37th ESMO – Vienna
ESMO/CSCO joint session – 29th September 2012

Is the neoadjuvant model an accelerated path towards BC treatment tailoring ? Experience of the NeoALTTO trial

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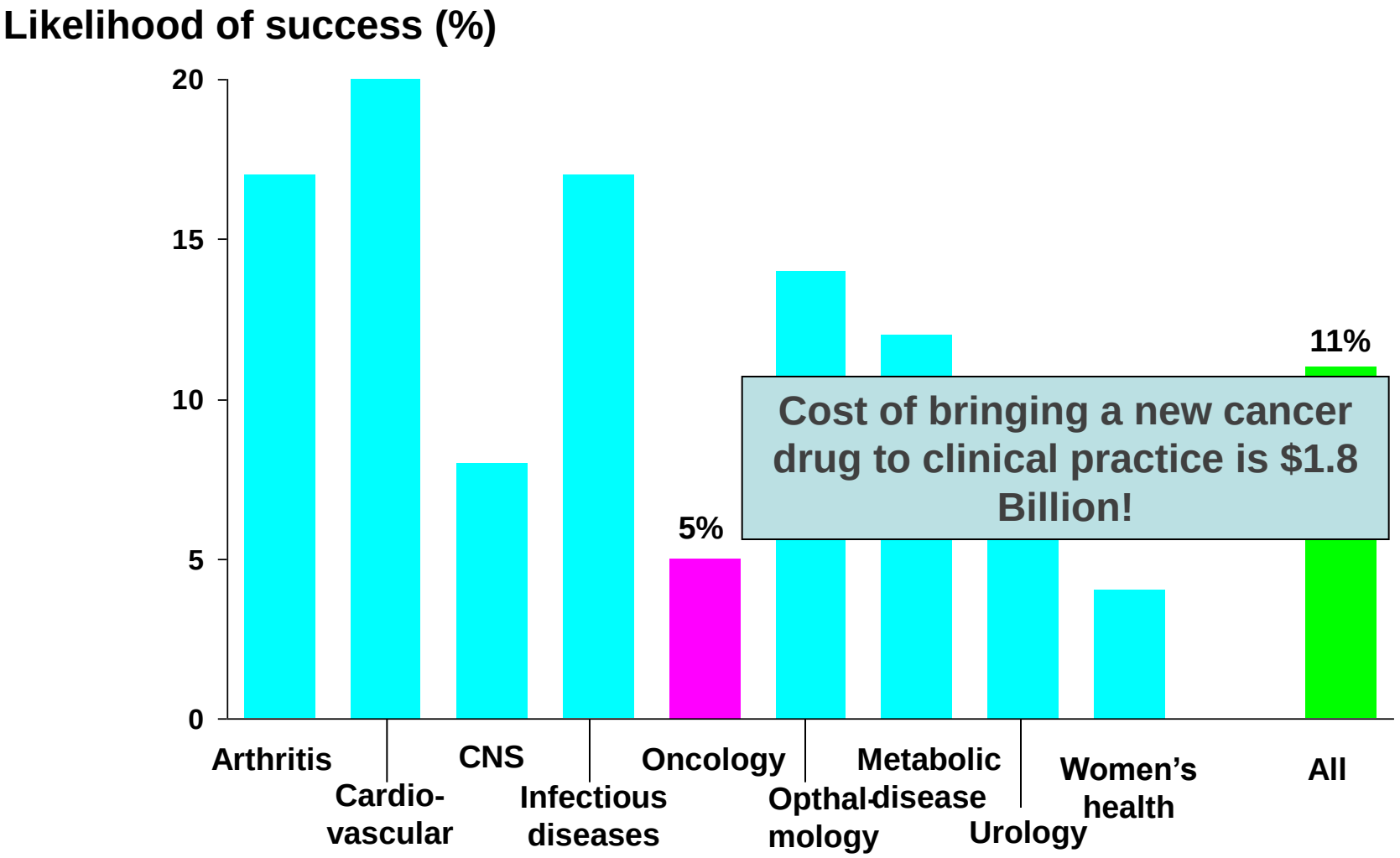
ULB Institut Jules Bordet réseau iris structuur Instituut

BIG BREASTINTERNATIONALGROUP

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

THE PIPELINE PROBLEM



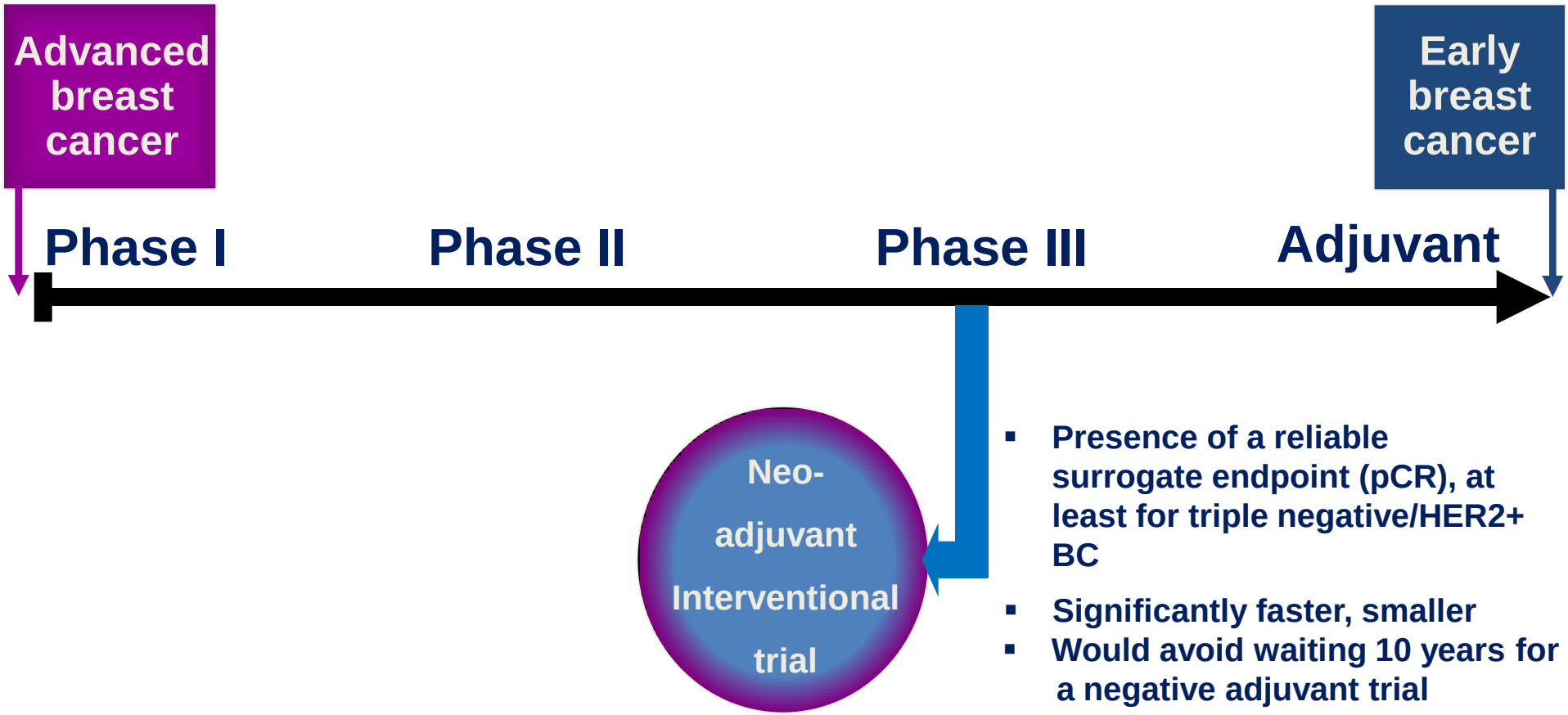
Kola Nat Rev Drug Discovery 2004

SPECIAL ISSUES IN NEW DRUG DEVELOPMENT FOR BC

- **The likelihood of success is low**
- **The cost is huge**
- **The understanding of who benefits is poor, even in the era of « personalized oncology »**

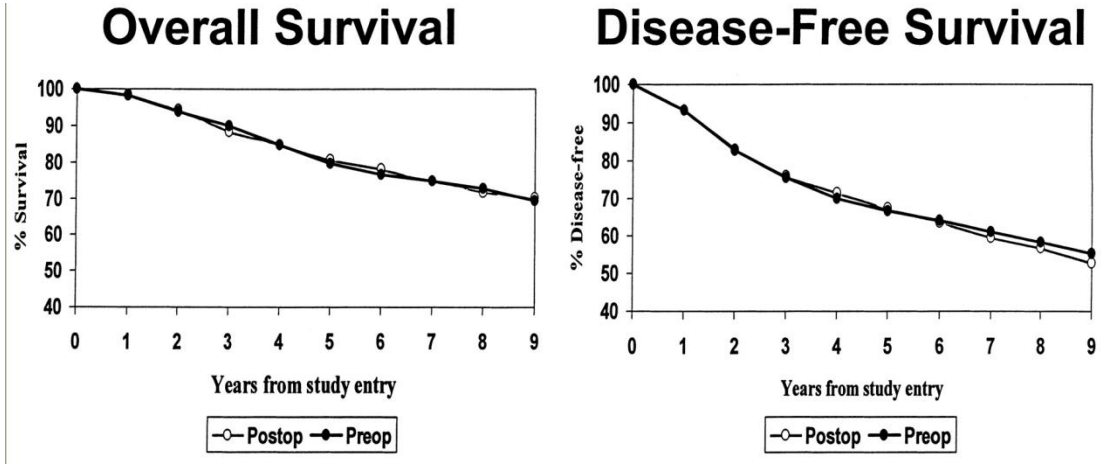
Kola Nat Rev Drug Discovery 2004

POTENTIAL WAYS OF ACCELERATING DRUG DEVELOPMENT AND REDUCING THE RISK OF « FAILURE »

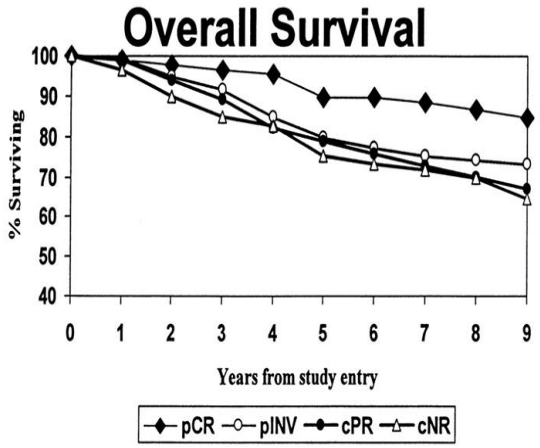


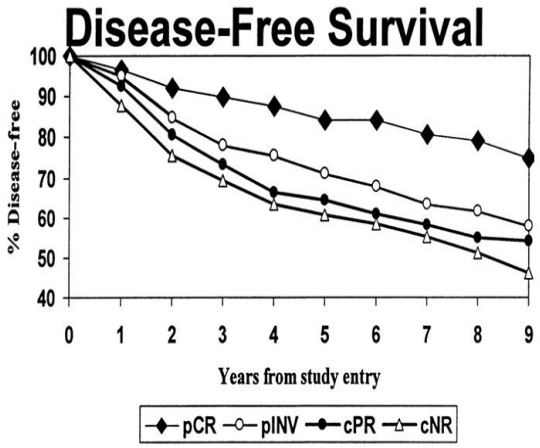
- Presence of a reliable surrogate endpoint (pCR), at least for triple negative/HER2+ BC
- Significantly faster, smaller
- Would avoid waiting 10 years for a negative adjuvant trial
- Easy integration of biomarker research

NSABP-B18: A LANDMARK TRIAL NEOADJUVANT VS ADJUVANT "AC"



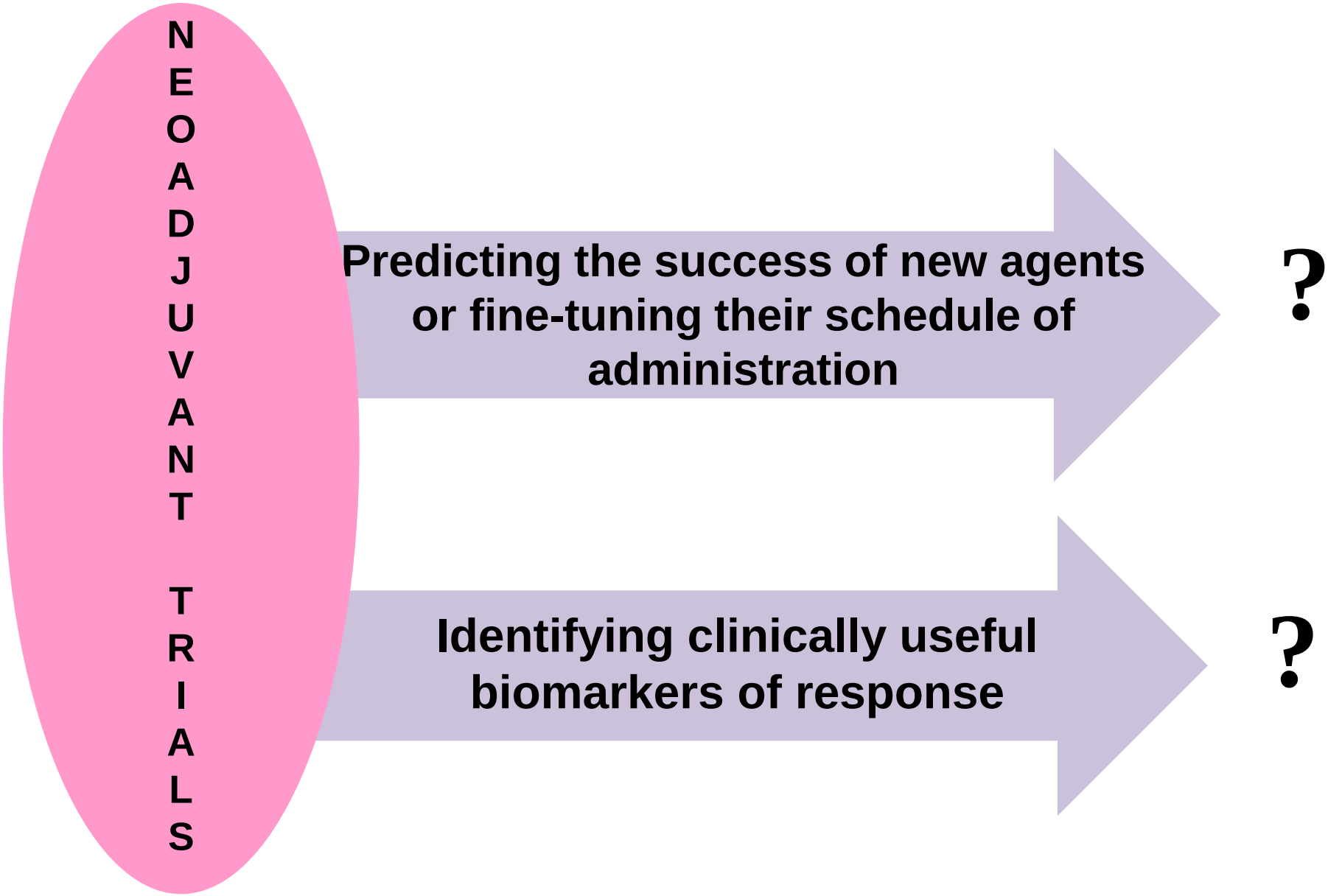
Neo-adjuvant
=
Adjuvant





pCR is a good surrogate marker for long-term outcome

Fisher et al JNCI 2001


NEOADJUVANT TRIALS
Predicting the success of new agents or fine-tuning their schedule of administration
?
Identifying clinically useful biomarkers of response
?

1. CYTOTOXIC AND ENDOCRINE AGENTS

LESSONS LEARNED FROM NEOADJUVANT TRIALS IN THE PRE-GENOMIC ERA

Predicting the success of new agents for the « average » patient…

or fine-tuning their schedule of administration

…

Preoperative trials	Key findings	Confirmation in postoperative trials
Aberdeen **N=162**	• **Docetaxel in sequence with anthracycline better than anthracycline alone (pCR)**	**Many adjuvant trials** **N ~ 44,000**
MD Anderson **N=258**	• **Paclitaxel q3wks better than weekly (pCR)**	**ECOG 1199 trial** **N=5,000**
M. Ellis / M. Dowsett **N=324 / N=330**	• **Aromatase inhibitor better than tamoxifen (clinical response)**	**Many adjuvant trials** **N>40,000**

LESSONS LEARNED FROM NEOADJUVANT TRIALS IN THE PRE-GENOMIC ERA

Identifying clinically useful biomarkers of response…

PREOPERATIVE ENDOCRINE THERAPY DOUBLE BLIND STUDIES

	Letrozole (L) vs Tamoxifen (T) M. ELLIS (N=324)	Anastrozole (A) vs Tamoxifen (T) M. DOWSETT (N=330)
CLINICAL	• Higher response rate with L • Higher rate of breast conservation with L	• Similar response rate • Trend for higher rate of breast conservation with A
MOLECULAR	• Benefit of L confined to tumors with HER-1/HER-2 receptors	• Trend for greater A benefit in HER2 +++ tumors • Significantly greater Ki67 drop at 2 wks with A

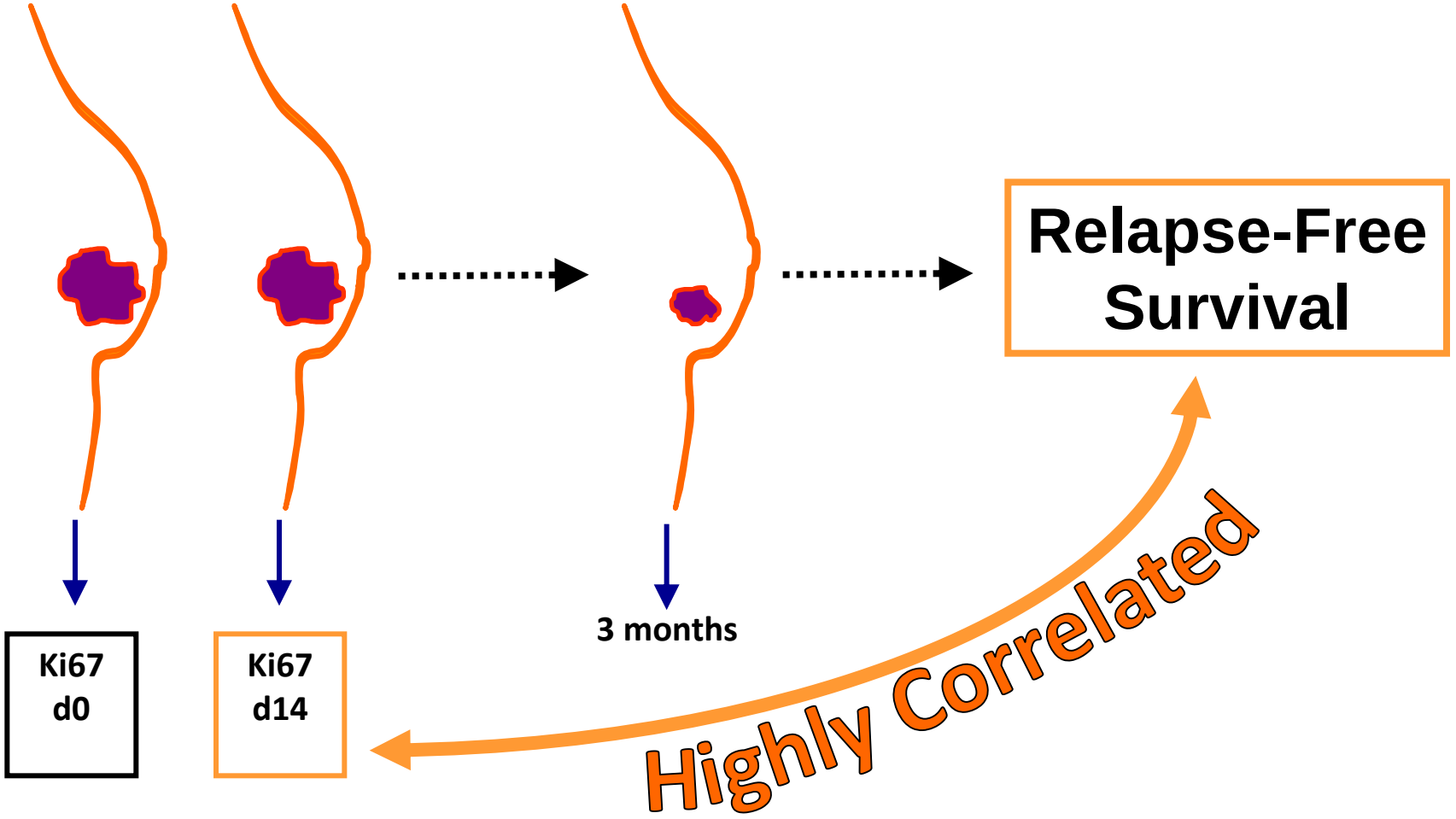
NOT confirmed in the large AI trials!

I. Smith

IMPACT Trial:

Tam vs Anastrozole vs Tam + Ana

M. Dowsett



Dowsett, JNCI 2007

2. TARGETED DRUGS

Lessons learned from neoadjuvant trials in the post-genomic era: predicting the success of new targeted agents

a) **Bevacizumab**

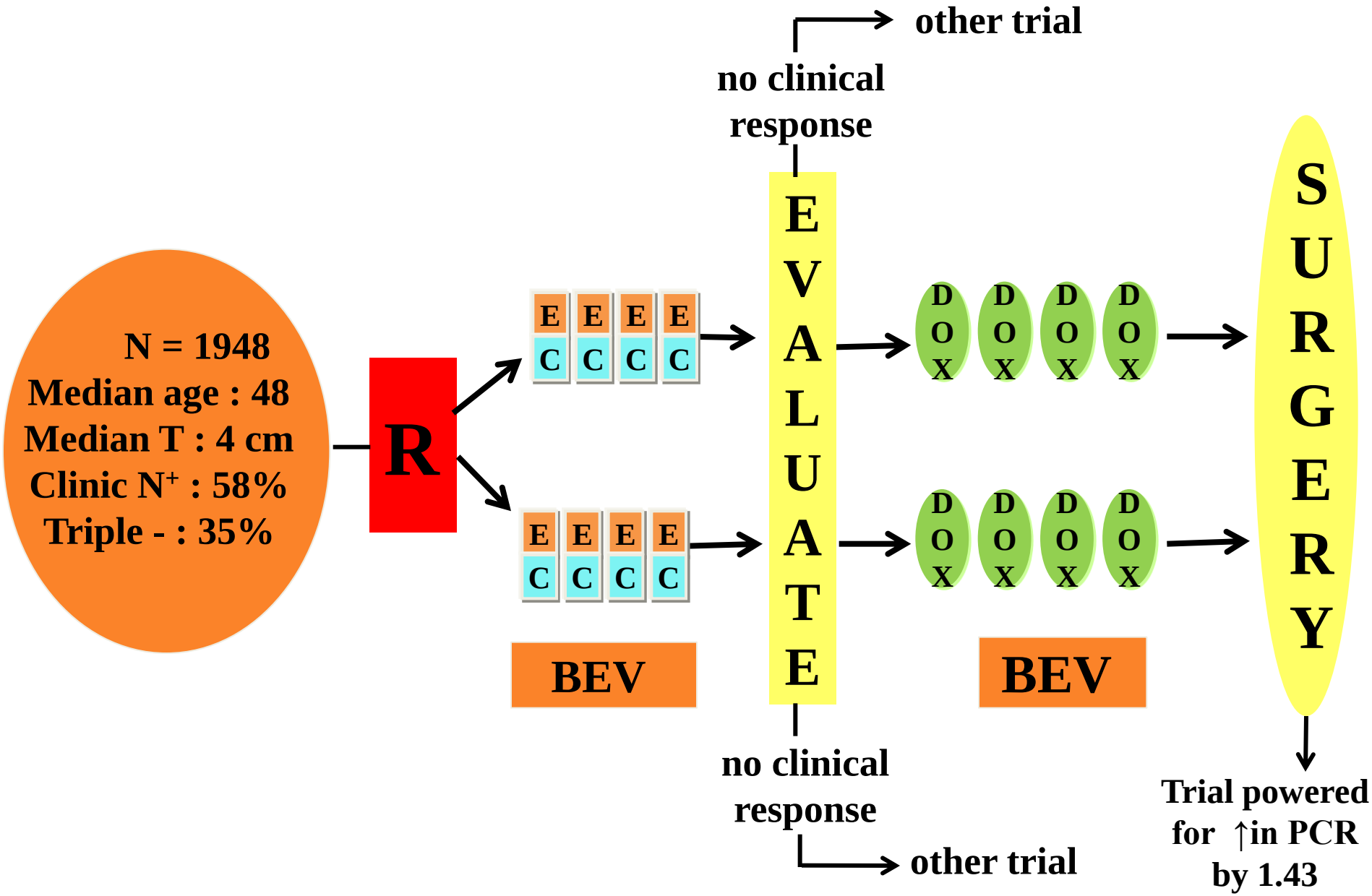
b) **Dual HER2 targeting**

Lessons learned from neoadjuvant trials in the post-genomic era

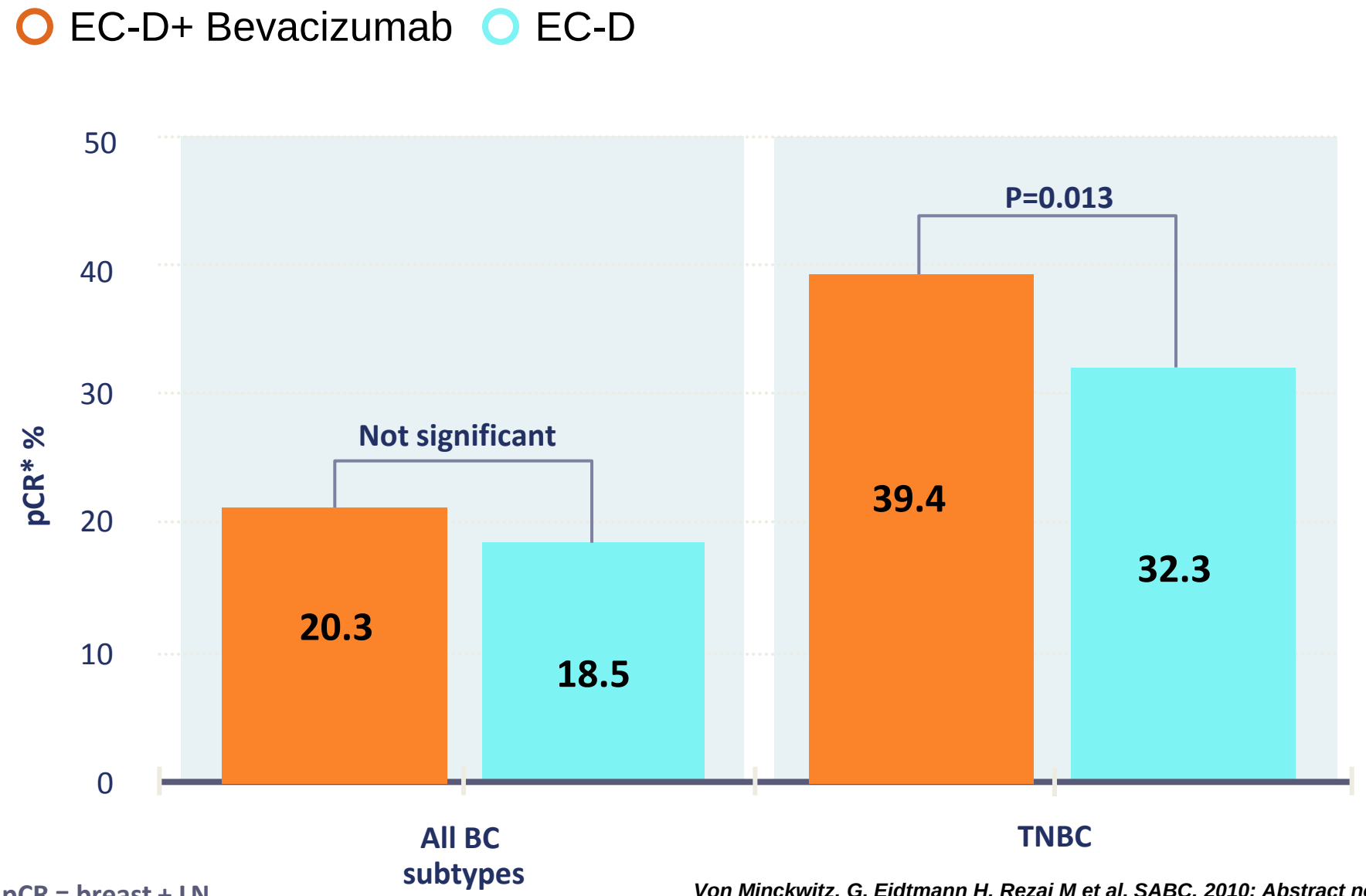
Predicting the success of new targeted agents…

and the subpopulation where the benefit will be substantial…

GEPARQUINTO trial in HER2 negative BC



Early signal in TNBC



*pCR = breast + LN

Von Minckwitz, G, Eidtmann H, Rezai M et al, SABC, 2010; Abstract no: S4-6

Gerber B, Eidtmann H, Rezai M et al, J Clin Oncol, 2011, 29(15_suppl):Abstract 1006

NSABP-B40

Neoadjuvant Bevacizumab in HER2 - BC
Phase III

Study dosing: q3w (4 cycles Docetaxel + 4 cycles AC)

Patients with operable HER2-BC

Chemo-naïve & primary tumors ≥2cm

N = 1206

RANDOMIZE

- **Bevacizumab Docetaxel → AC**
- **Docetaxel → AC**
- **Bevacizumab Xeloda +Docetaxel → AC**
- **Xeloda +Docetaxel → AC**
- **Bevacizumab Gemcitabine +Docetaxel → AC**
- **Gemcitabine+Docetaxel → AC**

SURGERY

- **Bevacizumab q3 wk x 10**
- **Bevacizumab q3 wk x 10**
- **Bevacizumab q3 wk x 10**

Neoadjuvant treatment

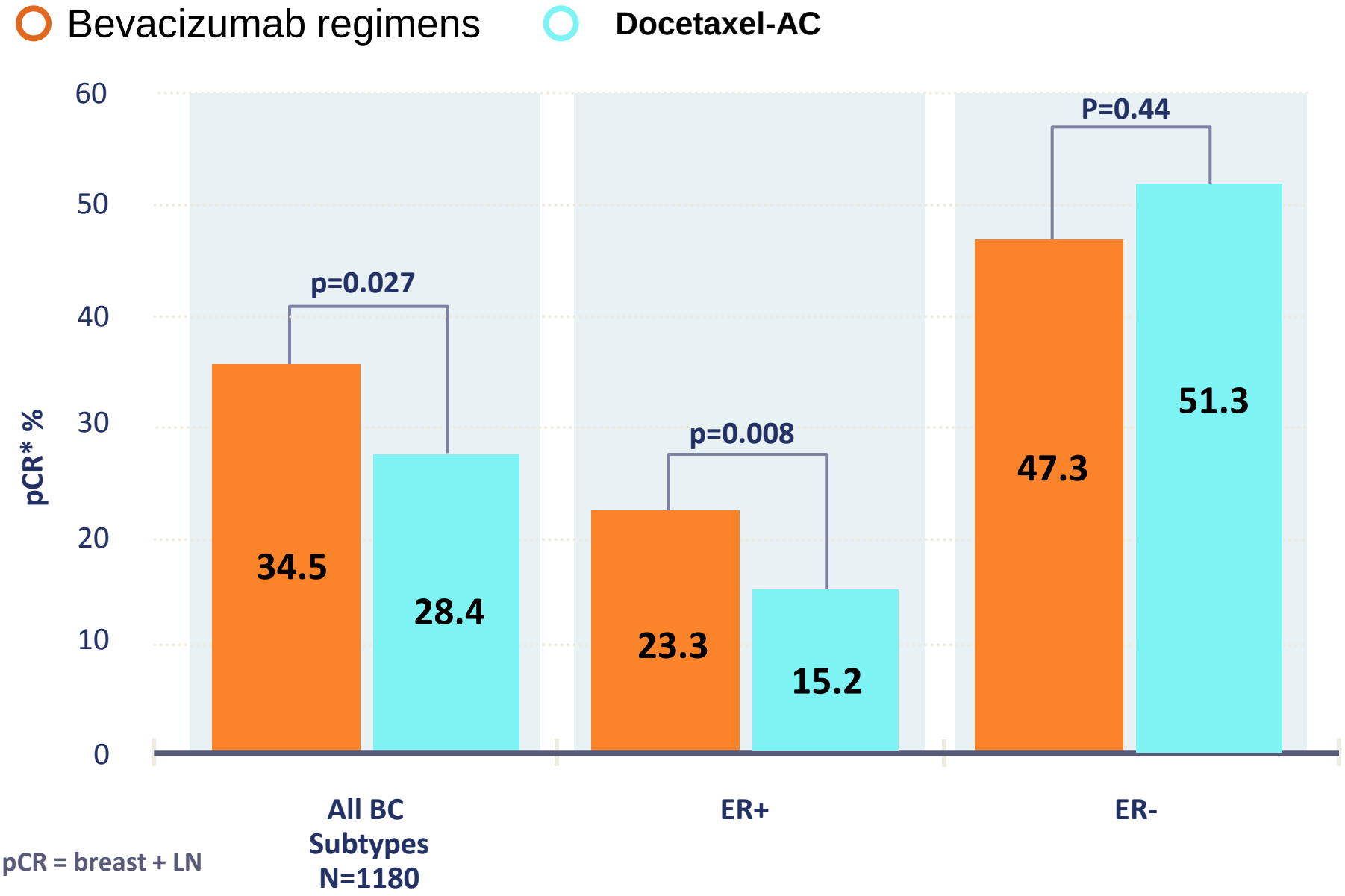
Adjuvant treatment

End points: pCR rate

AC, Adriamycin and cyclophosphamide

Bear HD, Tang G, Rastogi P, J Clin Oncol, 2011; 29 (suppl) Abstract LBA1005

EARLY SIGNAL IN HR+

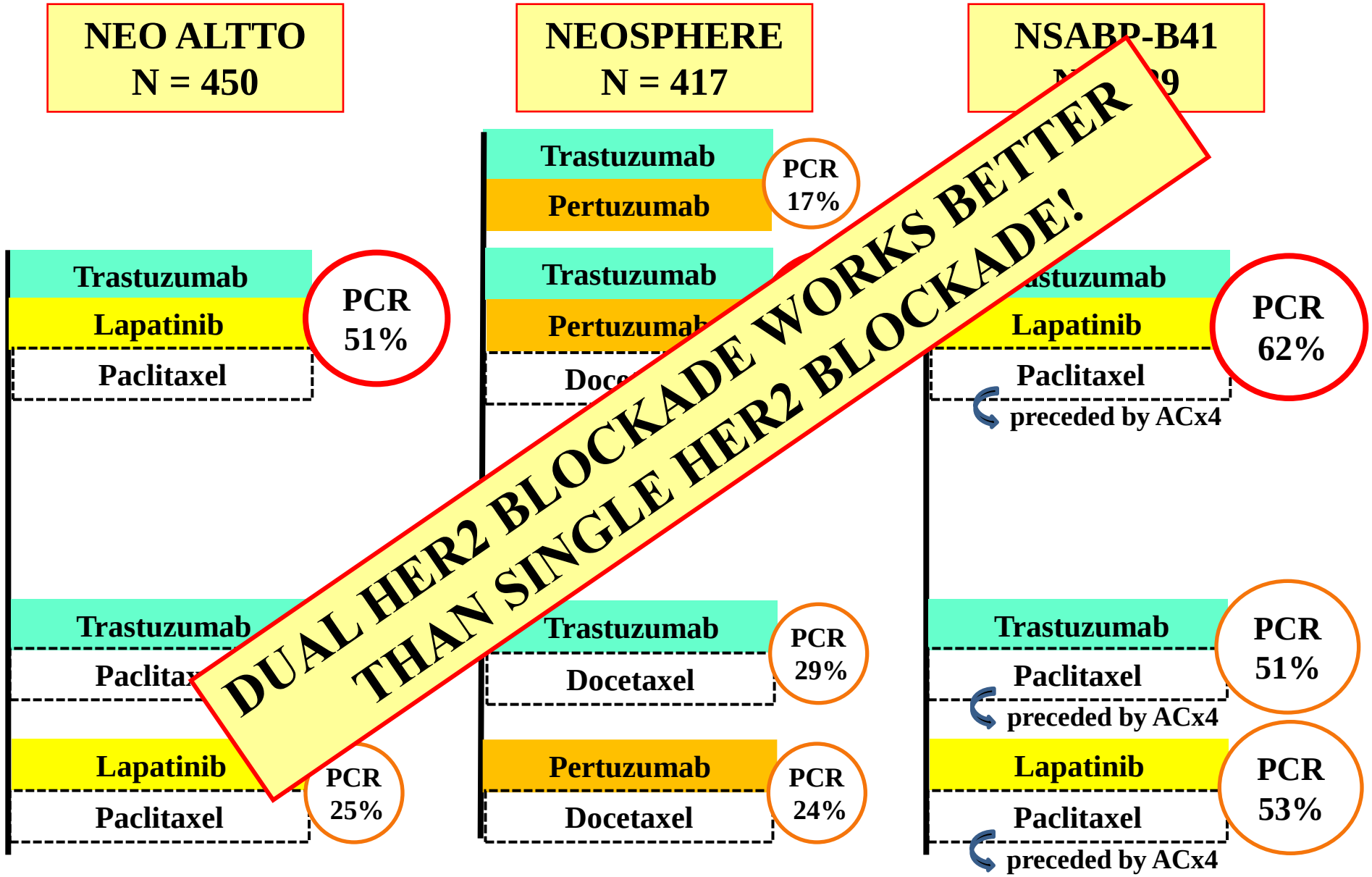


*pCR = breast + LN

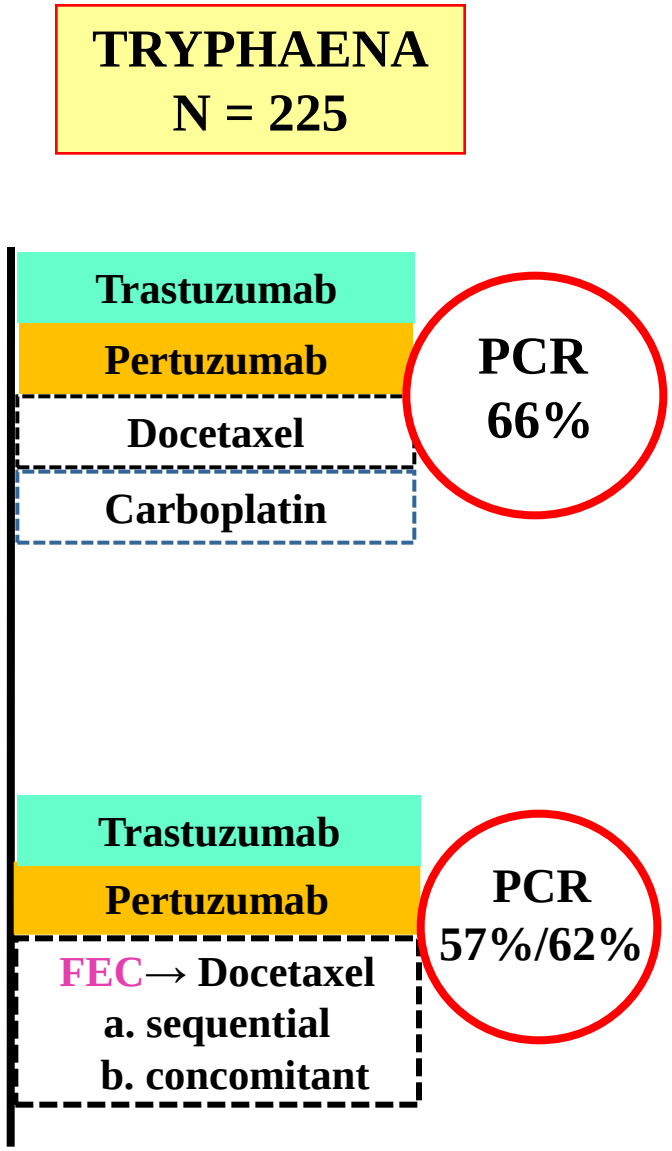
Neoadjuvant results with bevacizumab…

very confusing…and probably not helpful

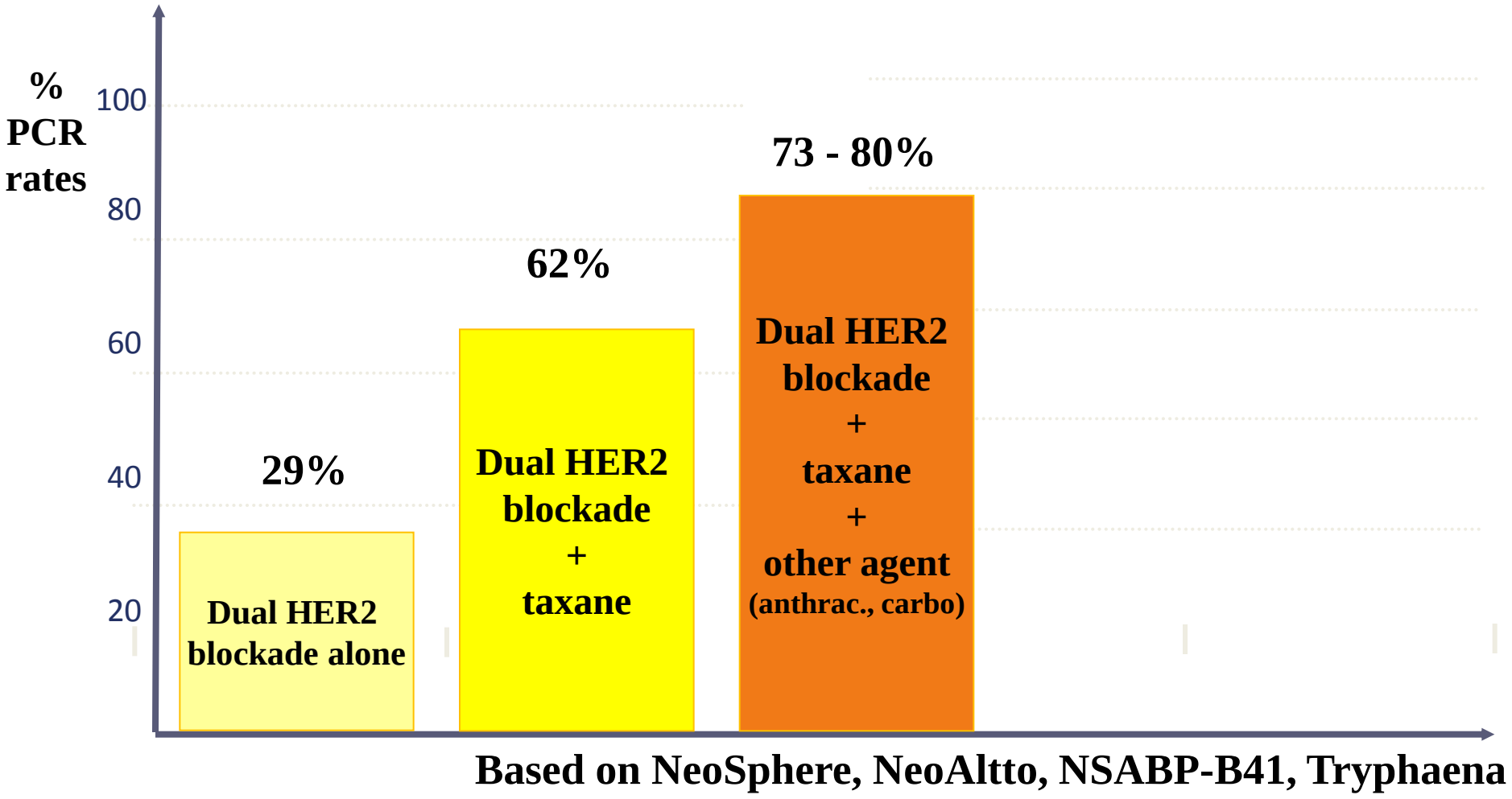
Lessons learned from neoadjuvant trials investigating dual HER2 blockade



Lessons learned from neoadjuvant trials investigating dual HER2 blockade



Results obtained with dual HER2 blockade alone or with chemotherapy in Hormone Receptor Negative Disease



HER2 positive B.C.

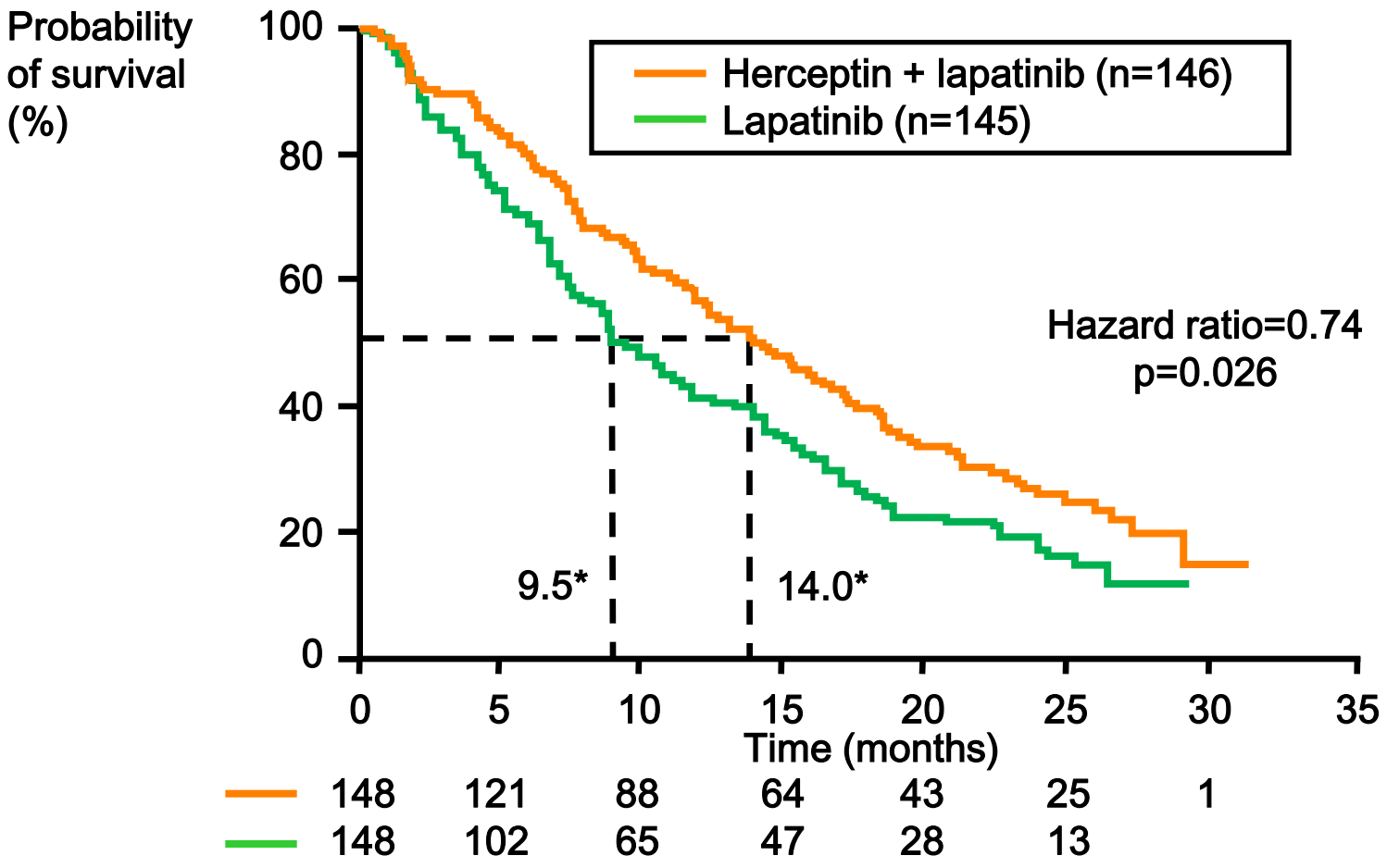
Neoadjuvant results with dual HER2 targeting :

- **Suggest that a subgroup of HER2 positive tumors, primarily HR negative, are exquisitely sensitive to dual HER2 blockade and may not need aggressive chemotherapy**

- **Are in line with results obtained in advanced BC**

- **Should predict the success of the strategy in the adjuvant setting… !**

EGF104900: significant OS benefit with Herceptin + lapatinib following disease progression



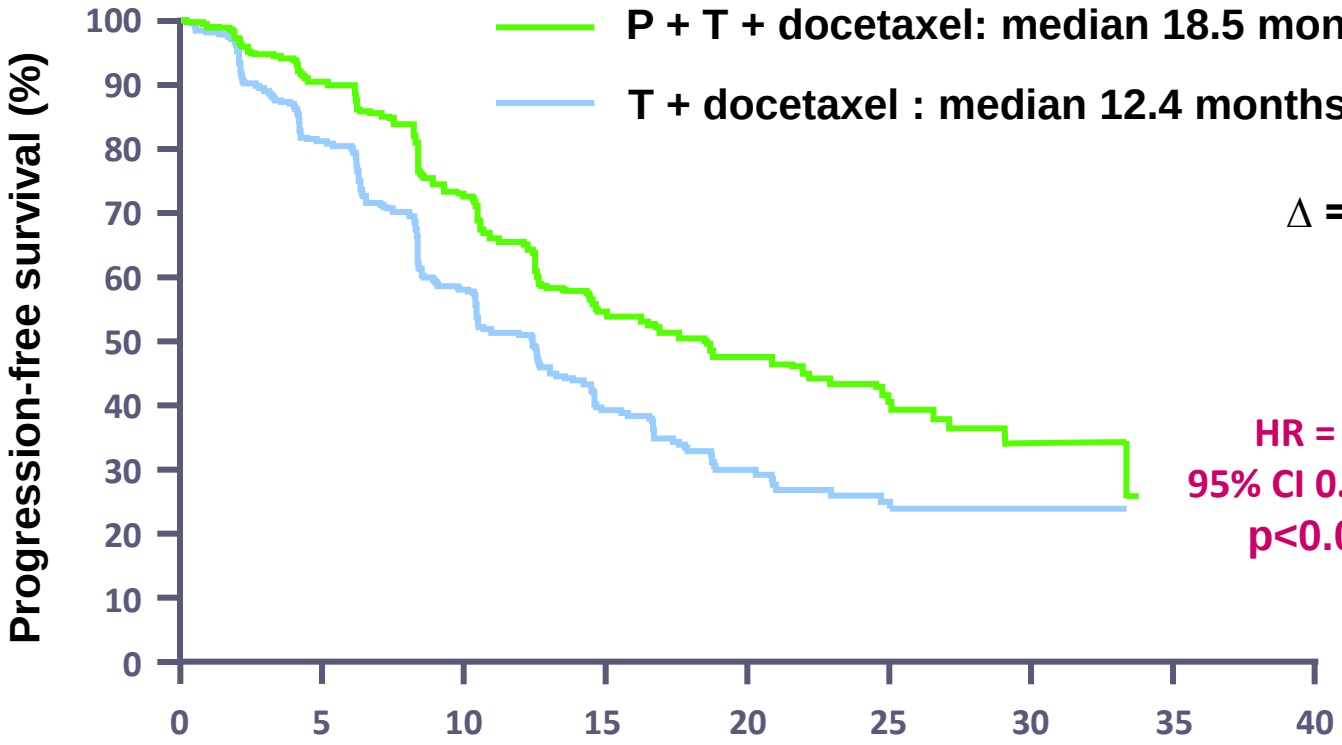
* Median OS (months)

Not within EMEA-approved indication for Herceptin

Blackwell et al 2010

Cleopatra trial in advanced HER2+ BC : pertuzumab plus trastuzumab superior to trastuzumab

Primary endpoint: Independently assessed PFS
n = 433 PFS events



n at risk

Ptz + T + D	402	345	267	139	83	32	10	0	0
Pla + T + D	406	311	209	93	42	17	7	0	0

D, docetaxel; PFS, progression-free survival; Pla, placebo; P, pertuzumab; T, trastuzumab

Baselga J, Kim S-B, Im S-A, et al, SABC, 2011; Abstract S5-5

THE ALTTO TRIAL

8000 women with HER2 positive breast cancer

Design 1 = sequential administration

CHEMOTHERAPY

Design 2 = concomitant administration

Trastuzumab x 1y

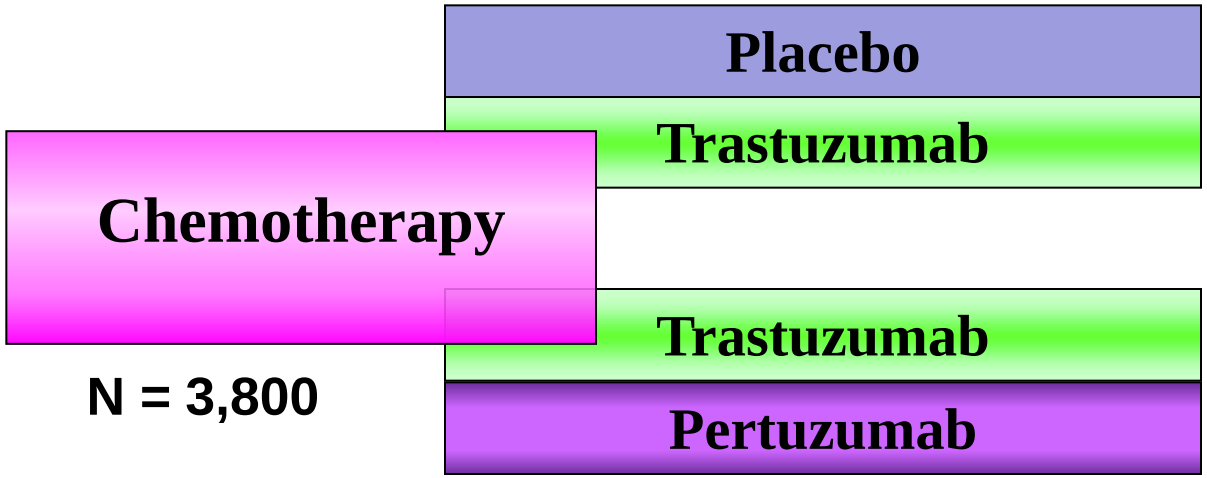
Lapatinib x 1y

Trastuzumab ↓ then lapatinib

Trastuzumab combined with lapatinib

THE NEW PIVOTAL BIG TRIAL FOR HER2+ BREAST CANCER:

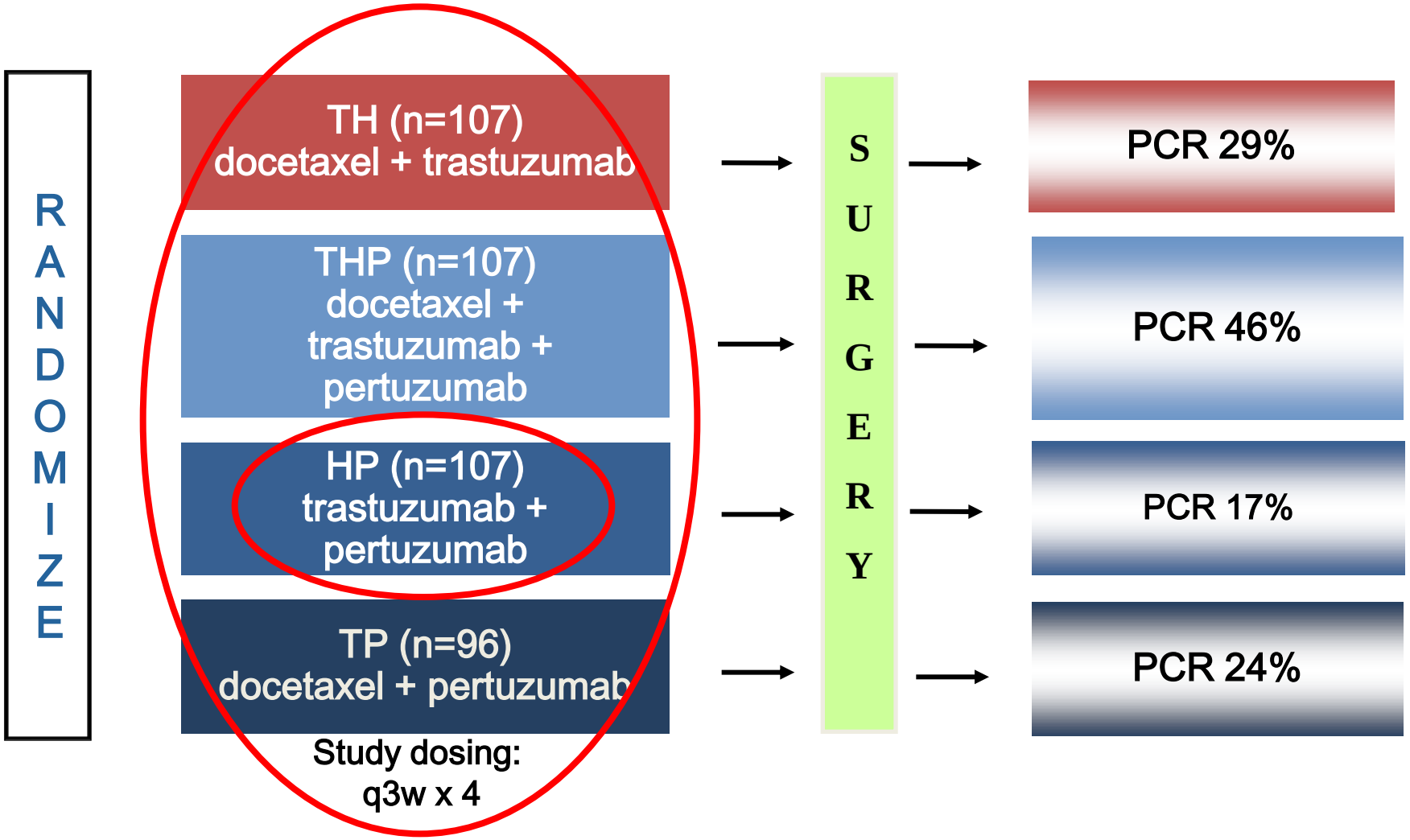
APHINITY



Lessons learned from neoadjuvant trials in the post-genomic era

Identifying clinically useful biomarkers of response…

NeoSPHERE study : N = 417 women



BC, breast cancer; FEC, 5-fluorouracil, epirubicin and cyclophosphamide
*Locally advanced=T2–3, N2–3, M0 or T4a–c, any N, M0; operable=T2–3, N0–1, M0; inflammatory = T4d, any N, M0
H, trastuzumab; P, pertuzumab; T, docetaxel

L. Gianni, SABCS 2010

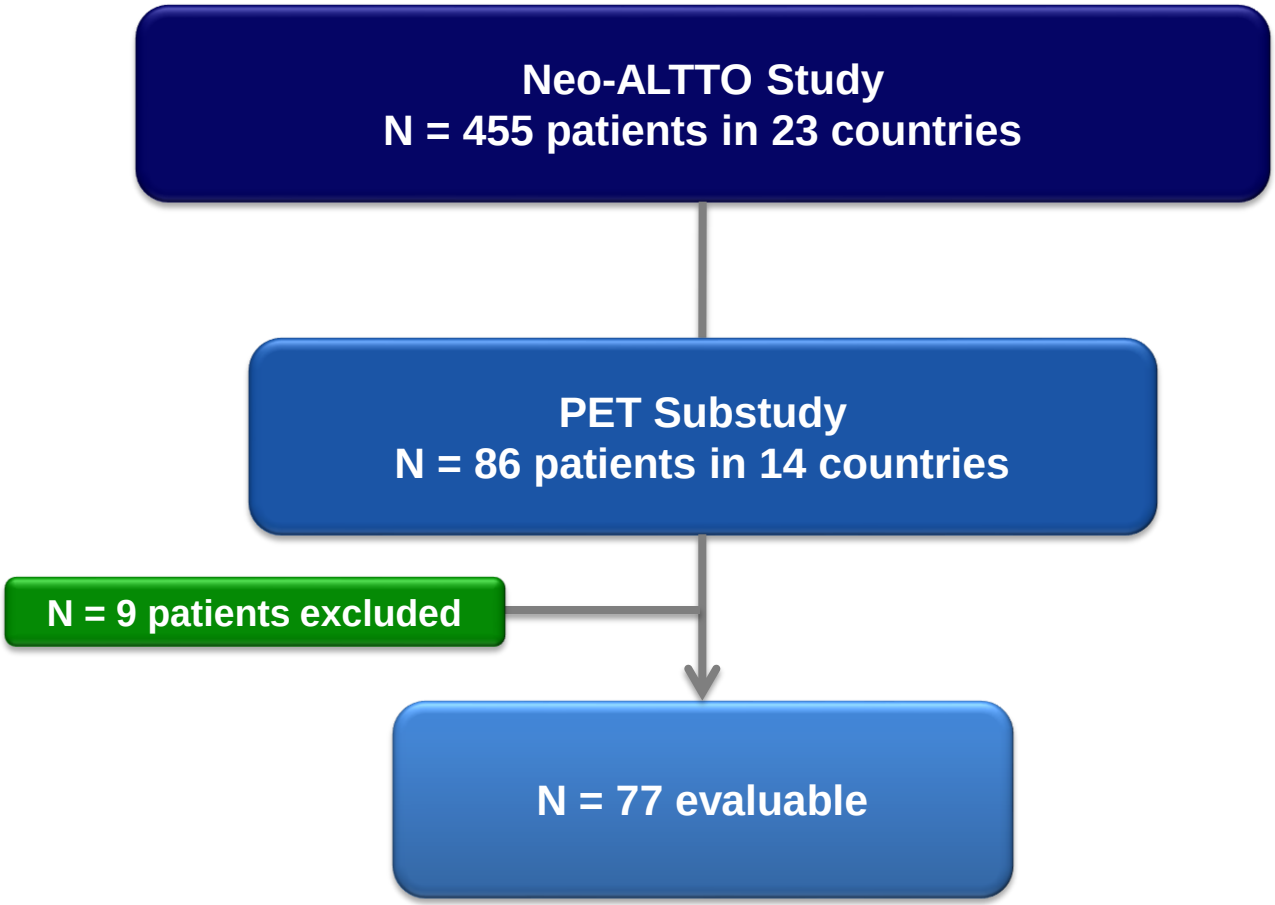
NEOSPHERE: huge biomarker (day 0) research eff

Assay method	Biomarker	
IHC	HER2 mem H-s	
	HER3 mem	377
	IGF1R	339
		373
		373
		299
		299
qRT-PCR		384
		384
	-CR	387
	EGFR-CR	377
	c-myc	275
ELI	sHER2 (ng/mL)	381
	Amphiregulin (pg/mL)	384
	TGF-alpha (pg/mL)	384
	EGF (pg/mL)	384
Mutational analyses	PIK3CA mutation	273

None of these markers found to be clinically useful!!!

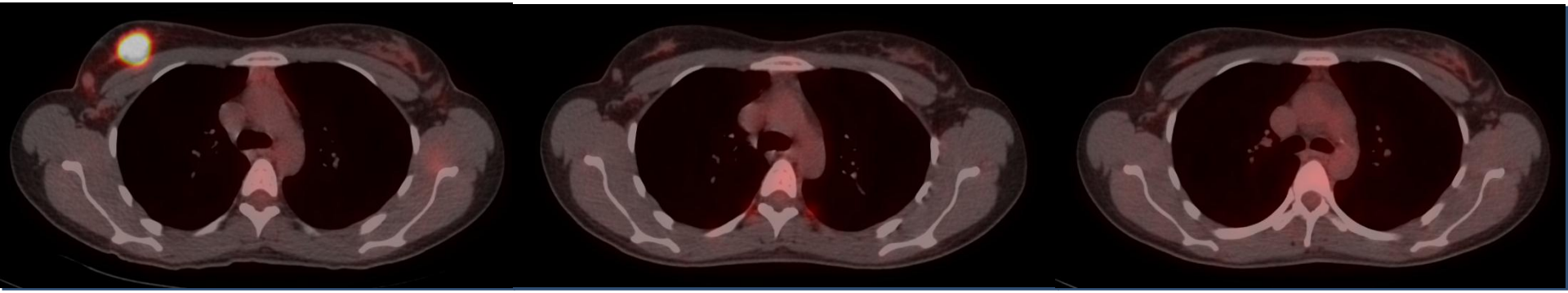
Courtesy L. Gianni, SABCS 2011

NEO ALTTO PET imaging substudy



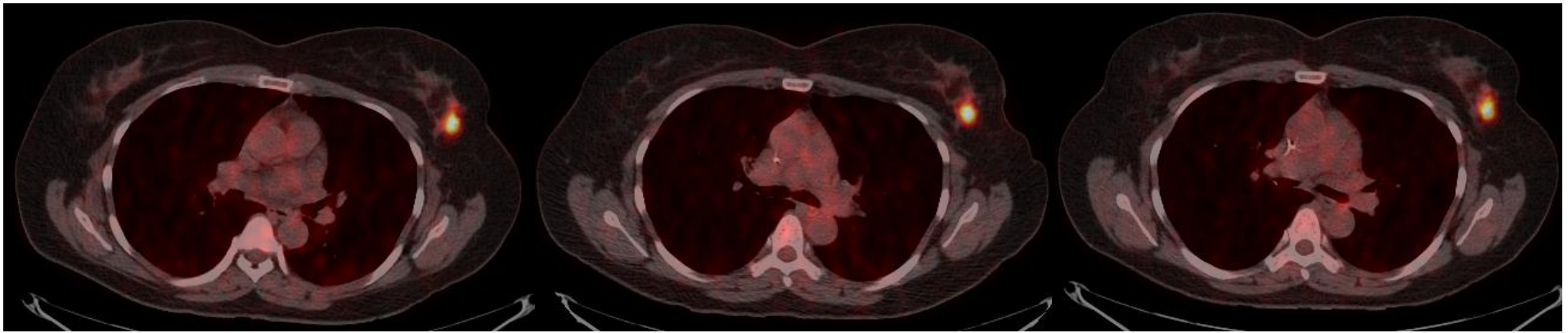
Metabolic Responder…

BASELINE | WEEK 2 | WEEK 6

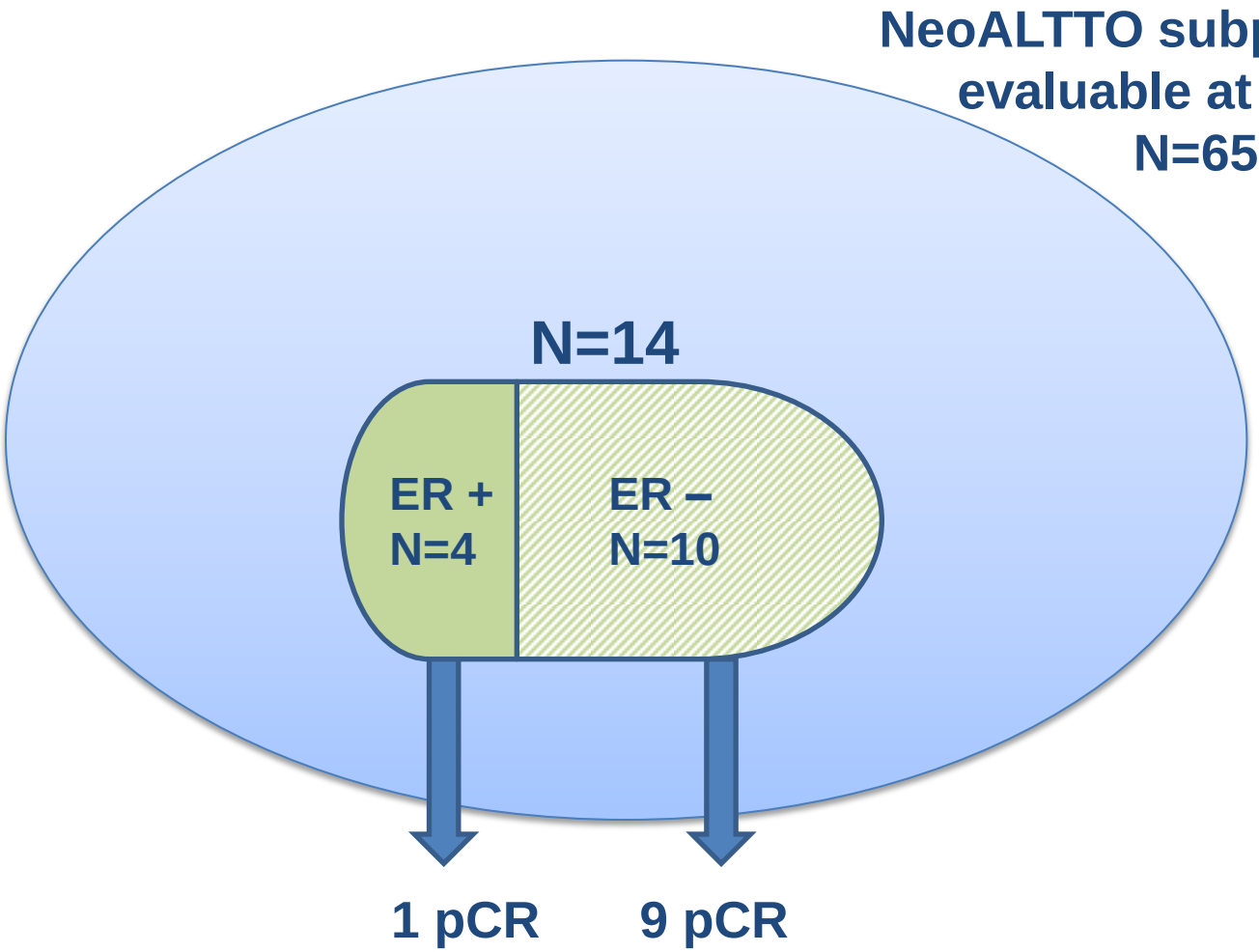


… and metabolic non-responder

BASELINE | WEEK 2 | WEEK 6



Complete Metabolic Response at week 6



Apparent higher rate of complete metabolic responses – linked to higher pCR probability – in ER negative HER2+ patients

Lessons learned from neoadjuvant trials

Conclusions

1. **In general, neoadjuvant trials are a very efficient tool to screen for new active drugs…**

2. **Biomarker research remains highly challenging, poorly efficient and needs new models of collaboration**

3. **Neoadjuvant trials contribute to an improved understanding of the disease…**
   …but do not tell the whole story !









BIG
BREASTINTERNATIONALGROUP

The Breat International Group Board Members


THANK YOU!

BACK-UP

CHALLENGES

Long, complex and resource intensive
→ $400-900 million
→ >10 years

High attrition rate in the later phases
→ 5% to marketing

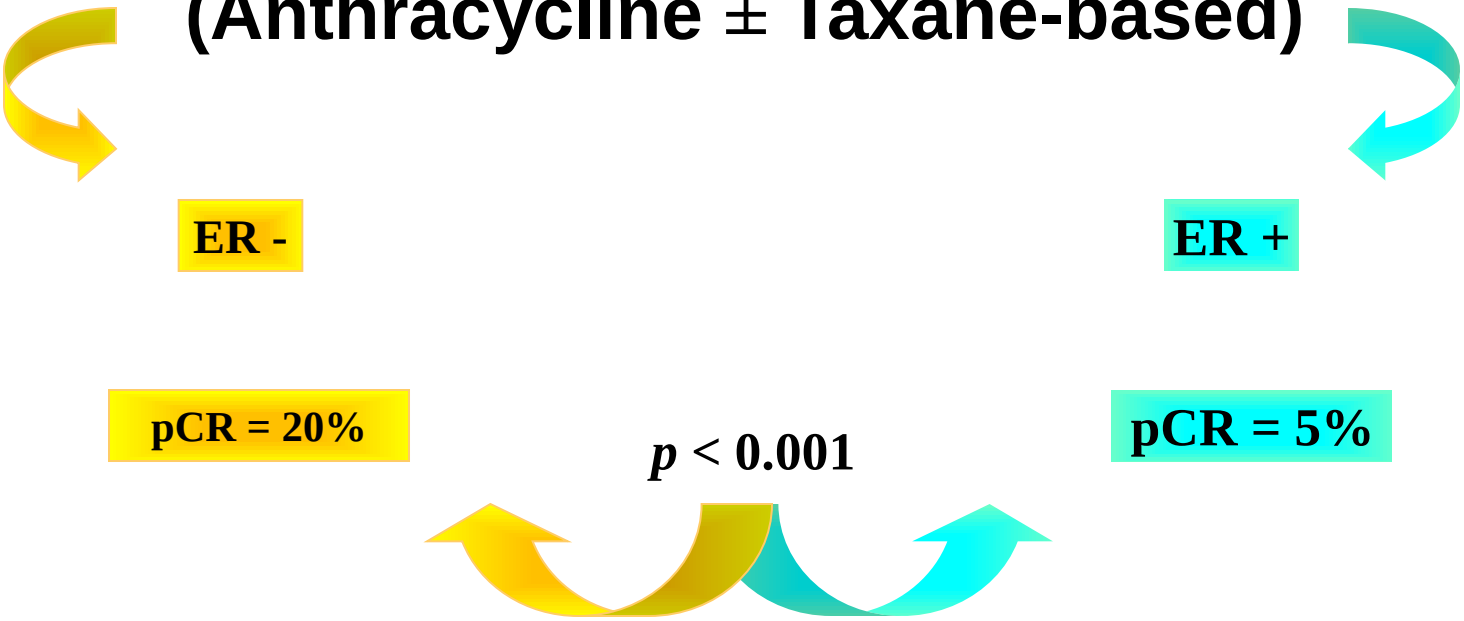
Drug Development Process

Many Bottlenecks

<u>For Patients</u>:
***Delayed* access and more *expensive* therapies**

PATHOLOGICALLY COMPLETE RESPONSE TO CHEMOTHERAPY IS RELATED TO HORMONE RECEPTOR STATUS : THE MD ANDERSON EXPERIENCE

N=1,018 women
receiving 6 preoperative CT regimens
(Anthracycline ± Taxane-based)



Buzdar, San Antonio, 2003

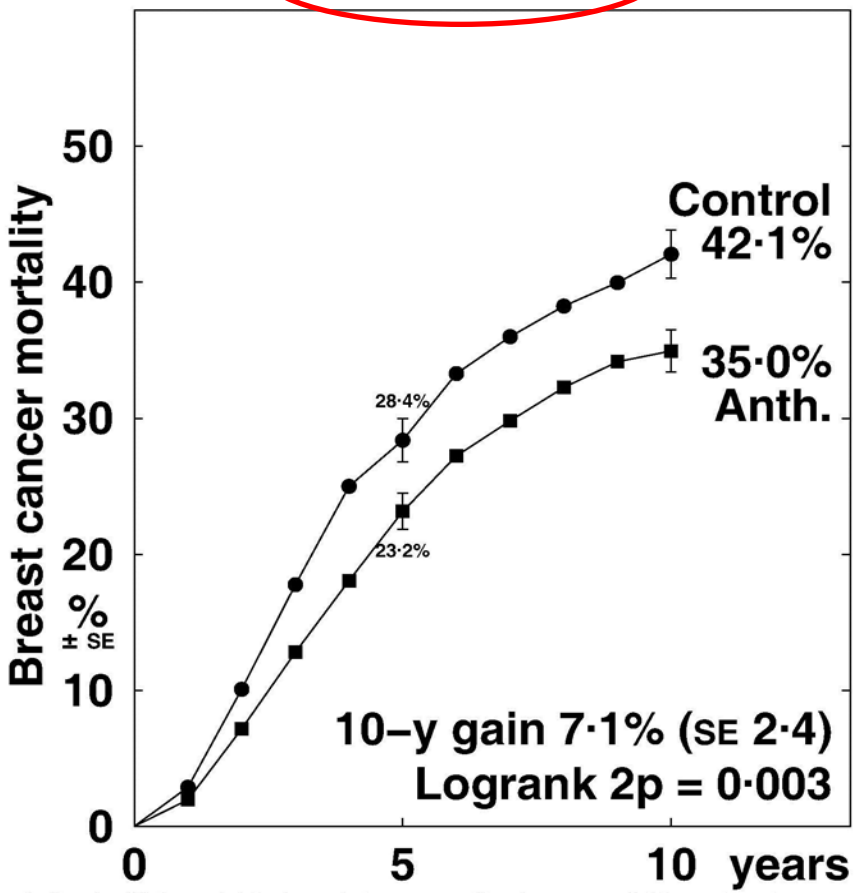
Caution: is pCR a good « surrogate marker » of survival in ER positive B.C. ?

Anthracycline-based regimen vs. No chemotherapy

Anthracycline–based regimen vs. No chemotherapy

BREAST CANCER MORTALITY

ER–poor



Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

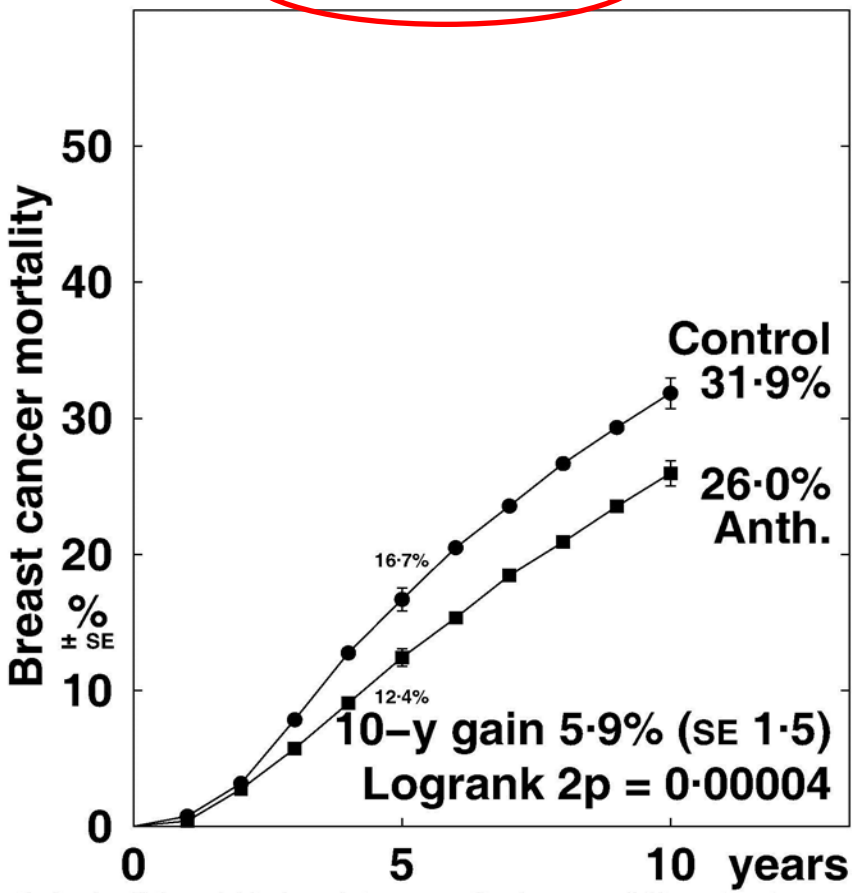
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anth.	5·01 SE 0·33	3·46 SE 0·33	2·67 SE 0·36
Control	6·85 SE 0·42	4·56 SE 0·43	2·96 SE 0·41
Rate ratio, from (O–E) / V	0·77 SE 0·08 −28·3 / 107·3	0·79 SE 0·13 −11·2 / 48·6	0·98 SE 0·20 −0·5 / 24·1

18:39:50 29 September 2010
Not for publication or citation

Anthracycline–based regimen vs. No chemotherapy

BREAST CANCER MORTALITY

ER+

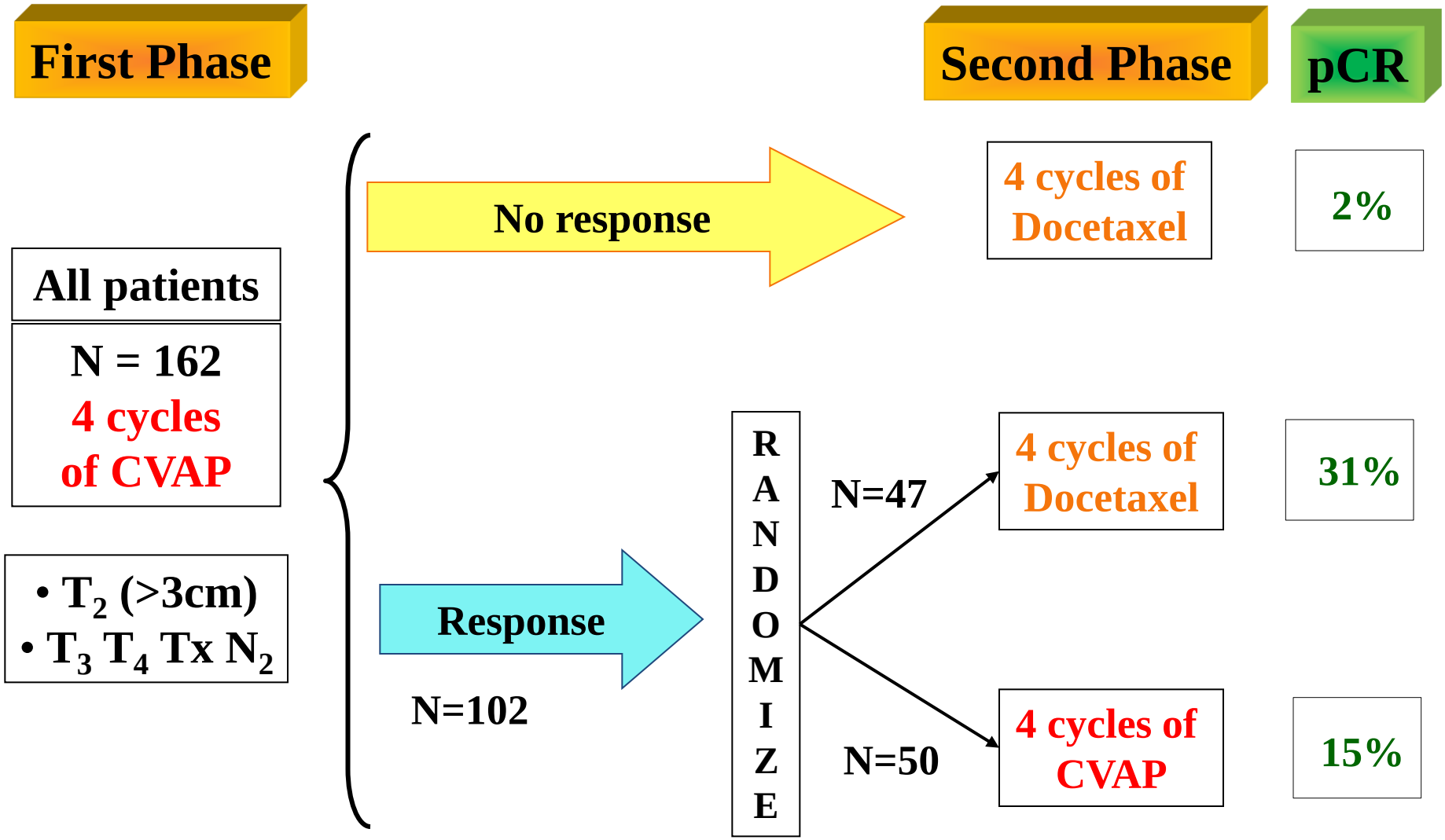


Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anth.	2·63 SE 0·14	3·44 SE 0·19	3·01 SE 0·26
Control	3·61 SE 0·19	4·13 SE 0·26	3·05 SE 0·30
Rate ratio, from (O–E) / V	0·72 SE 0·07 −49·2 / 151·2	0·83 SE 0·08 −22·6 / 119·2	0·97 SE 0·14 −1·7 / 47·2

EBCTCG September 2010

ABERDEEN NEOADJUVANT STUDY (I)



Hutcheon AW, San Antonio 2003

PREOPERATIVE ENDOCRINE THERAPY DOUBLE BLIND STUDIES

CLINICAL

Letrozole (L) vs Tamoxifen (T)	Anastrozole (A) vs Tamoxifen (T)
M. ELLIS (N=324)	M. DOWSETT (N=330)
• Higher response rate with L • Higher rate of breast conservation with L	• Similar response rate • Trend for higher rate of breast conservation with A
Did predict for the results of BIG 01-98	Did predict for the results of ATAC

NEOADJUVANT PACLITAXEL → FAC WEEKLY VERSUS Q3 WEEKS

Pathologic Complete Response

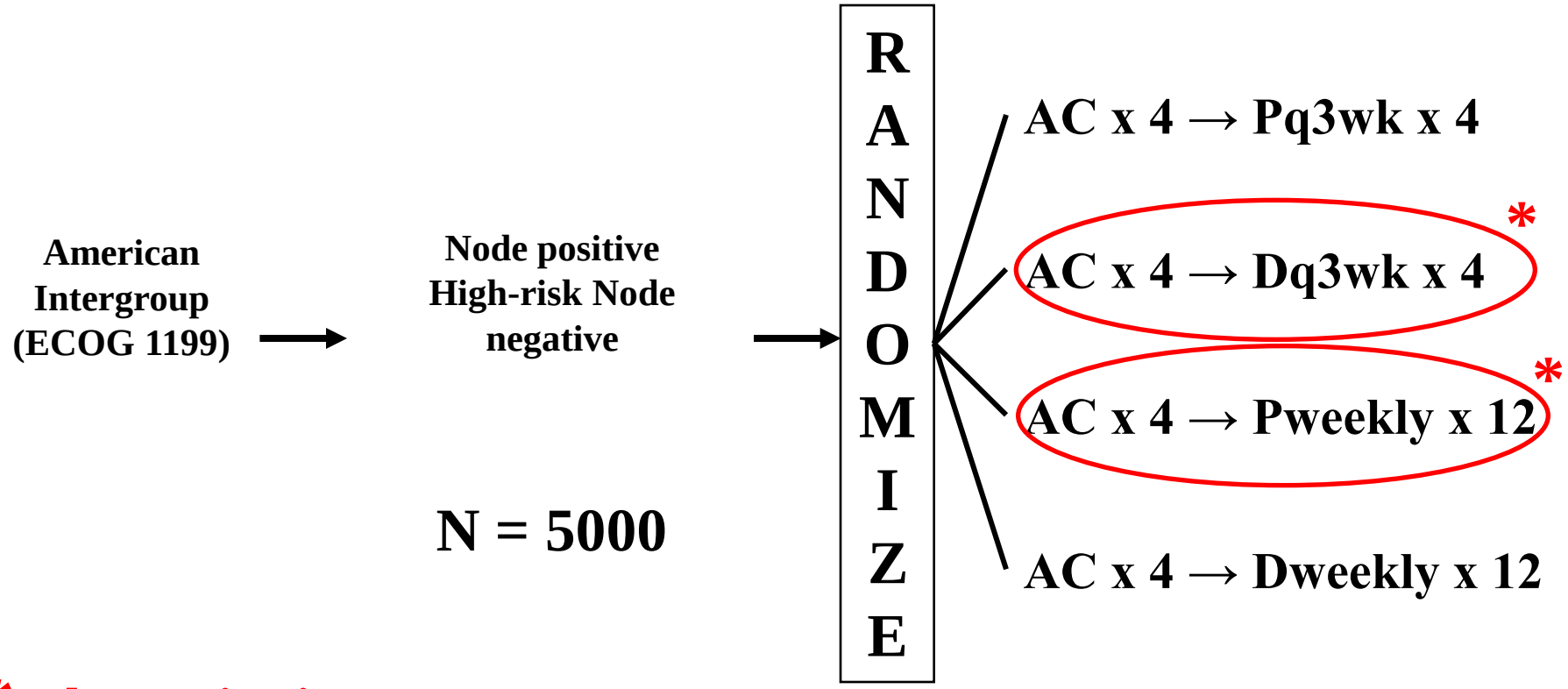
	Node positive		Node Negative	
	Weekly (n=50)	Q3 weeks (n=51)	Weekly (n=68)	Q3 weeks (n=67)
PCR	28.0%	13.7%	29.4%	13.4%

P < 0.01*

*** Weekly versus q3 weeks/clinical nodal status**

Green MC, ASCO 2002

SECOND GENERATION OF RANDOMIZED CLINICAL TRIALS
DOCETAXEL (D) VERSUS PACLITAXEL (P)
3-WEEKLY versus WEEKLY ADMINISTRATION



* The « winning arms » !

A Note of CAUTION

Which is correct?

GeparQuinto
Bevacizumab achieves higher pCR rates in TNBC

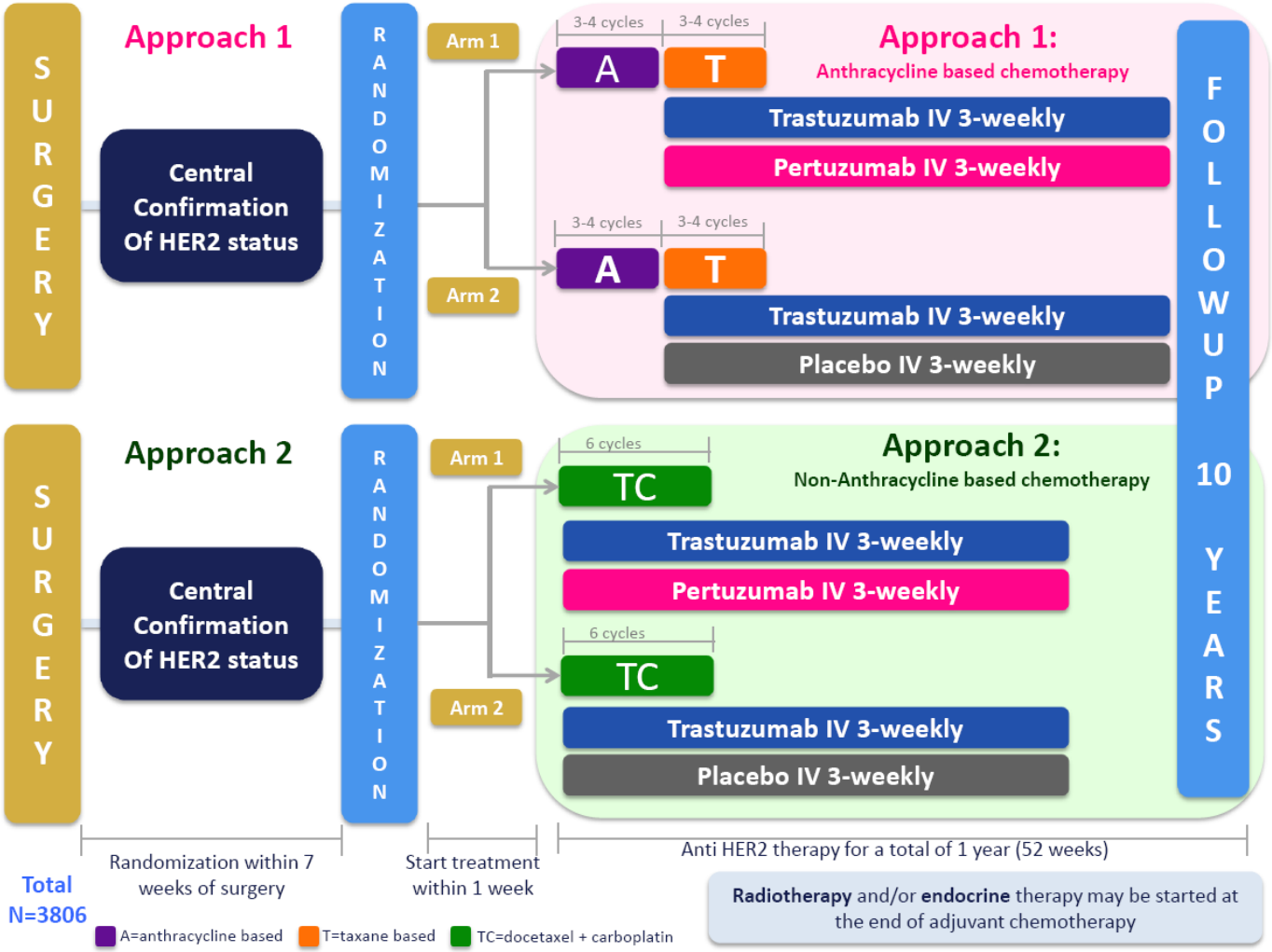
NSABP-40
Bevacizumab achieves higher pCR rates in ER+

Early signal & guide to adjuvant therapies

HER2+ EBC

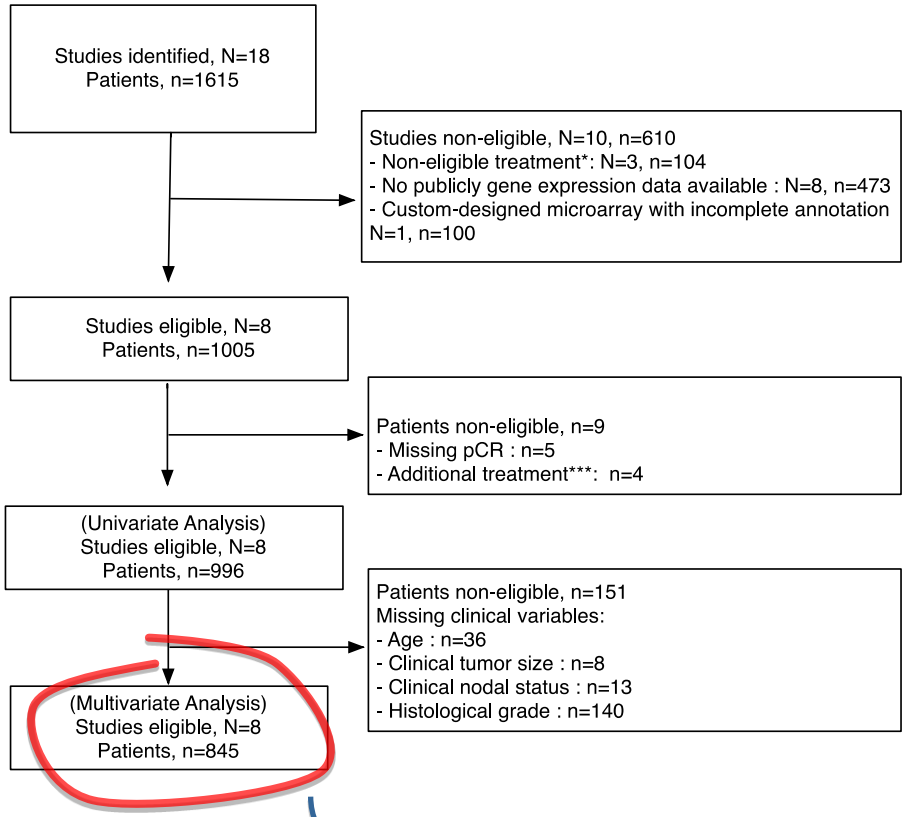
The APHINITY Study: Adjuvant Pertuzumab and Herceptin in Initial Therapy

BIG 4-11 / BO25126 / TOC4939g



www.clinicaltrials.gov, NCT01358877

Pooled analysis of gene expression studies to predict neoadjuvant (taxanes and/or anthracyclines) chemotherapy response



Several molecular processes (including immune signatures) and molecular pathways

? Response to chemotherapy

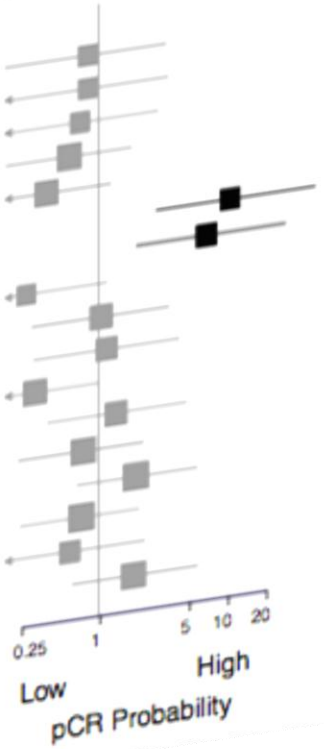
M Ignatiadis

Mainly seen in HER2+ and ER-/HER2- BC

HER2+

(N=118 pts; pCR=42)

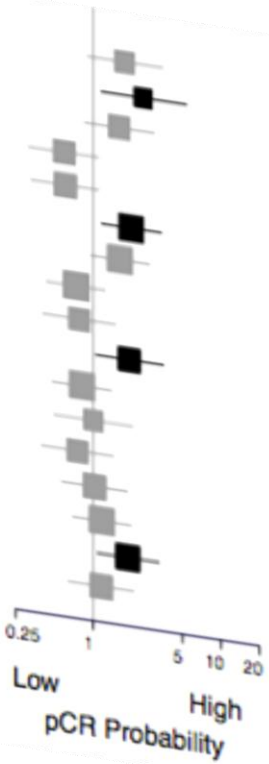
	OR	95% CI	P	FDR
GGI	0.86	(0.25,2.72)	8.0E−01	8.7E−01
Gene70	0.85	(0.24,2.8)	8.0E−01	8.7E−01
CIN70	0.76	(0.22,2.41)	6.4E−01	8.4E−01
Stroma1	0.65	(0.25,1.62)	3.5E−01	7.5E−01
Stroma2	0.46	(0.17,1.19)	1.2E−01	4.0E−01
Immune1	7.13	(2.38,25.51)	1.0E−03	1.8E−02
Immune2	5.01	(1.77,16.35)	4.1E−03	3.5E−02
RAS_Bild	0.34	(0.09,1.12)	8.7E−02	3.7E−01
MAPK	1.04	(0.37,2.84)	9.4E−01	9.4E−01
PTEN	1.13	(0.38,3.31)	8.2E−01	8.7E−01
AKTmTOR	0.39	(0.14,0.99)	5.4E−02	3.1E−01
PIK3CA	1.3	(0.47,3.69)	6.2E−01	8.4E−01
IGF1	0.79	(0.3,1.94)	6.2E−01	8.4E−01
SRC	1.74	(0.73,4.33)	2.2E−01	6.1E−01
MYC	0.77	(0.31,1.82)	5.6E−01	8.4E−01
E2F3	0.65	(0.21,1.97)	4.5E−01	8.4E−01
BetaCatenin	1.68	(0.68,4.35)	2.7E−01	6.5E−01



ER-/HER2-

(N=394 pts; pCR=120)

	OR	95% CI	P	FDR
GGI	1.59	(0.91,2.81)	1.0E−01	2.2E−01
Gene70	2.11	(1.12,4.03)	2.2E−02	1.6E−01
CIN70	1.47	(0.88,2.47)	1.4E−01	2.7E−01
Stroma1	0.65	(0.38,1.08)	9.7E−02	2.2E−01
Stroma2	0.66	(0.4,1.08)	9.9E−02	2.2E−01
Immune1	1.76	(1.13,2.76)	1.3E−02	1.6E−01
Immune2	1.49	(0.96,2.31)	7.4E−02	2.2E−01
RAS_Bild	0.77	(0.5,1.19)	2.4E−01	4.1E−01
MAPK	0.81	(0.47,1.38)	4.3E−01	5.7E−01
PTEN	1.71	(1.04,2.85)	3.7E−02	1.6E−01
AKTmTOR	0.84	(0.54,1.3)	4.3E−01	5.7E−01
PIK3CA	1	(0.55,1.8)	9.9E−01	9.9E−01
IGF1	0.79	(0.46,1.34)	3.8E−01	5.7E−01
SRC	1.02	(0.62,1.65)	9.5E−01	9.9E−01
MYC	1.13	(0.73,1.75)	5.7E−01	6.9E−01
E2F3	1.67	(1.06,2.67)	2.9E−02	1.6E−01
BetaCatenin	1.12	(0.69,1.82)	6.4E−01	7.3E−01



M Ignatiadis

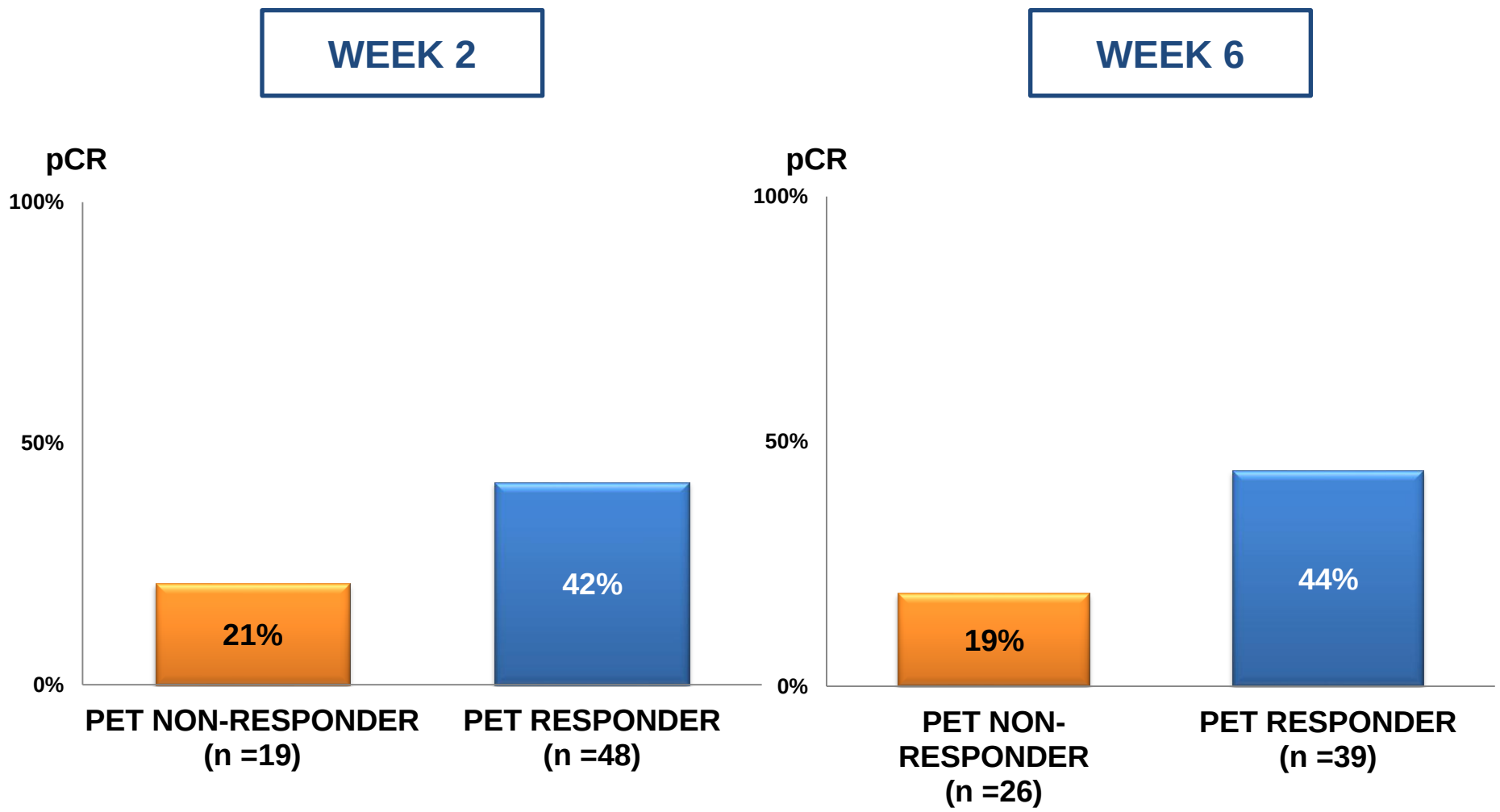
Lessons learned from neoadjuvant trials in the post-genomic era

2. Identifying clinically useful biomarkers of response…

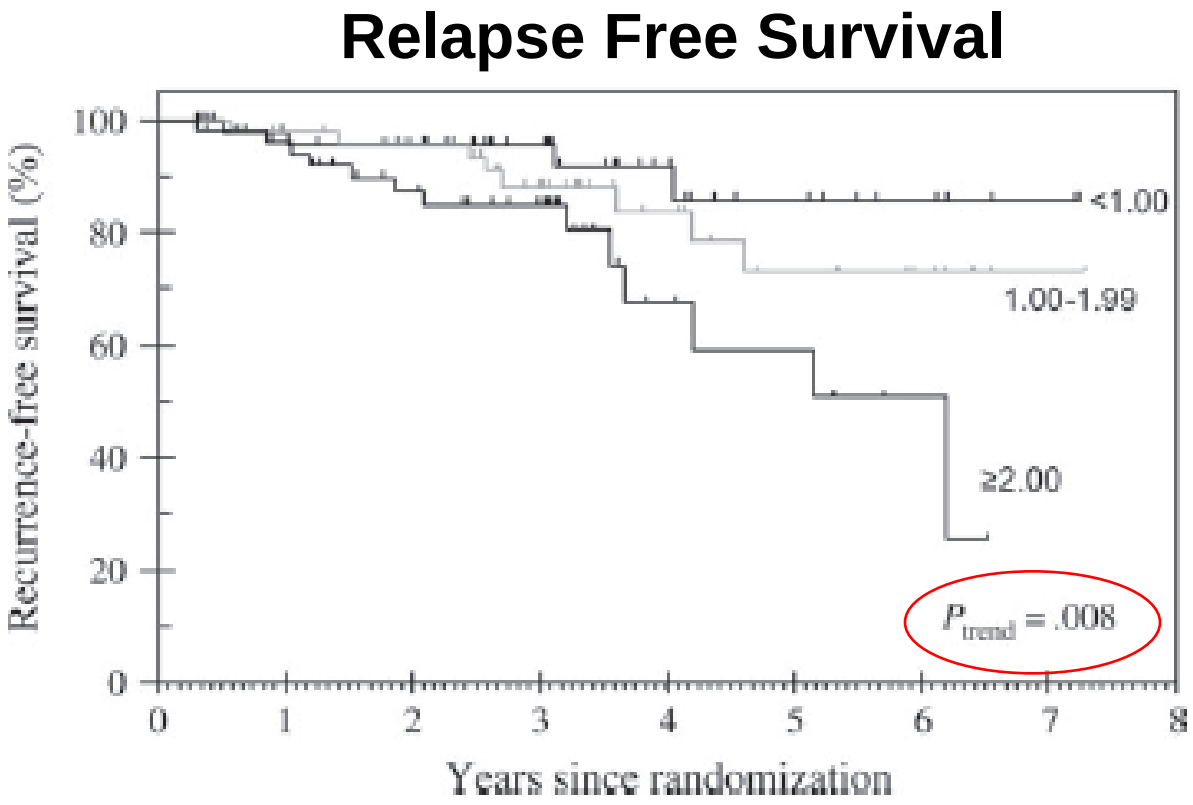
→ to chemotherapy

→ to targeted drugs

pCR by Metabolic Response in Primary Tumor



Absolute value of day 14 Ki67 is prognostic



Day 14 Ki67

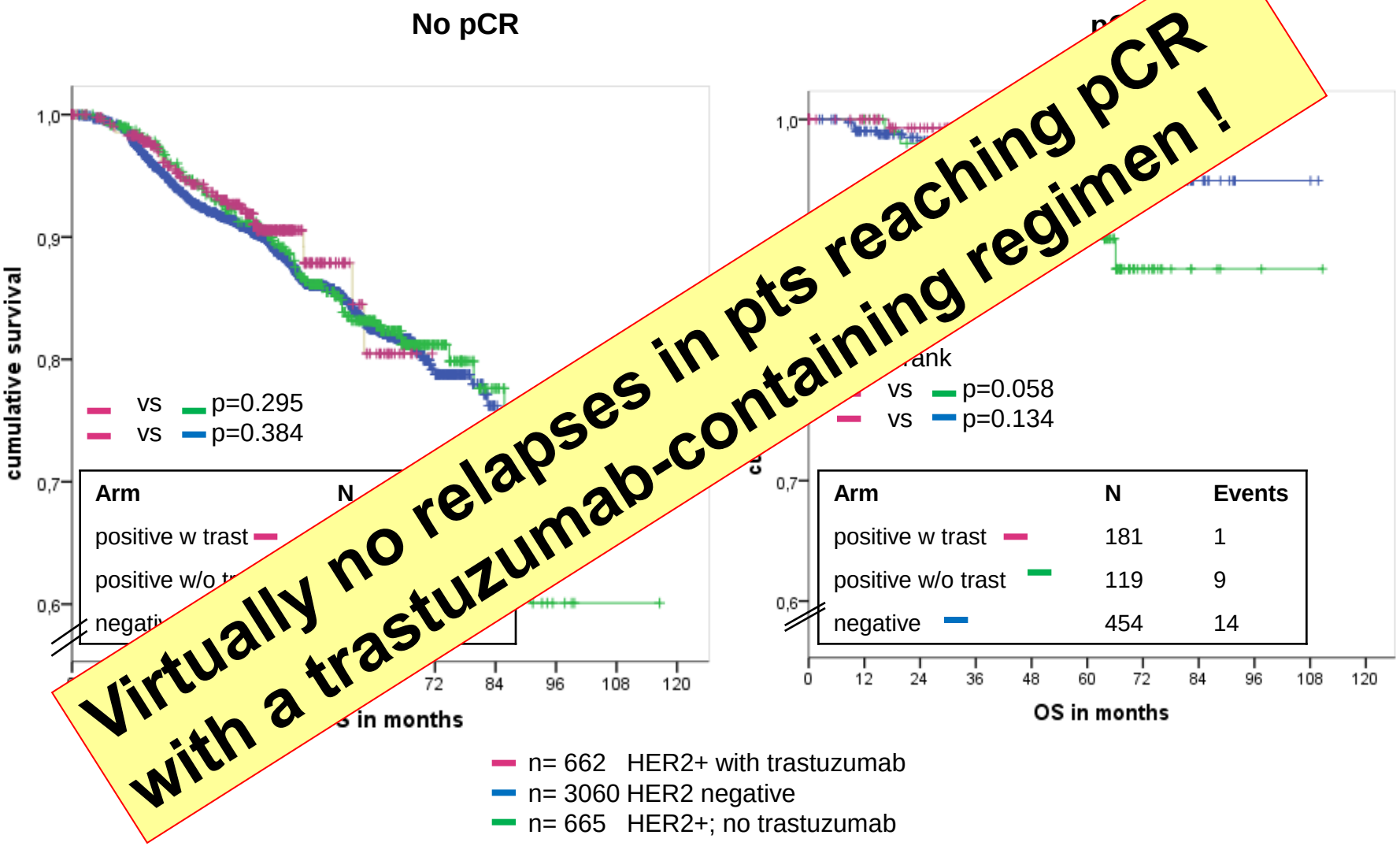
<2.7%

2-7-7.3%

>7.3%

Dowsett et al. JNCI 2007

OS analysis by pCR

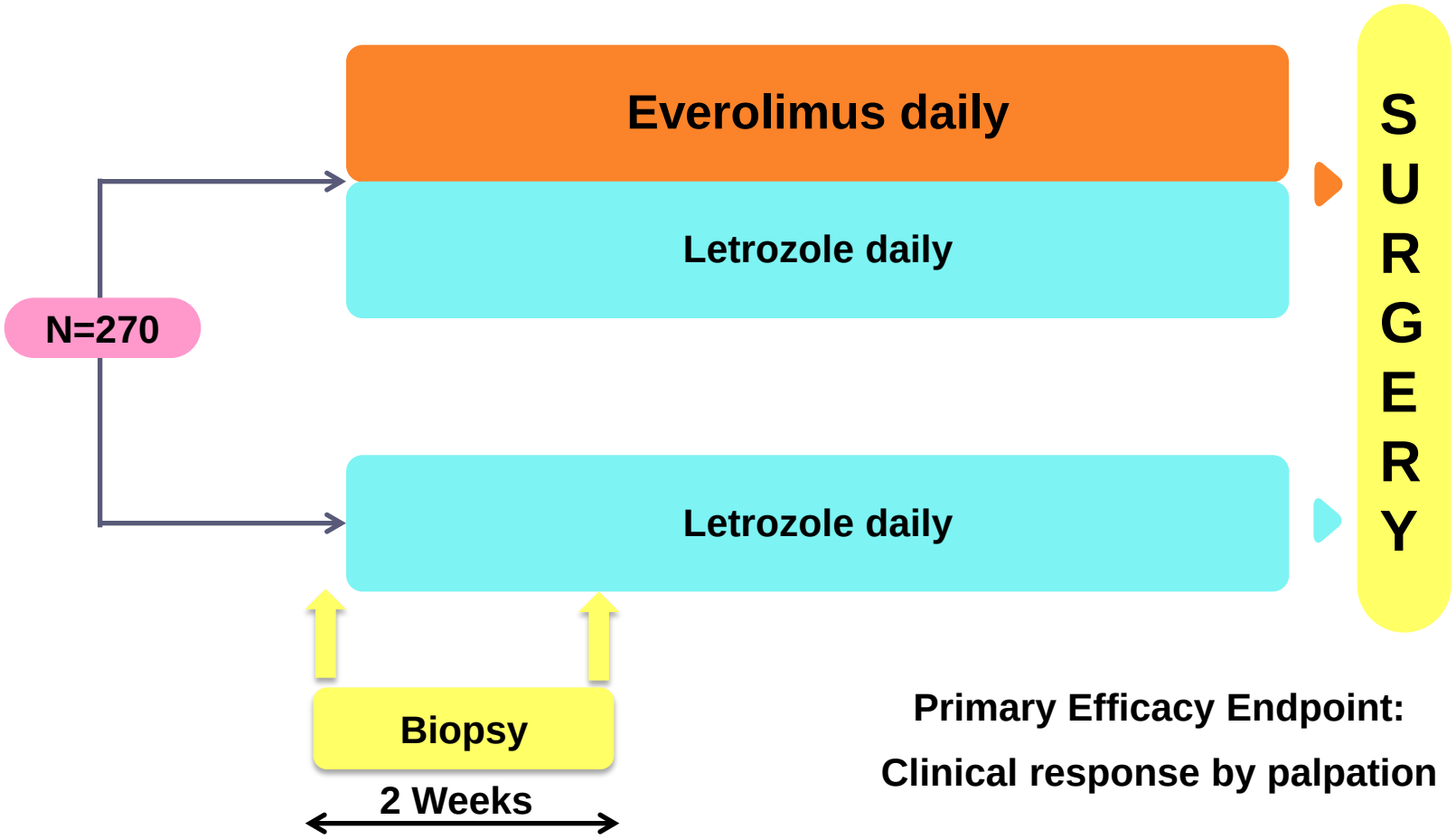


Virtually no relapses in pts reaching pCR with a trastuzumab-containing regimen !

Lessons learned from neoadjuvant trials in the post-genomic era

The neoadjuvant letrozole ± Everolimus study

Randomized 1:1, 2-Arm, Open-Label, Multicenter Trial

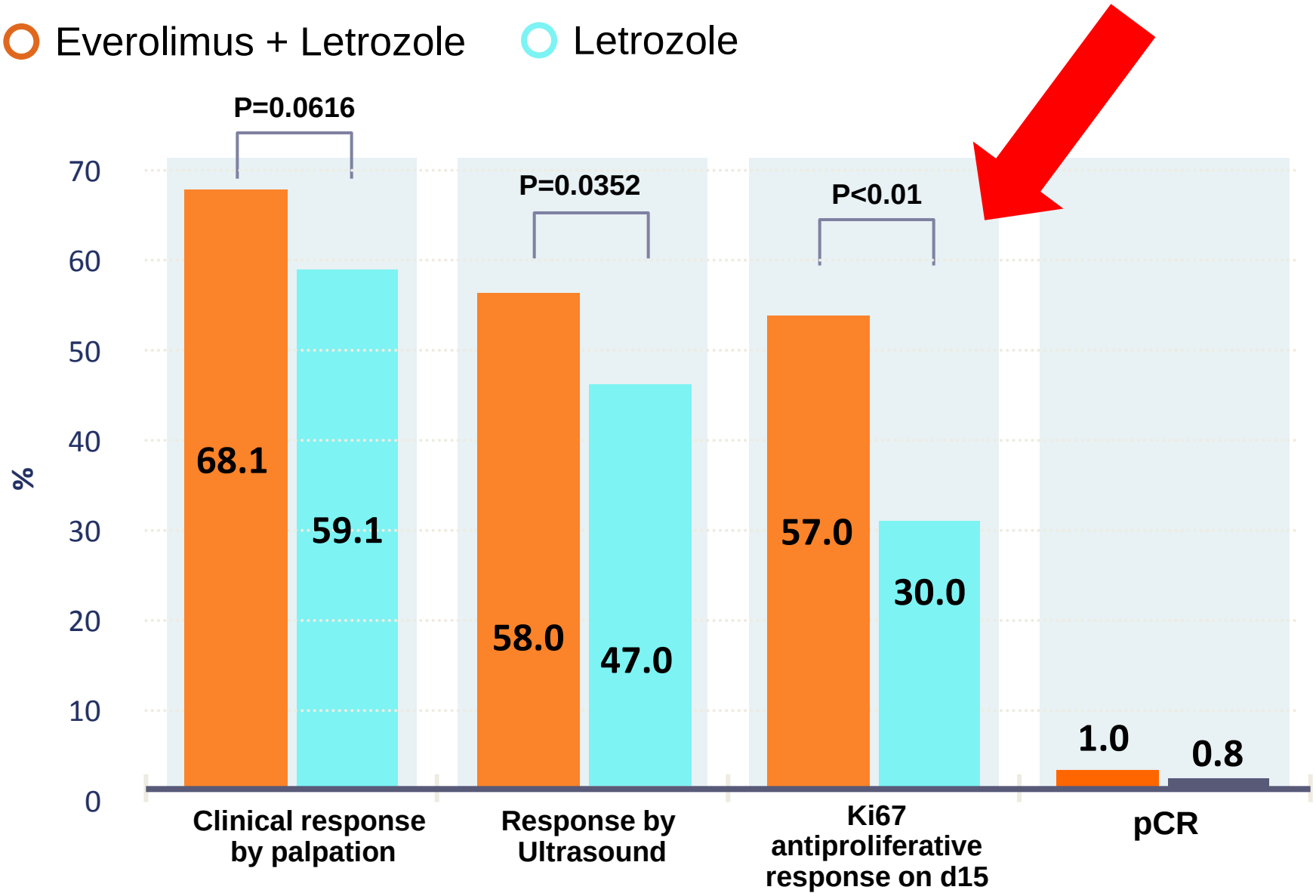


Primary Efficacy Endpoint:

Clinical response by palpation

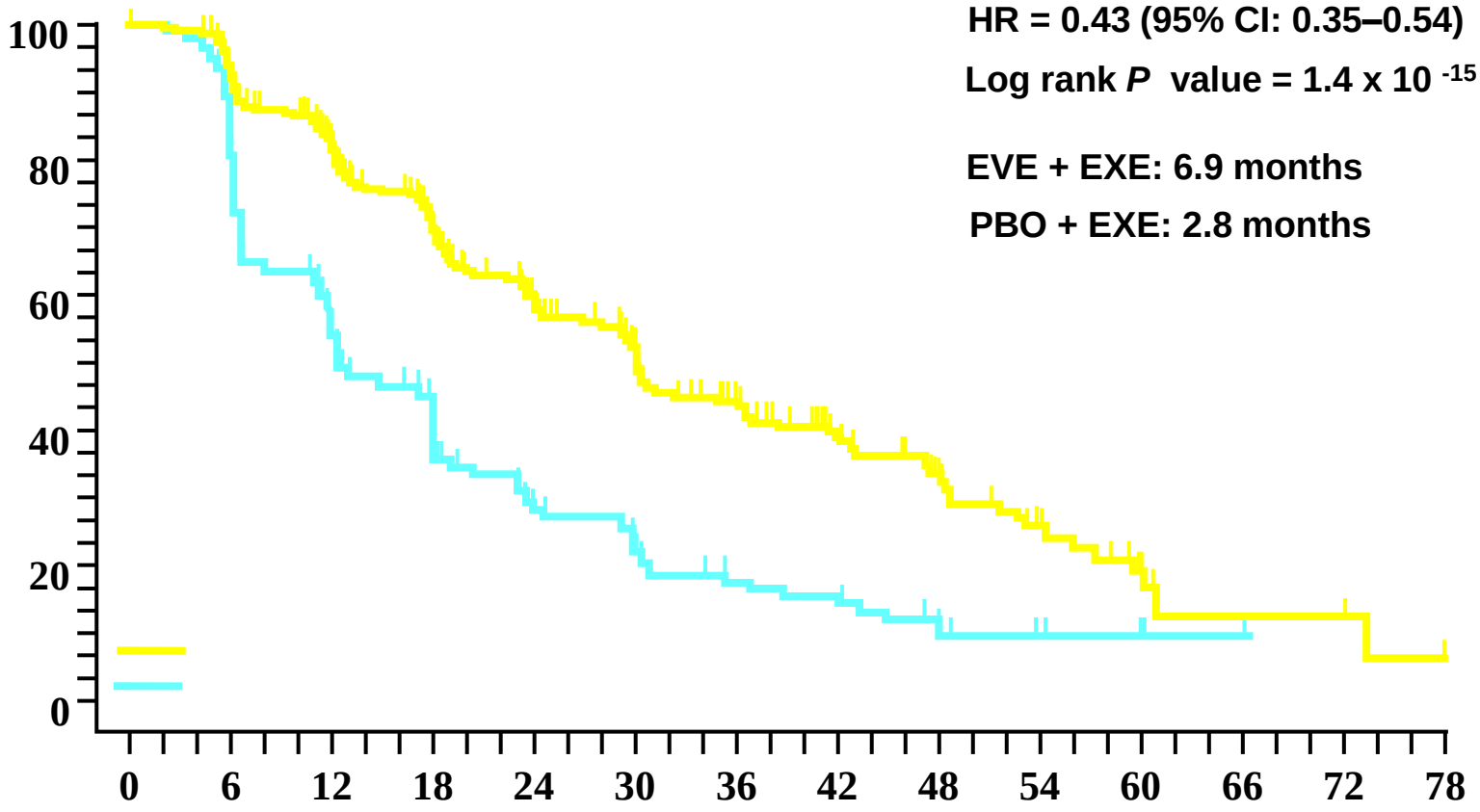
Baselga J, Semiglazov V, van Dam P et al, J Clin Oncol, 2009; 27(16):2630-2637

mTOR inhibitor + Letrozole versus Letrozole



(significance threshold P≤0.10)

BOLERO-2 Primary Endpoint: PFS Local Assessment



No. of Patients Still at Risk:

Everolimus	485	398	294	212	144	108	75	51	34	18	8	3
Placebo	239	177	109	70	36	26	16	14	9	4	3	1

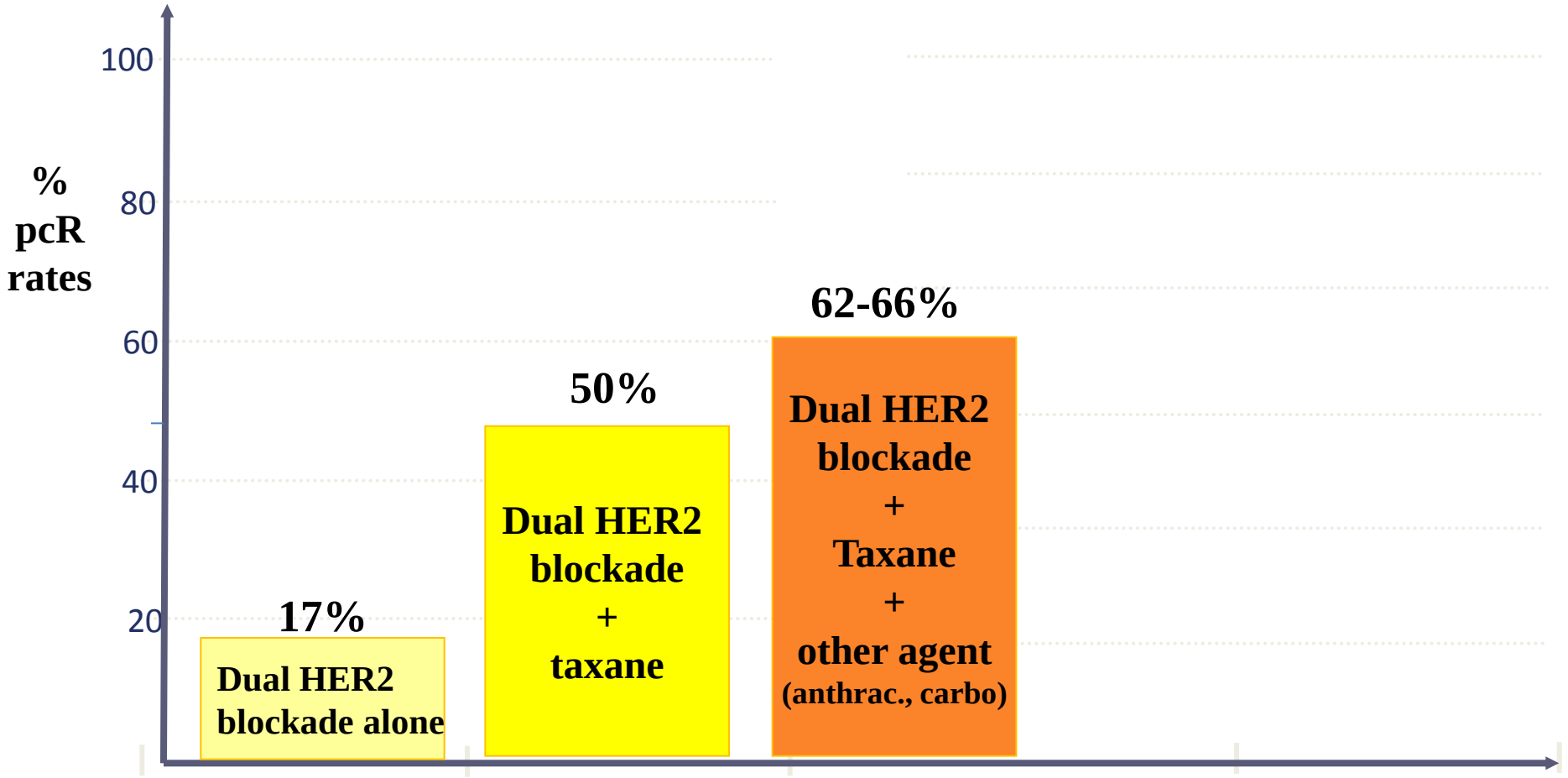
Presented by J. Baselga at the 2011 European Multidisciplinary Cancer Congress (ECCO/ESMO), September 26, 2011. Abstract: 9LBA.

Luminal B.C.

Neoadjuvant results with Everolimus :

- **Are in line with results obtained in advanced BC particularly the Ki67 proliferative response**
- **Should predict the success of mtor inhibitors in combination with endocrine therapy in the adjuvant setting**

Results obtained with dual HER2 blockade alone or with chemotherapy



Based on NeoSphere, NeoAltto, NSABP-B41, Tryphaena