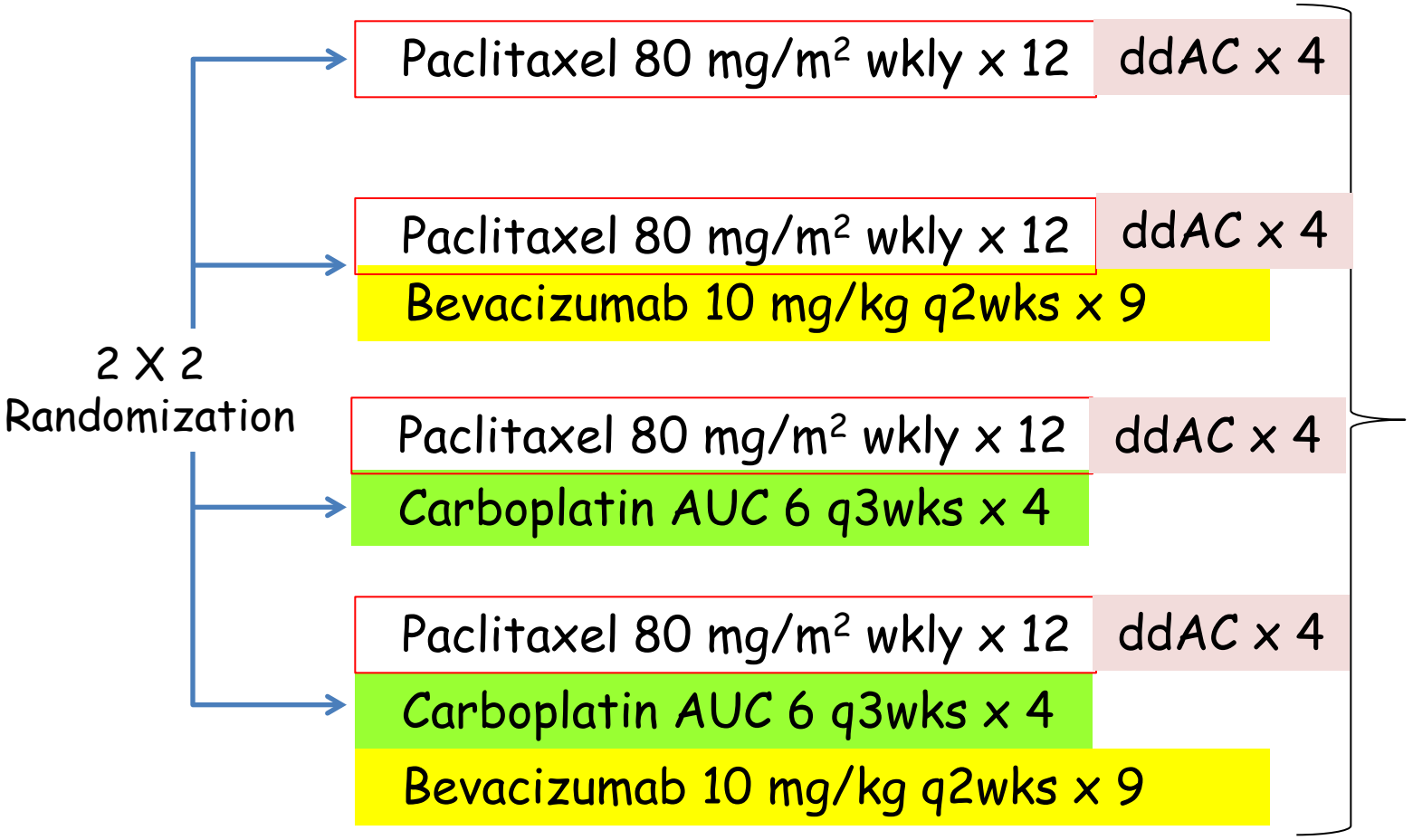
CALGB 40603: Schema – Randomized phase II



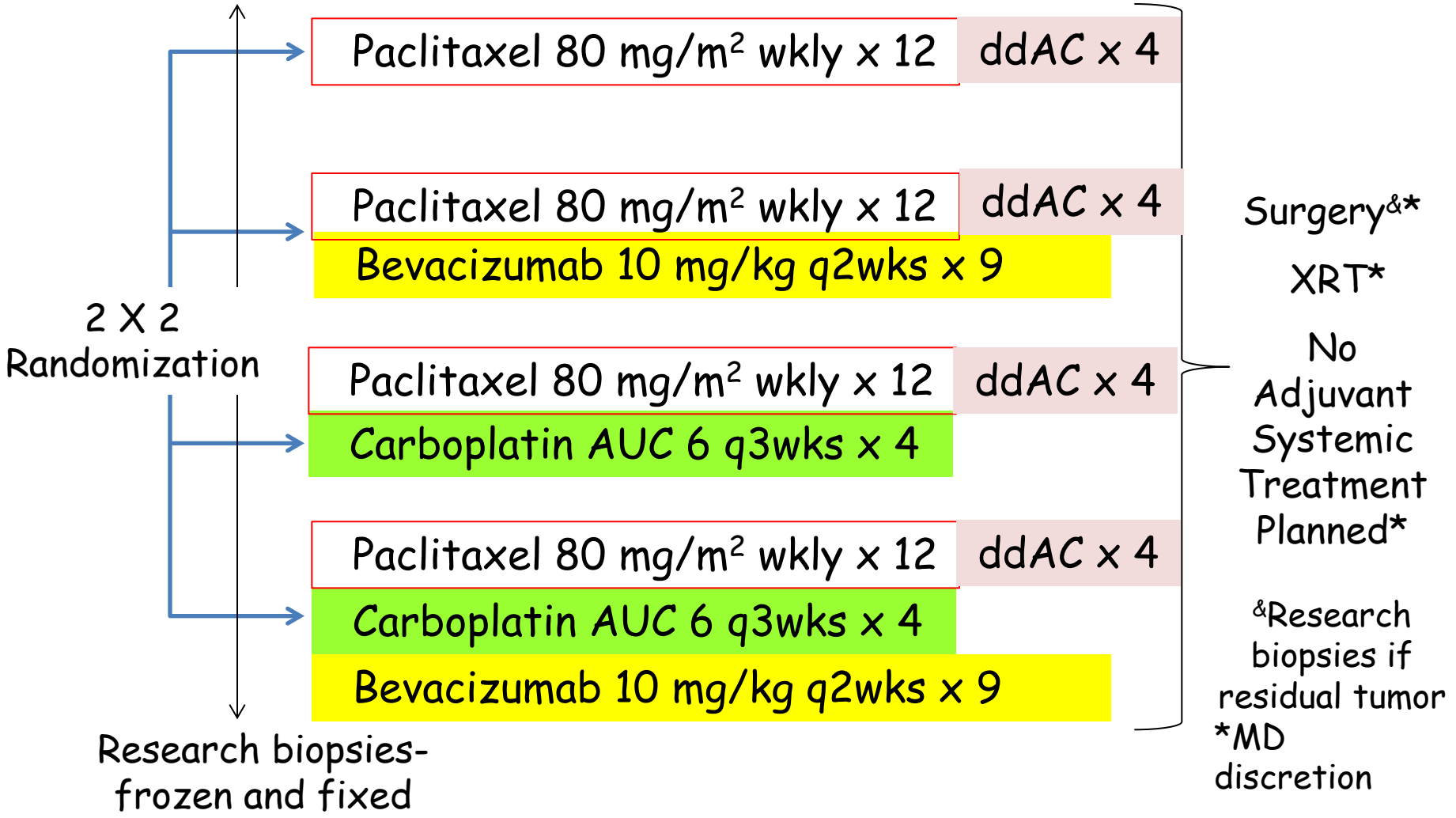
CALGB 40603: Schema – Randomized phase II



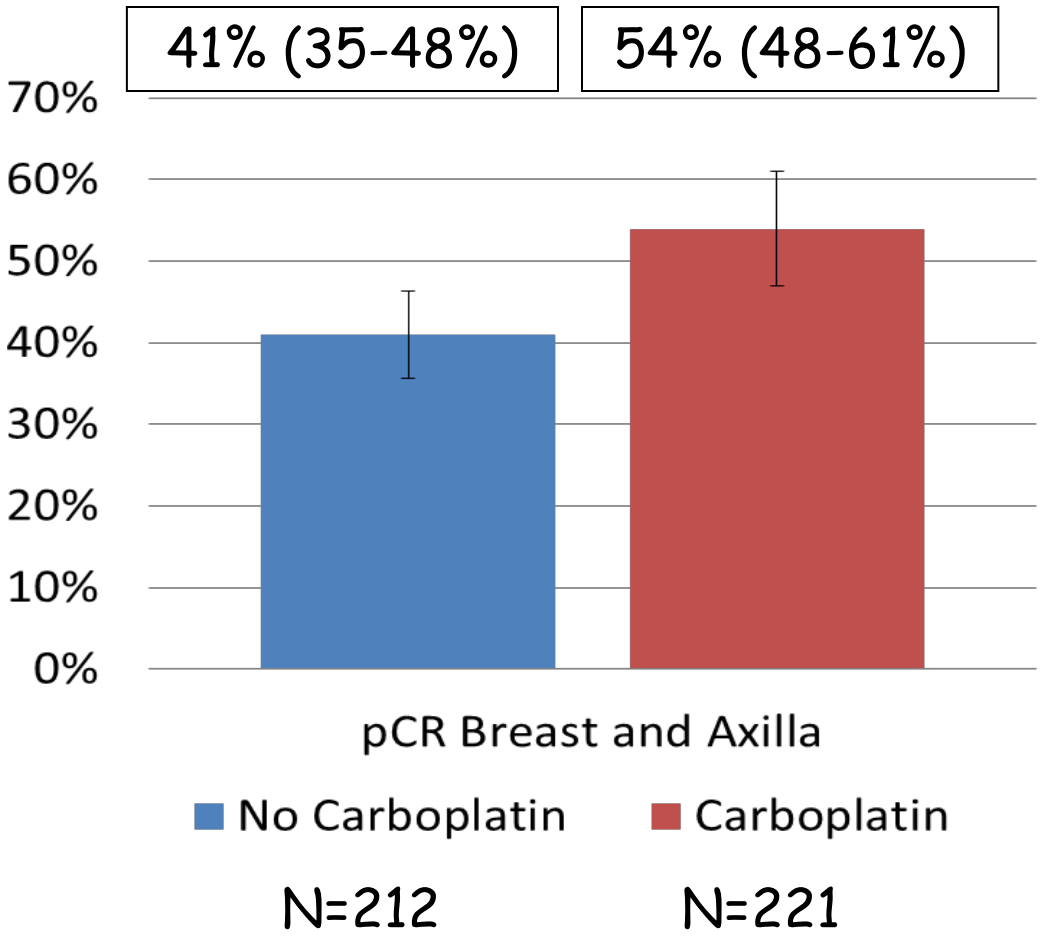
CALGB 40603: Schema – Randomized phase II



CALGB 40603: Schema – Randomized phase II



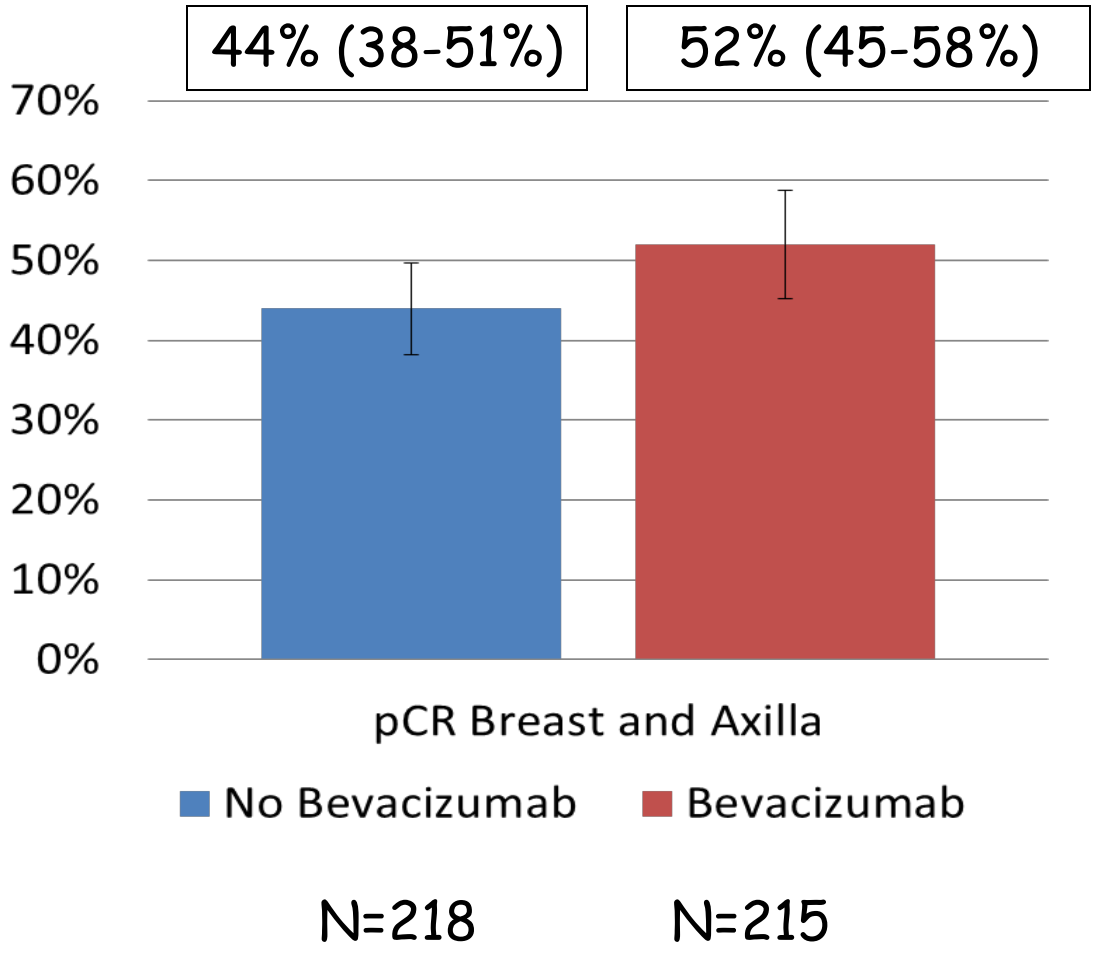
CALGB 40603: pCR Breast/Axilla (ypT0/is N0)



Odds ratio: 1.71
p = 0.0029

pCR Breast/Axilla (ypT0/is N0) +/- Bevacizumab

Odds ratio: 1.36
p = 0.0570



CALGB 40603: Select Grade ≥3 Toxicities

	Chemo	Chemo + Bev	Chemo + Carbo	Chemo + Carbo + Bev
Neutropenia	22%	27%	56%	67%
Thrombocytopenia	4%	3%	20%	26%
Febrile neutropenia	7%	9%	12%	24%
Hypertension	2%	12%	0%	10%*
Nausea / Vomiting	4% / 2%	4% / 2%	3% / 2%	8% / 4%
Fatigue	10%	12%	10%	20%
Stopped treatment due to toxicity	0%	10%	6%	12%

* One cardiac death attributed to uncontrolled HTN

Protocol Design

HER2 (-) BC
Stage II/IIIA
18-70 years
PS 0/1
Good Organ function
Written IC

R

CP-CEF

Paclitaxel
80 mg/m² qwk x 12

Carboplatin
AUC5
q3wks x 4

CEF
500/100/500 mg/m²
q3wks x 4

P-CEF

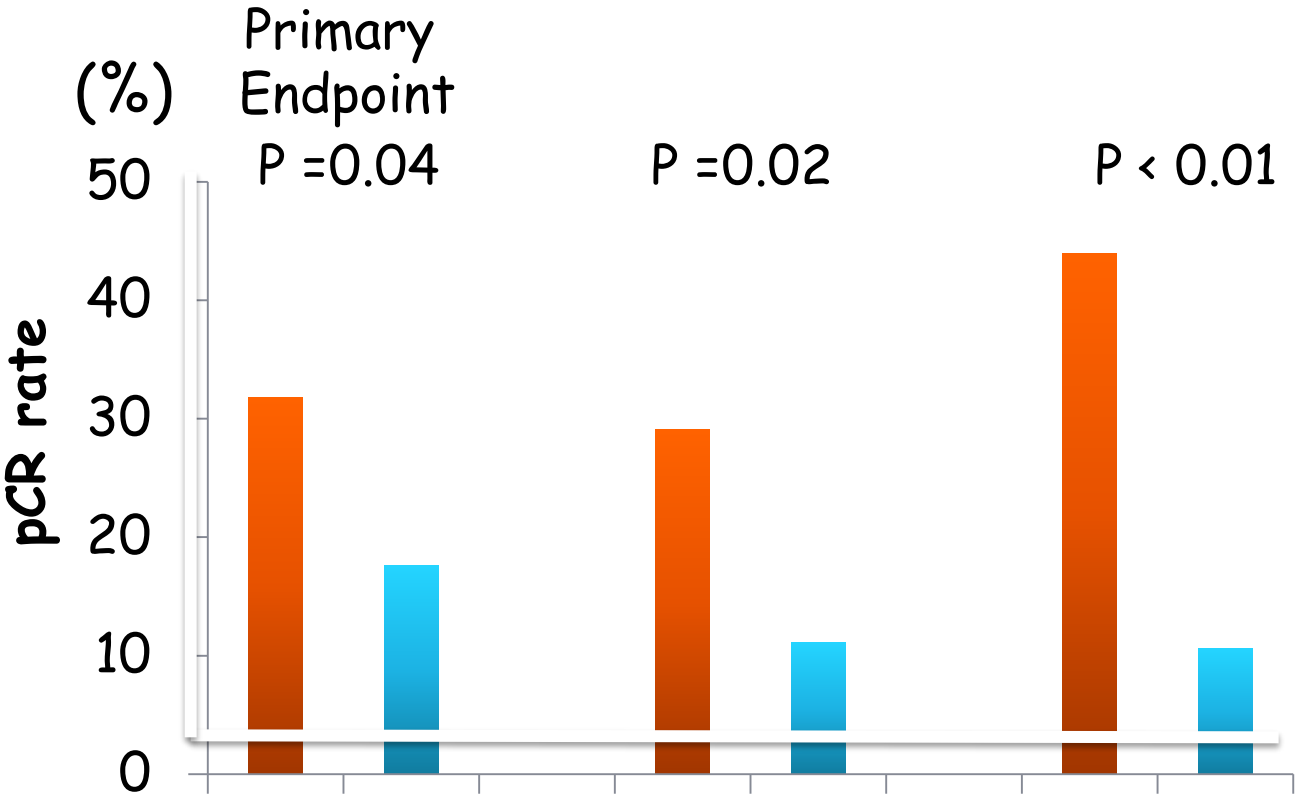
Paclitaxel
80 mg/m² qwk x 12

CEF
500/100/500 mg/m²
q3wks x 4

SURGERY

Tamura Proc ASCO 2014

pCR rates by sub groups



Odds ratio	0.46	0.30	0.15

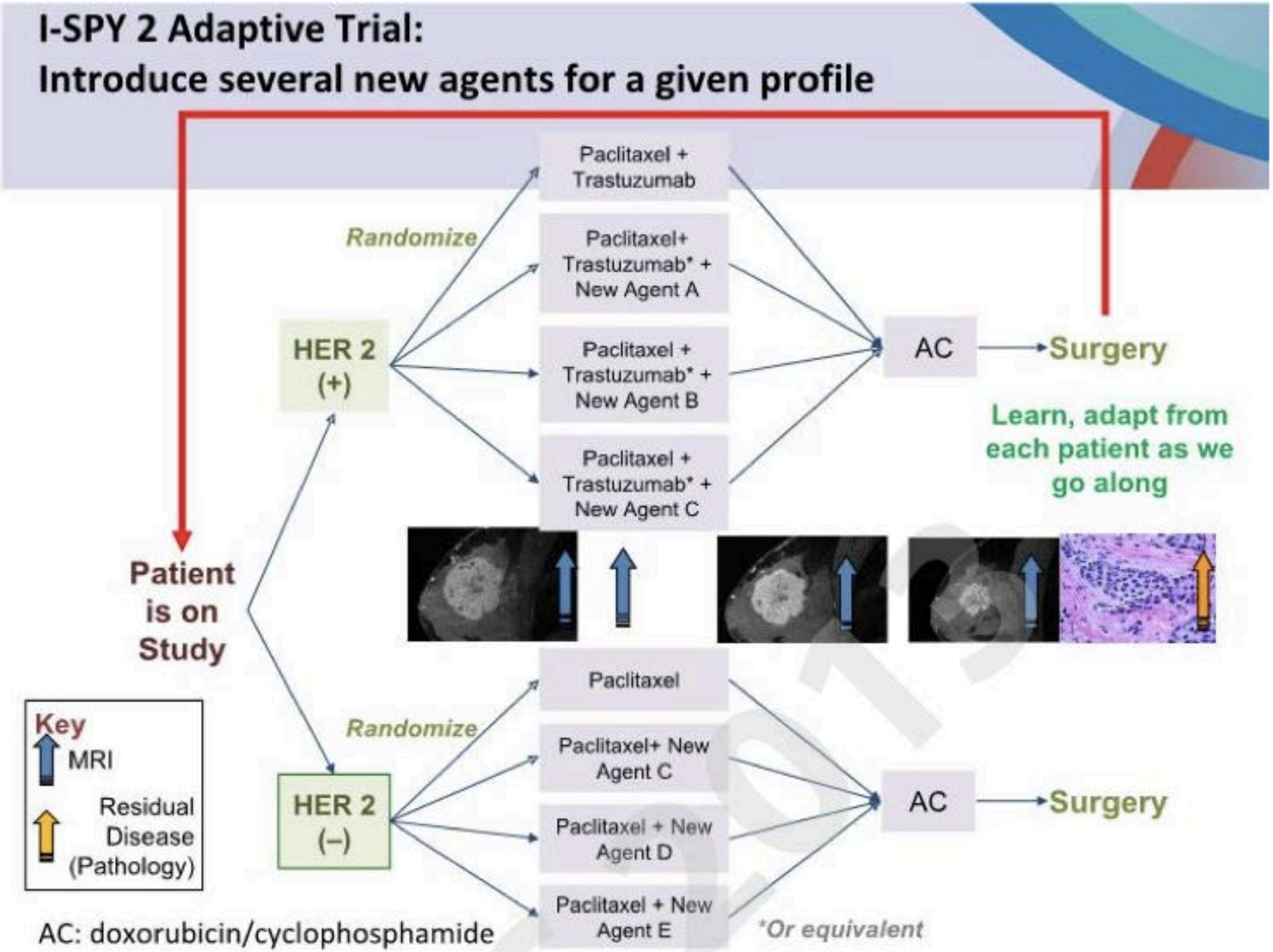
Tamura Proc ASCO 2014

Adverse Events

Treatment arm	CP-CEF				P-CEF			
	All		CP phase		All		P phase	
Adverse events	G3%	G4%	G3%	G4%	G3%	G4%	G3%	G4%
Anemia	18.2	1.1	14.8	1.1	1.1	0	0	0
Neutropenia	46.6	19.3	52.3	5.7	17.6	20.9	8.8	1.1
Thrombocytopenia	1.1	0	1.1	0	0	0	0	0
Febrile neutropenia	20.5	0	2.3	0	15.4	0	0	0
Nausea	3.4	0	2.3	0	2.2	0	0	0
Vomiting	2.3	0	1.1	0	0	0	0	0
Fatigue	2.3	0	2.3	0	1.1	0	0	0
Infection	4.4	0	2.2	0	1.1	0	0	0
Sensory neuropathy	1.1	0	1.1	0	1.1	0	1.1	0

Tamura Proc ASCO 2014

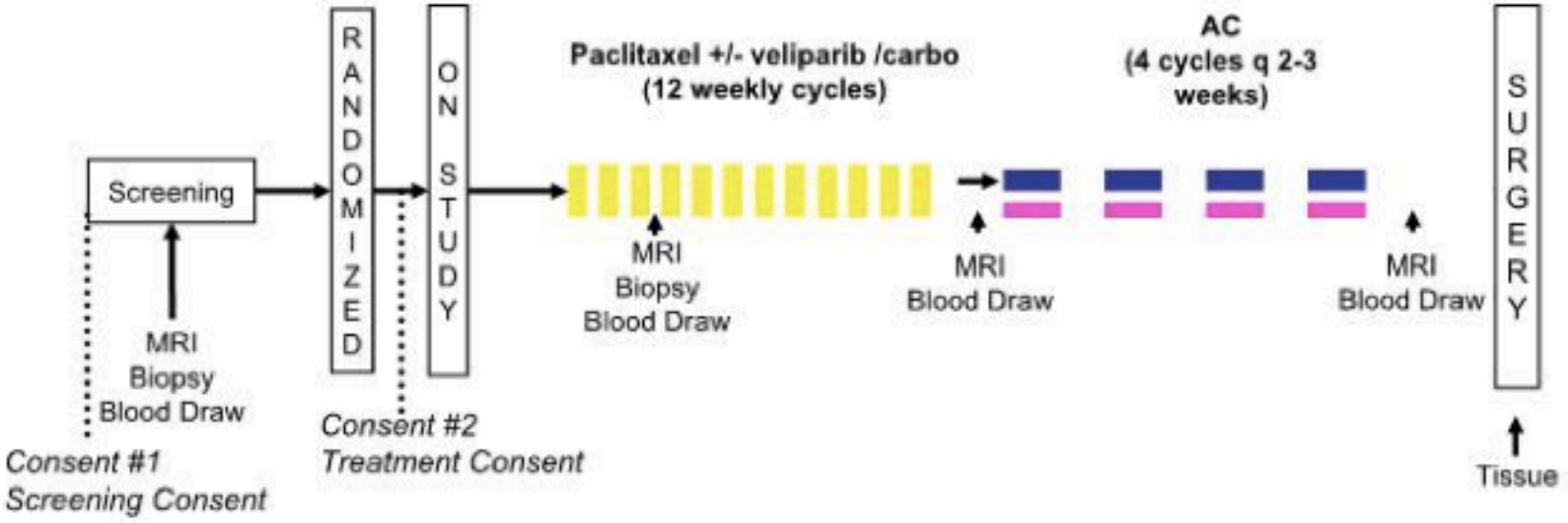
I-SPY 2 Adaptive Trial:
Introduce several new agents for a given profile



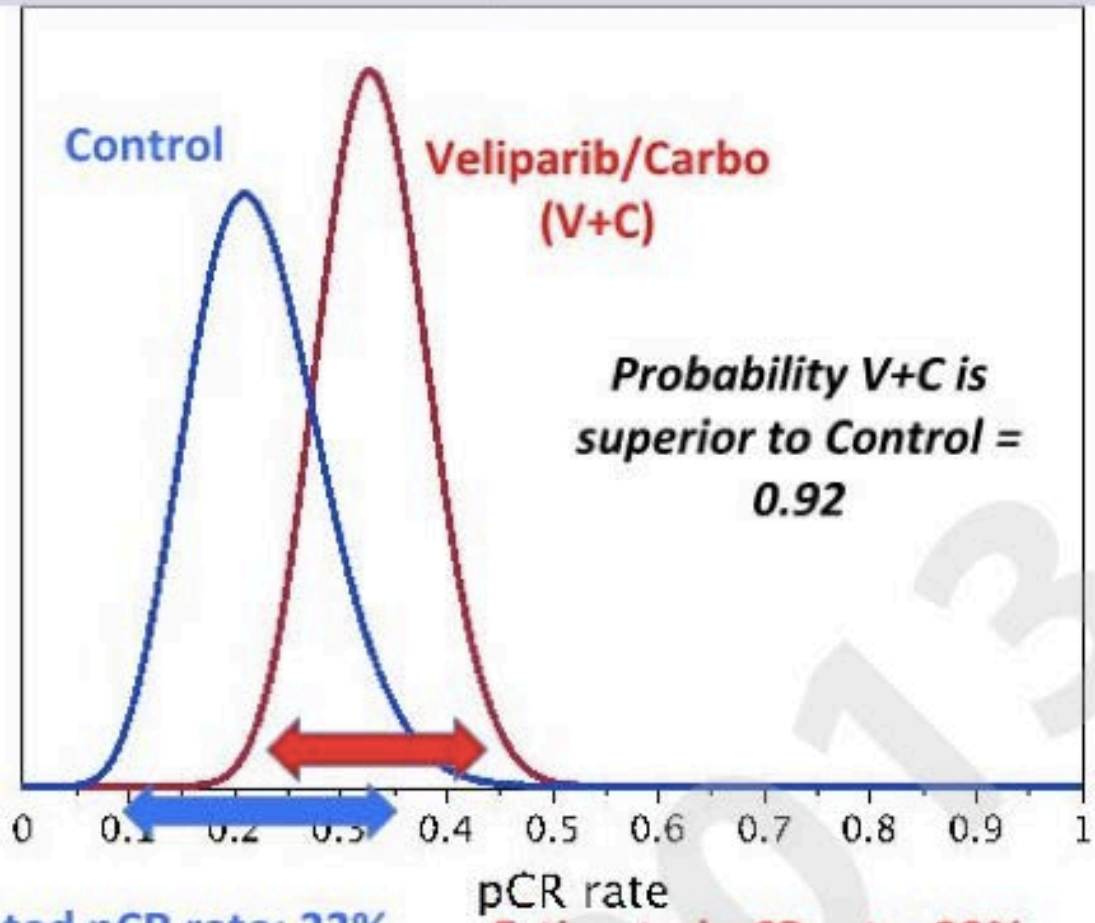
Experimental Arm 1: Veliparib/Carboplatin

- Veliparib (ABT888) is a potent PARP inhibitor.
- For this analysis, patients were ADAPTIVELY randomized to receive:
  - Veliparib 50 mg po BID x 12 weeks/carboplatin AUC 6 q 3 weeks x 4

  OR with weekly paclitaxel followed by AC
  - Weekly paclitaxel followed by AC
- Enrollment open **only** to patients **with HER2 negative disease**
- Eligible to graduate in 3 signatures: **all HER2-, HR+/HER2-, TN**



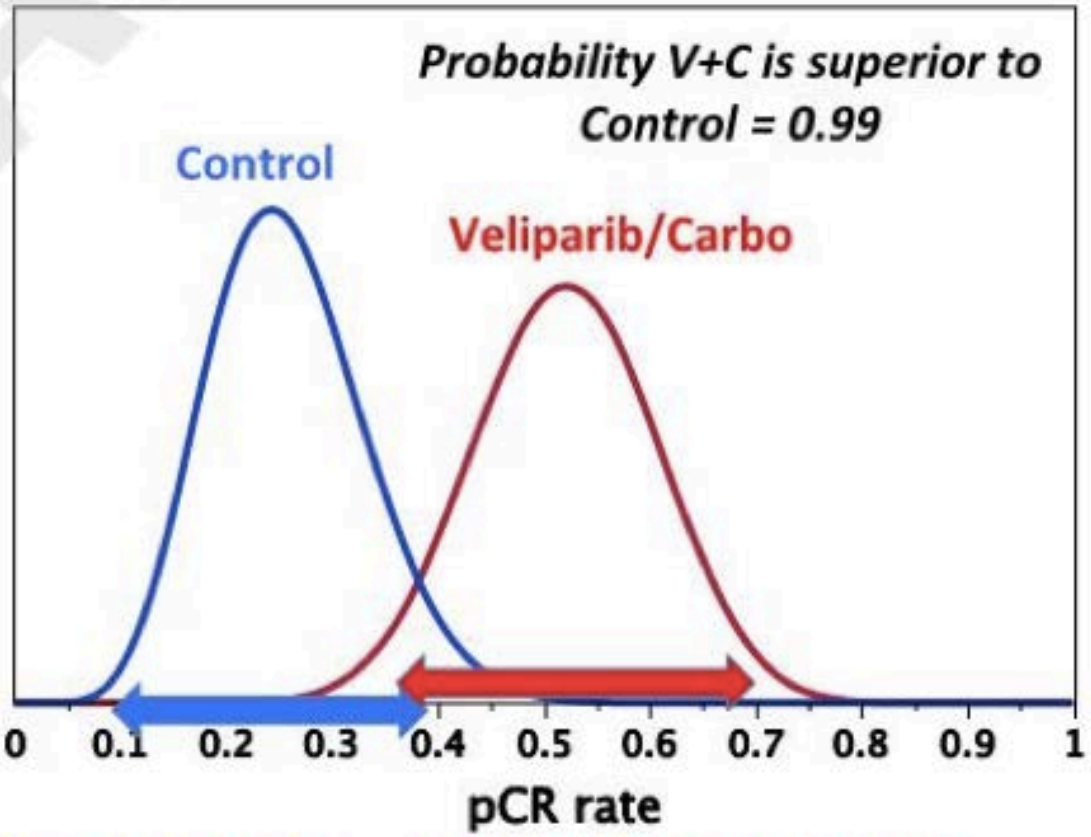
Estimated pCR Rate: All HER2 Negative Signature



Estimated pCR rate: 22%
95% Probability Interval: 10% to 35%

Estimated pCR rate: 33%
95% Probability Interval: 23% to 43%

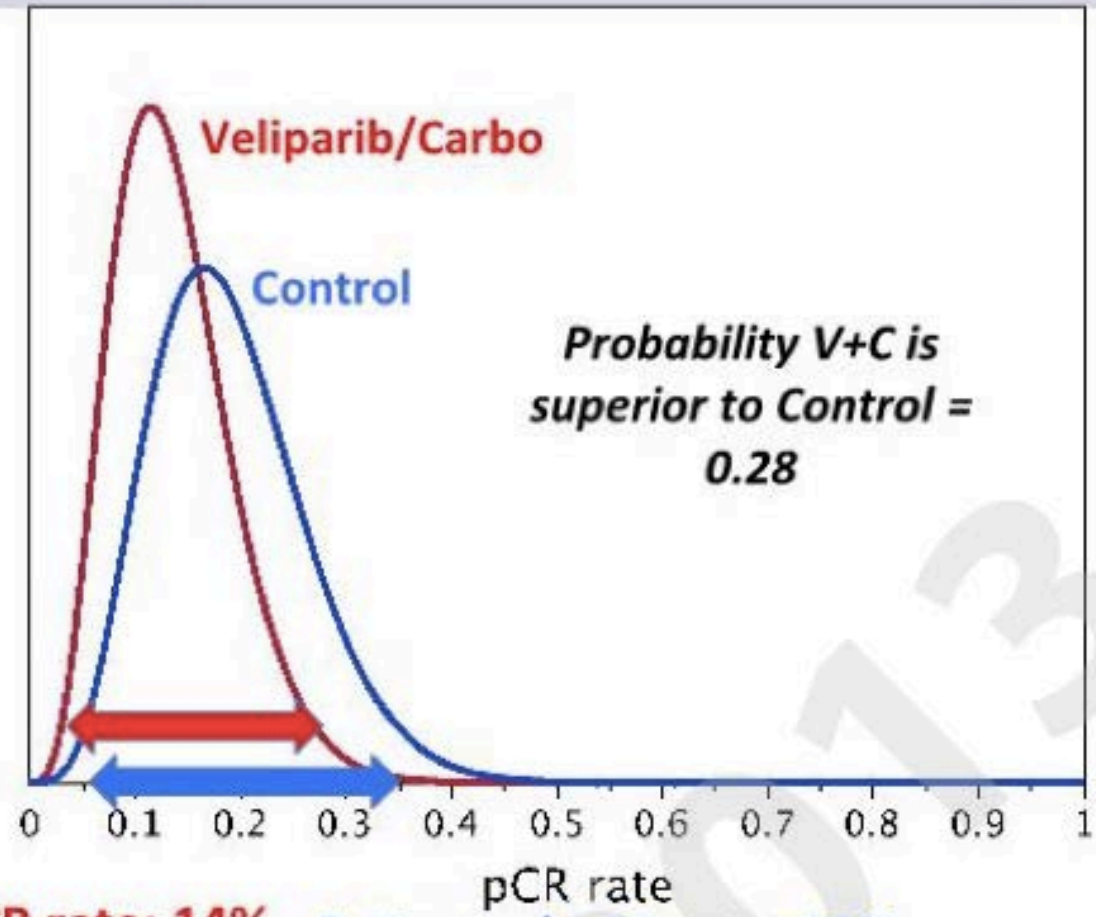
Estimated pCR Rate: Triple Negative Signature



Estimated pCR rate: 26%
95% probability interval:
11% to 40%

Estimated pCR rate: 52%
95% probability interval:
35% to 69%

Estimated pCR Rate: HER2 Negative/HR Positive Signature



Estimated pCR rate: 14%
95% probability interval: 4% to 27%

Estimated pCR rate: 19%
95% probability interval: 6% to 35%

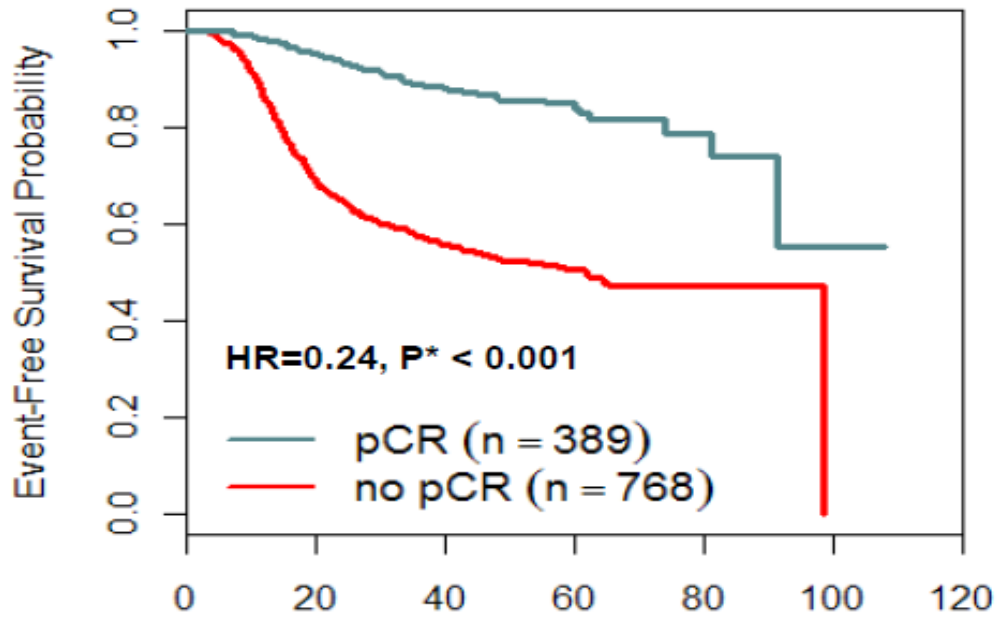
Case History

- Patient receives pre-operative AC followed by taxol
- Patient undergoes right mastectomy and ALND
- Final pathology: ypT1C (19mm), N1 (2 nodes with macro-mets)
- Receives post-mastectomy radiation
- Any role for further systemic therapy?

CALGB 40603: Background

Neoadjuvant Chemotherapy for TNBC

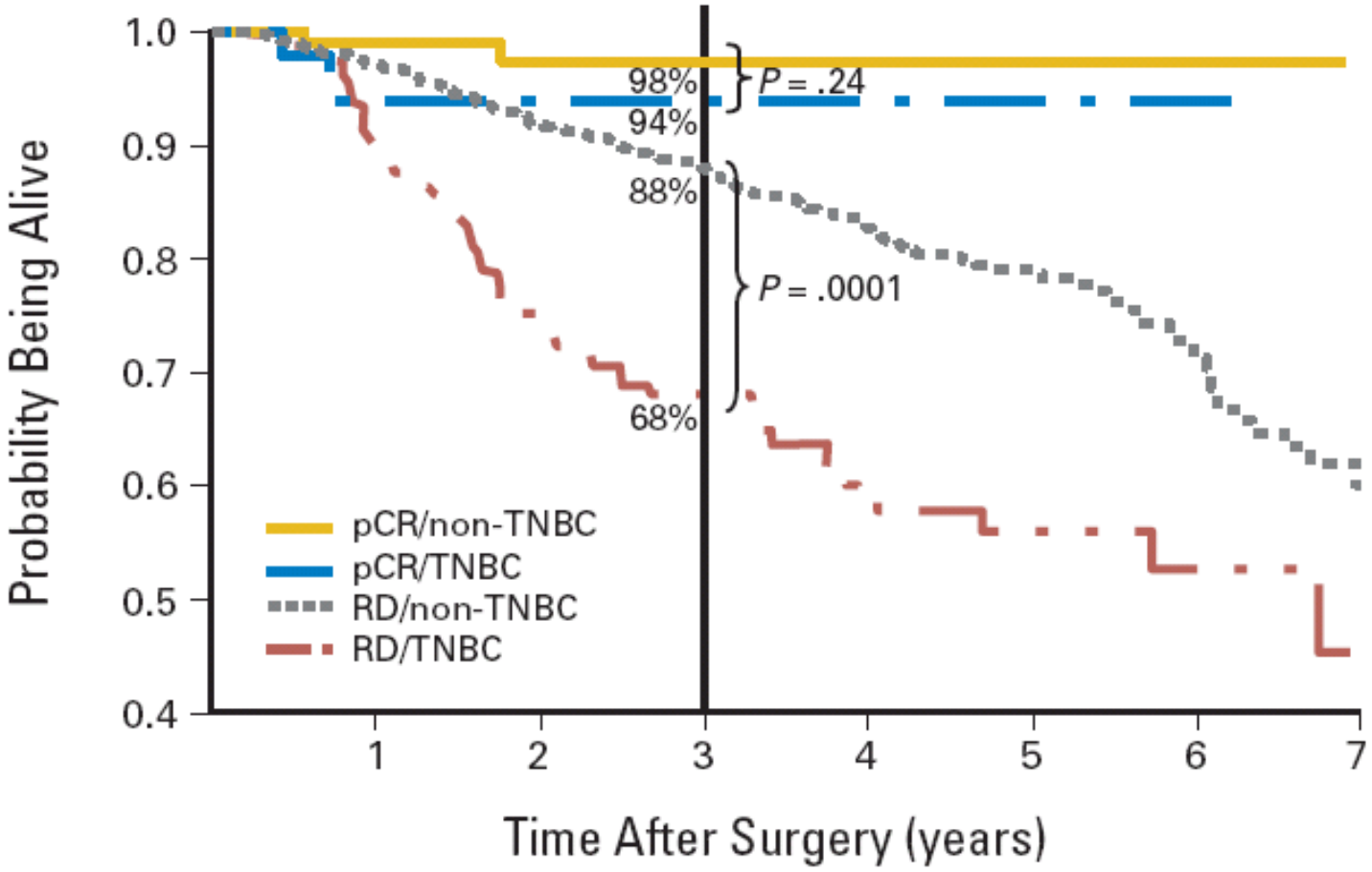
- pCR (ypT0/is N0) rate: 34% (meta-analysis)



Cortazar et al SABCS 2012

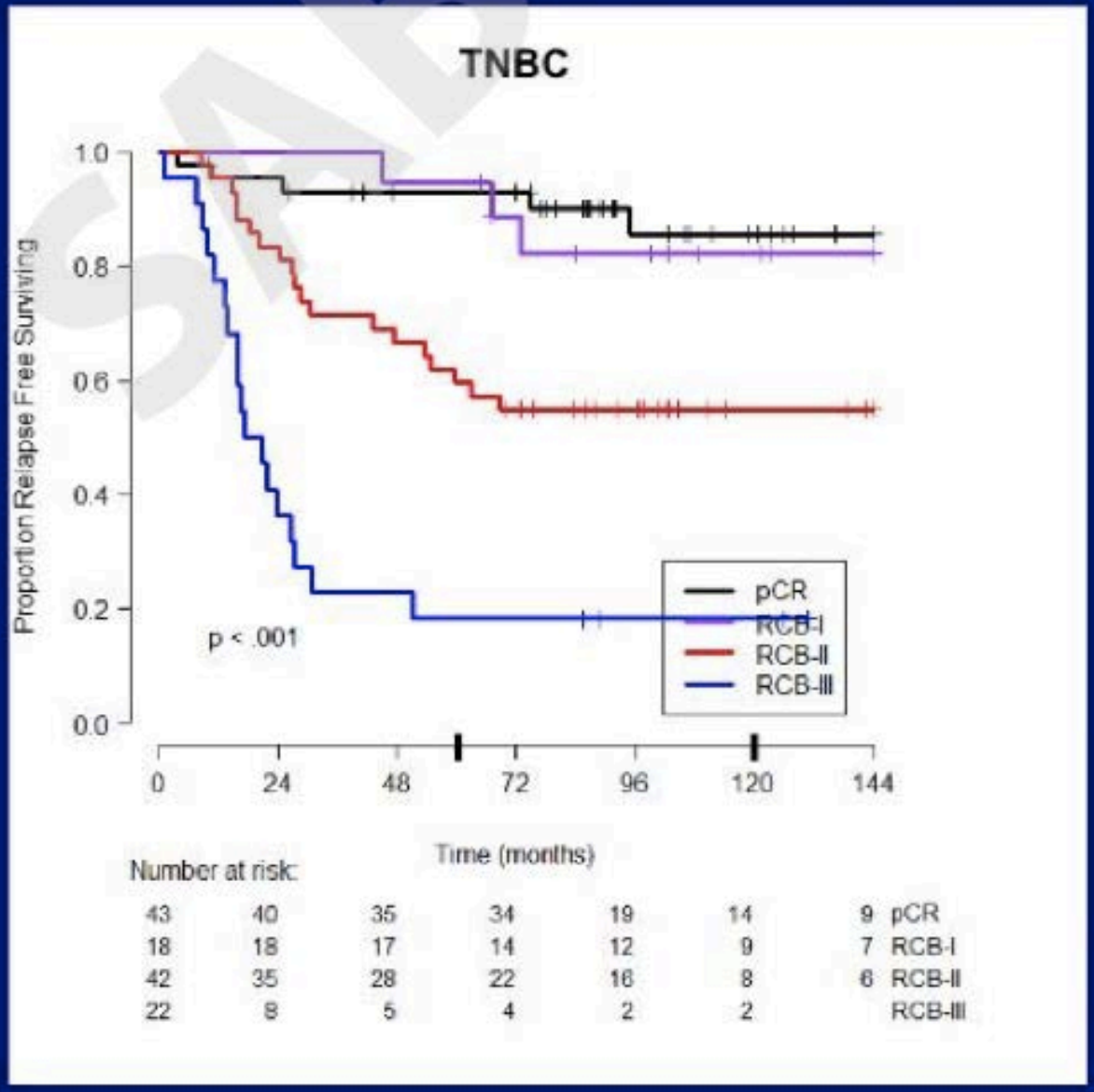
Importance of Pathologic CR

Overall Survival



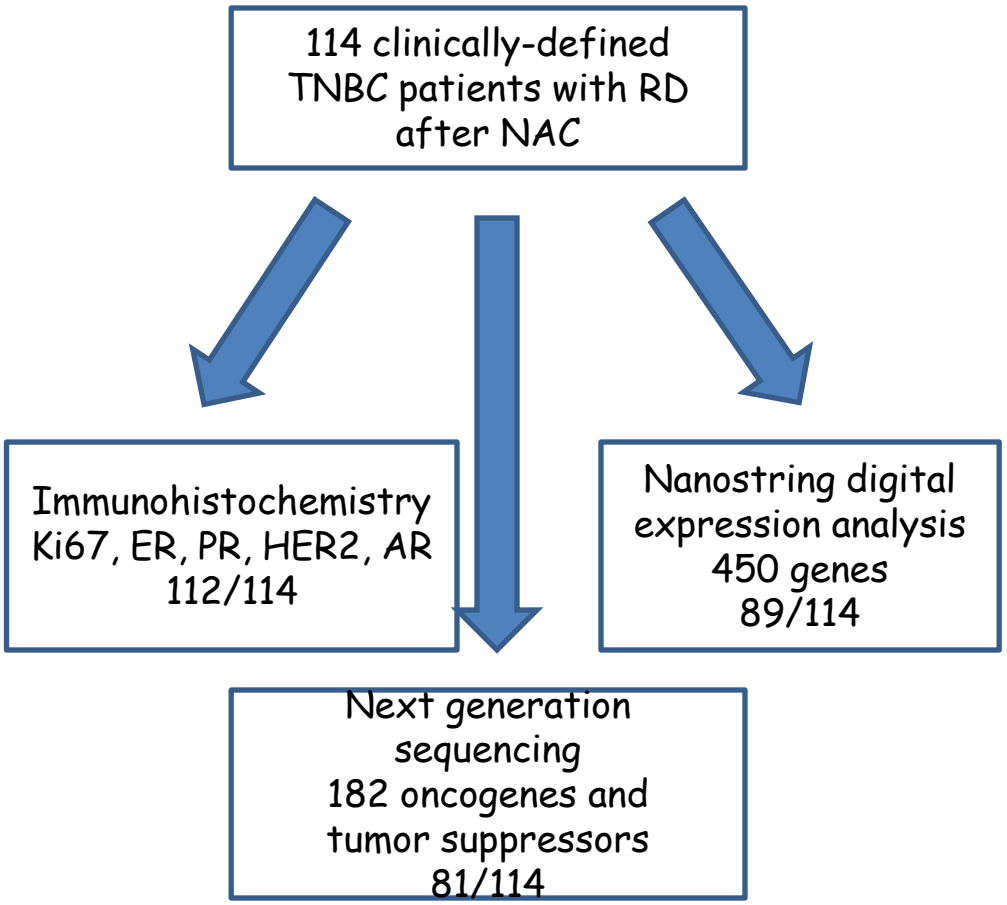
Liedtke et al. *JCO* 2008; 26(8): 1275-81

RCB Categories: Combined T/FAC Cohorts (RFS)



Class	N	%
pCR	43	34
RCB-I	18	14
RCB-II	42	34
RCB-III	22	18

Cohort

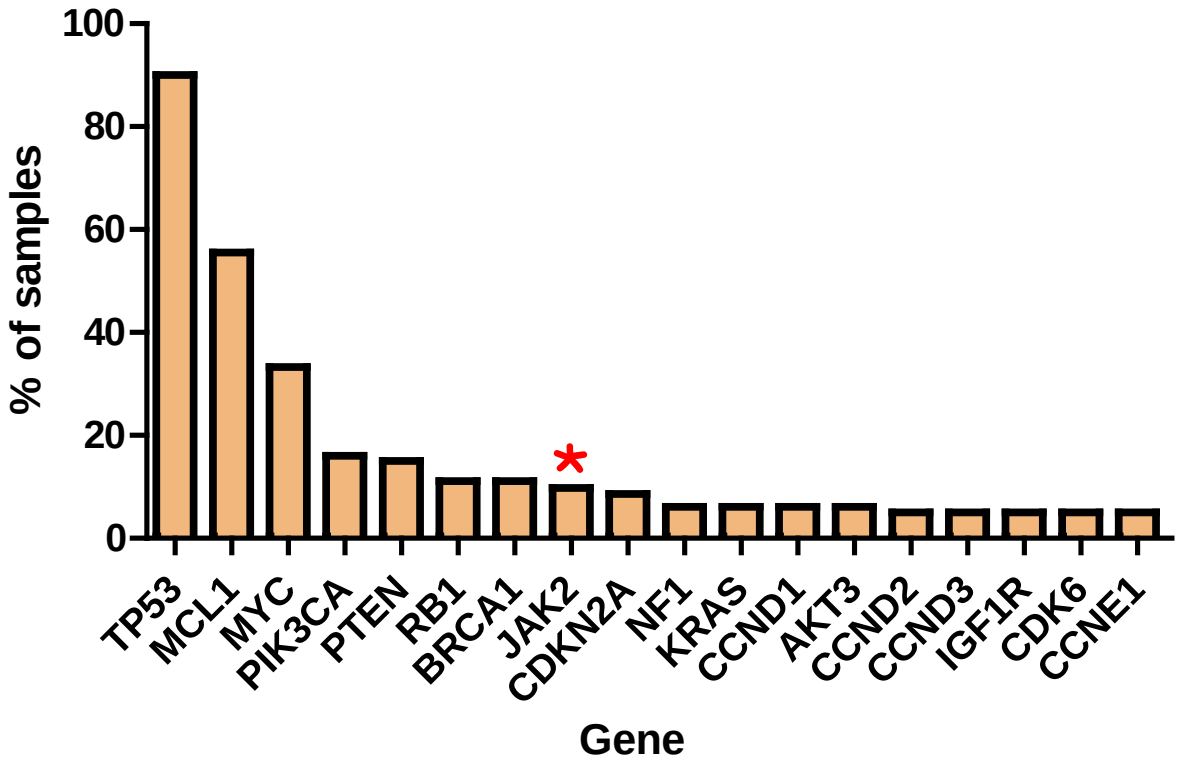


	Median	Min	Max
Age	48	24	78
		N	%
Stage	IIa	3	3%
	IIb	5	5%
	IIIa	13	12%
	IIIb	77	69%
	IIIc	10	9%
	NA	3	3%
Taxane	Yes	55	50%
	No	53	48%
	NA	3	3%
Menopause	Pre	55	50%
	Post	53	48%
	NA	3	3%
Node status	Pos	70	63%
	Neg	37	33%
	NA	4	4%

Balko et al, Cancer Discovery, in press.

Deep sequencing of the residual disease in NAC-treated TNBC

- 182 oncogenes and tumor suppressors in a CLIA certified lab (Foundation Medicine, Cambridge MA)
- Data were evaluable for 81 tumors, with a sufficient coverage to determine CNAs in 72/81



Balko et al, Cancer Discovery, in press.

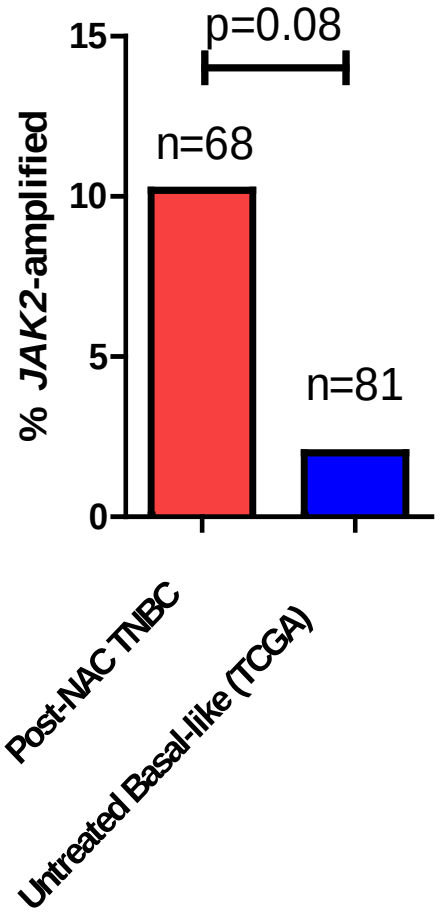
JAK2

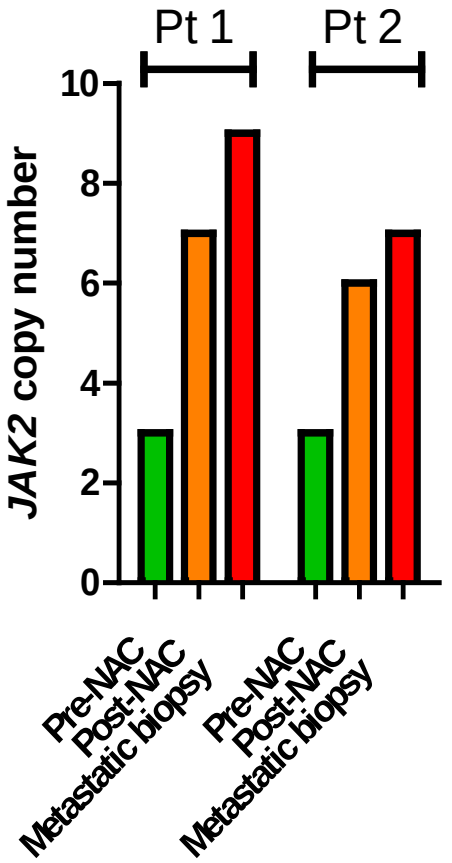
- Janus-kinase 2 (JAK2) is a receptor-coupled tyrosine kinase which transmits cytokine-mediated signals to the STAT pathway to drive proliferation and differentiation
- JAK2/STAT signaling has been shown to play a role in promoting breast cancer 'stemness' and driving the proliferation of CD44+/CD24- basal-like breast cancer cells.

Marotta LL et al. J Clin Invest. 2011;121(7):2723-35.

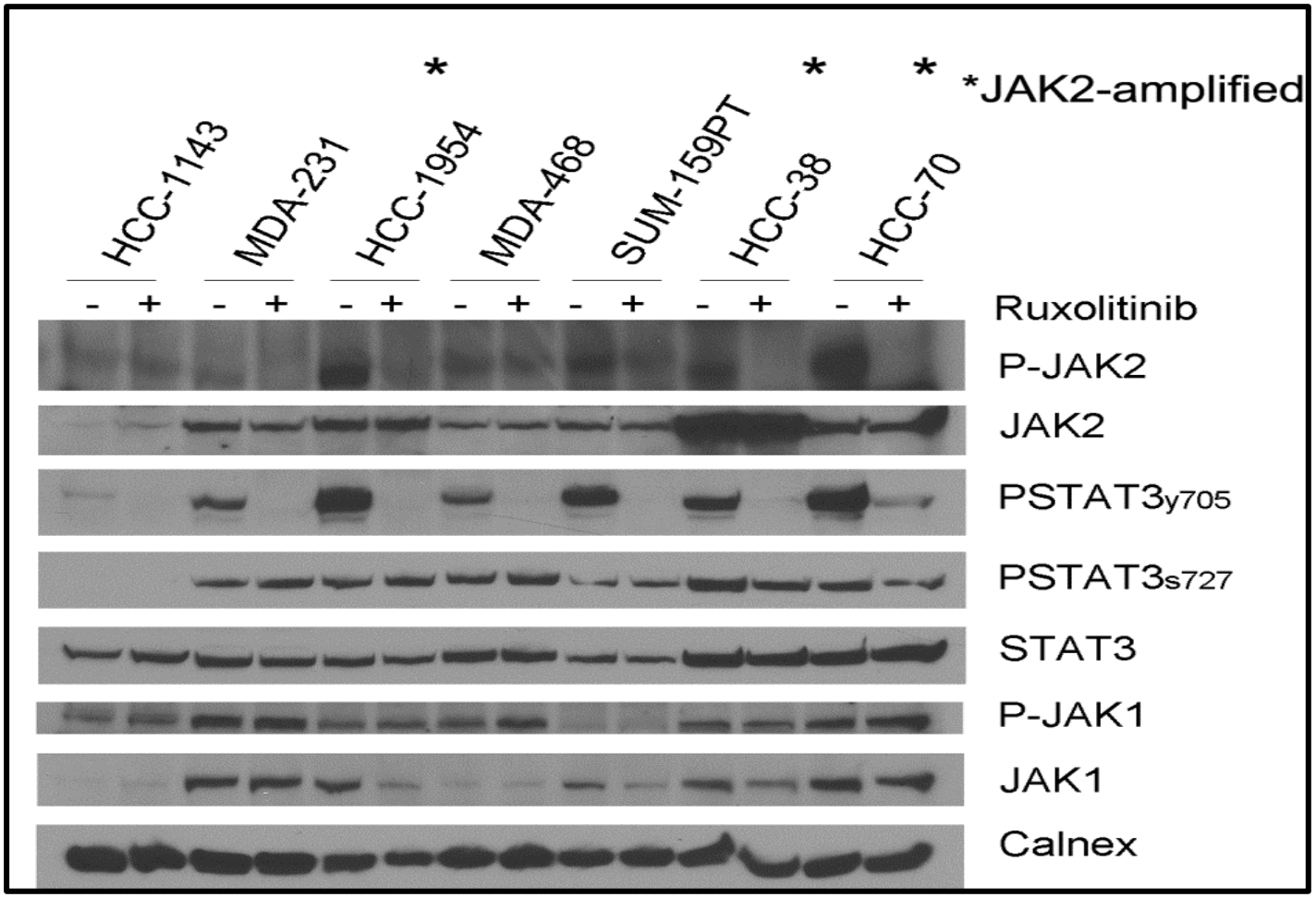
JAK2 copy number increases with treatment and metastatic progression

- JAK2 gains and amplifications were more frequent in NAC-treated TNBC than in primary untreated BLBC (TCGA)

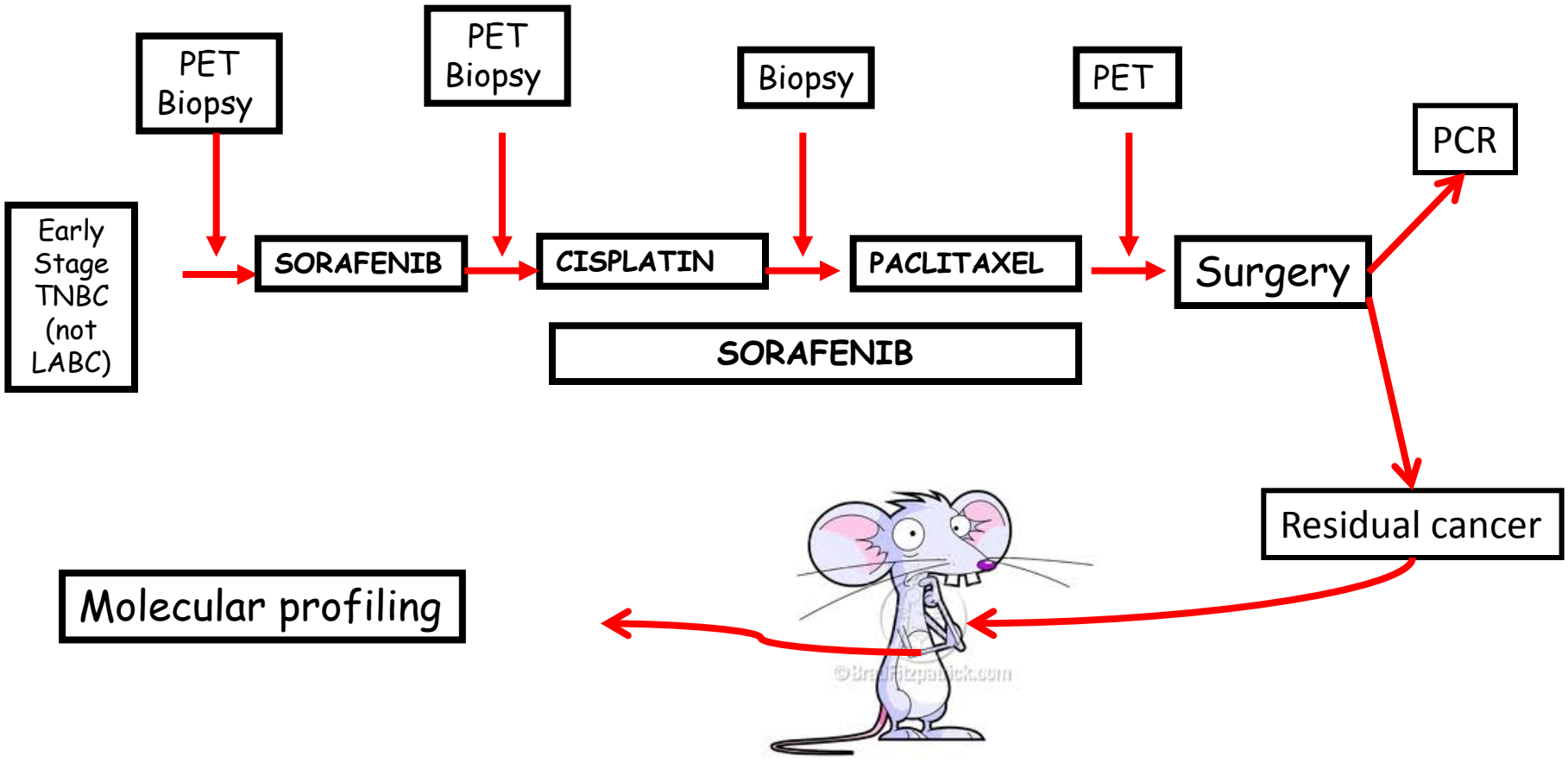




Ruxolitinib inhibits JAK2 pathway in TNBC with JAK2 amplifications



Winship pre-operative trial in triple negative breast cancer

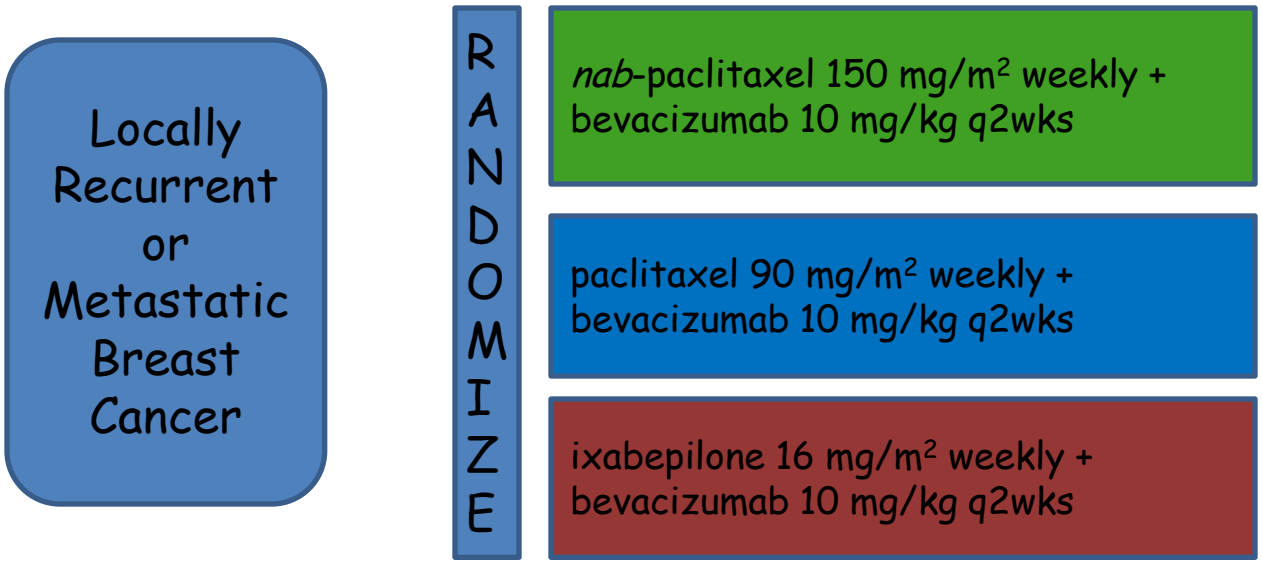


Case History

- Patient does fine for 18-months when she develops shortness of breath
- Imaging shows lung nodules and liver metastases
- Liver biopsy: adenocarcinoma, ER/PR/HER2-negative

CALGB 40502: Schema

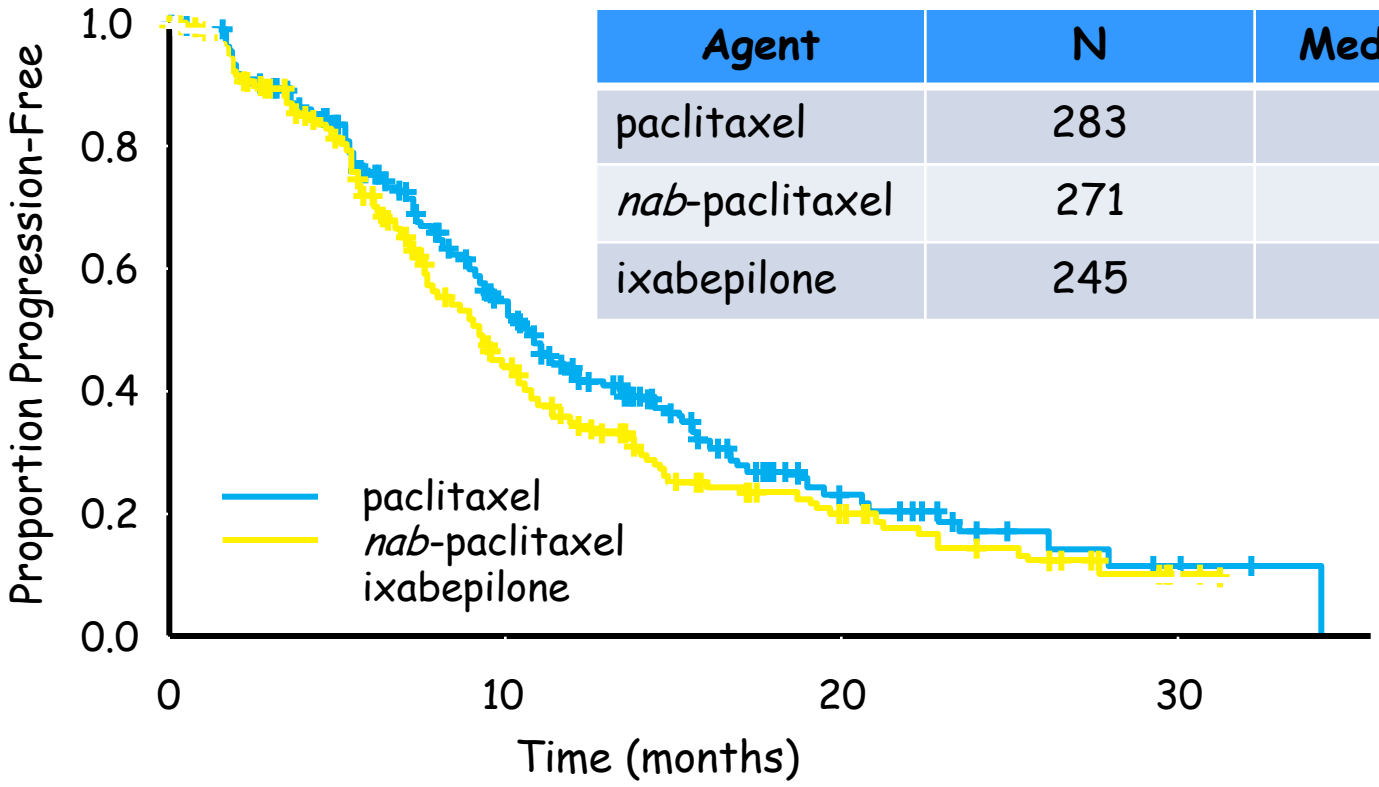
- Open-label, phase III trial of first-line therapy for locally recurrent breast cancer or metastatic breast cancer (N = 799)
- Randomized 1:1:1



- All chemotherapy given on a 3-weeks on, 1-week off schedule
  - Patients could discontinue chemotherapy and continue bevacizumab alone after 6 cycles if stable or responding disease
  - 98% received bevacizumab
- Primary endpoint: PFS of each experimental arm compared with control

Rugo H, et al. *J Clin Oncol.* 2012;30(suppl). Abstract CRA 1002.

CALGB 40502: PFS by Treatment Arm



Agent	N	Median PFS
paclitaxel	283	10.6
nab-paclitaxel	271	9.2
ixabepilone	245	7.6

- Neither weekly *nab* or ixabepilone are superior to weekly paclitaxel
- Weekly paclitaxel appears to offer better PFS survival than ixabepilone
- At this dose and schedule, there is no advantage with either *nab*-paclitaxel or ixabepilone

Rugo H, et al. *J Clin Oncol*. 2012;30(suppl). Abstract CRA 1002.

Phase III EMBRACE Trial Study Design

Patients (N = 762)

- Locally recurrent or MBC
- 2-5 prior chemotherapies
  - ≥ 2 for advanced disease
  - Prior anthracycline and taxane
- Progression ≤ 6 months of last chemotherapy
- Neuropathy ≤ grade 2
- ECOG ≤ 2

Eribulin mesylate

1.4 mg/m^2, 2-5 min IV
Day 1, 8 q21d

Randomization 2:1

Treatment of physician's choice (TPC)

Any monotherapy (chemotherapy, hormonal, biological)* or supportive care only†

Primary Endpoint

- OS

Secondary Endpoints

- PFS
- ORR
- Safety

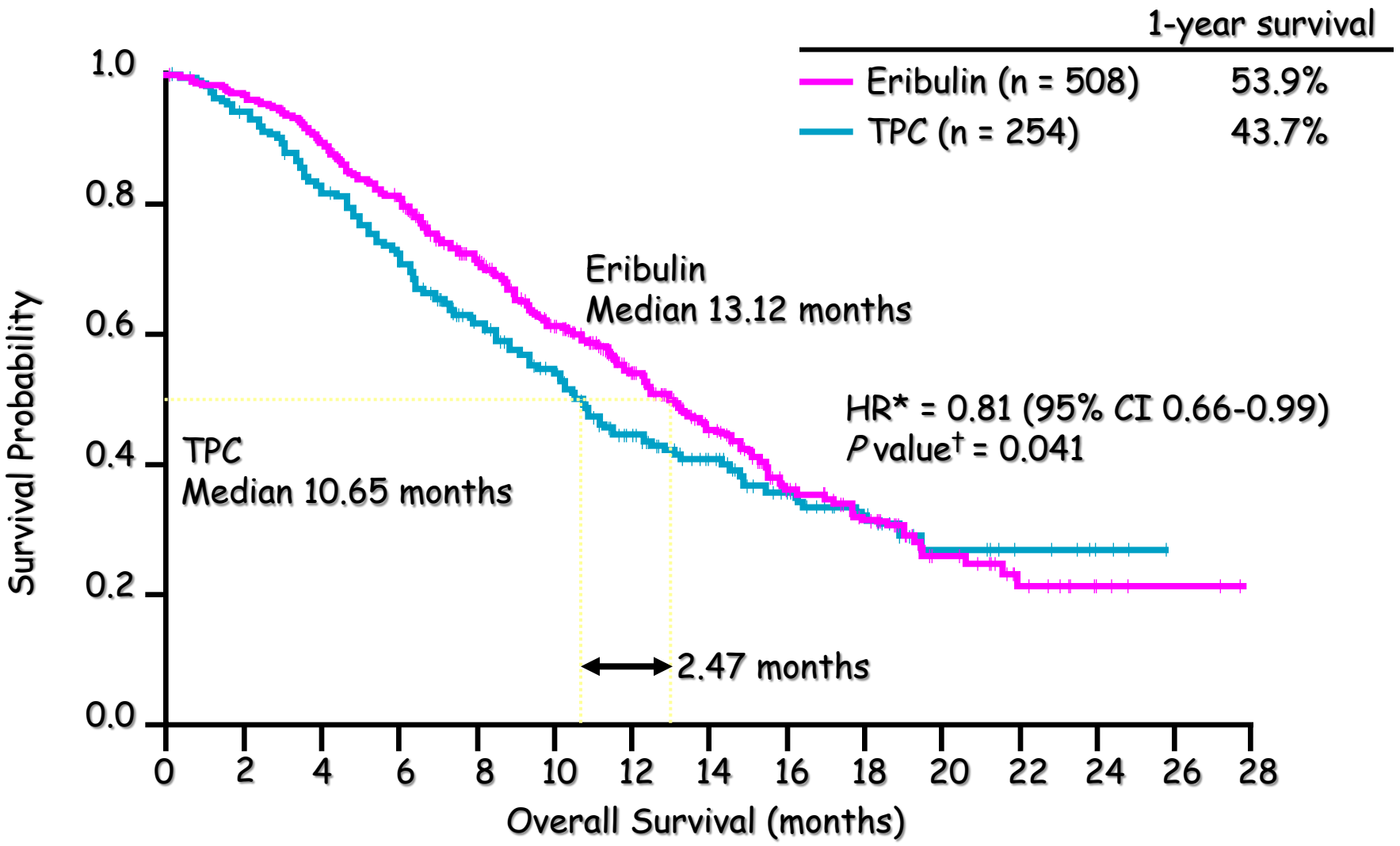
- **Stratification:**
  - **Geographical region**
  - **Prior capecitabine**
  - **HER2 / *neu* status**

- Exploratory subgroups:
  - Hormone receptor expression status (ER, PR, HER2, triple-negative)
  - Number of organs involved
  - Sites of disease

*Approved for treatment of cancer administered according to local practice; †Palliative treatment or radiotherapy, if applicable.

Cortes J, et al. *Lancet.* 2011;377(9769):914-933.

EMBRACE: Overall Survival



*HR Cox model including geographic region, HER2 status, and prior capecitabine therapy as strata. †*P* value from stratified log-rank test (pre-defined primary analysis).

Cortes J, et al. *Lancet.* 2011;377(9769):914-933.

Eribulin 301

Global, randomized, open-label phase III trial (Study 301)

Patients (N = 1102)

Locally advanced or MBC

- ≤ 3 prior chemotherapy regimens (≤ 2 for advanced disease)
- Prior anthracycline and taxane in (neo)adjuvant setting or for locally advanced or MBC

Eribulin mesylate
1.4 mg/m^2 2- to 5-min IV
Day 1 & 8 q21 days

Randomization 1:1

Capecitabine
1250 mg/m^2 BID orally
Days 1-14, q21 days

Co-primary endpoint

- OS and PFS

Secondary endpoints

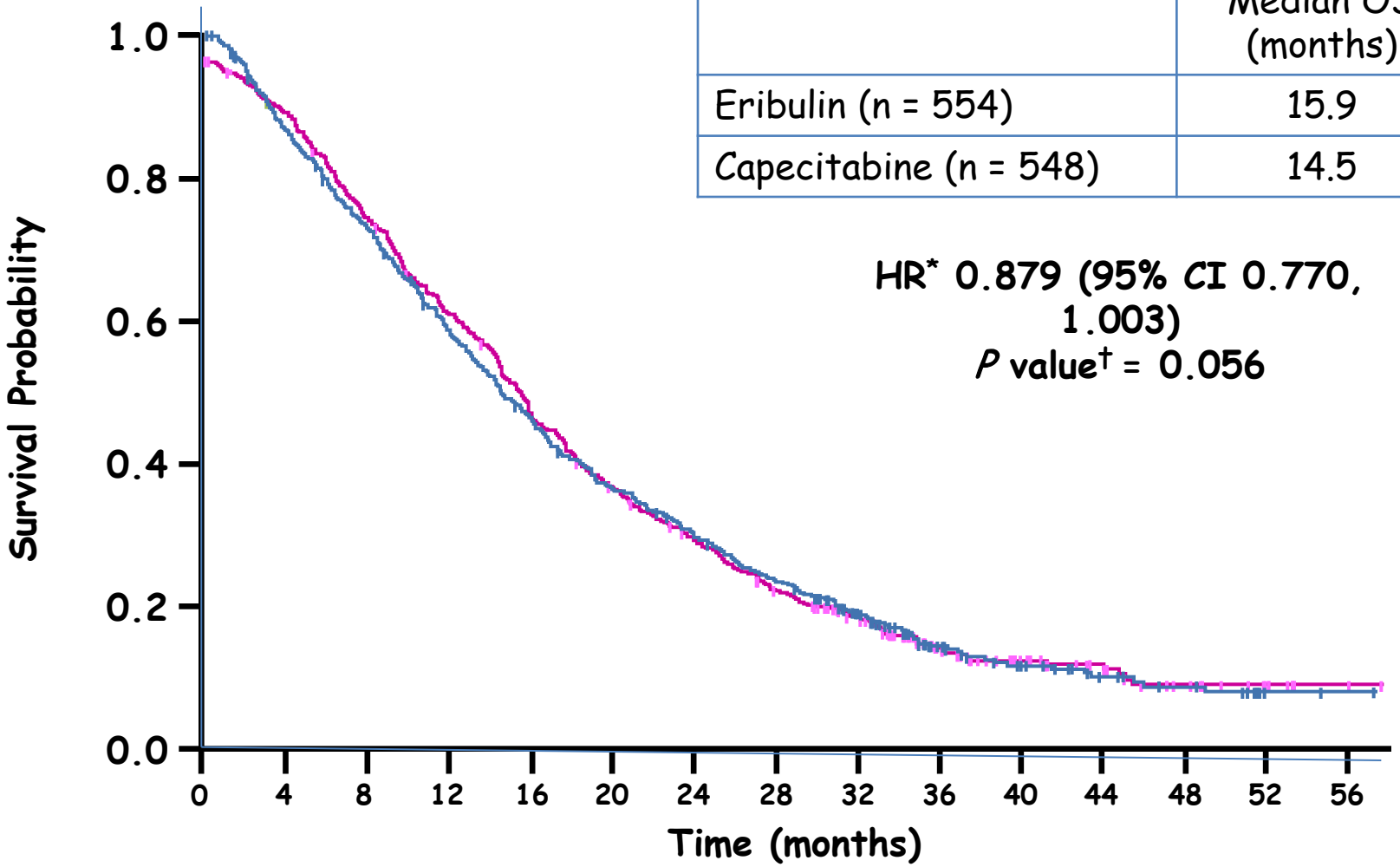
- Quality of life
- ORR
- Duration of response
- 1-, 2-, and 3-year survival
- Tumor-related symptom assessments
- Safety parameters
- Population PK

Kaufman PA, et al. SABCS December 7, 2012. Abstract S6-6.

Eribulin 301: Overall Survival

	Median OS (months)
Eribulin (n = 554)	15.9
Capecitabine (n = 548)	14.5

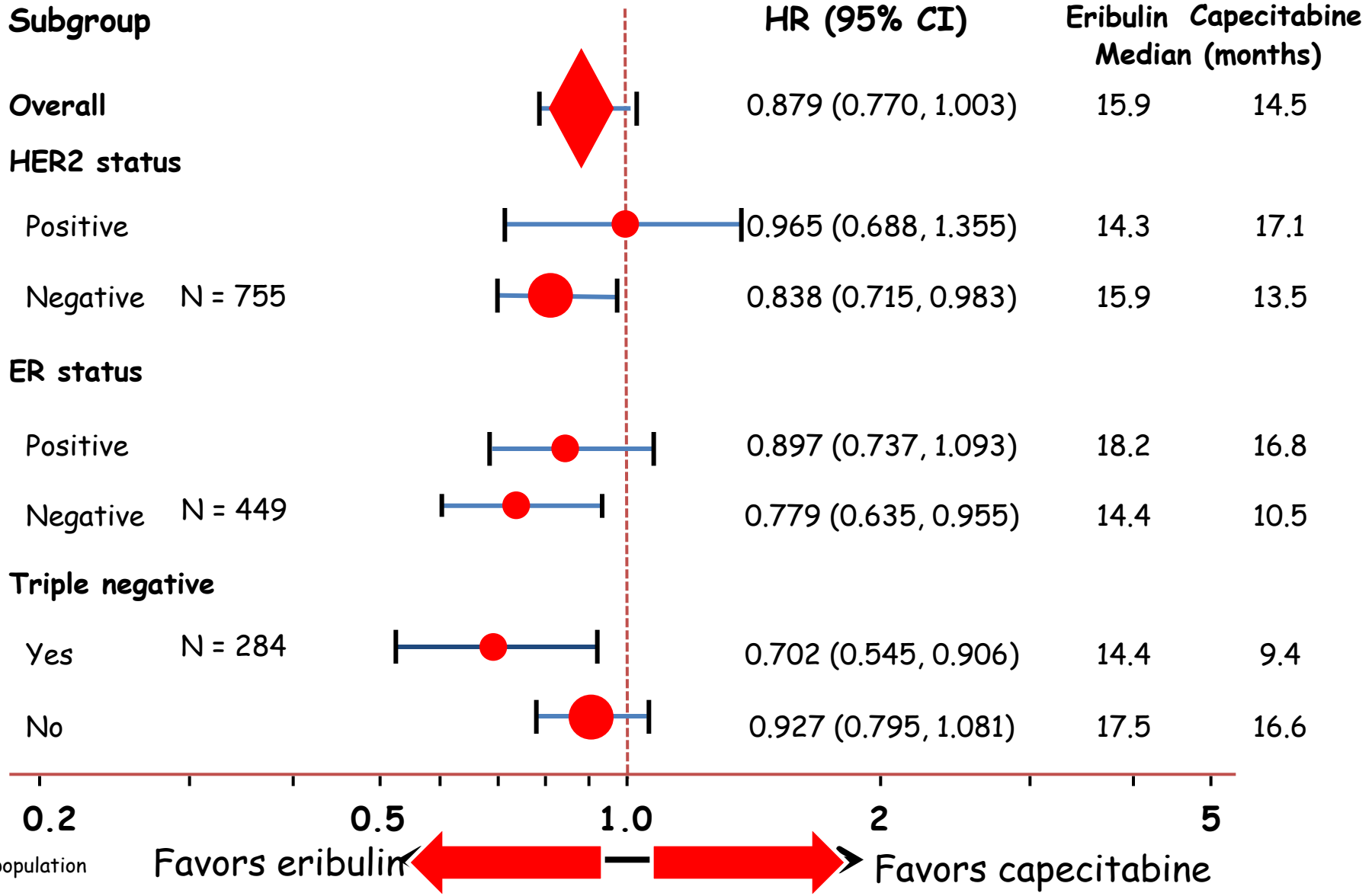
HR* 0.879 (95% CI 0.770, 1.003)
***P* value† = 0.056**



ITT population; *HR Cox model including geographic region and HER2 status as strata.
†*P* value from stratified log-rank test based on clinical database.

Kaufman PA, et al. SABCS December 7, 2012. Abstract S6-6.

Eribulin 301: Overall Survival By Receptor Status



Kaufman PA, et al. SABCS December 7, 2012. Abstract S6-6.

Kaufman et al, SABCS– December 7, 2012

Capecitabine ± Ixabepilone in Triple Negative MBC

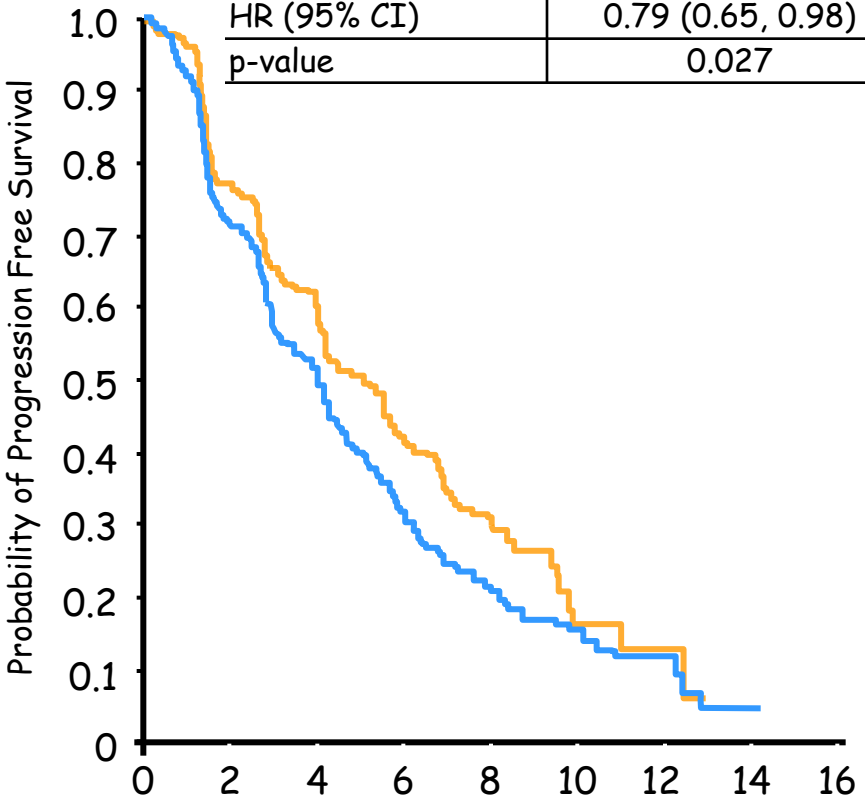
Efficacy	Ixa + Cape (n = 191)	Cape (n = 208)
ORR	31%	15%
CR	3%	1%
PR	28%	14%
Median PFS	4.2 mos	1.7 mos
HR	0.63	
P value	< .0001	
Median OS	10.3 mos (n = 213)	9.0 mos (n = 230)
HR	0.87	
P value	.18	

Pooled triple negative subgroup (n = 443)

Rugo et al. SABCS 2008, Abstract 3057

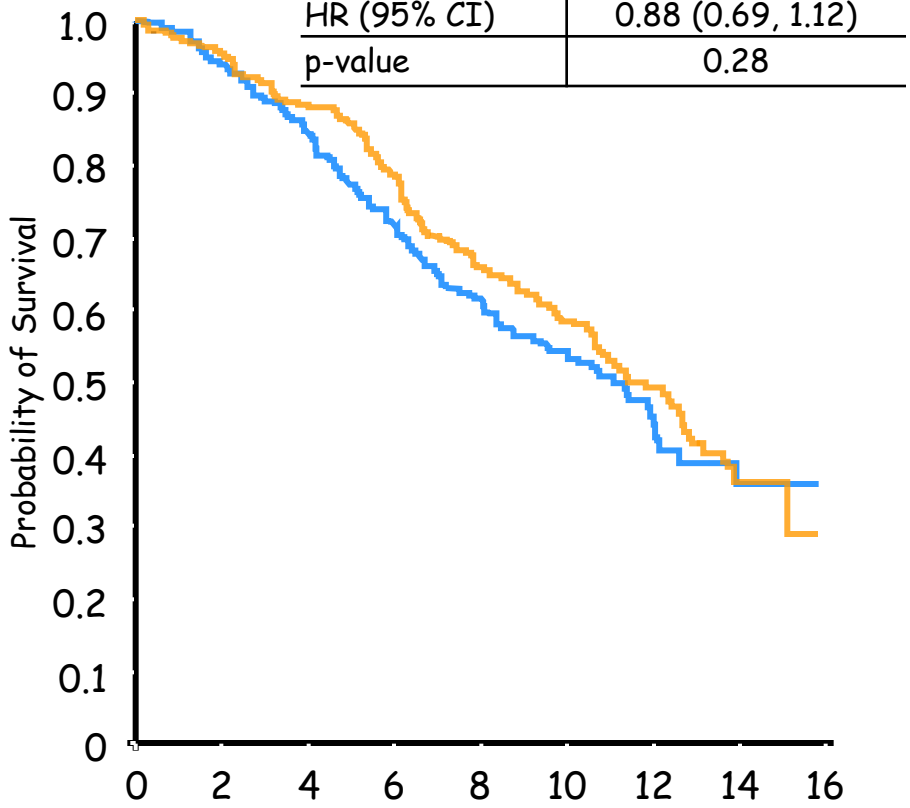
Iniparib does not improve outcome in unselected metastatic triple negative breast cancer

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

O' Shaughnessy PASCO 2011

PARP Inhibitor Trials – Activity Seen Only in BRCA1/2 Mutation Carriers

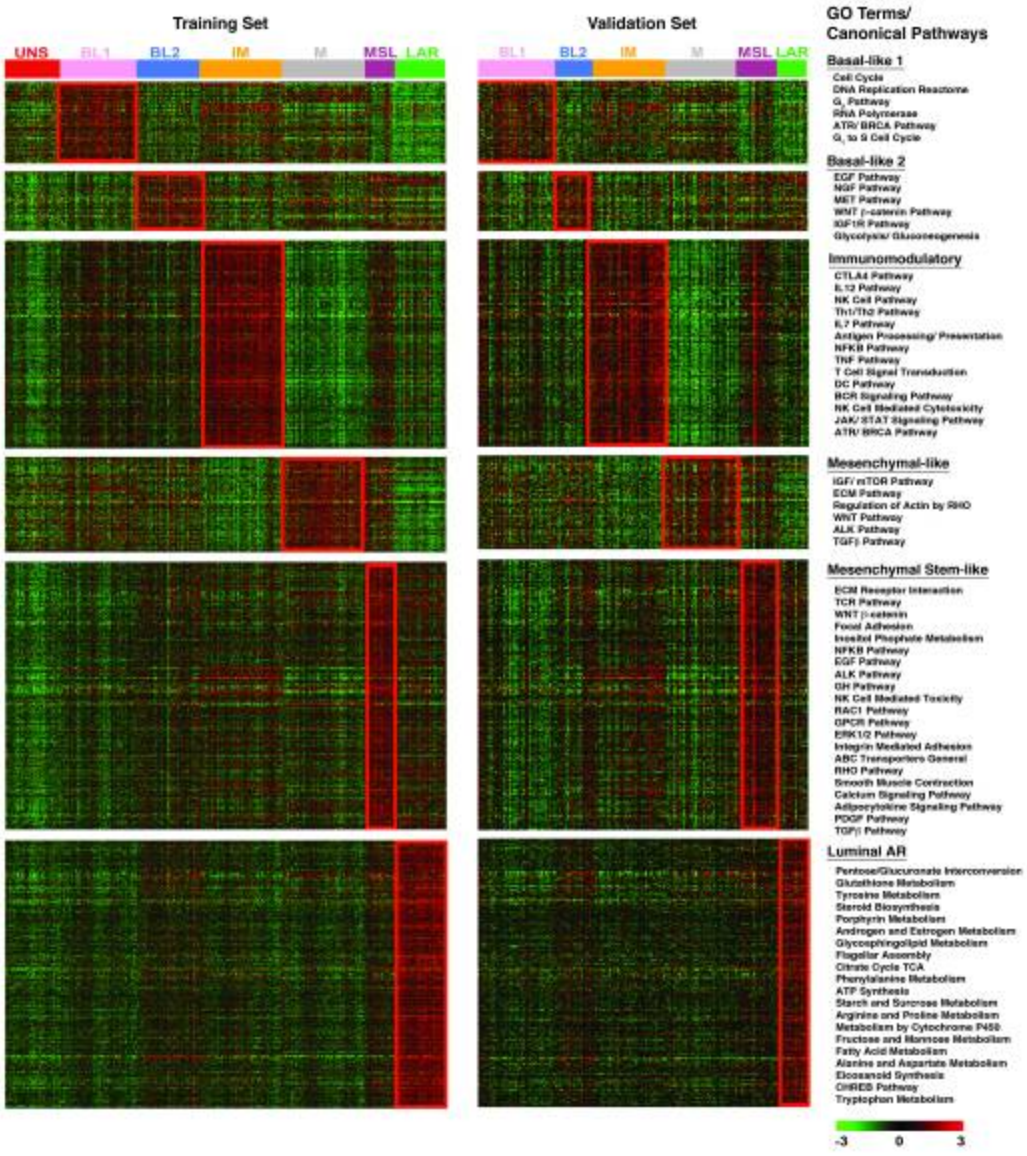
Agent	Author	BRCA1/BRCA2	TNBC	Response Rate
Olaparib (phase I; mixture tumor types)	Fong	60 patients 37% -BRCA1/2 mutations	N/A	63% clinical benefit rate (only in BRCA associated cancers)
Olaparib 400 mg po BID	Tutt	27 patients BRCA1 67% BRCA2 33%	50%	41%
ABT888 +temozolomide	Isakoff	41 patients BRCA1: 7.3% BRCA2: 12%	56%	BRCA 1 and 2: 37.5% **No response in normal BRCA status**

1. Fong PC, et al. N Engl J Med. 2009; 361:123-34; 2. Tutt, et all. Lancet 2010. Vol. 376 No. 9737 pp 235-244; 3. Isakoff et al. J Clin Oncol 28:15s, 2010 (suppl; abstr 1019) ;

Sub-types of triple negative breast cancer

- Evaluated gene expression profiles from 21 breast cancer data sets (14 training and 7 validation = 587 cases of TNBC)
- Used cluster analysis to sub-divide TNBC into 6 sub-types displaying unique gene expression and ontologies
- Identified breast cancer cells lines representative of each subtype

Lehmann et al JCI 2011



Lehmann et al JCI 2011

Basal-like 1: cell cycle, DNA repair and proliferation genes

Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)

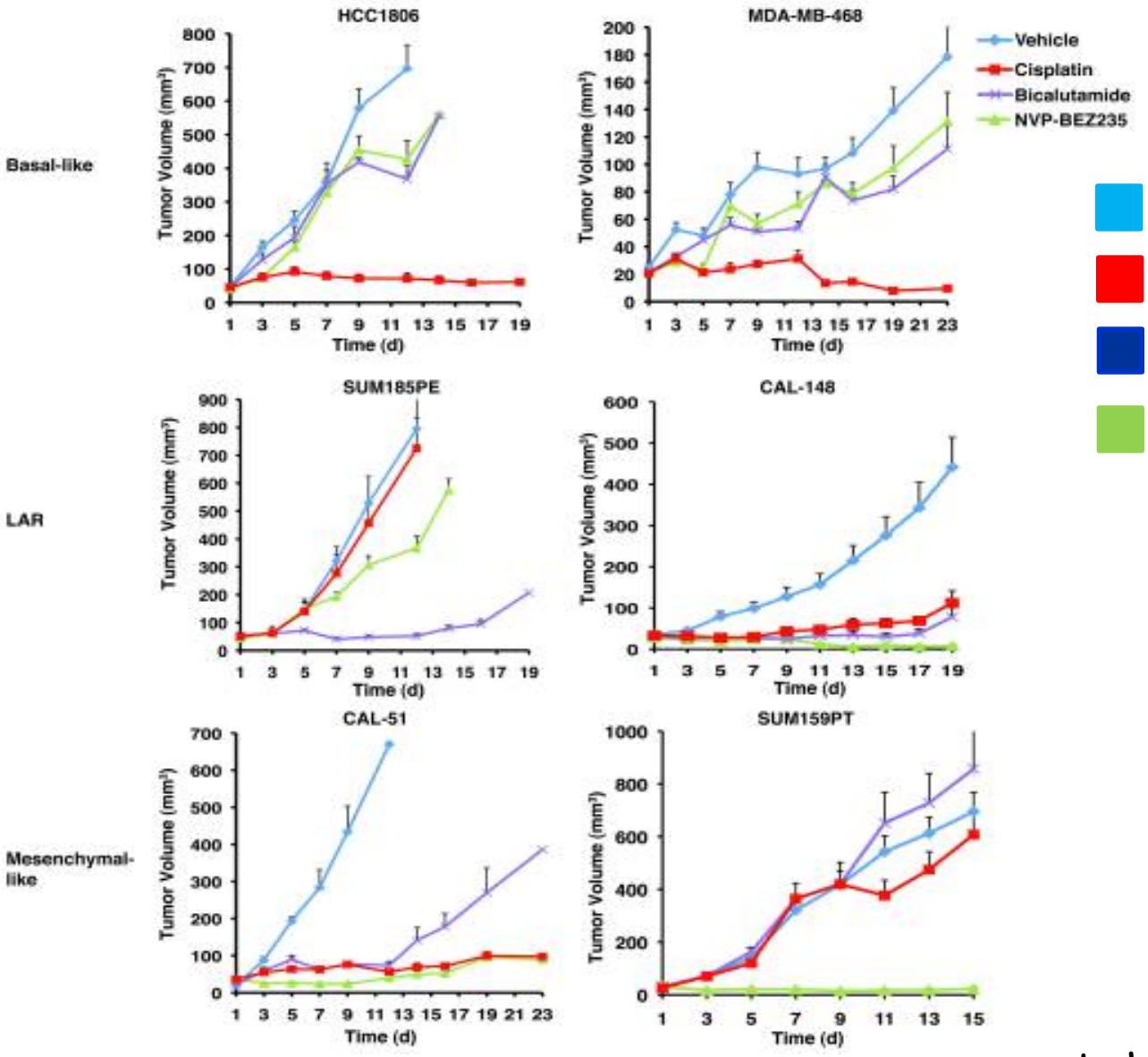
IM: immune cell processes (medullary breast cancer)

M: Cell motility and differentiation, EMT processes

MSL: similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

LAR: Androgen receptor and downstream genes, luminal features

Sub-types demonstrate differential response to therapies *in vivo*



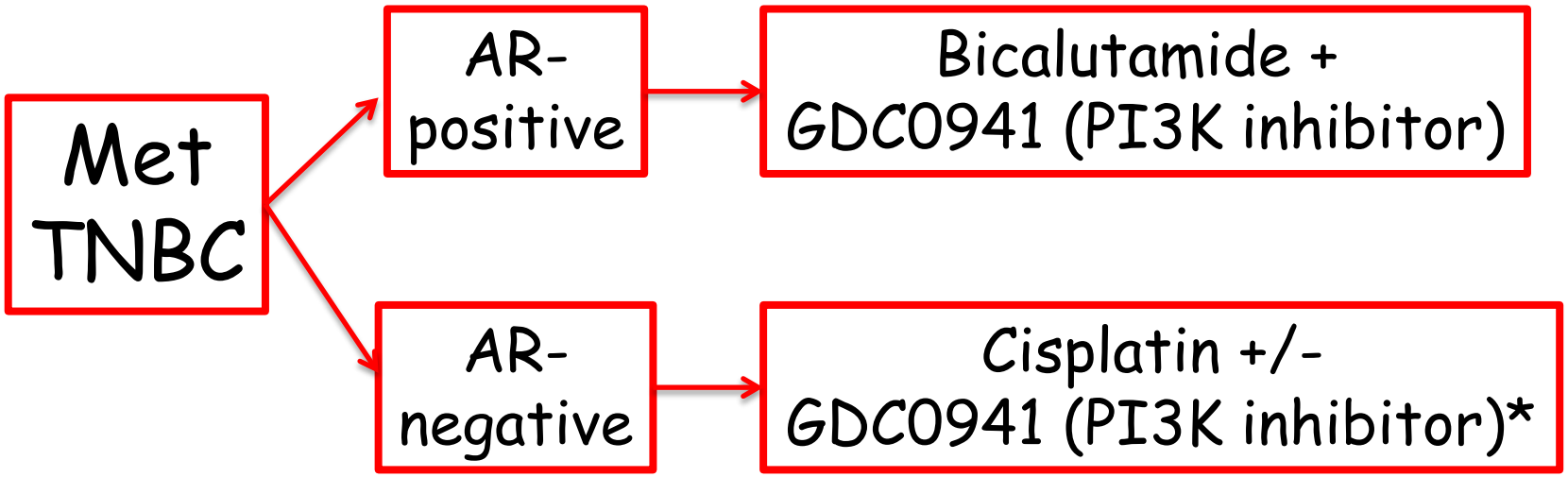
Lehmann et al JCI 2011

Phase 2 trial of bicalutamide in AR+ ER- PR- MBC

- Screening 452 patients with TNBC: 51 (12%) were AR+
- 26 patients were treated with bicalutamide 150mg daily
- No responses, stable disease > 6-months in 5 patients
- Median PFS 12-months

Gucalp et al Proc ASCO 2012 Abstract 1006

Vanderbilt TNBC trials



*NCT01918306