Studio TBCRCO23: quali potranno essere le future ricadute nella pratica clinica?

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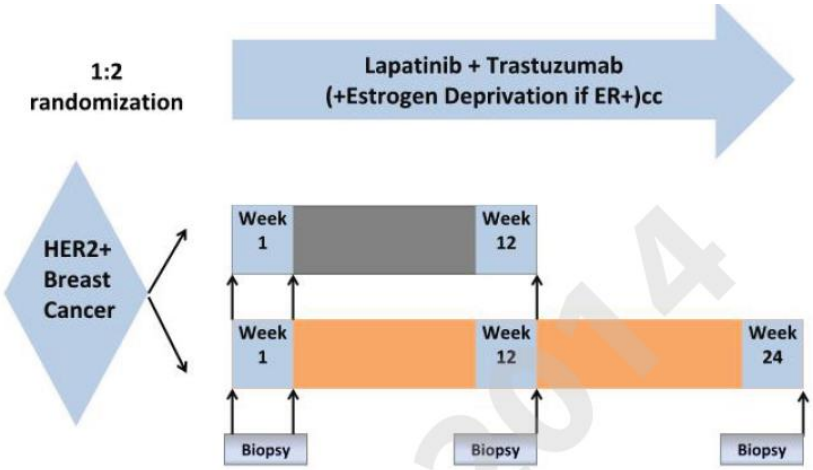
TBCRC023: Lapatinib-trastuzumab + HT



Pathologic Response

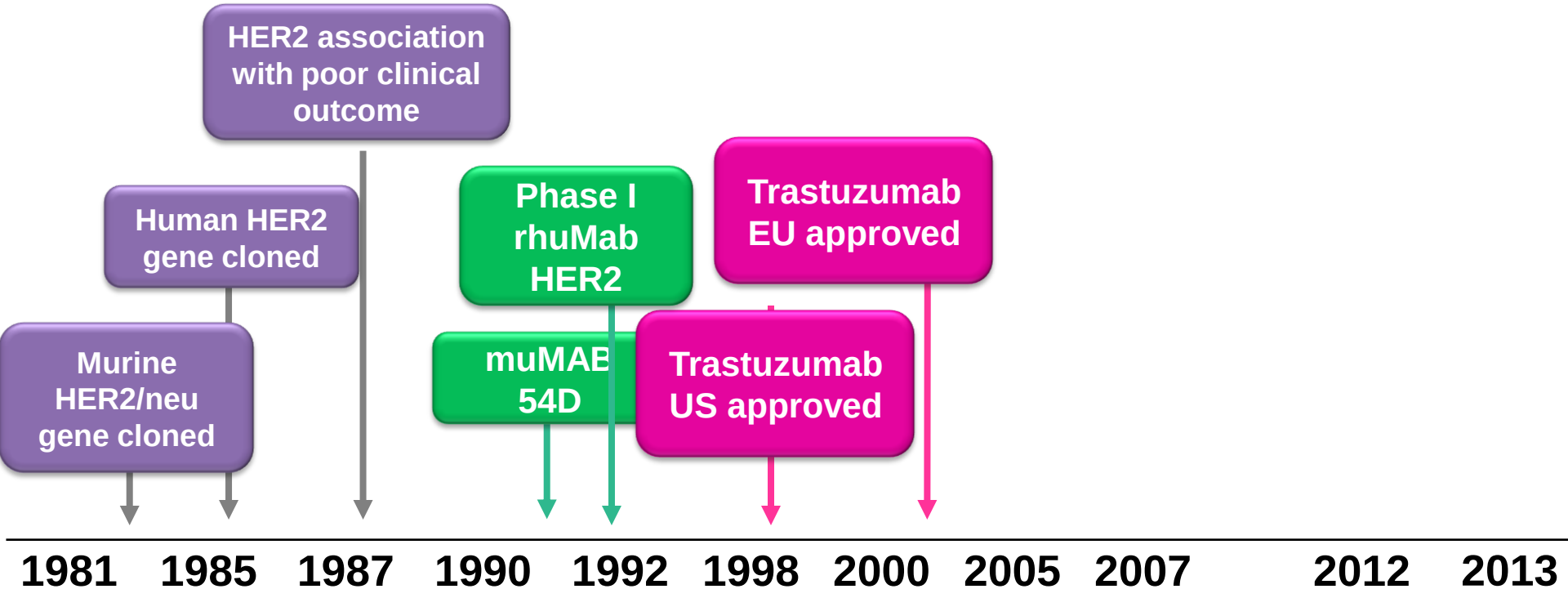
Path CR (ypT_{0-is})	12 weeks (n=33)	24 weeks (n=61)
Overall	4 (12%)	17 (28%)
ER-positive	2 (9%)	13 (33%)
ER-negative	2 (20%)	4 (18%)

For Monday clinic: 6 months of neoadjuvant therapy better than 3 months in terms of pCR for the HR+ subgroup

Rate of yT_{0-is},N0?
Rate of breast conserving surgery?
Rate of disease progression?

Rimawi et al, SABCS 2014

Milestones in the treatment of HER2^{+} BC



First line, anti-HER2 single agent (w/o CT)

	Trastuzumab w	Trastuzumab q3w	Lapatinib
n	114*	105	138
ORR	26%	23%	24%
Clinical Benefit Rate	38%	36%	31%
TTP	3.8 mos	3.4 mos	7 mo
Survival (median)	24 mos	-	-

*HER2 2+/3+

Vogel et al, et al. J Clin Oncol 2002; Baselga et al, J Clin Oncol 2005; Gomez et al, J Clin Oncol 2008

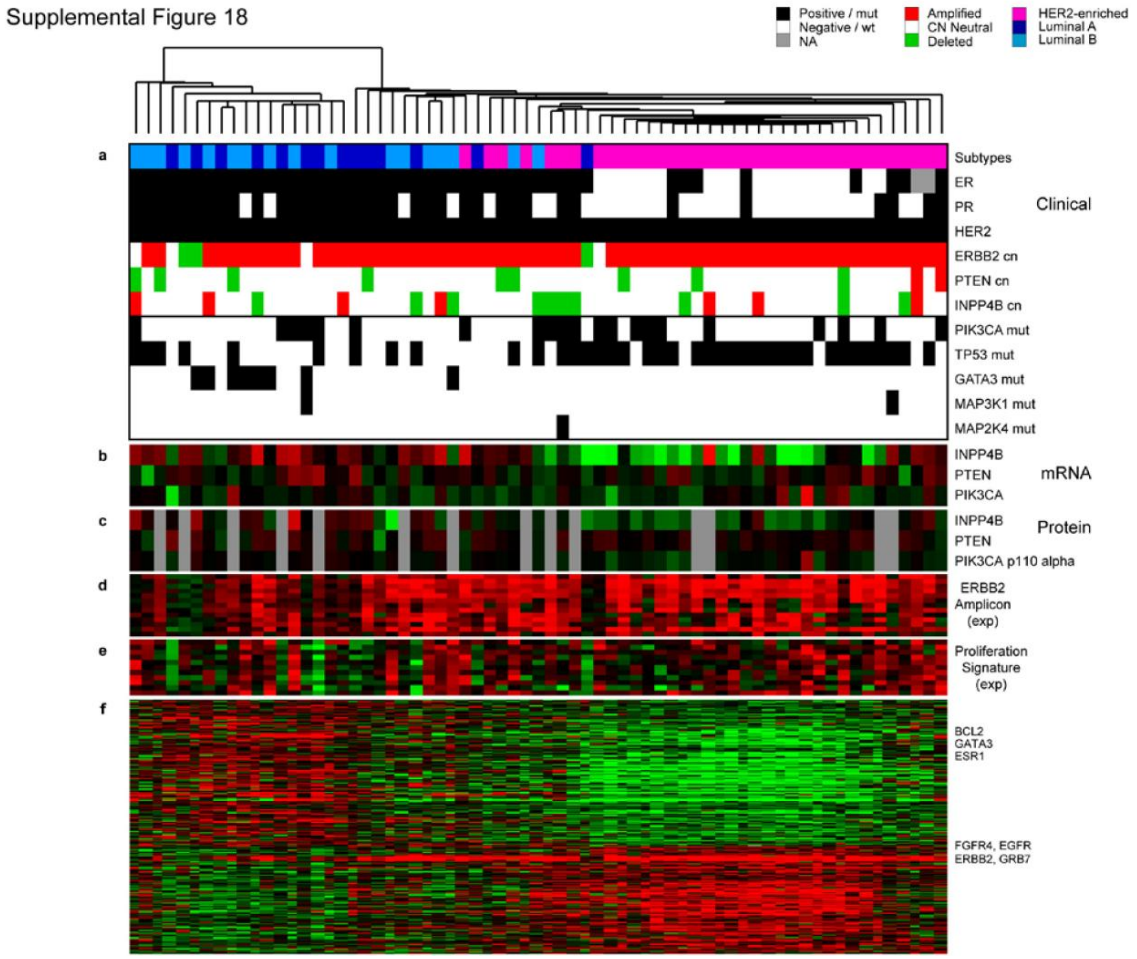
ONCE/LPD/0062/13. Date of preparation: October 2013

Randomized study of trastuzumab +/- Chemotherapy

	Slamon N=469		Marty N=186	
	CT	**CT +Trastuzumab**	**CT**	**CT +Trastuzumab**
ORR	32%	**50%**	34	**61**
PFS	4.6 mos	**7.4 mos**	6.1 mos	**11.7 mos**
OS	20.3 mos	**25.1 mos**	22.7 mos	**31.2 mos**

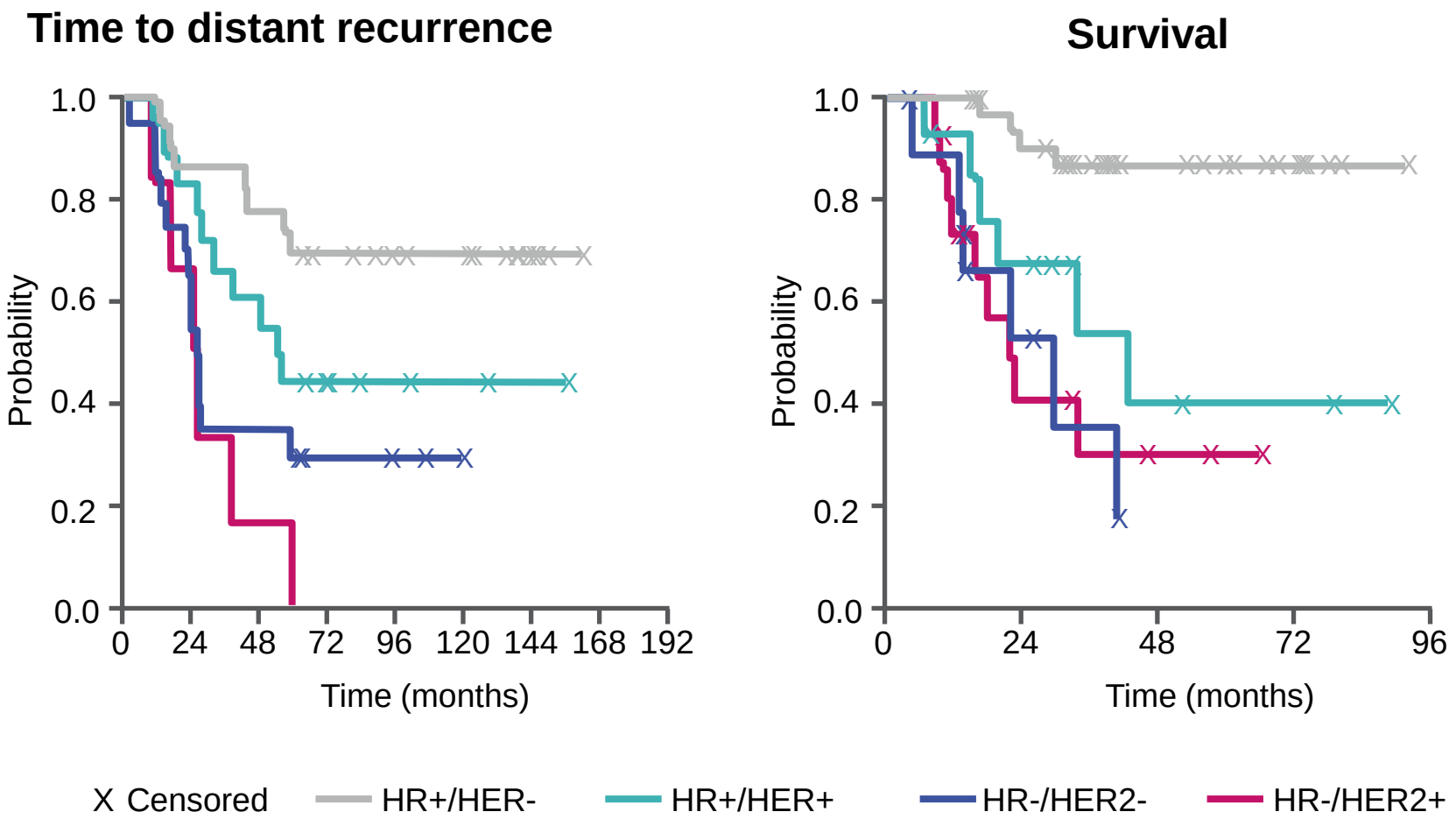
ONCE/LPD/0062/13. Date of preparation: October 2013

At least two types of clinically defined HER2+ tumours



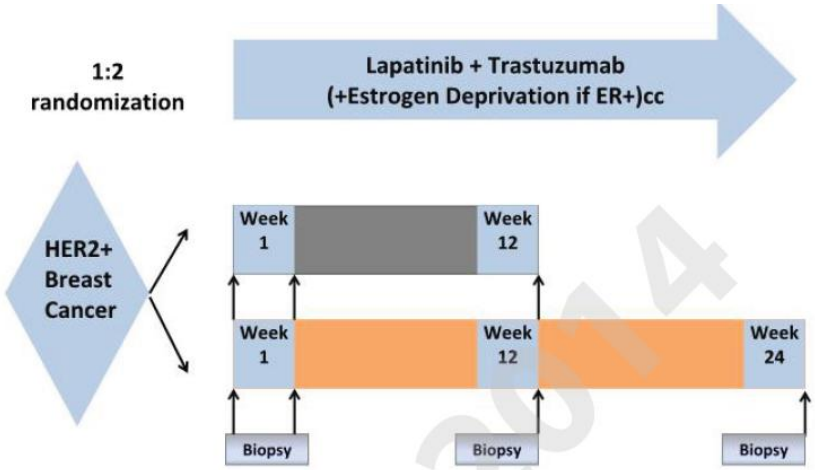
The Cancer Genome Atlas Network, Nature 2012

Heterogeneity of BC



Sorlie et al. Proc Natl Acad Sci USA 2003;100:8418.

TBCRC023: Lapatinib-trastuzumab +/- HT



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Rimawi et al, SABCS 2014

Background

NeoSphere: Study design and main results

TH (n=107)
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)

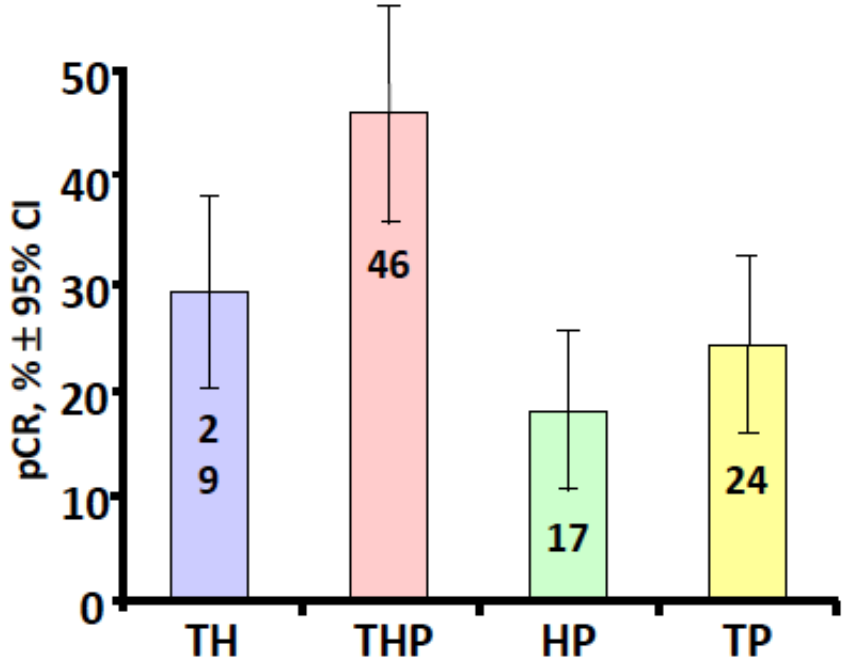
THP (n=107)
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

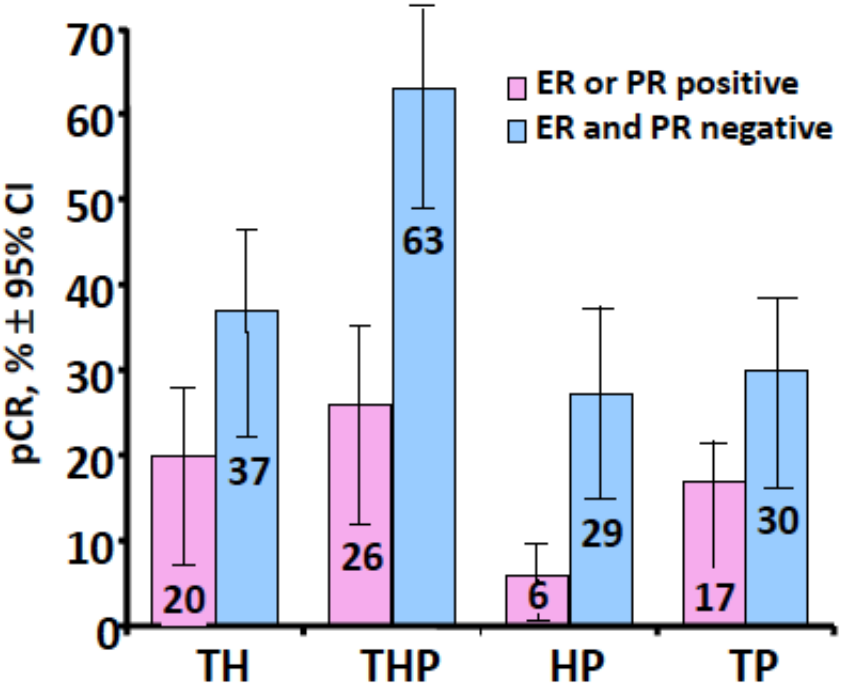
HP (n=107)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

TP (n=96)
docetaxel (75→100 mg/m²)
pertuzumab (840→420 mg)

SURGERY

Study dosing: q3w x 4



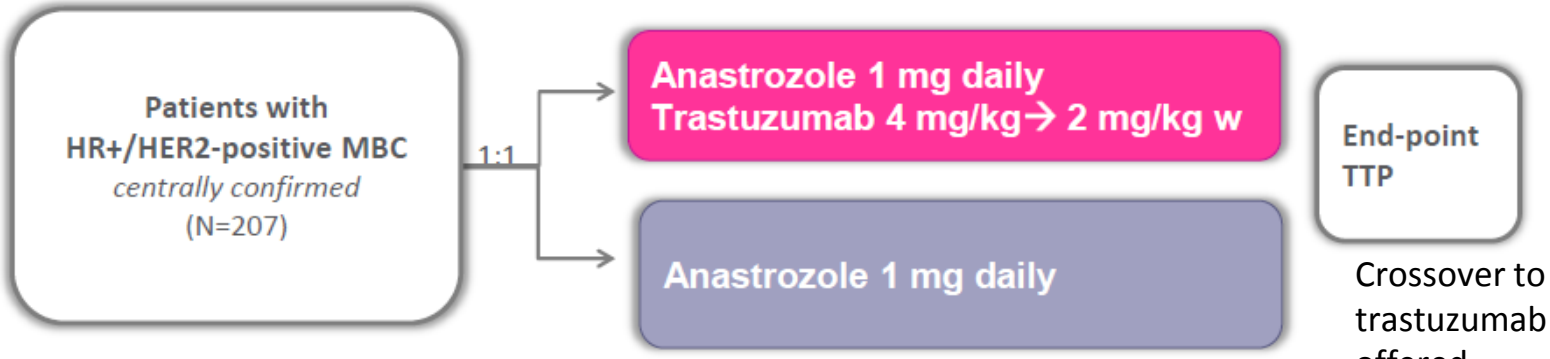


Gianni L, et al. Lancet Oncol 2011 DOI:10.1016/S1470-2045(11)70336-9

Response to neoadjuvant CT+anti-HER2 according to HR status

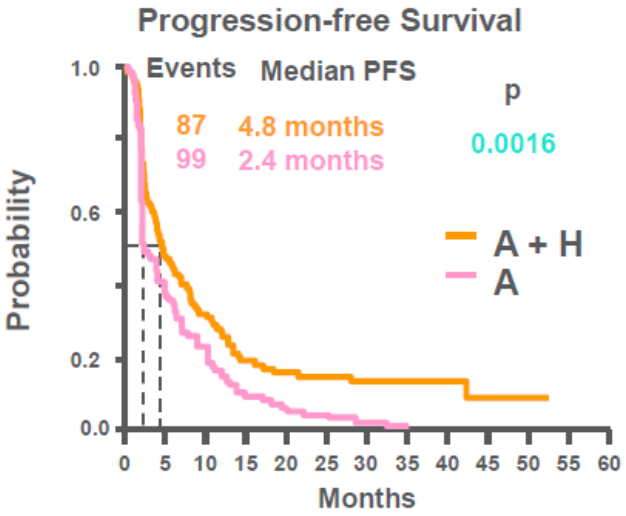
Trial	pts #	HR + %	tpCR %		
			HR-	HR+	Δ
MDACC (w/o antiHER2)	321	57	**29**	**15.3**	**13.7**
MDACC	89	48	**61**	**47**	**14**
Neo-ALLTO	455	51	**43.9**	**26.7**	**17.2**
NeoSphere	417	47	**39.8**	**17.3**	**22.5**
CherLob	121	60	**44**	**27**	**17**

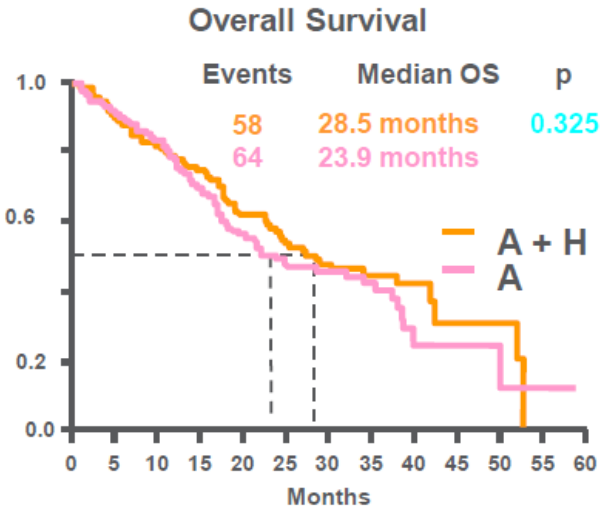
TAnDEM: phase III study of anastrozole +/- trastuzumab as first-line therapy for ER+/HER2+ MBC



Crossover to trastuzumab actively offered

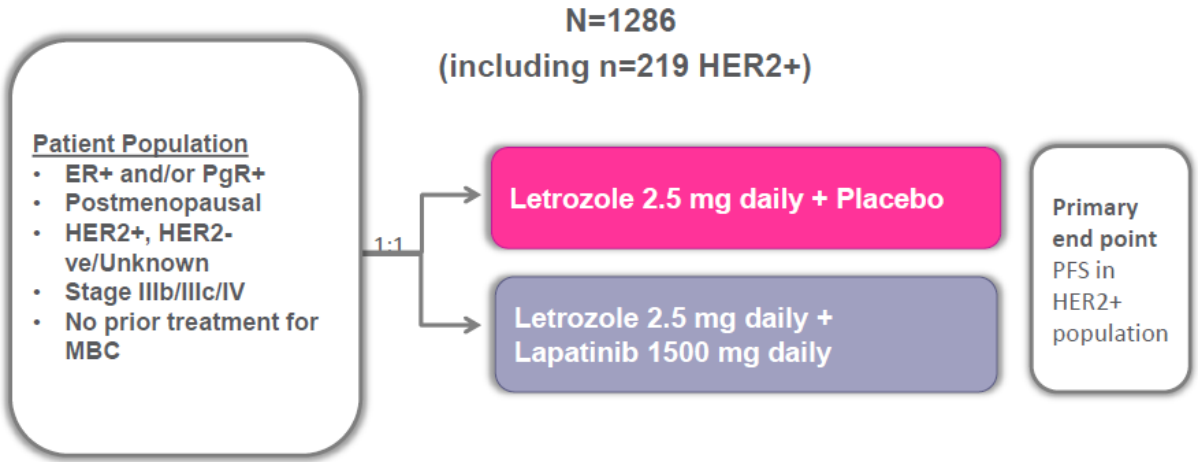
	Anastrozole	Anast.+Trastuzumab	
OR (%)	7	20	p=0.018
CBR (%)	28	43	p=0.026

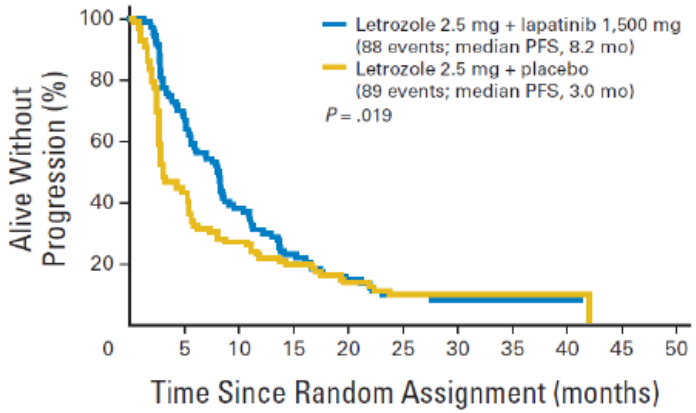


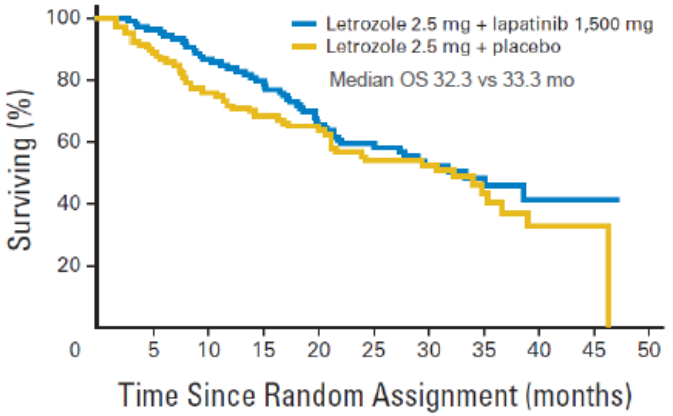


Kaufman et al. J Clin Oncol 2009; 27:5529-37

EGF 30008: Phase III study of letrozole v letrozole-lapatinib as first-line therapy for HR+ advanced BC



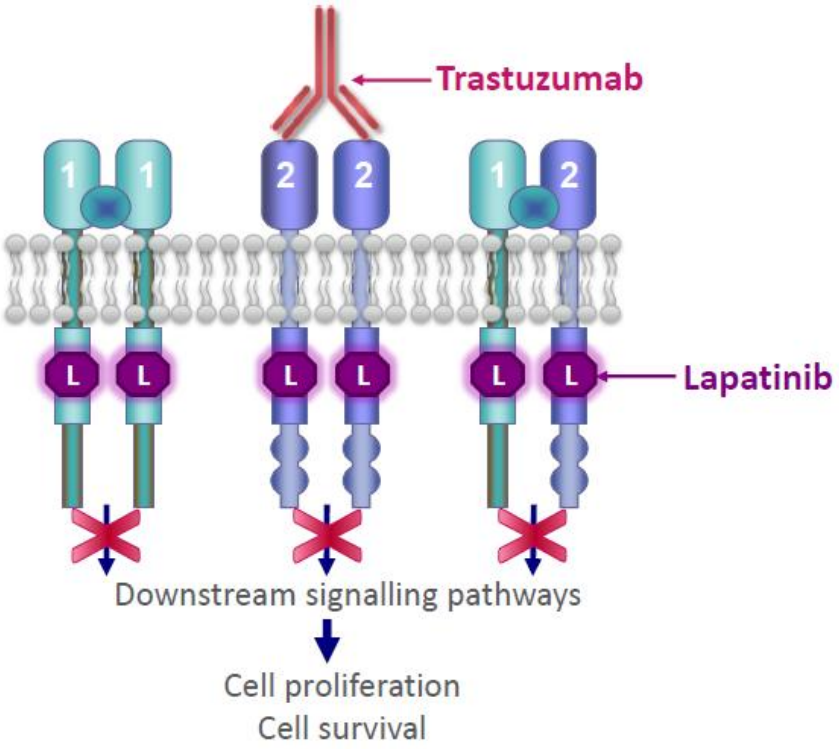




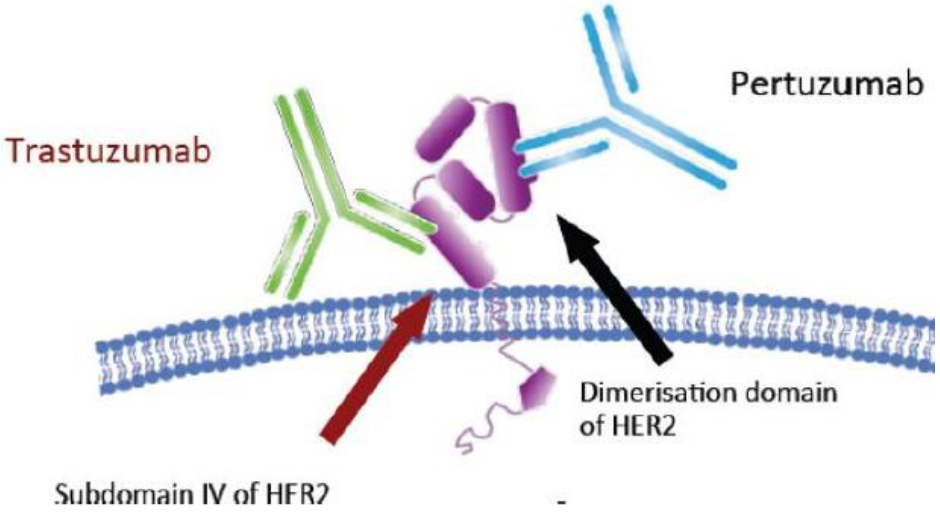
Johnston et al, J Clin Oncol 2009 27; 5538-46

Dual HER2 receptor blockade

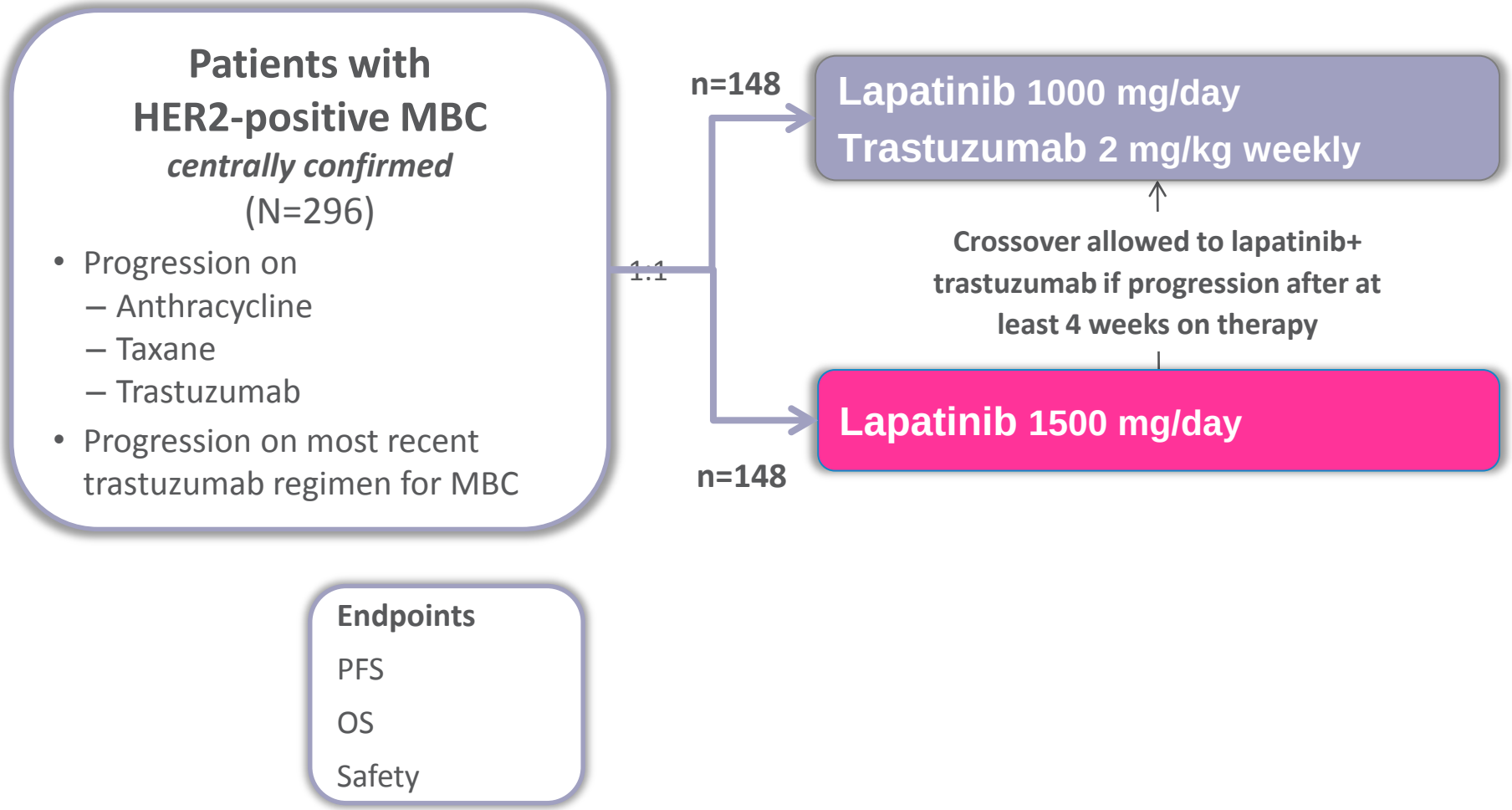
"Vertical targeting"



"Horizontal targeting"



Vertical dual blockade of the HER2 receptor with lapatinib+trastuzumab: EGF104009



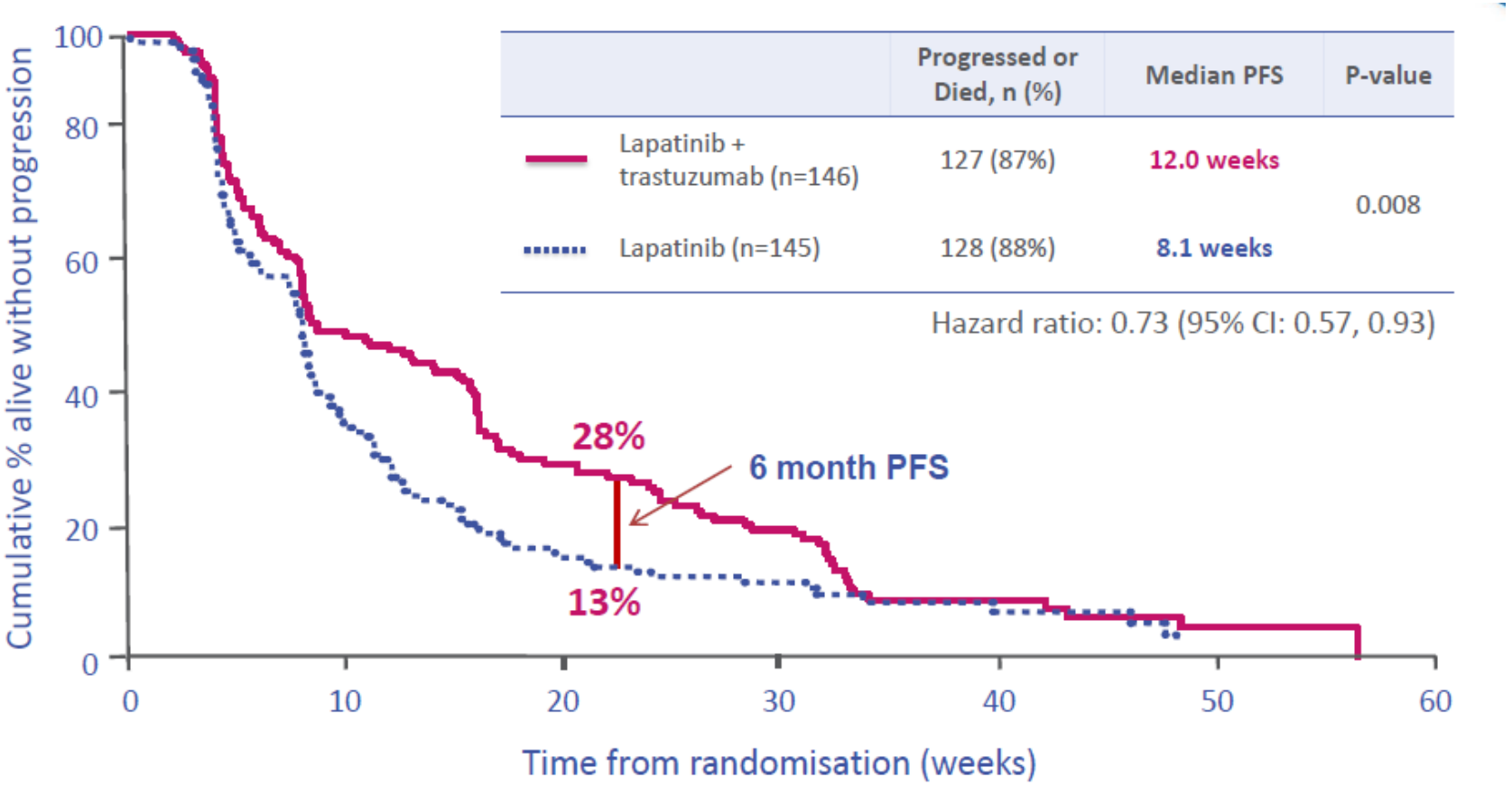
Blackwell et al. J Clin Oncol 2010;28:1124; Blackwell at al. J Clin oncol 2012. .

EGF104009: patients characteristics

	Lapatinib (n=148)	Lapatinib+ trastuzumab (n=148)
Median Age (range)	51 (29-78)	52 (26-81)
ECOG PS		
0	69 (47%)	80 (54%)
1	73 (49%)	61 (41%)
2	6 (4%)	7 (5%)
Median # of prior CT regimens	4	5
≥ 6 prior regimens	41 (28%)	50 (34%)
Visceral disease	110 (74%)	105 (71%)

Pivot et al. ESMO 2012

Vertical dual blockade of the HER2 receptor with lapatinib+trastuzumab

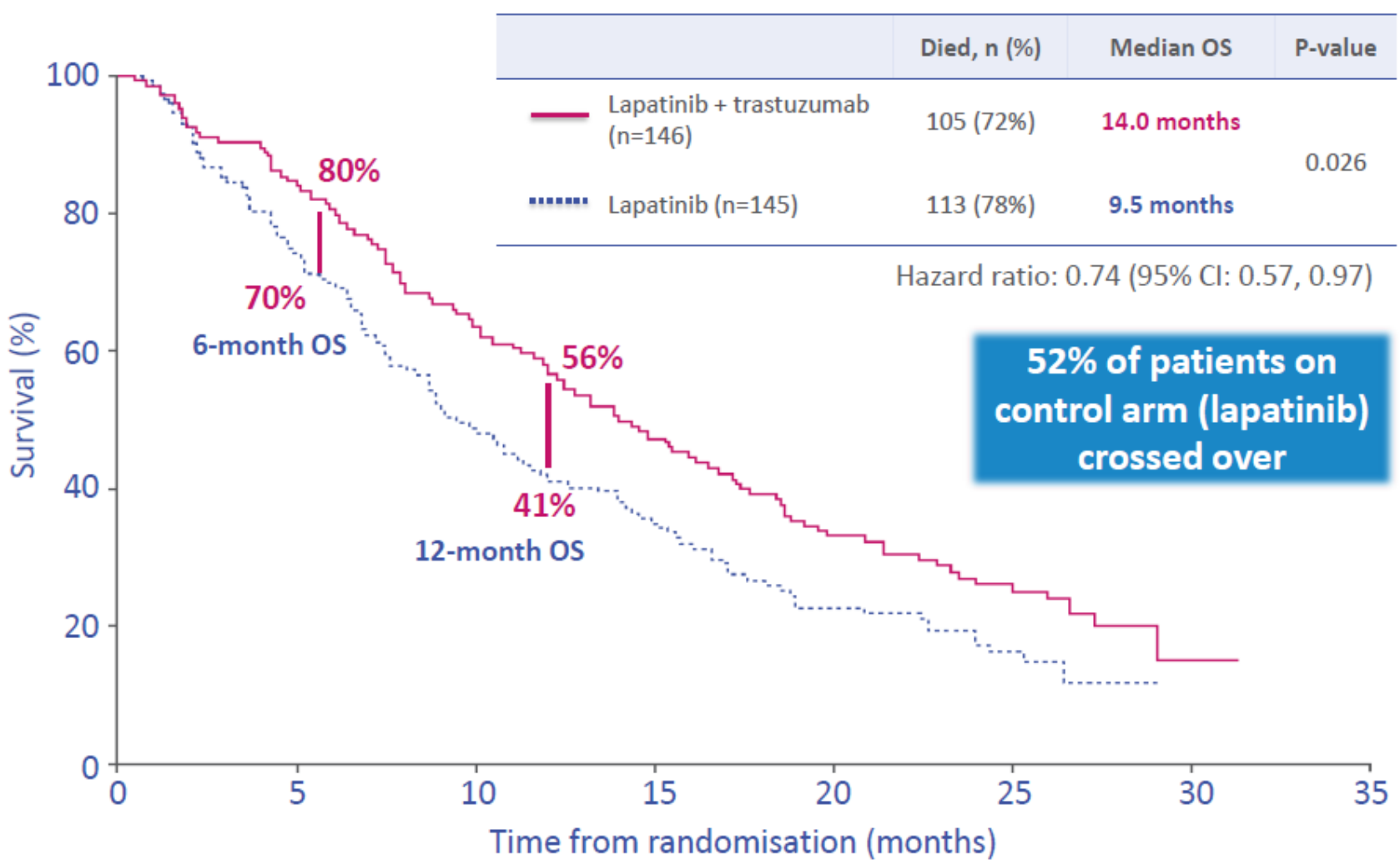


	Progressed or Died, n (%)	Median PFS	P-value
Lapatinib + trastuzumab (n=146)	127 (87%)	12.0 weeks	0.008
Lapatinib (n=145)	128 (88%)	8.1 weeks	

Hazard ratio: 0.73 (95% CI: 0.57, 0.93)

Blackwell et al. J Clin Oncol 2010

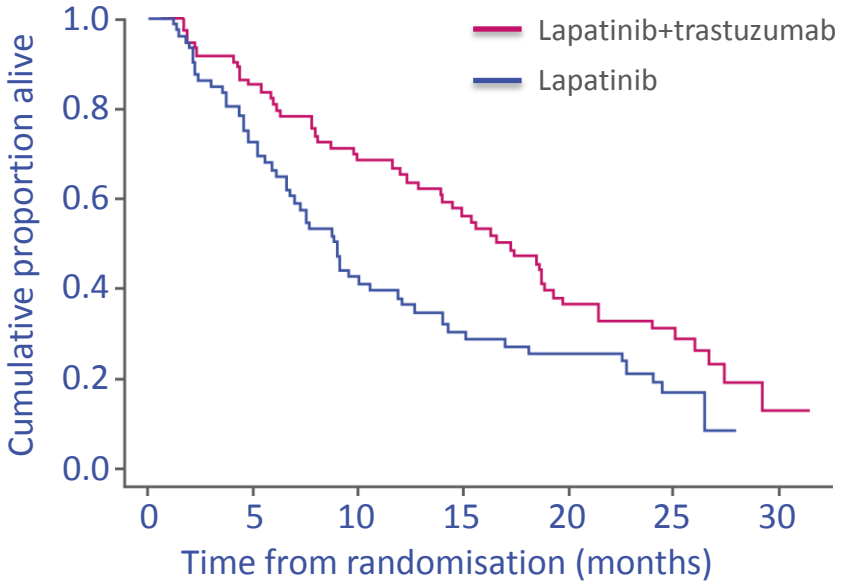
Vertical dual blockade of the HER2 receptor with lapatinib+trastuzumab



Blackwell at al. J Clin Oncol 2012.

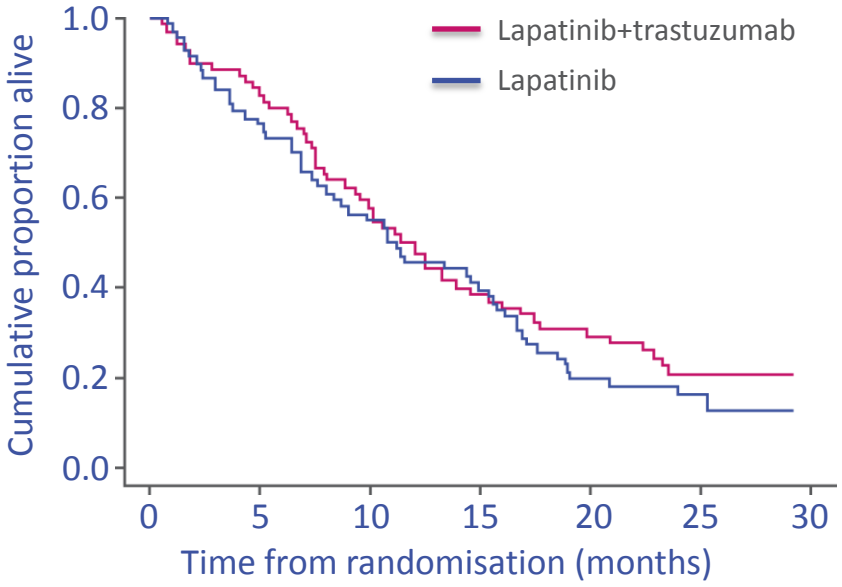
OS by Hormone receptor status

HR-negative



	Lap+Tras N=75	Lap N=75	OS hazard ratio (95% CI)
Median OS, months	**17.2**	**8.9**	**0.62** (0.42, 0.90)

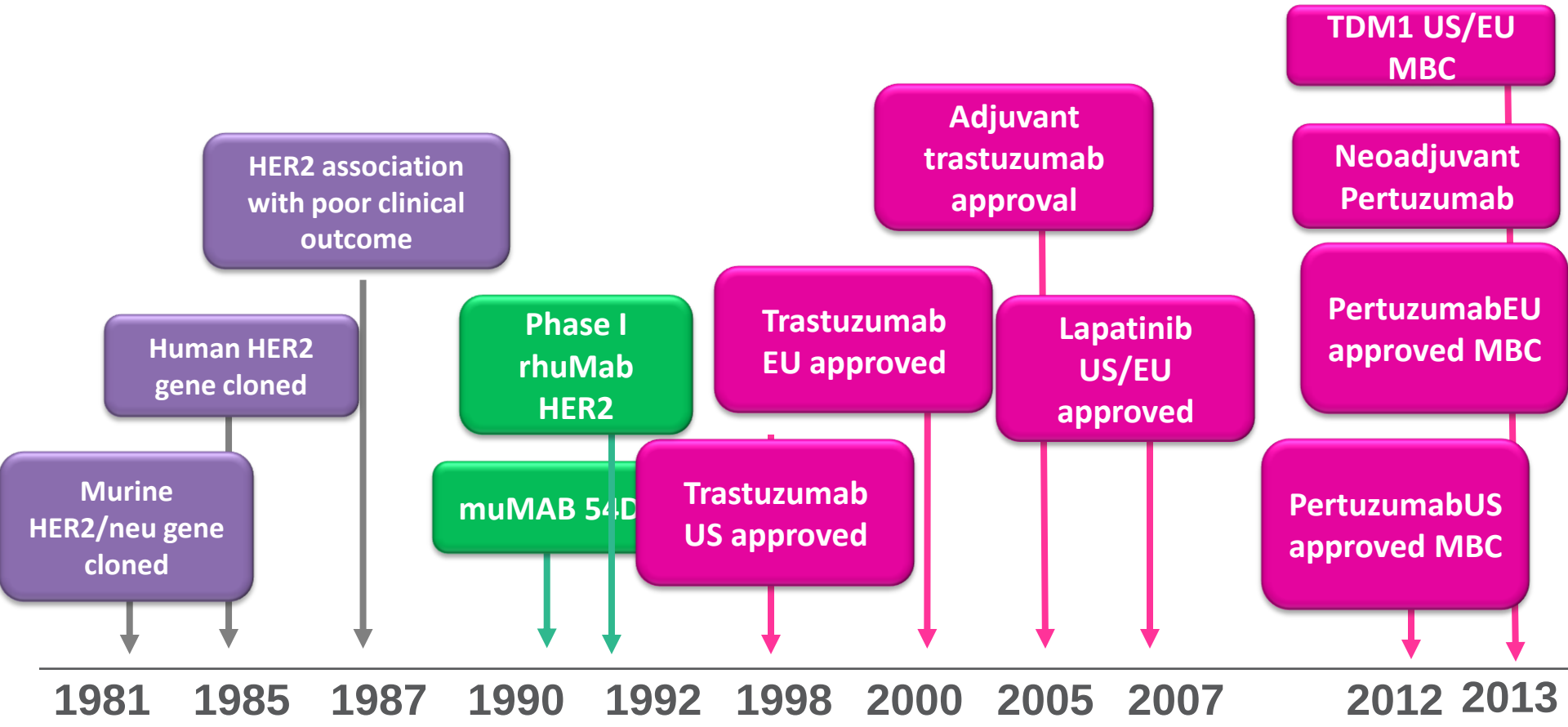
HR-positive



	Lap+Tras N=75	Lap N=75	OS hazard ratio (95% CI)
Median OS, months	12.0	11.2	0.84 (0.58, 1.23)

Tyverb Assessment report EMEA/H/C/000795/II/0022 27 June 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000795/WC500147870.pdf. Accessed October 2013.

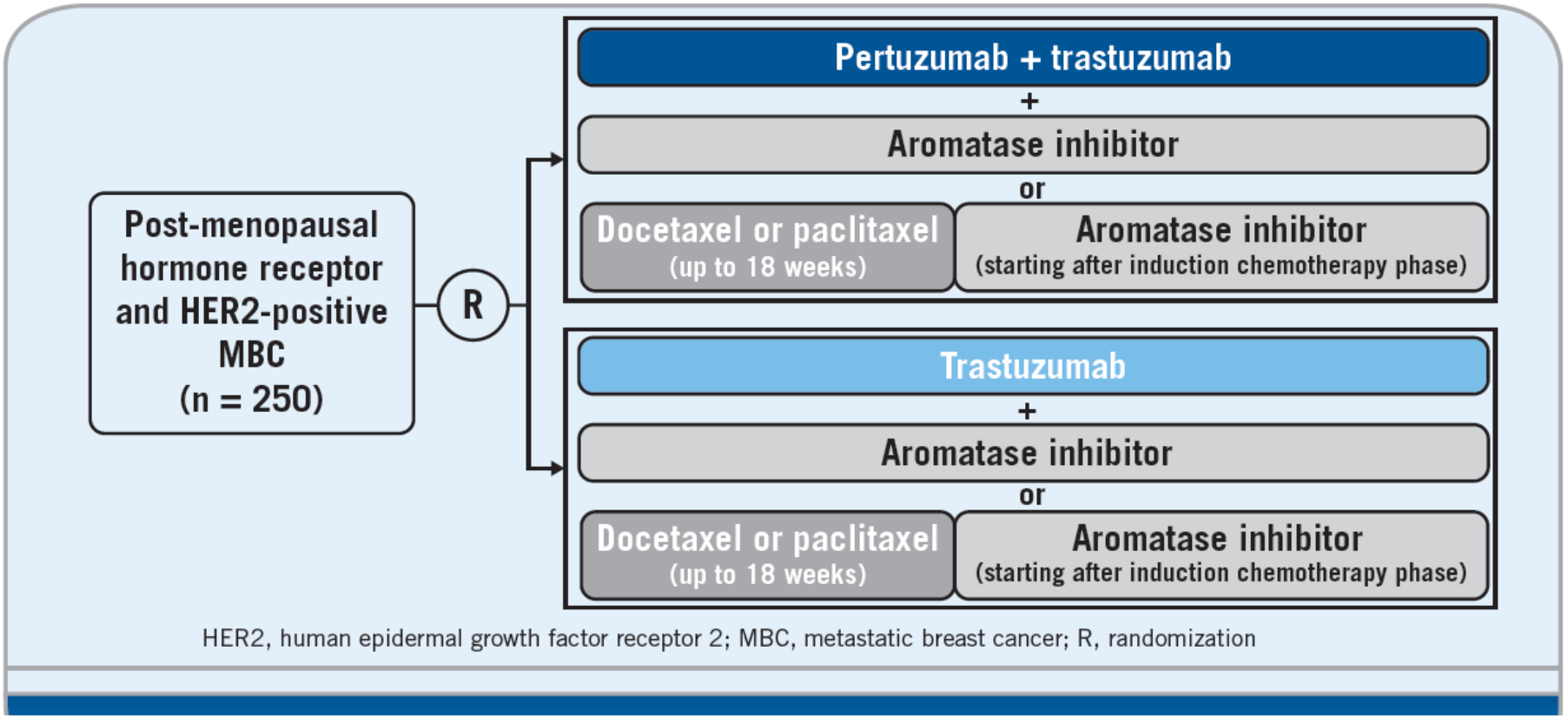
Milestones in the treatment of HER2+ BC



Closing Credits for Chemotherapy in HER2+ disease?

- **HER2+ BC shows molecular heterogeneity which translate in very different clinical behaviour**
- **combining hormonal therapy + anti-HER2 agents is a chemo-free option with good balance between efficacy and tolerability**
- **dual-HER2 inhibition is superior to single anti-HER2 block→ ceiling effect for the companion?**

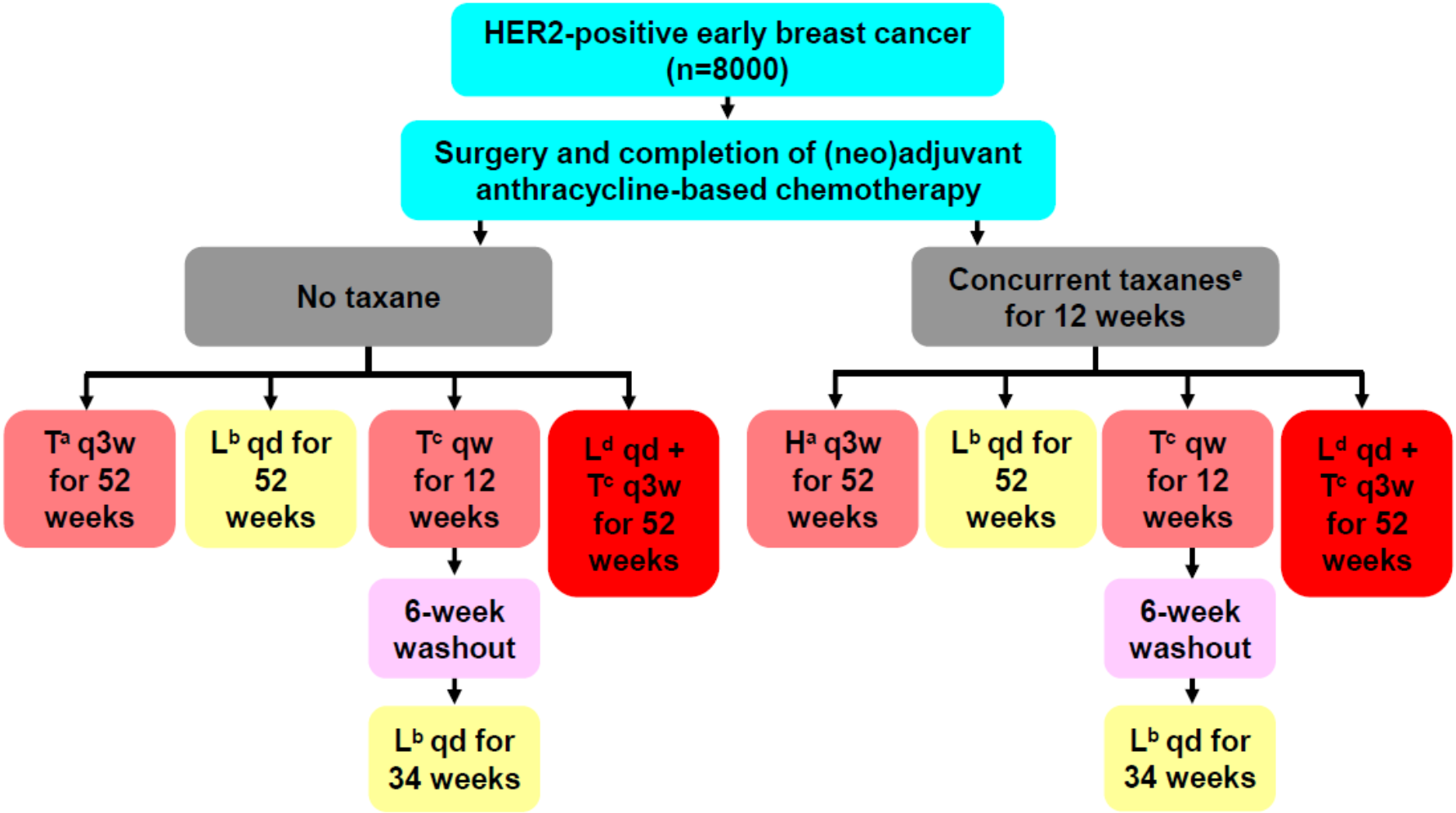
PERTAIN: randomized phase II study



HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; R, randomization

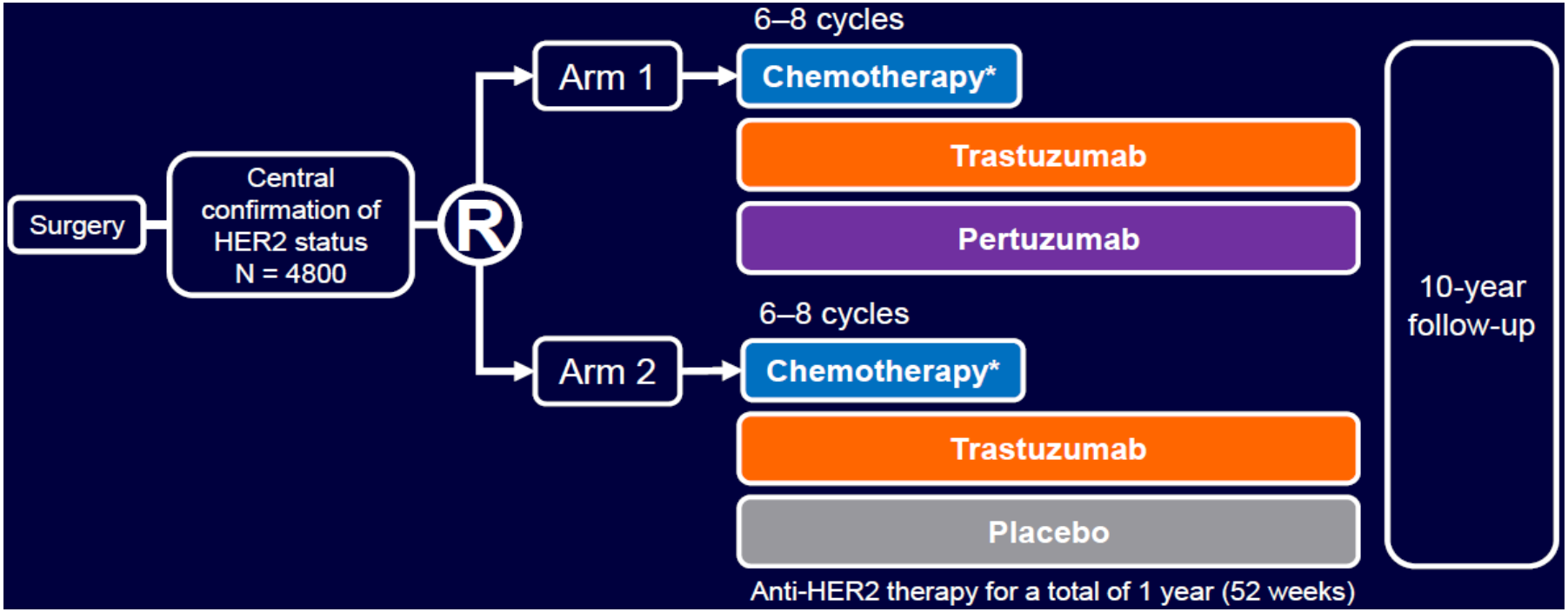
Rimawi MF, Poole C, Ferrero J-M,de la Haba-Rodriguez J, Mitchell L, Pelizon C, Arpino G
ASCO 2012

ALLTO: phase III randomised open-label trial comparing adjuvant Lapatinib +/- Trastuzumab



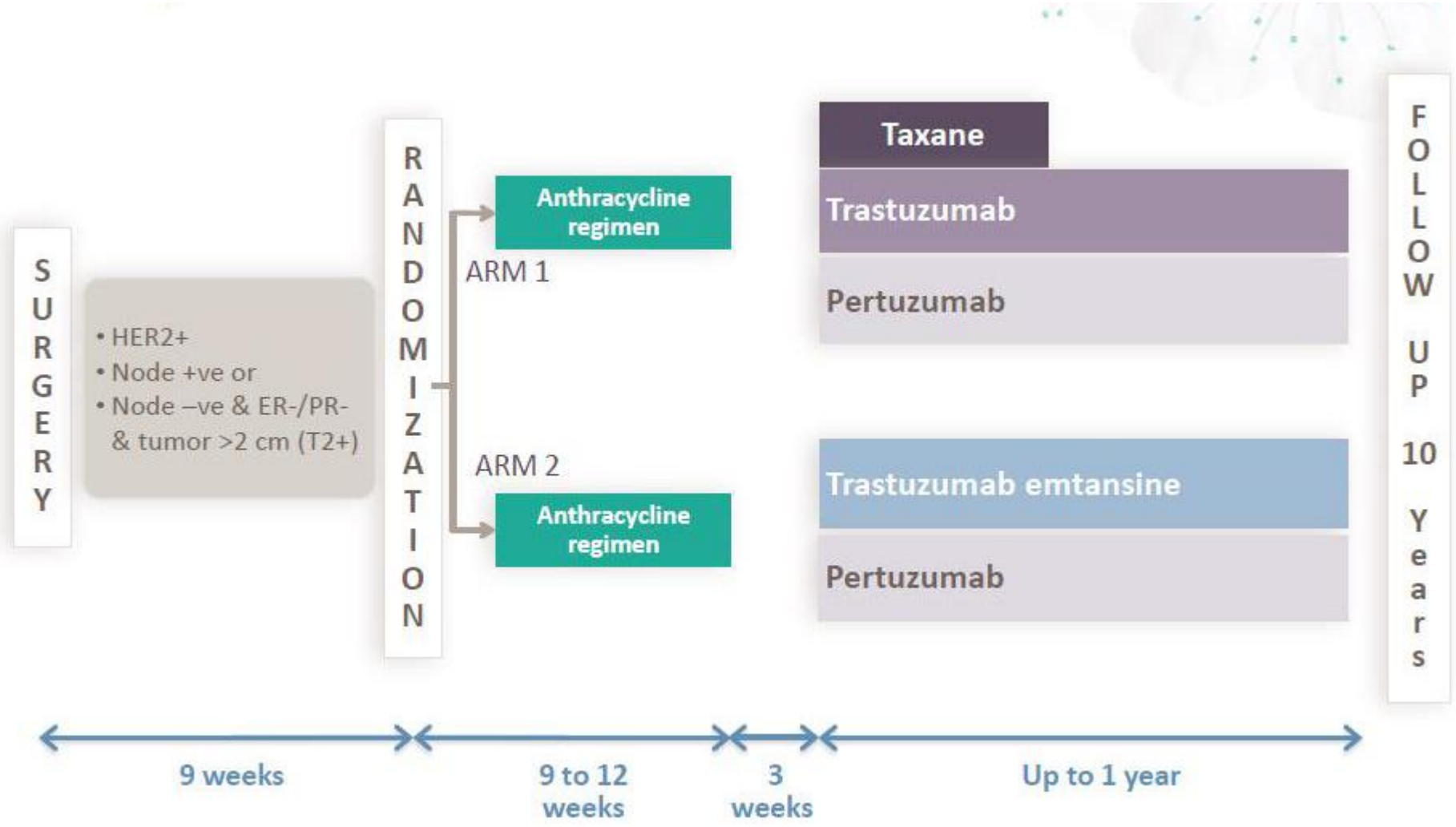
[a] Trastuzumab 8 mg/kg iv loading dose followed by 6 mg/kg q3w; [b]Lapatinib 1500 mg; [c]Trastuzumab 4 mg/kg iv loading dose followed by 2 mg/kg qw; [d]Lapatinib 1000 mg; [e]Paclitaxel 80 mg/m^2 qw or docetaxel q3w

Aphinity: Phase III trial of adjuvant chemotherapy + trastuzumab +/- pertuzumab



www.clinicaltrials.gov, BO25126/TOC4939g

Adjuvant Trastuzumab Emtasine: Kaitlin trial



PER-ELISA: HR+/HER2+ operable breast cancer

Clinical Study Protocol AS.T.R.O BC01-13
Eudract 2013-002662-40, PI V. Guarneri