Progetto CANOA

CARCINOMA MAMMARIO:

QUALI NOVITÀ PER IL 2015?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

III SESSIONE:

Trattamento neoadiuvante del carcinoma mammario HER2-positivo/recettori ormonali positivi

Lo studio TBCRC-023:

Commento sulla metodologia

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Disclosures

- Advisory Boards/Honoraria/Consultant for:
  - Celgene
  - Astra-Zeneca
  - Helsinn
  - Eli-Lilly
  - BMS
- Research Support / Grants from:
  - A.I.R.C. (Associazione Italiana Ricerca sul Cancro)
  - I.A.S.L.C. (International Association for the Study of Lung Cancer)

AIRC

IASLC
International Association for the Study of Lung Cancer

Lo studio TBCRC023:

‘Comments’ upon Methodology

- **Protocol Analysis**
  - Presentation from SABCS 2014
- **Supporting background & Rationale**
  - Preclinical evidences
  - Single arm Phase II [TBCRC06]
  - Was the benchmarking appropriate?
- **Demographics**
  - Do patients characteristics overlap TBCRC06?
- **Choice of end-point**
  - **pCR**
    - Achieved or not?
    - What’s now on?
  - **Data Attrition**
    - Safety, Biopsy rate

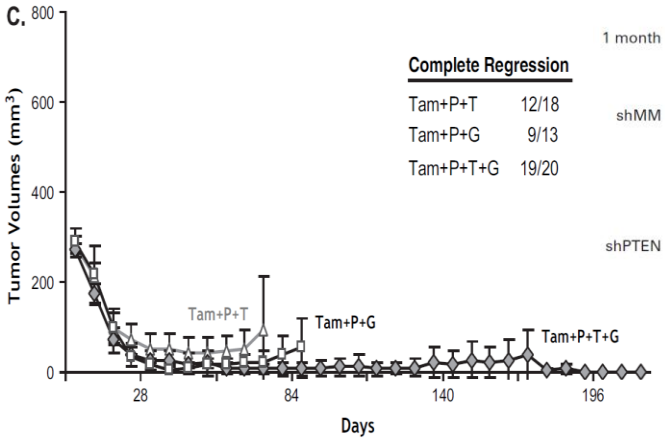
Lo studio TBCRC023:

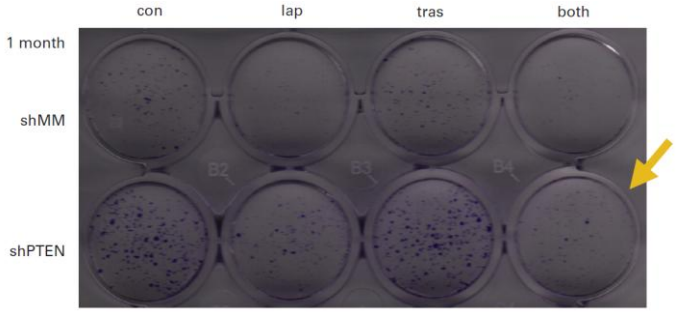
Supporting Background & Rationale

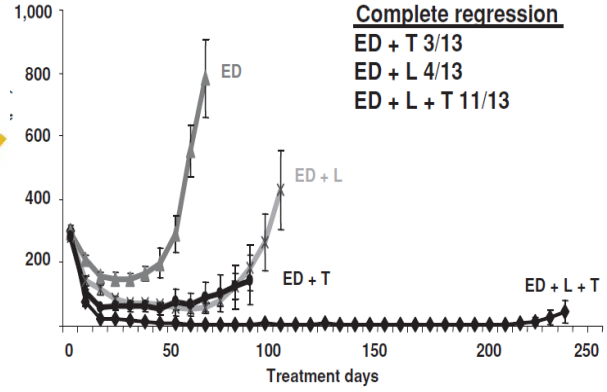
3-drugs block HER-dymers much more than any single, **eradicating HER2-overexpressing xenografts** in mice

PTEN loss and *PI3K* mutations are **associated with resistance to TRAST but not LAP**

LAP and **TRAST** were also effective in **eradicating HER2-overexpressing xenografts**







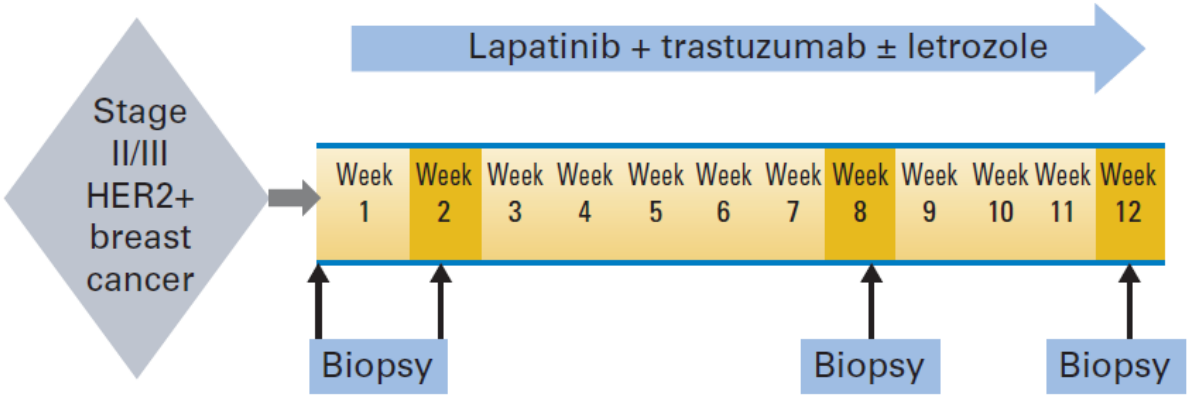
Arpino, JNCI 2007

Dave, JCO 2011

Rimawi, CCR 2011

Multicenter Phase II Study of Neoadjuvant Lapatinib and Trastuzumab With Hormonal Therapy and Without Chemotherapy in Patients With Human Epidermal Growth Factor Receptor 2–Overexpressing Breast Cancer: TBCRC 006

Single-Arm Phase II



Biopsies Performed

Time Point	%
Baseline	95
Week 2	89
Week 8	78
Total	88

- **pCR:** from **10%** expected with trastuzumab to **35%** in each stratum (*ER positive, ER negative*).
- Simon optimal two-stage, one-sided alpha 5%, power 85%.

ER Status	pCR	
	No.	%
Positive	8	21
Negative	9	36
Total	17	27

Rimawi, JCO 2013

Hypothesis

- We hypothesized that in HER2+ breast cancer, longer treatment with anti-HER2 therapy and endocrine therapy, if tumors are also ER+, will result in higher pCR rate.

Study Design

- **Randomized Unblinded Phase II**
- **No-Profit Fashion**

tbcrc Translational Breast Cancer Research Consortium

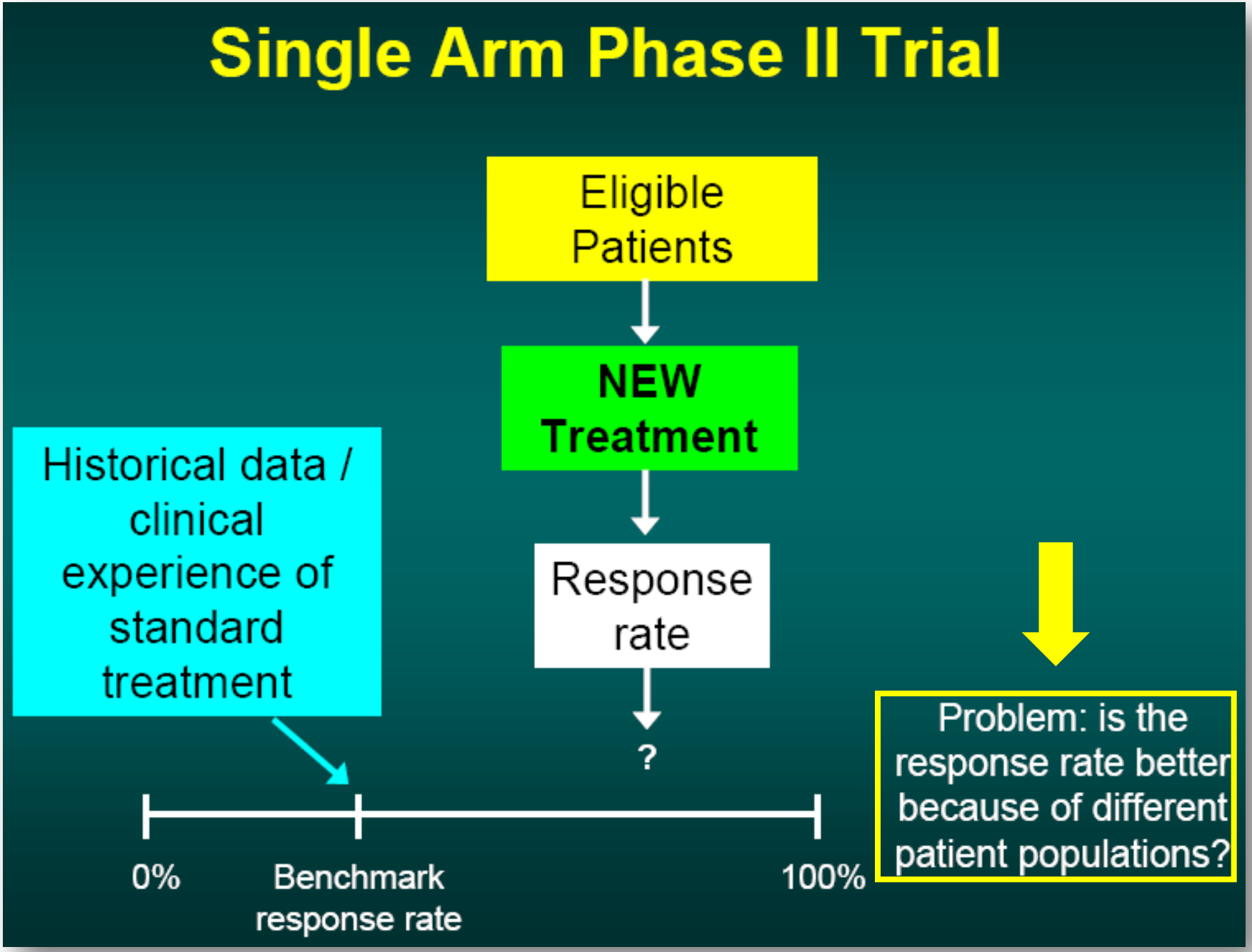
AVON Foundation for Women

The Breast Cancer Research Foundation

Susan G. Komen for the Cure

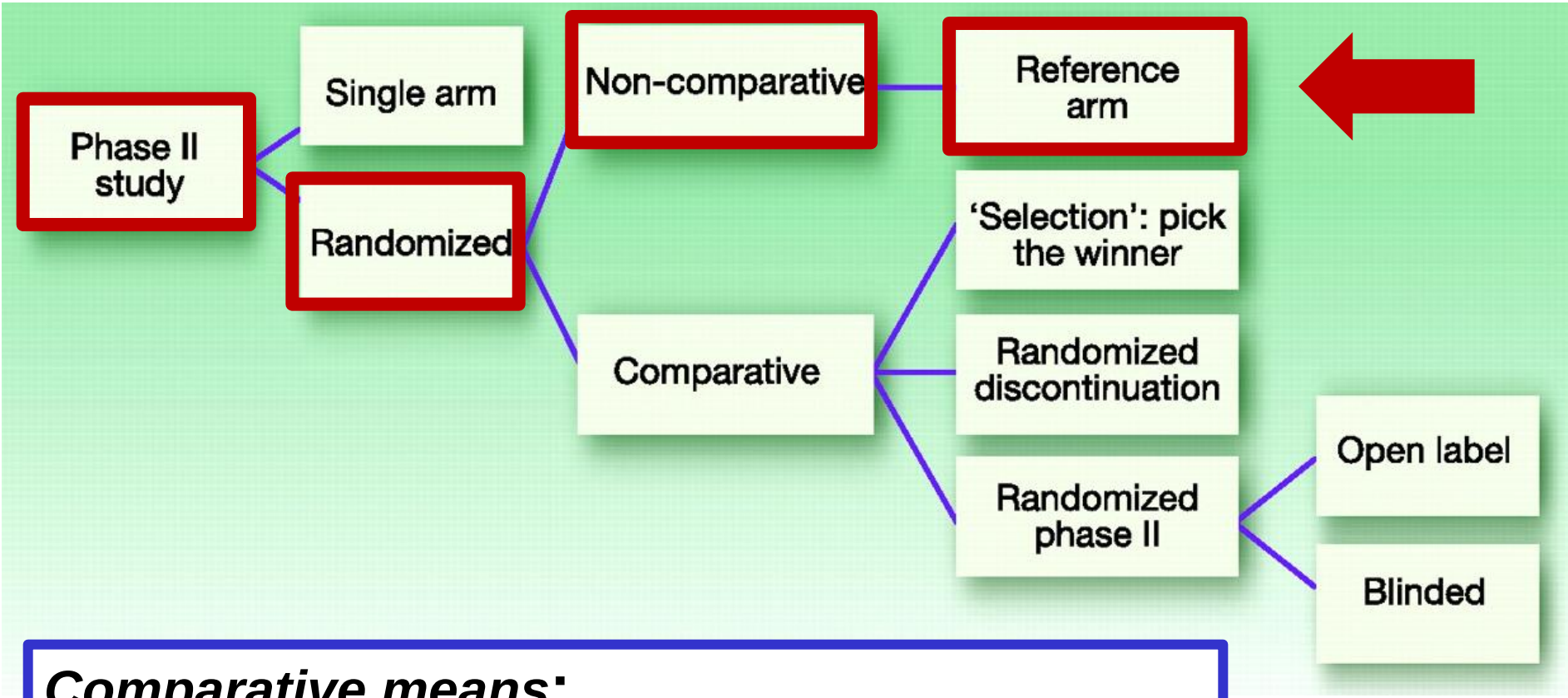
Rimawi, SABCS 2014

Single Arm Phase II Trial



Courtesy of Billingham C, 2008

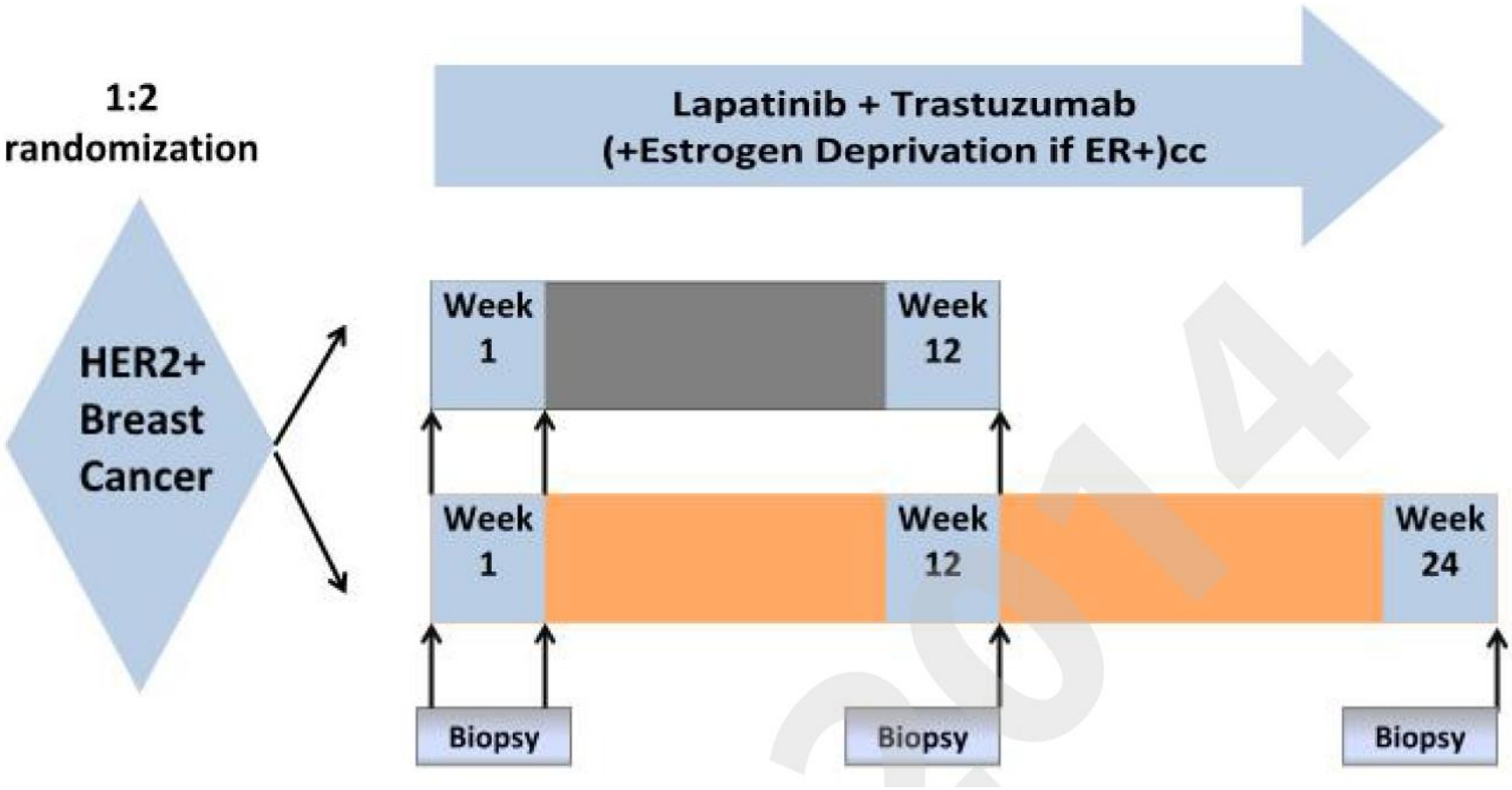
Types of phase II studies



***Comparative means*:**
The winner enters the Phase III fashion

Seymour L, CCR 2010

TBCRC023 Schema



Study Timeline

- **Nov. 2011-Nov. 2013:** Accrual to main study cohort.
- **April 2013:** Addition of expansion cohort (to meet correlative objectives)

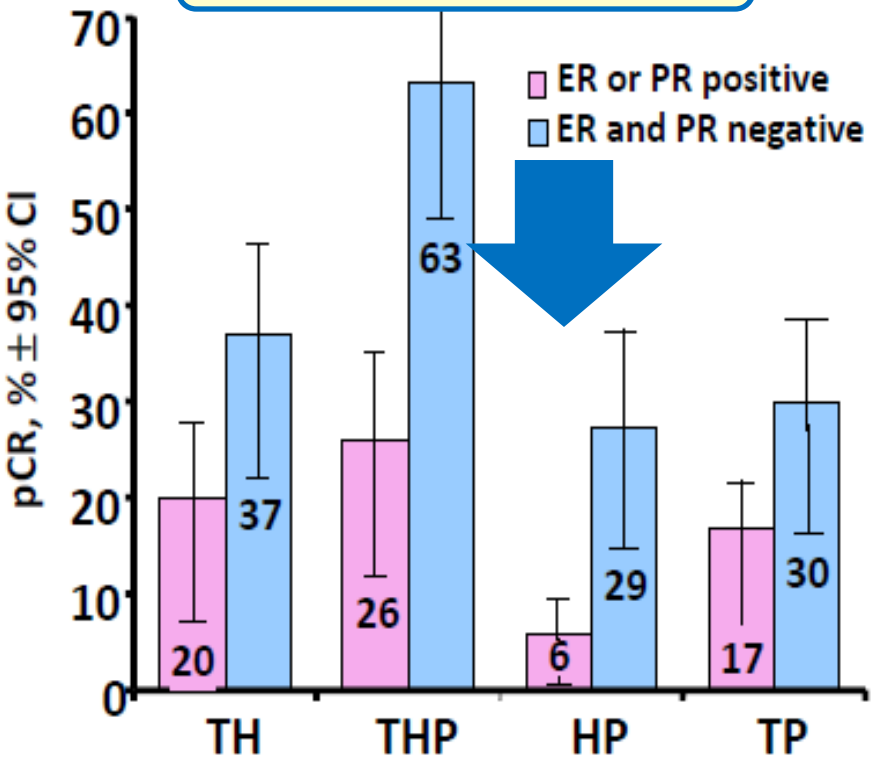
Rimawi, SABCS 2014

Lo studio TBCRC023:

‘Benchmarking’ the Activity: [HER2+]–Dual Blockade

LABC/IBC/Operable

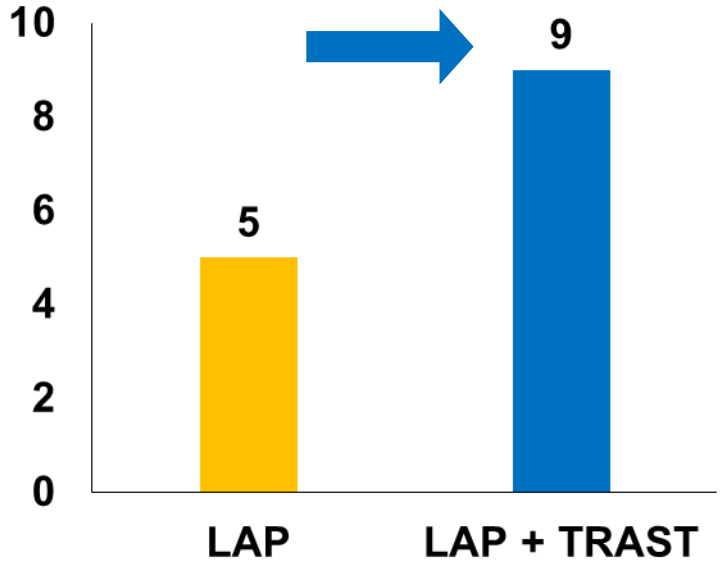
NeoSphere



Gianni, Lancet Oncol 2011

Heavily Metastatic

EGF104900

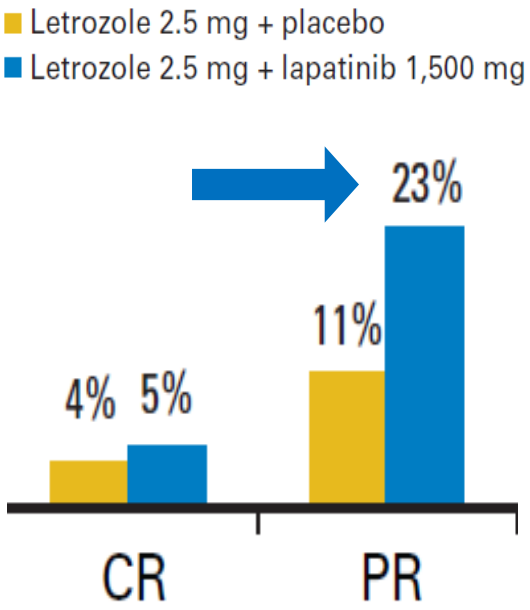


Blackwell, JCO 2010

‘Benchmarking’ the Activity: [HER2+] - ER-Positive

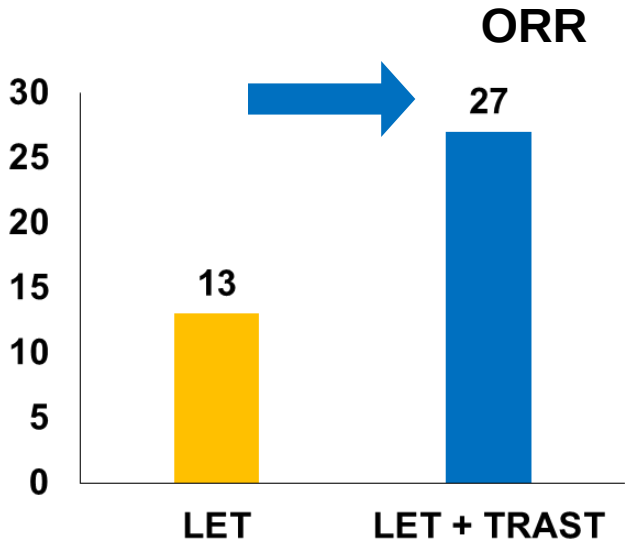
Metastatic Disease - Letrozole

LAP-Trast



Johnston, JCO 2009

ELECTRA



Huober, The Breast 2012

‘Benchmarking’ the Activity: [HER2+] - ER-Positive

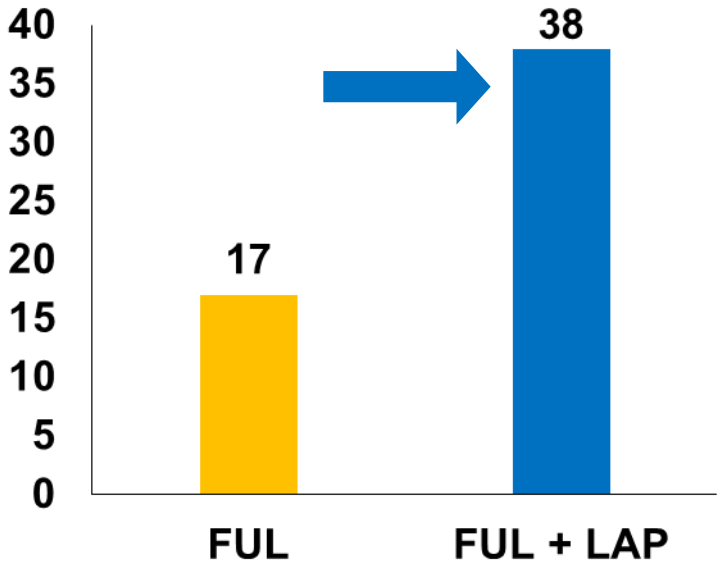
Metastatic Disease [Other Hormonal]

TANDEM

Response	Trastuzumab + Anastrozole (n = 74)	
	No. of Patients	%
Complete response*	0	0
Partial response	15	20.3†
Stable disease	28	37.8
Progressive disease	30	40.5
Not evaluable	1	1.4

Kaufman, JCO 2009

CALGB 40302



Burnstein, JCO 2014

Study Design

- Primary endpoint is pathologic complete response (pCR) in the breast ($ypT_{0\text{-}is}$ ypN_x).
- Secondary endpoints included: safety and tolerability, time to first recurrence, and overall survival.
- 88-96 patients were needed to detect an increase in pCR from 27% reported in TBCRC006 to 45%, with a power of 85% and type I error of 10%.
- Study arms were not powered to be directly comparable.

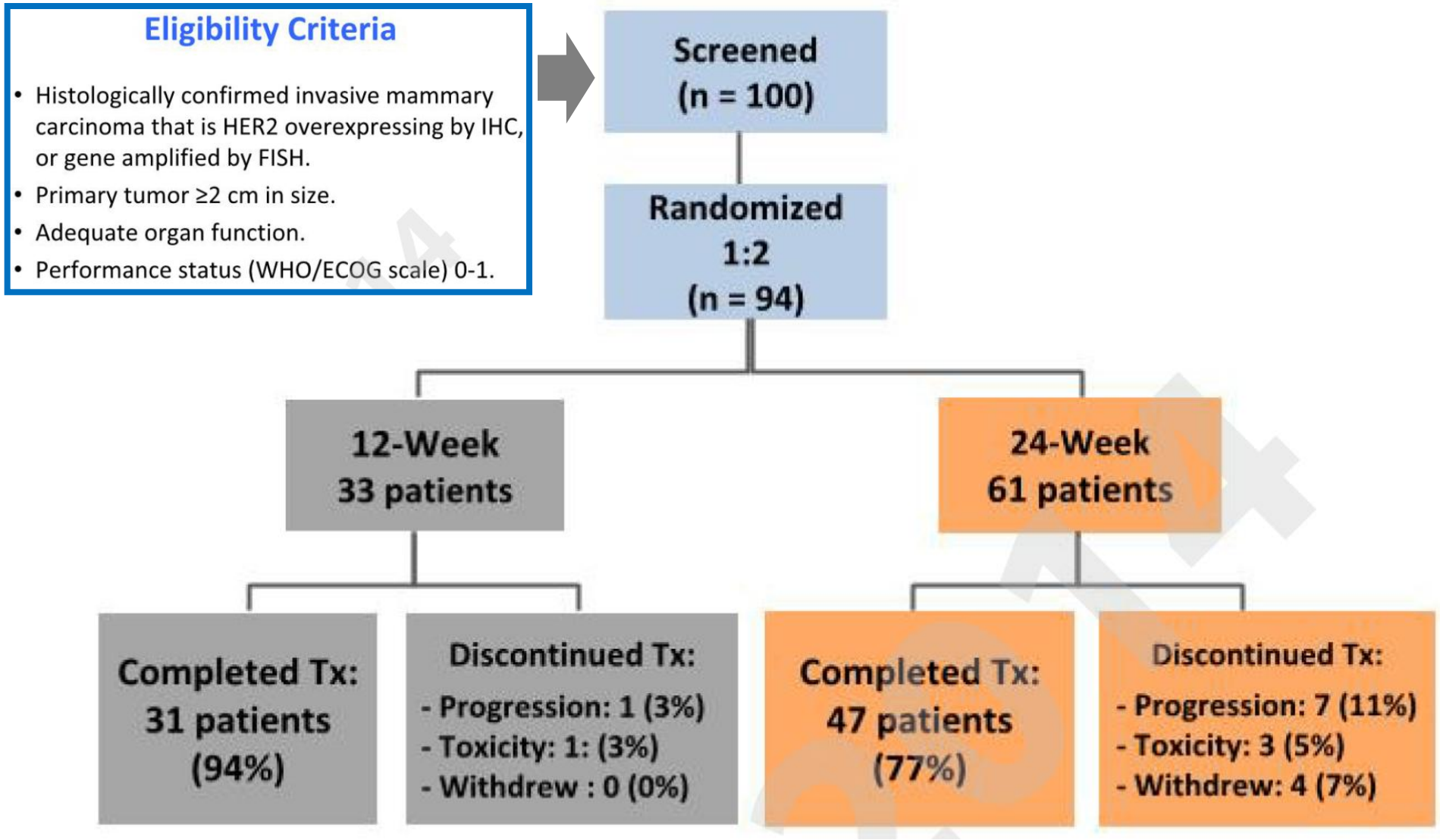
Rimawi, SABCS 2014

False Positive Rates of Randomized Phase II Designs

- **Purpose of Randomized Phase II:**
  - Selecting a treatment for eventual Phase III
  - 'Pilots' to Phase III evaluations.
  - One should not regard them as conclusive.
  - **Control arms may yield erroneous inferences.**
- **Frequent misapplications:**
  - **In presence of 'impressive' difference in binary outcomes, the 'false-positive' rates range from 20% to over 40%.**

Liu PY, Control Clin Trials 1999

Study Flow Diagram



Rimawi, SABCS 2014

Lo studio TBCRC023:

Demographics: 06 *vs.* 023

TBCRC06

Age, years			
≤ 50	34		52
> 50	31		48
Median		49	
Range		31-74	
Race			
White	48		74
Black	14		21.5
Asian	1		1.5
American Indian	1		1.5
Unknown	1		1.5
Ethnicity			
Hispanic	21		32
Non-Hispanic	43		66
Unknown	1		1.5
Menstrual status			
Premenopausal	35		54
Postmenopausal	30		46

TBCRC023

Age	≤50	39	41%
	>50	55	59%
	Median (range)	51	(23-80)
Race	White	73	78%
	Black	16	17%
	Others/Unkown	5	5%
Ethnicity	Hispanic	19	20%
	Not Hispanic	74	79%
	Unknown	1	1%
Menstrual Status	Premenopausal	42	45%
	Postmenopausal	52	55%

Rimawi, JCO 2013

Rimawi, SABCS 2014

Lo studio TBCRC023:

Demographics: 06 *vs.* 023

TBCRC06		TBCRC023	
ECOG status			
0	61		94
1	4		6
Tumor size, cm			
≤ 5	25		38
> 5	40		62
Median		6	
Range		1.5-30	
ER			
Positive	40		62
Negative	25		38
PR			
Positive	29		45
Negative	36		55

Clinical Stage	II	66	70%
	III	27	29%
Tumor Size	≤5cm	57	61%
	>5cm	36	38%
	Median (range)	5 cm	(0-15)
ER	Positive	62	66%
	Negative	32	34%
Histologic grade	I	1	1%
	II	26	28%
	III	67	71%

Rimawi, JCO 2013

Rimawi, SABCS 2014

Lo studio TBCRC023:

Safety: 06 *vs.* 023

TBCRC06

Adverse Event	Grades 3 and 4 No.	Grades 3 and 4 %
GI		
Diarrhea	2	3
Nausea	0	0
Heartburn/dyspepsia	0	0
Mucositis/stomatitis	0	0
Hepatic		
ALT	3	5
AST	4	6
Alkaline phosphatase	0	0
Elevated bilirubin	1	2
Skin		
Rash	1	2
Dry skin/other	0	0
Constitutional		
Fatigue	0	0
Hot flashes	0	0
Anorexia	0	0
Laboratory		
Anemia	0	0
Hypokalemia	0	0
Hyperglycemia	1	1.5
Hypocalcemia	0	0
Hyponatremia	0	0

Rimawi, JCO 2013

TBCRC023

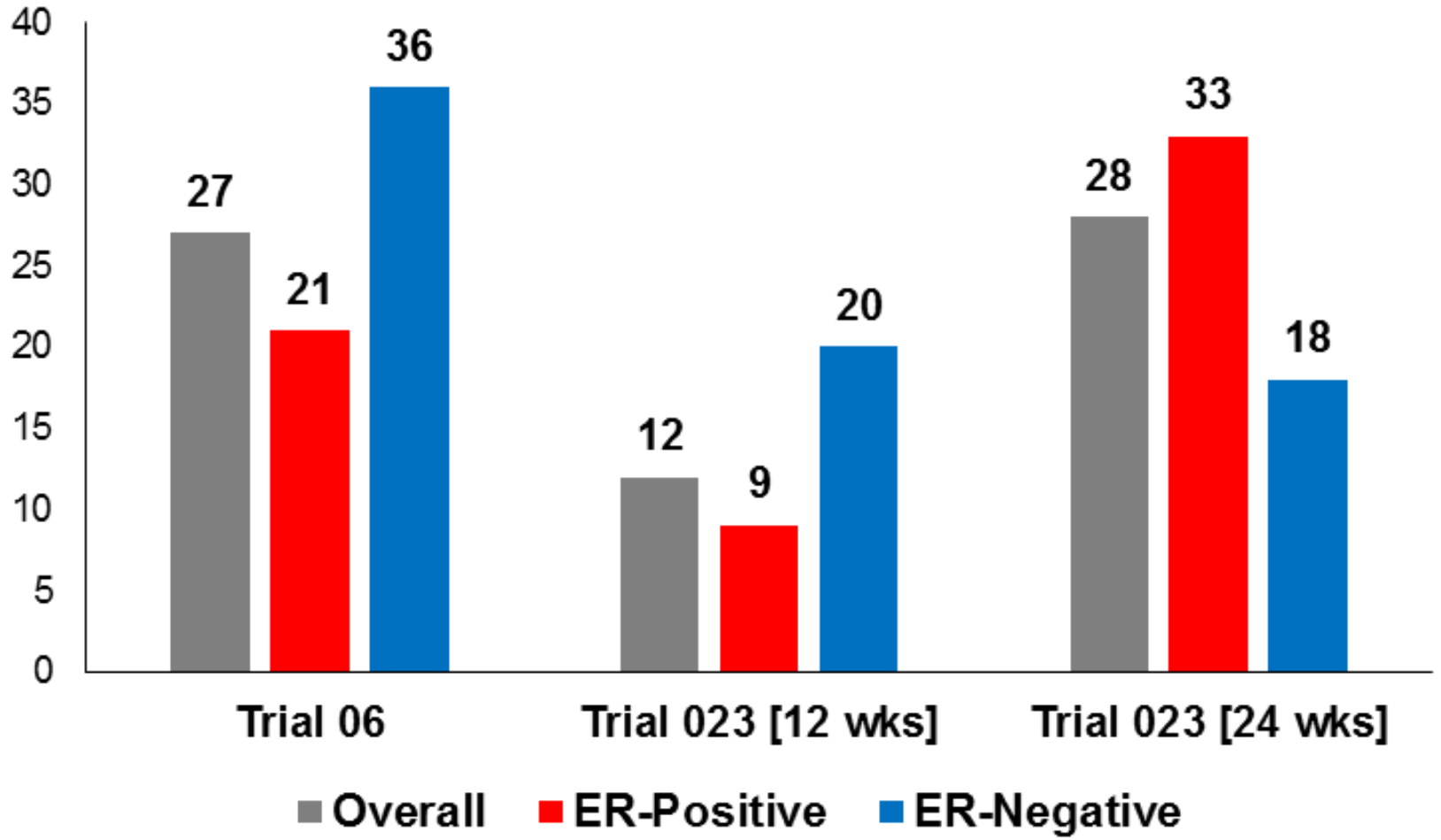
Grade 3 Toxicity	12 Week N (%)	24 Week N (%)
Elevated LFT	–	**5 (9%)**
Diarrhea	–	**1 (2%)**
Mucositis	–	**1 (2%)**
Anemia	**1 (3%)**	–
Renal calculi (SAE)	**1 (3%)**	–

No grade 4 toxicity

Rimawi, SABCS 2014

Lo studio TBCRC023:

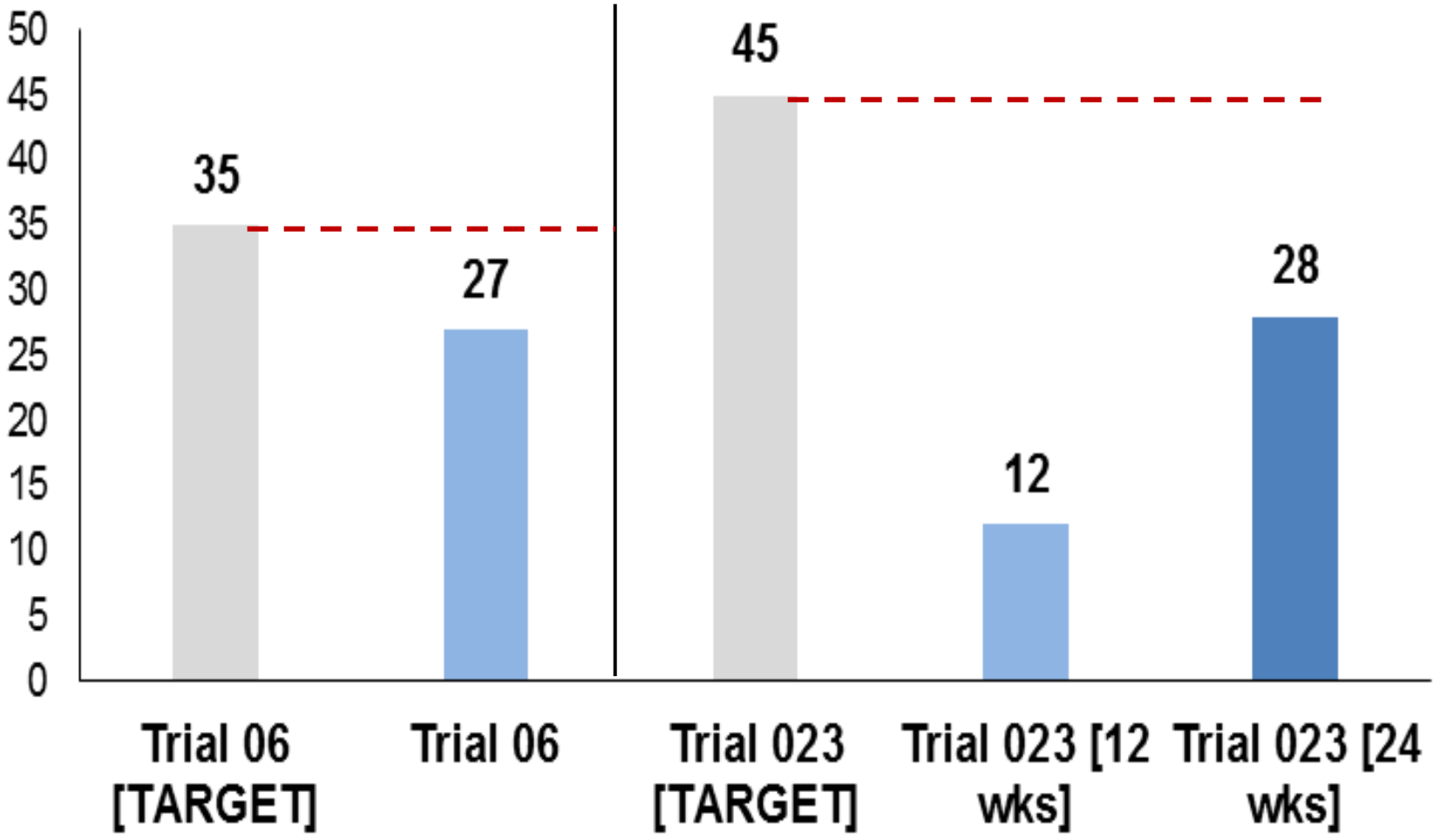
pCR according to ER: 06 *vs.* 023



Rimawi, JCO 2013; Rimawi, SABCS 2014

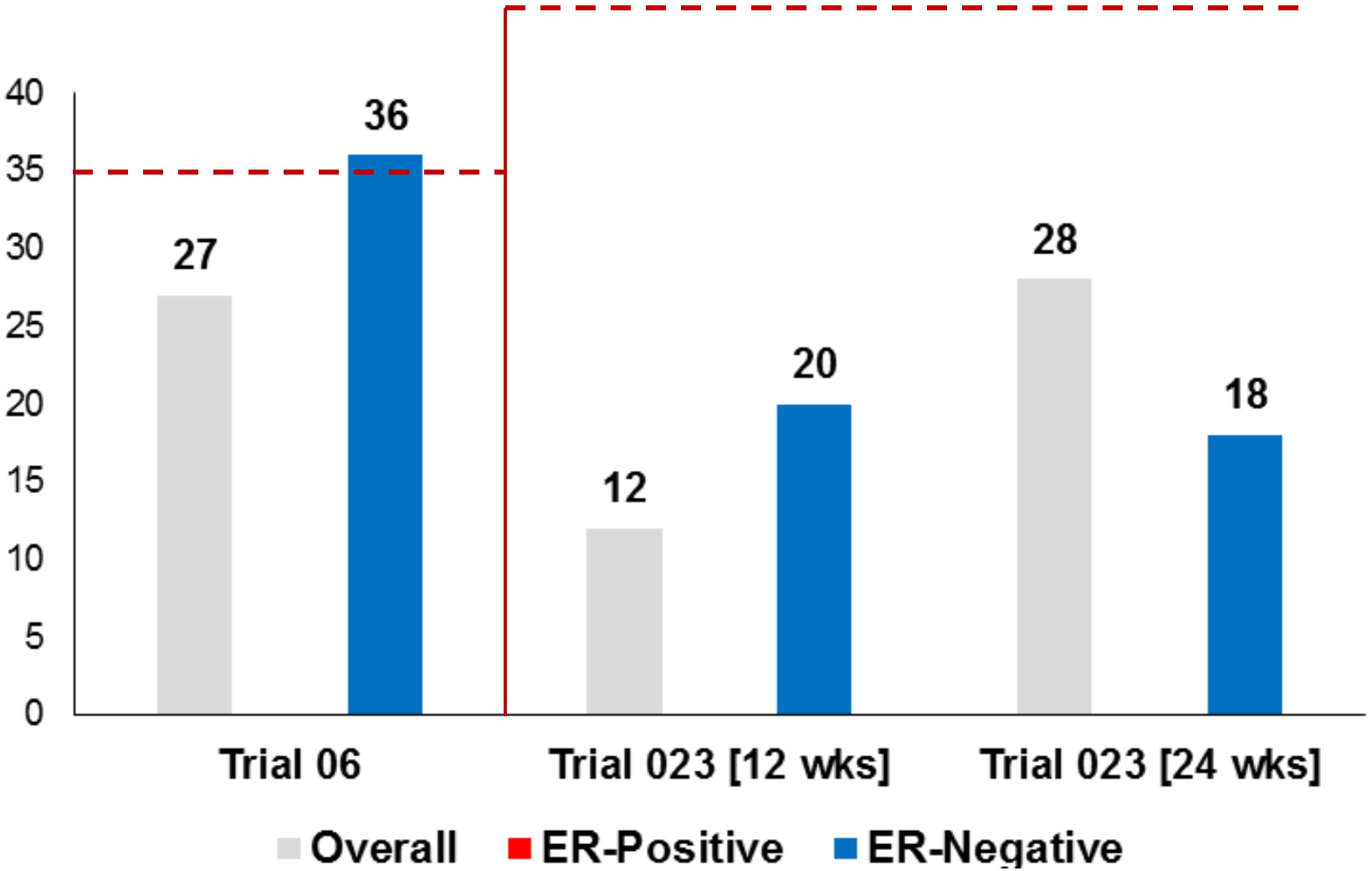
Lo studio TBCRC023:

TARGET pCR: 06 *vs.* 023



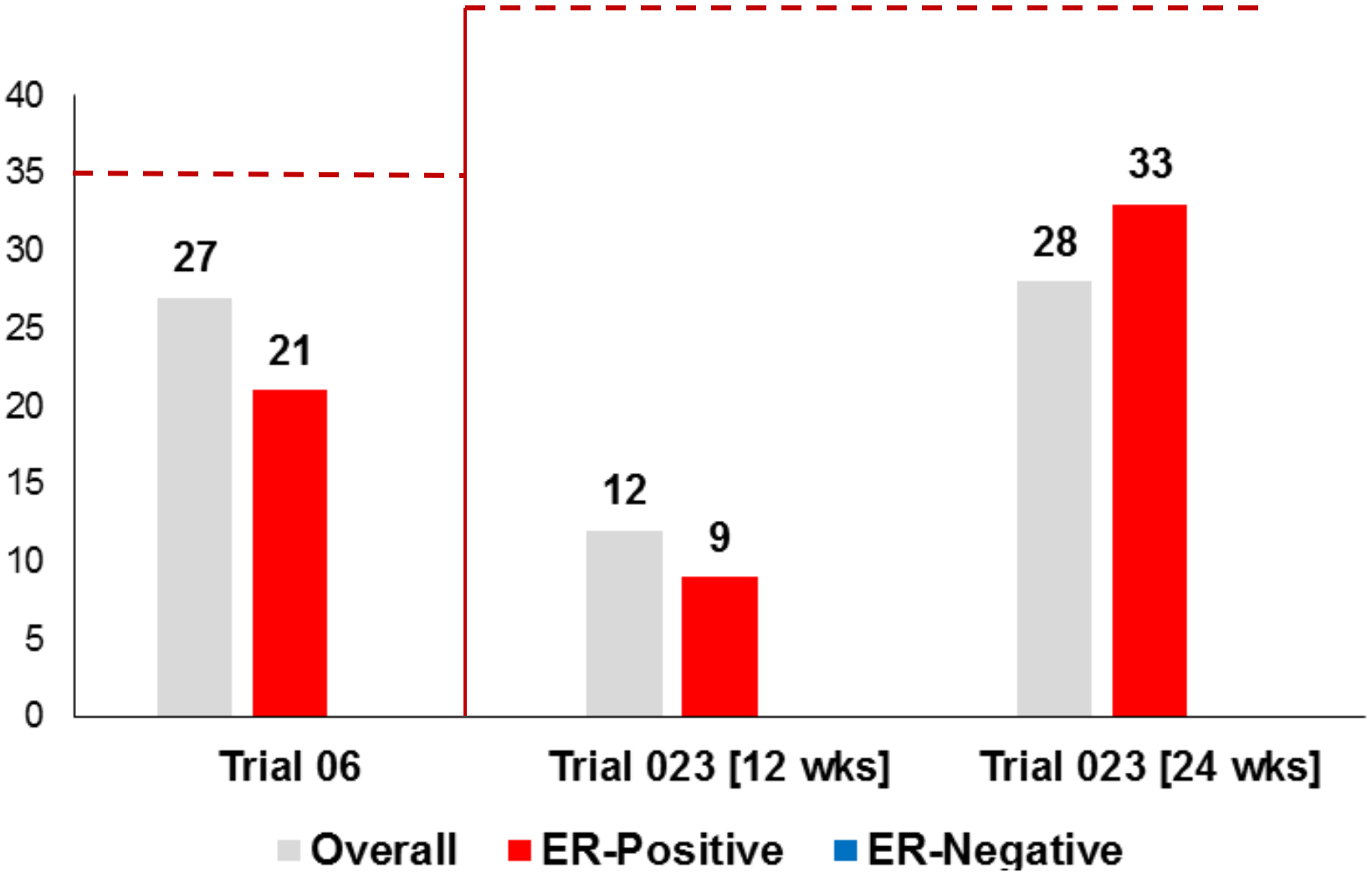
Lo studio TBCRC023:

pCR [ER-Negative]: 06 *vs.* 023



Lo studio TBCRC023:

pCR [ER-Positive]: 06 *vs.* 023



Lo studio TBCRC023:

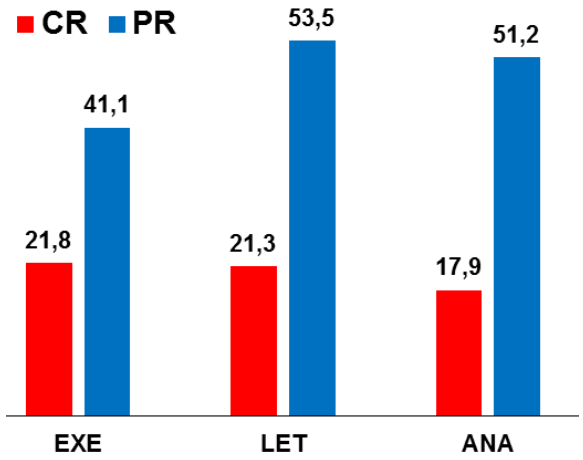
(Endocrine) Neoadjuvant Treatment Duration

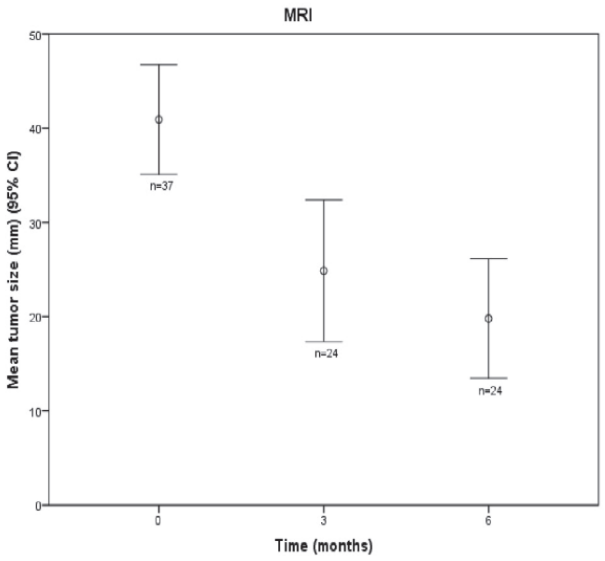
Median time to reach **maximum response >4 months**; >35% of pts **improved response after 6 months**

45-60% of clinical response with **AIs** after **16 to 18 weeks of treatment**

Best **MRI response** after **6 months** than after **3**

N=56	%
Clinical response evaluation	100
Patients with no response	23.2
Patients with response	76.8
Complete clinical response	25.0
Radiological response evaluation	51.8
	Median
Time to response (months)	3.9





Llombart-Cussac CTO 2012

Ellis JCO 2011

Fontein EJC 2014

Lo studio TBCRC023:

(Endocrine) Neoadjuvant Treatment Duration

Neoadjuvant endocrine trials.

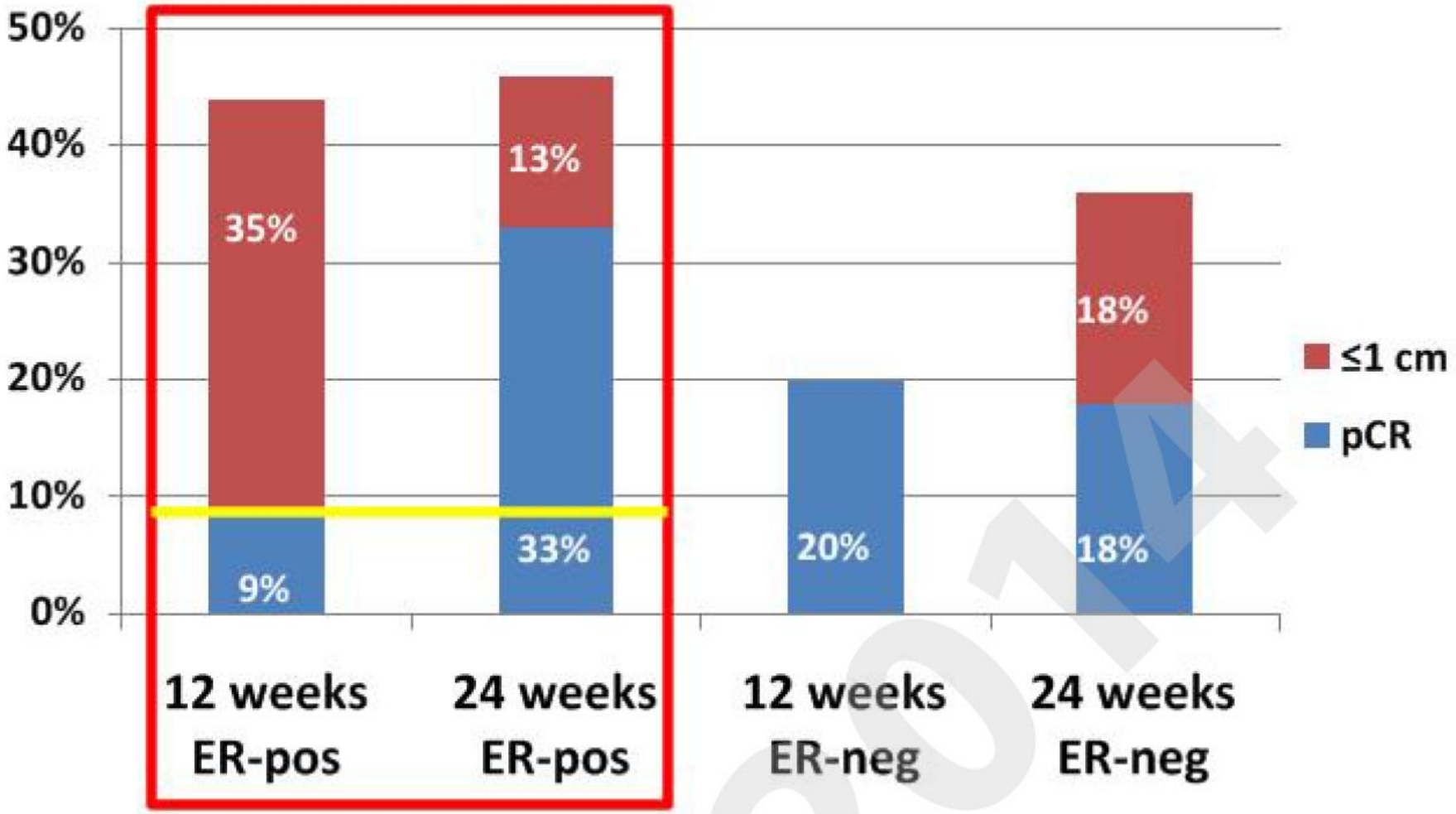
Author or trial name	Number of patients	Design	Duration (month)	Clinical ORR[e]
IMPACT[2]	330	ANA[a] vs TAM[b] vs ANA + TAM	3	37%, 36%, 39%
PROACT[3]	451	ANA vs TAM	3	49.7%, 39.7%
PO24 Trial[4]	337	LET[c] vs TAM	4	55%, 36%
GENARI Trial[5]	29	EXE[d]	4	37.0%
French study[6]	45	EXE	14–27 weeks	70.6%
Gil Gil (Spain)[7]	55	EXE	6	50%
Mustacchi[8]	44	EXE	6	66%

- **Data almost exclusively gathered from trials with AIs in HER2 negative disease!**

Hojo, The Breast 2013

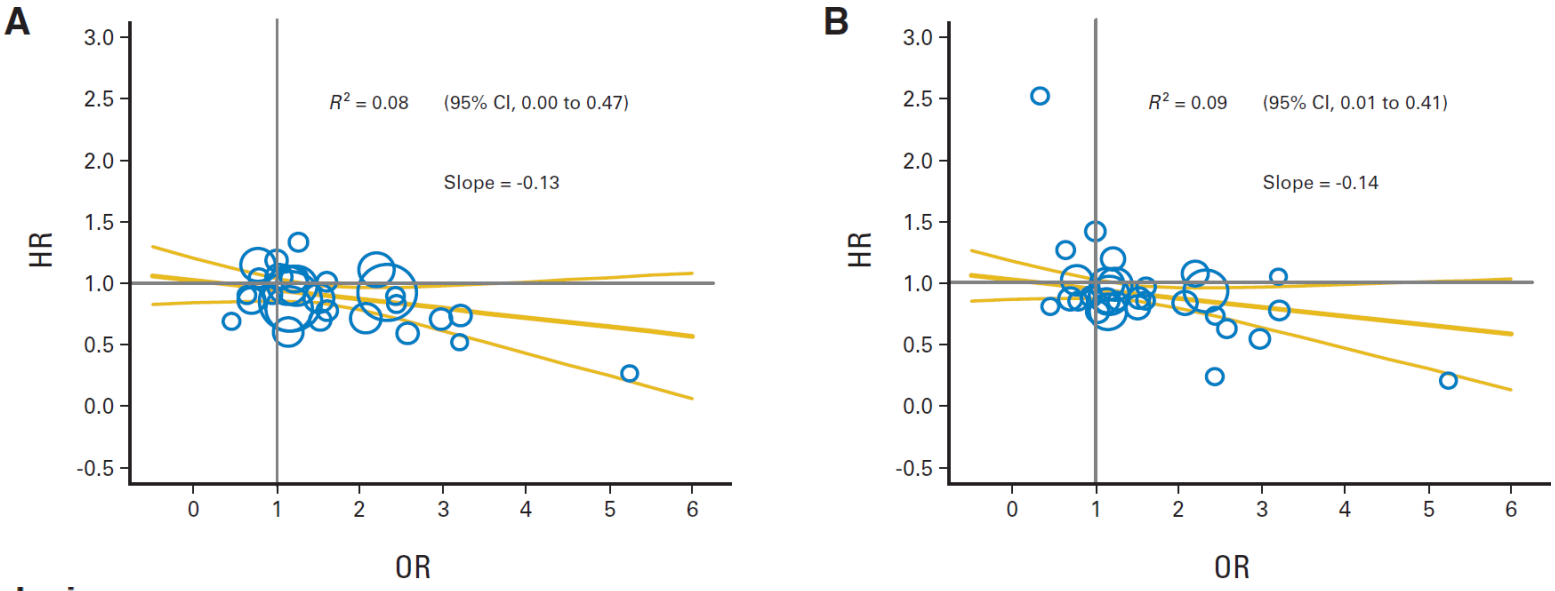
Lo studio TBCRC023:

Small residual [≤1 cm] according to ER



Rimawi, SABCS 2014

Pathologic Complete Response As a Potential Surrogate for the Clinical Outcome in Patients With Breast Cancer After Neoadjuvant Therapy: A Meta-Regression of 29 Randomized Prospective Studies



Conclusion

This meta-regression analysis of 29 heterogeneous neoadjuvant trials does not support the use of pCR as a surrogate end point for DFS and OS in patients with breast cancer. However, pCR may potentially meet the criteria of surrogacy with specific systemic therapies.

- **Endocrine therapy–based trials were excluded because pCR is uncommon after short-term preoperative endocrine therapy**
  - *Burzykowski T, et al. The Evaluation of Surrogate Endpoints. New York, NY, Springer, 2005*

Berruti A, JCO 2014

Conclusions

- TBCRC023 did not meet its primary endpoint of increasing pCR to 45%. This was mainly due to lower than expected pCR in both arms.
- However, our study demonstrated a twofold numeric increase in pCR in the 24 weeks arm over the 12 week arm. That increase was more than threefold in the ER+ subgroup.
- This is the first trial to show that longer treatment with dual anti-HER2 therapy in combination with endocrine therapy, and without chemotherapy, *leads to a meaningful increase in pCR rate in ER+/HER2+ breast cancer.*

Rimawi, SABCS 2014

Conclusions

- **First: let's wait for the final paper….**
  - **Additional data missing, safety (crucial anyway for phase II), biopsy rate, etc.**
- **Primary end-point not met!**
  - **Less than what expected in the control arm**
    - **Patients' selection bias?**
  - **Overall smaller difference than expected between 12 and 24 wks**
  - **ER-Negative did benefit more from dual HER2 blockade**
    - **Similar data from Trial 06 and Trial 023…….and consistent with NeoSphere**
  - **ER-Positive did benefit more from longer treatment**
    - **Hormonal therapy: the longer, the better!**
    - **Treatment duration for triple-positive disease still unclear**
- **Is pCR really useful as a 'pre-requisite' (not a surrogate) for overall outcome in the context of hormonal therapy, as well as for chemotherapy?**