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

- Lo studio TBCRC023 -

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Progetto CANOA

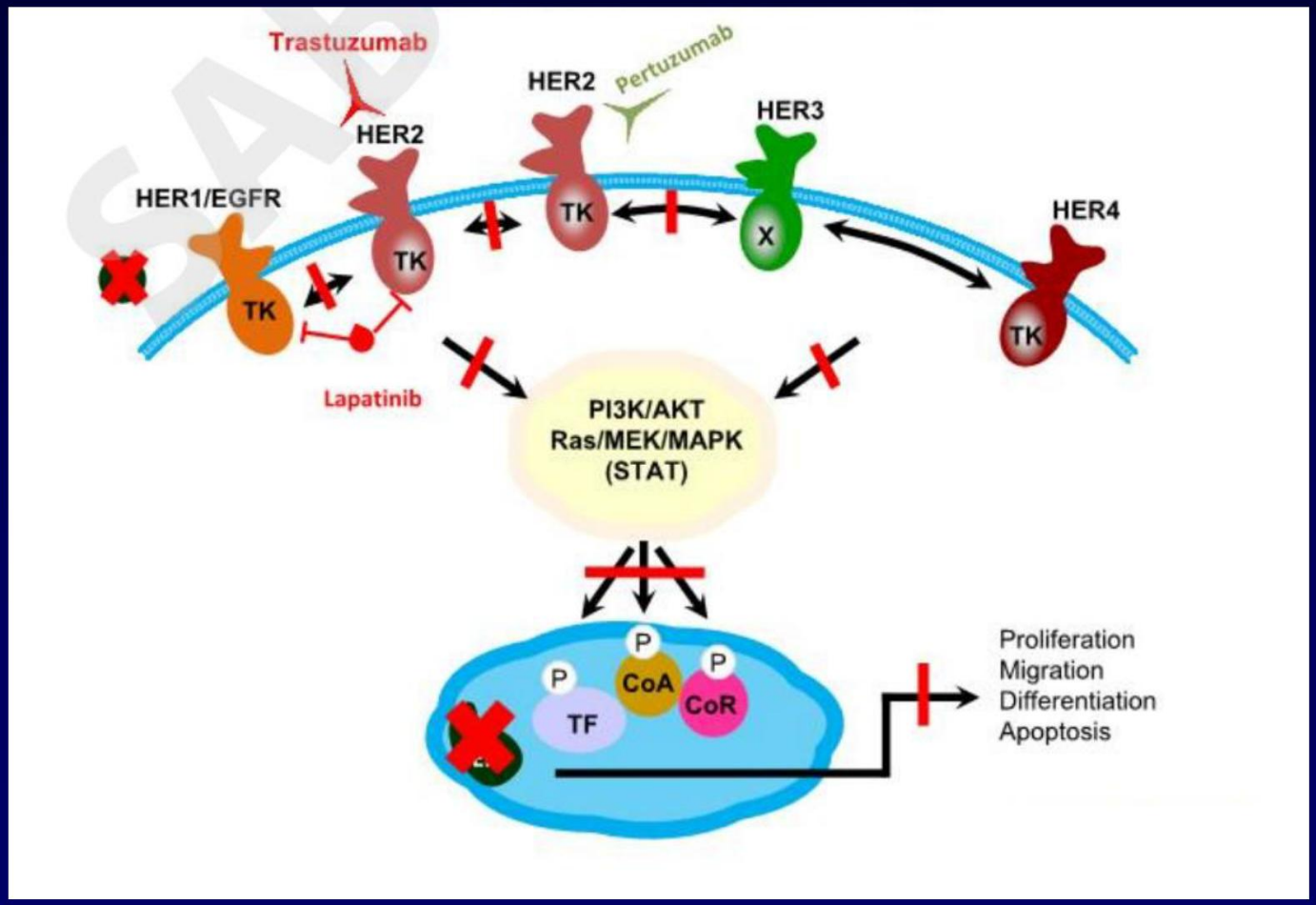
Ospedaletto di Pescantina, 10 Aprile 2015

TBCRC023: A Randomized Multicenter Phase II Neoadjuvant Trial of Lapatinib, Trastuzumab, With or Without Endocrine Therapy for 12 Weeks vs 24 Weeks in Patients With HER2 Overexpressing Breast Cancer

Abstract S6-02

Rimawi MF, Niravath PA, Wang T, Rexer B, Forero A, Wolff AC, Nanda R, Storniolo AM, Krop I, Goetz MP, Nangia JR, Jiralerspong S, Pavlick AC, Gutierrez C, Schiff R, Hilsenbeck SG, Osborne CK, on behalf of TBCRC

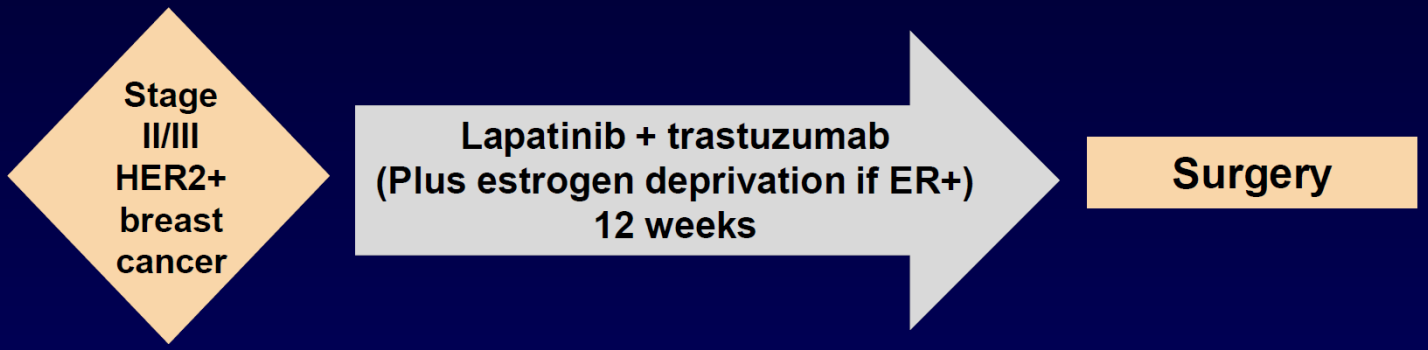
Targeting HER2 Pathway



Arpino G, et al. *J Natl Cancer Inst*. 2007;99(9):694-705. Rimawi MF, et al. *Clin Cancer Res*. 2011;17(6):1351-1361.

Rimawi MF, et al. Presented at: 2014 San Antonio Breast Cancer Symposium; December 9-13, 2014; San Antonio, Texas. Abstract S6-02.

TBCRC 006



N = 64
Median tumor Size = 6 cm

	Path CR (ypT_{0-is})	Residual CA≤ 1cm
Total	17 (27%)	14 (22%)
ER+	8 (21%)	13 (33%)
ER-	9 (36%)	1 (4%)

Rimawi MF, et al. *J Clin Oncol*. 2013;31(14):1726-1731.

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Hypothesis

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

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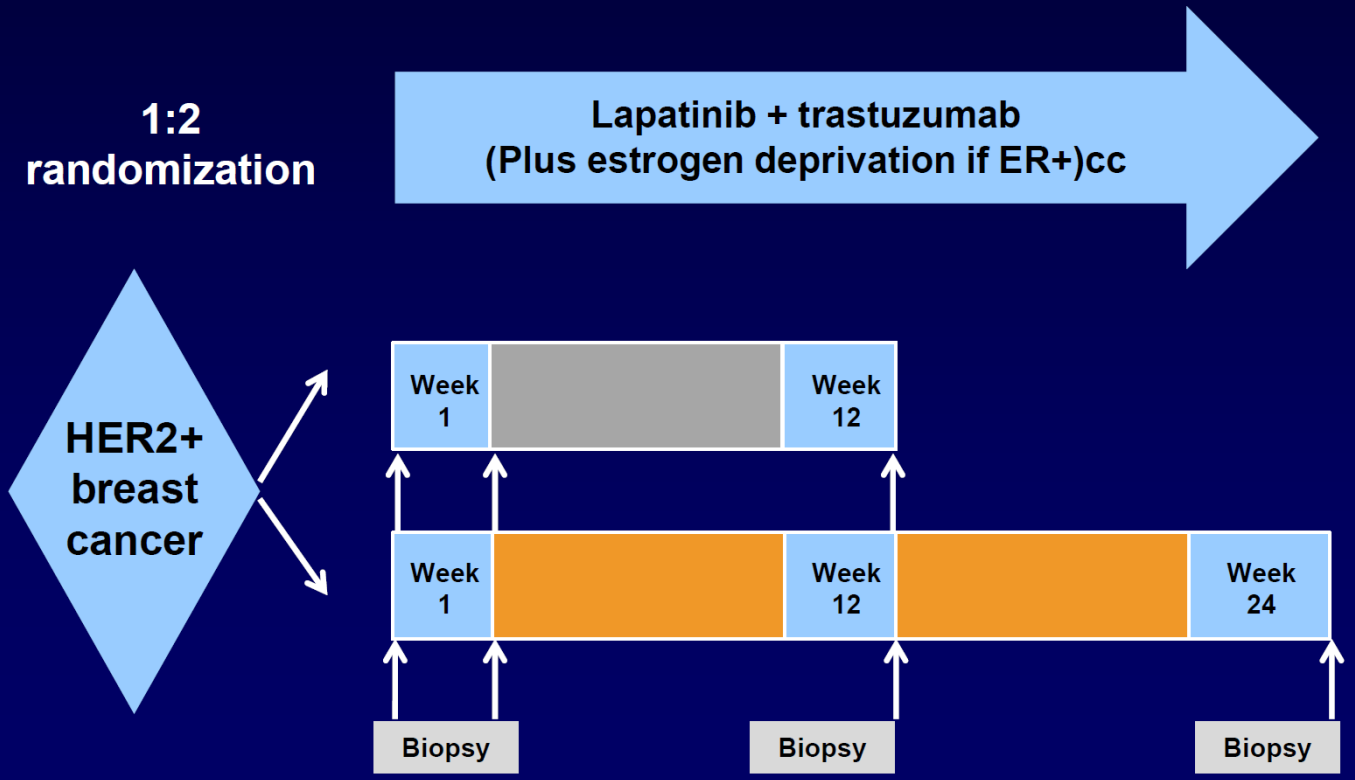
TBCRC023 Schema



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TBCRC023 Study Design

- Primary endpoint is pathologic complete response (pCR) in the breast ($ypT_{0\text{-}is}$ ypN_x).
- 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 et al. SABCS 2014 Abstract S6-02

Study Endpoints

- Primary endpoint
  - Pathologic complete response (pCR) in the breast ($ypT_{0\text{-}is}ypN_x$)
- Secondary endpoints
  - Safety and tolerability
  - Time to first recurrence
  - Overall survival

Rimawi MF, et al. Presented at: 2014 San Antonio Breast Cancer Symposium; December 9-13, 2014; San Antonio, Texas. Abstract S6-02.

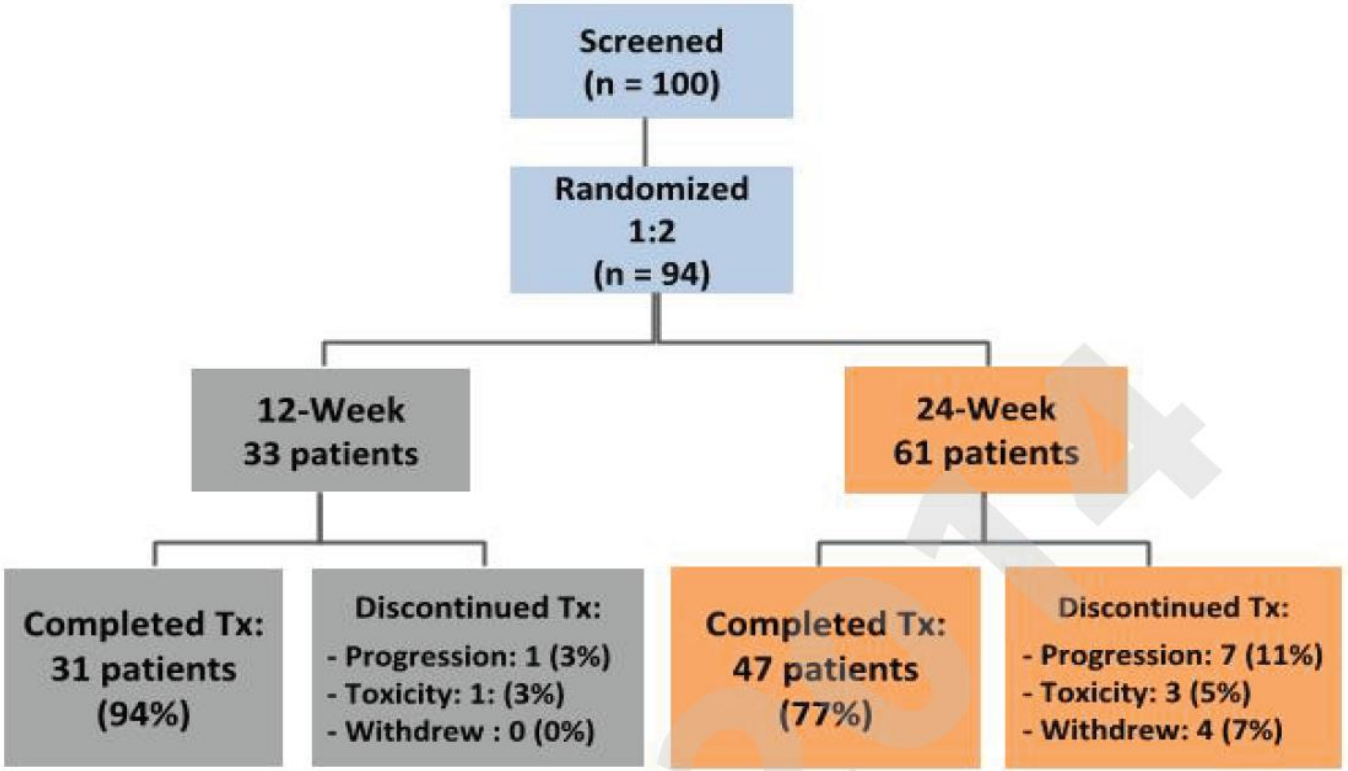
Eligibility Criteria

- Histologically confirmed invasive mammary carcinoma that is HER2 overexpressing by IHC, or gene amplified by FISH.
- Primary tumor ≥2 cm in size.
- Adequate organ function.
- Performance status (WHO/ECOG scale) 0-1.

Study Timeline

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

Study Flow Diagram



Patient Demographics

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

Tumor Characteristics

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

Toxicity

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

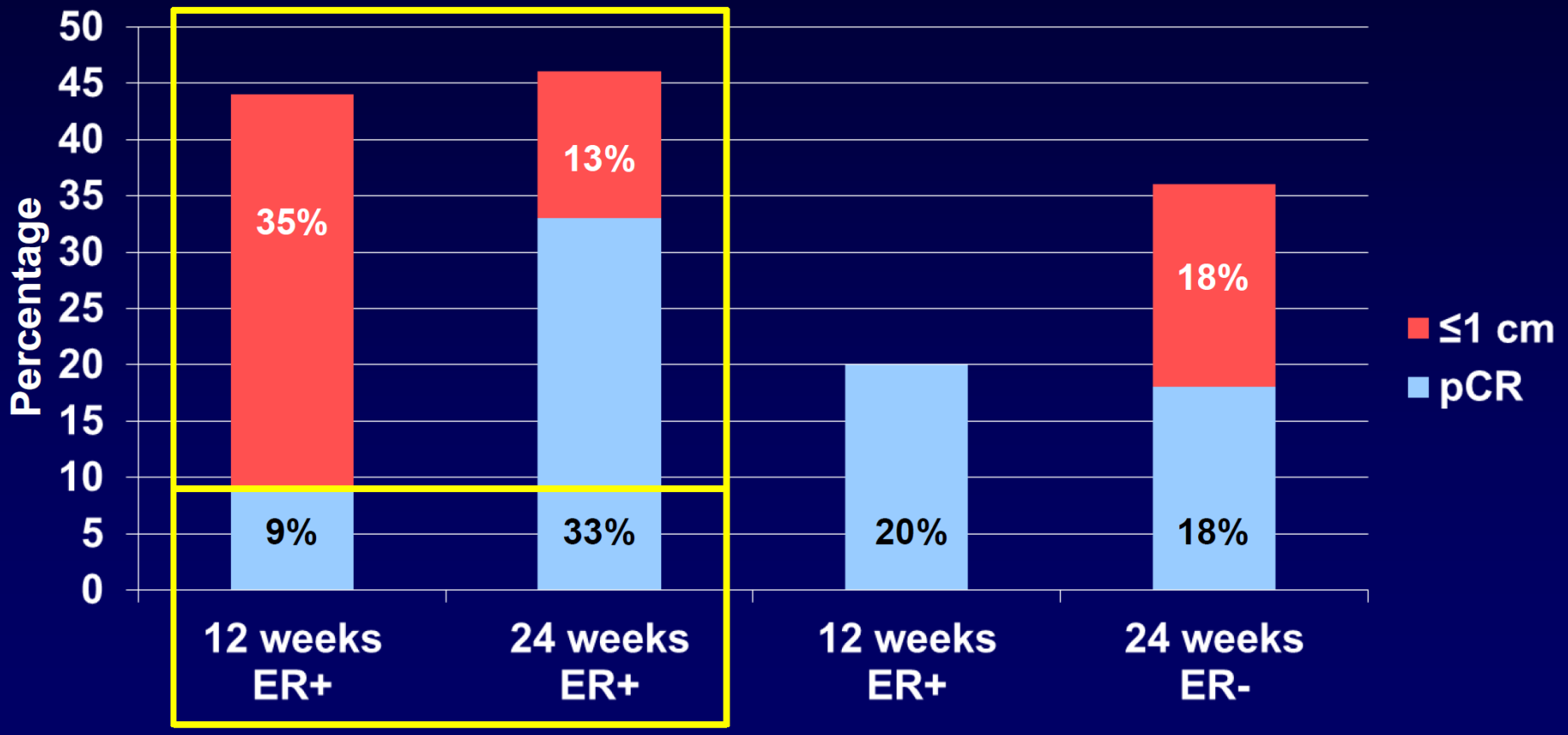
Rimawi MF, et al. Presented at: 2014 San Antonio Breast Cancer Symposium; December 9-13, 2014; San Antonio, Texas. Abstract S6-02.

TBCRC023 Pathologic Response

Path CR (ypT_{0-is})	12 weeks (n=33)	24 weeks (n=61)
Overall	4 (12%)	17 (28%)
ER-positive	2 (9%)	13 (33%)
ER-negative	2 (20%)	4 (18%)

Rimawi et al. SABCS 2014 Abstract S6-02

Pathologic Response



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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, the 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-positive 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-positive and HER2-positive breast cancer.

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Conclusions

- Molecular studies may help identify resistant/sensitive tumors.
- Targeted therapy without chemotherapy may offer a promising treatment strategy to patients with ER+/HER2+ breast cancer, and warrants further study.

Back-up slides

TBCRC023: A Randomized Multicenter Phase II Neoadjuvant Trial of Lapatinib, Trastuzumab, with or without Endocrine Therapy for 12 weeks vs. 24 weeks in patients with HER2 Overexpressing Breast Cancer

Mothaffar F Rimawi, Polly A Niravath, Tao Wang, Brent Rexer, Andres Forero, Antonio C Wolff, Rita Nanda, Anna M Storniolo, Ian Krop, Matthew P Goetz, Julie R Nangia, Sao Jiralerspong, Anne C Pavlick, Carolina Gutierrez, Rachel Schiff, Susan G Hilsenbeck, and C. Kent Osborne, *on behalf of TBCRC*

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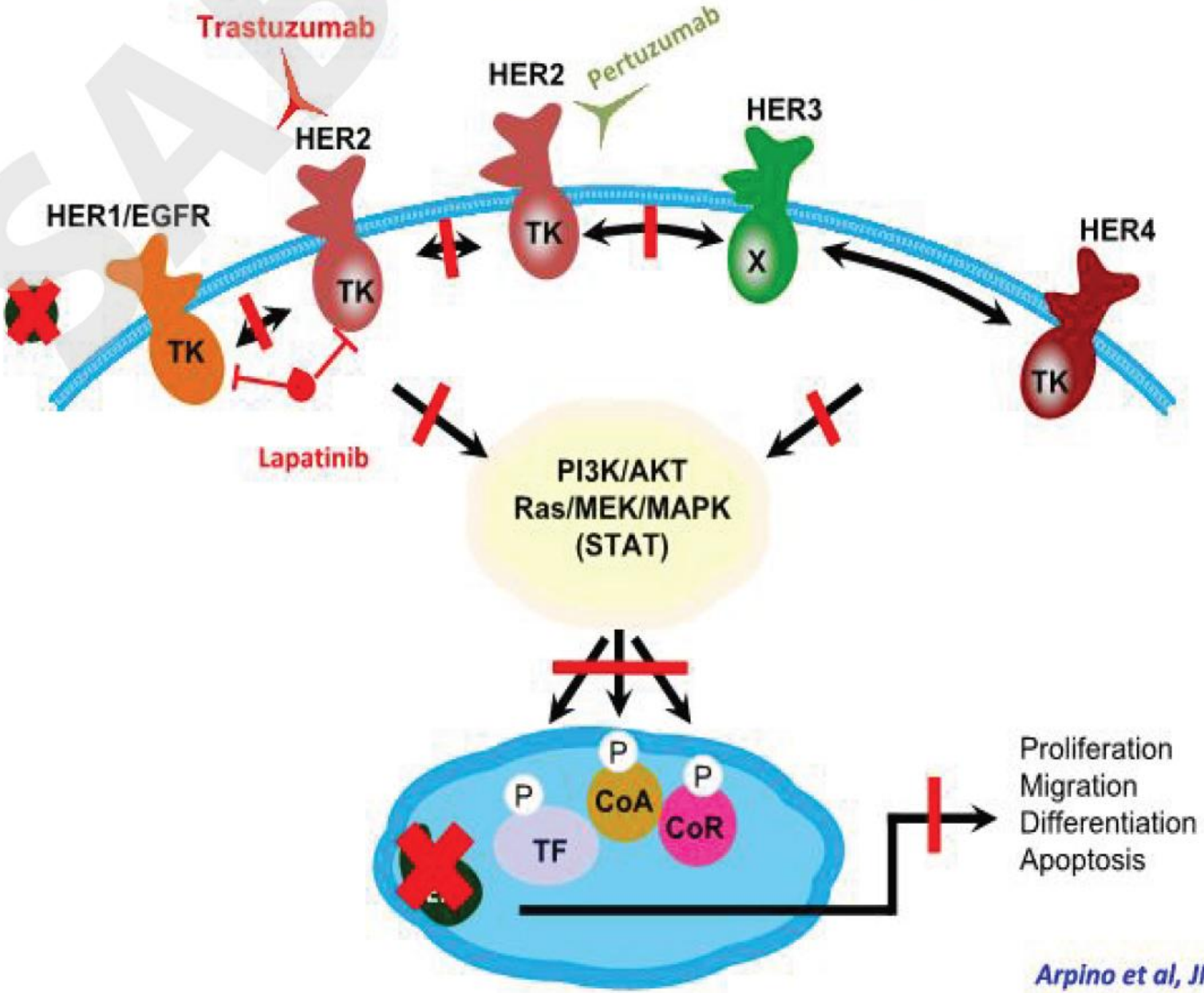
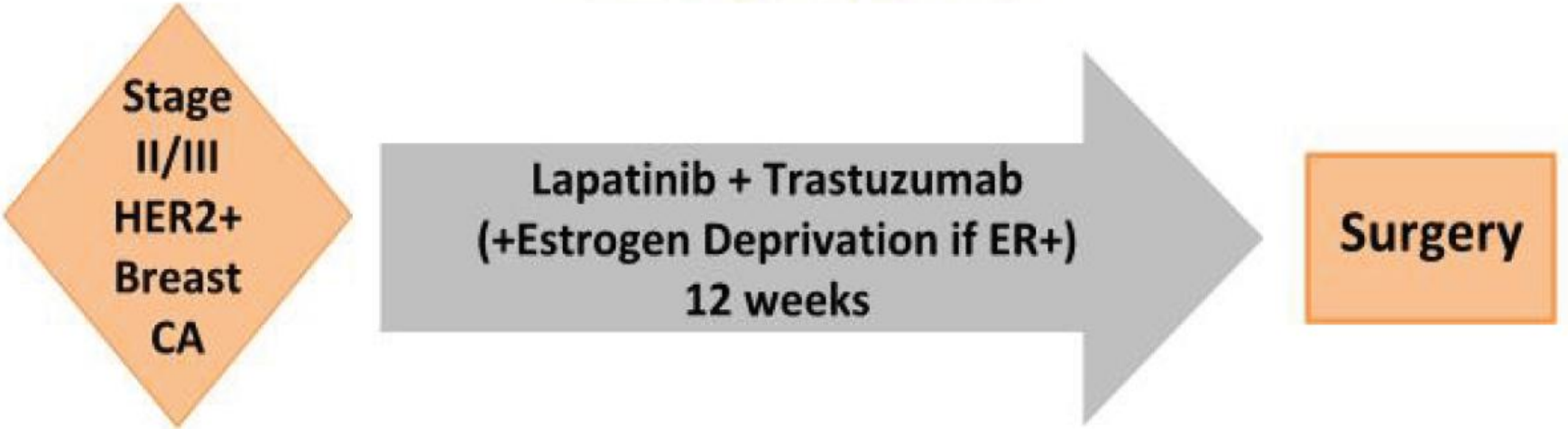


Arpino et al, JNCI 2007
Rimawi et al, CCR 2011

TBCRC 006



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Rimawi et al, JCO 2013

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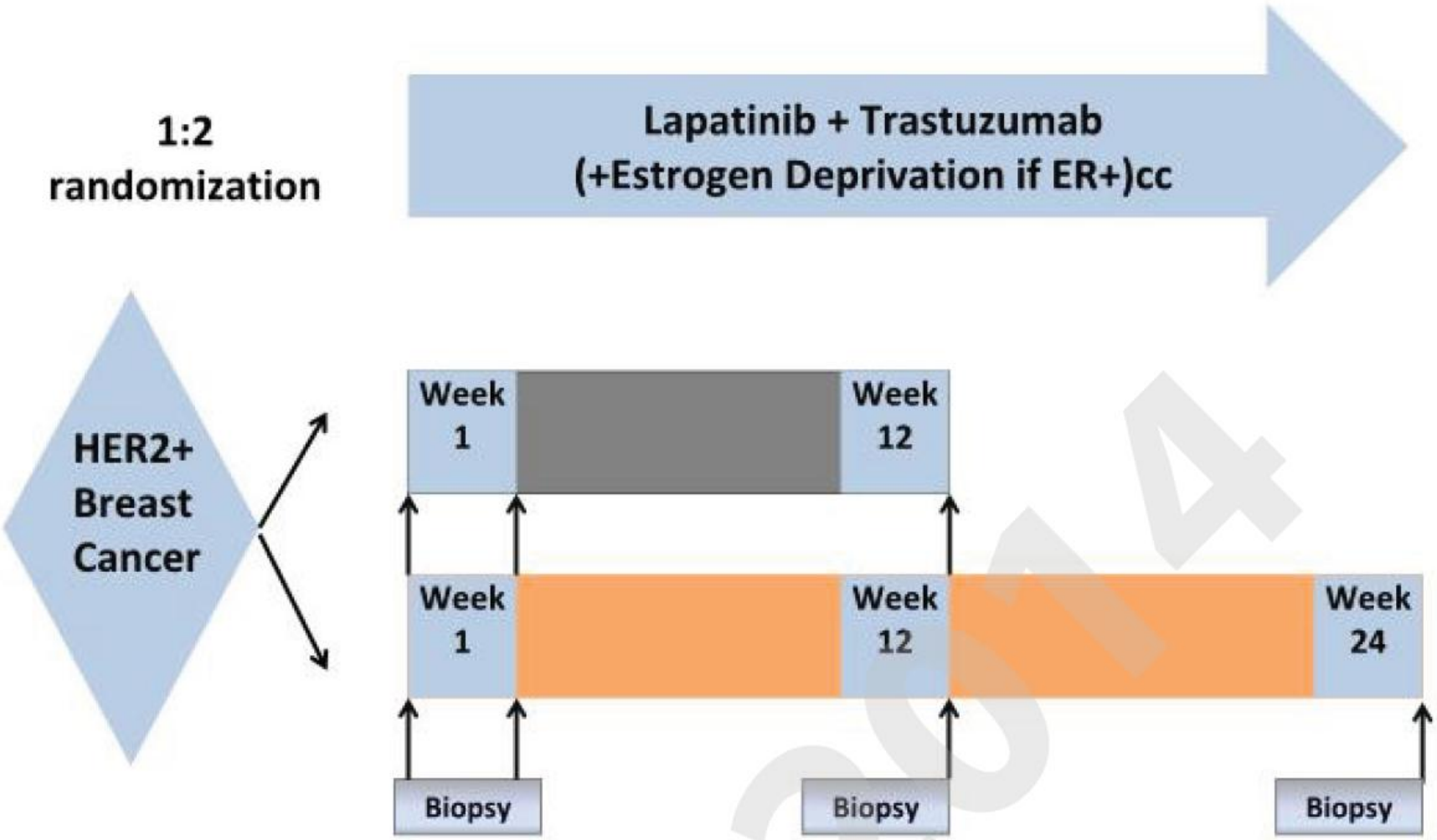
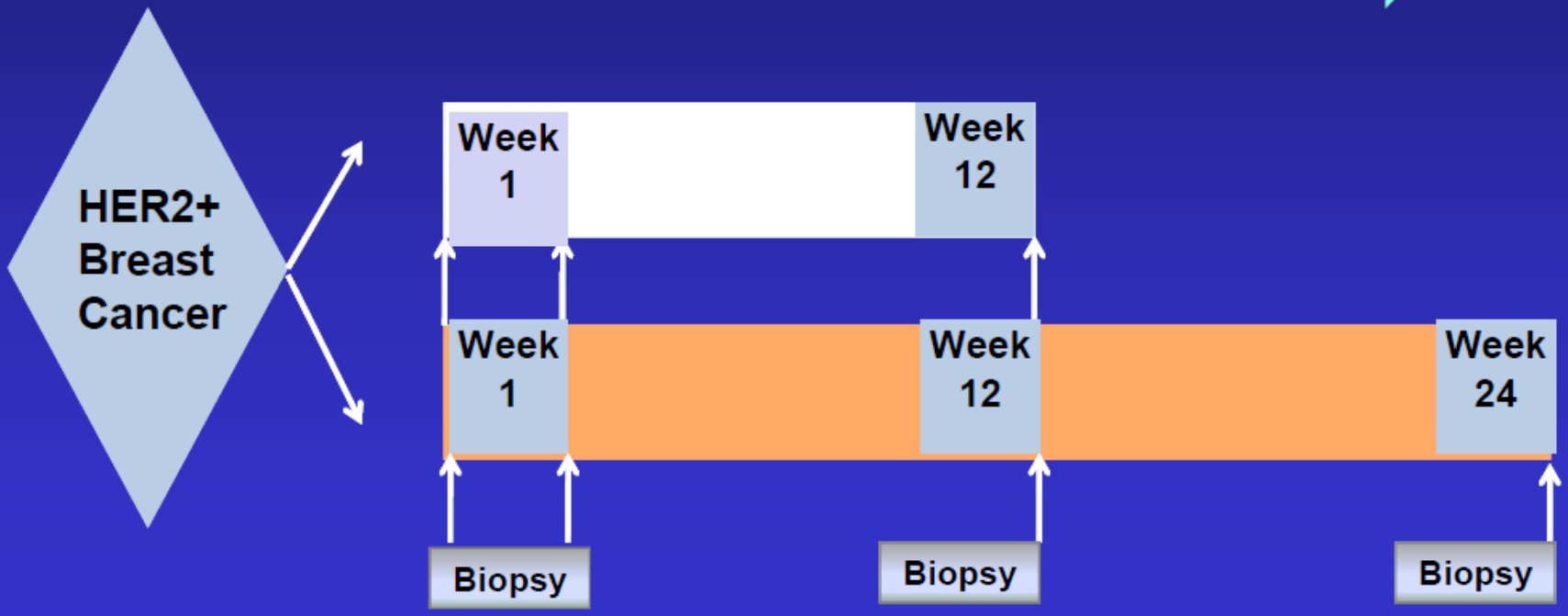


TBCRC023 Randomized Phase II Pilot anti-HER Doublet Duration

1:2 randomization

Lapatinib + Trastuzumab
(+ estrogen deprivation if ER+)



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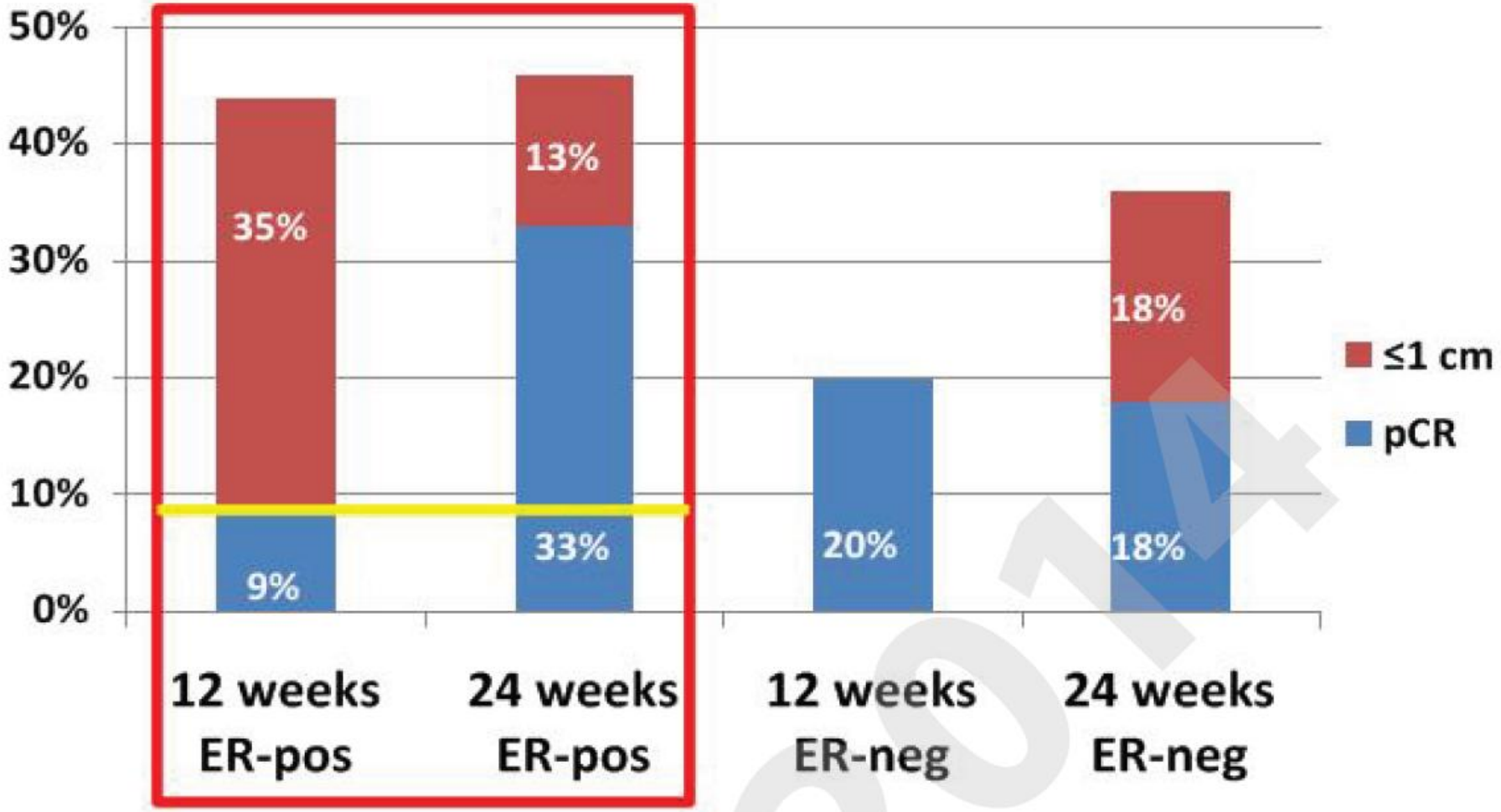

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- This is the first trial to show that longer treatment with dual anti-HER2 therapy in combination with endocrine therapy, and without chemotherapy, *leads to a meaningful increase in pCR rate in ER+/HER2+ breast cancer.*

Toxicity

- This trial collected targeted toxicity data:
  - All grade 3 and 4 AEs, regardless of causality
  - All liver toxicity, regardless of grade
  - All ≥ grade 2 cardiac or pulmonary toxicity
  - All clinically significant laboratory abnormalities.
  - All serious adverse events (SAEs).