Breast Cancer Research Worldwide : Quo Vadis

?

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Breast International Group (BIG aisbl), Chair

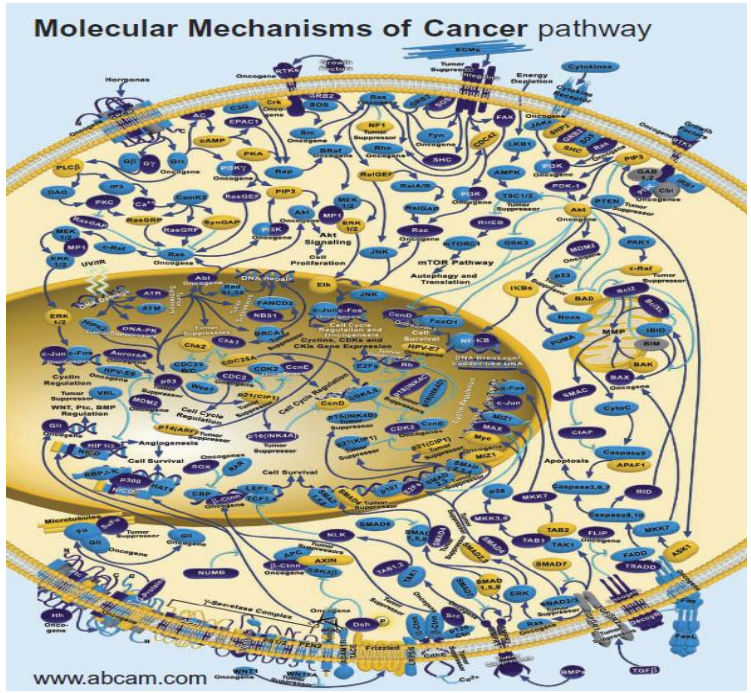
Disclosures

- Board member: PharmaMar
- Consultant (honoraria): Amgen, Astellas, AstraZeneca, Bayer, Eli Lilly, Invivis, MSD, Novartis, Pfizer, Roche-Genentech, sanofi Aventis, Symphogen, Synthon, Verastem
- Research grants to my Institute: most companies
- Speakers bureau/stock ownership: none

CLINICAL RESEARCH in oncology

The « guardian » ensuring that patients' needs remain top priority in randomized clinical trials

The only chance to beat an enemy that relies on a highly complex, adaptable network for its survival…

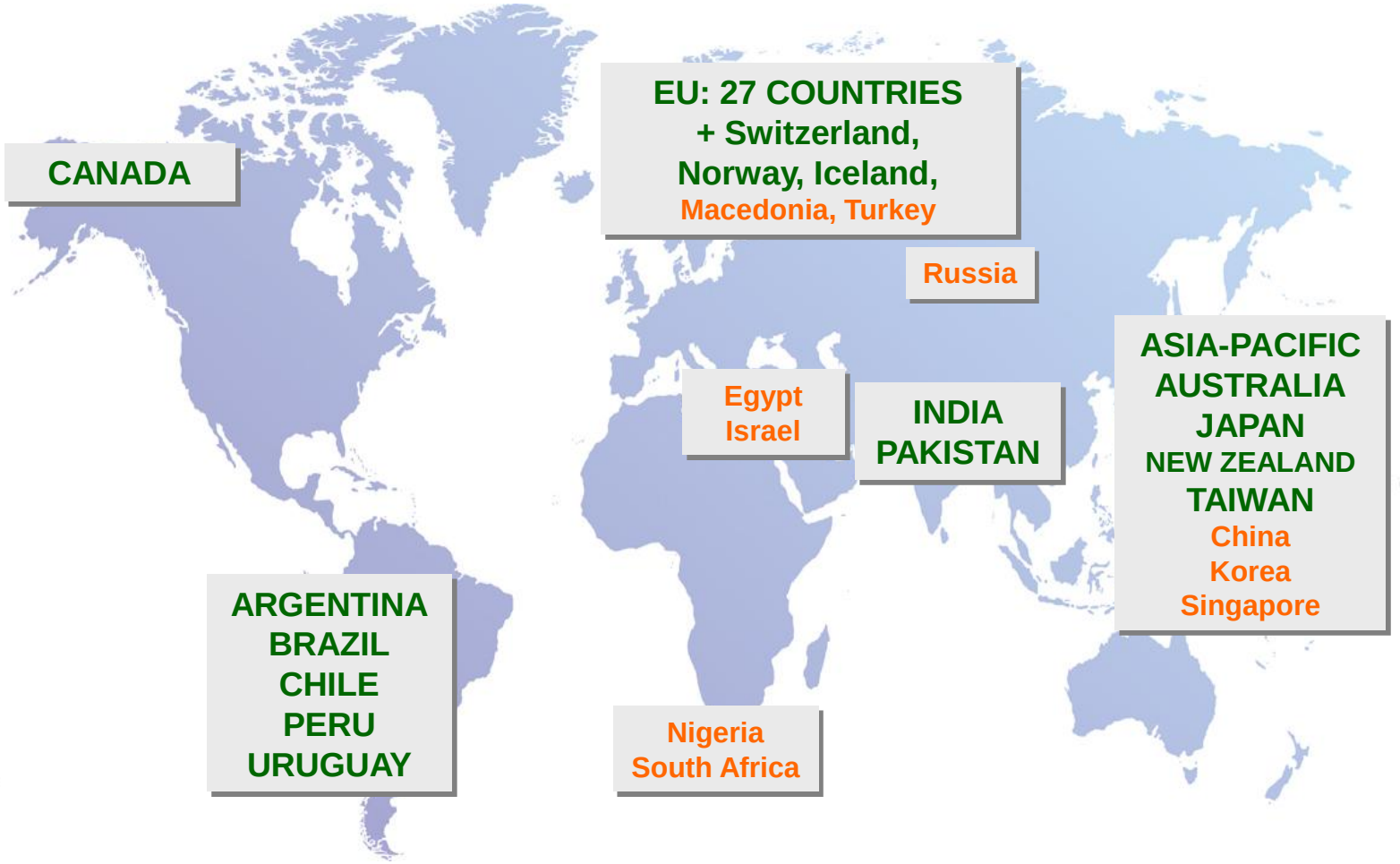


55 groups
covering
5 continents

… is through the building of a similarly STRONG, interconnected network of research groups !

1996 : the « BIG » concept is born
1999 : BIG becomes an international non-profit organisation

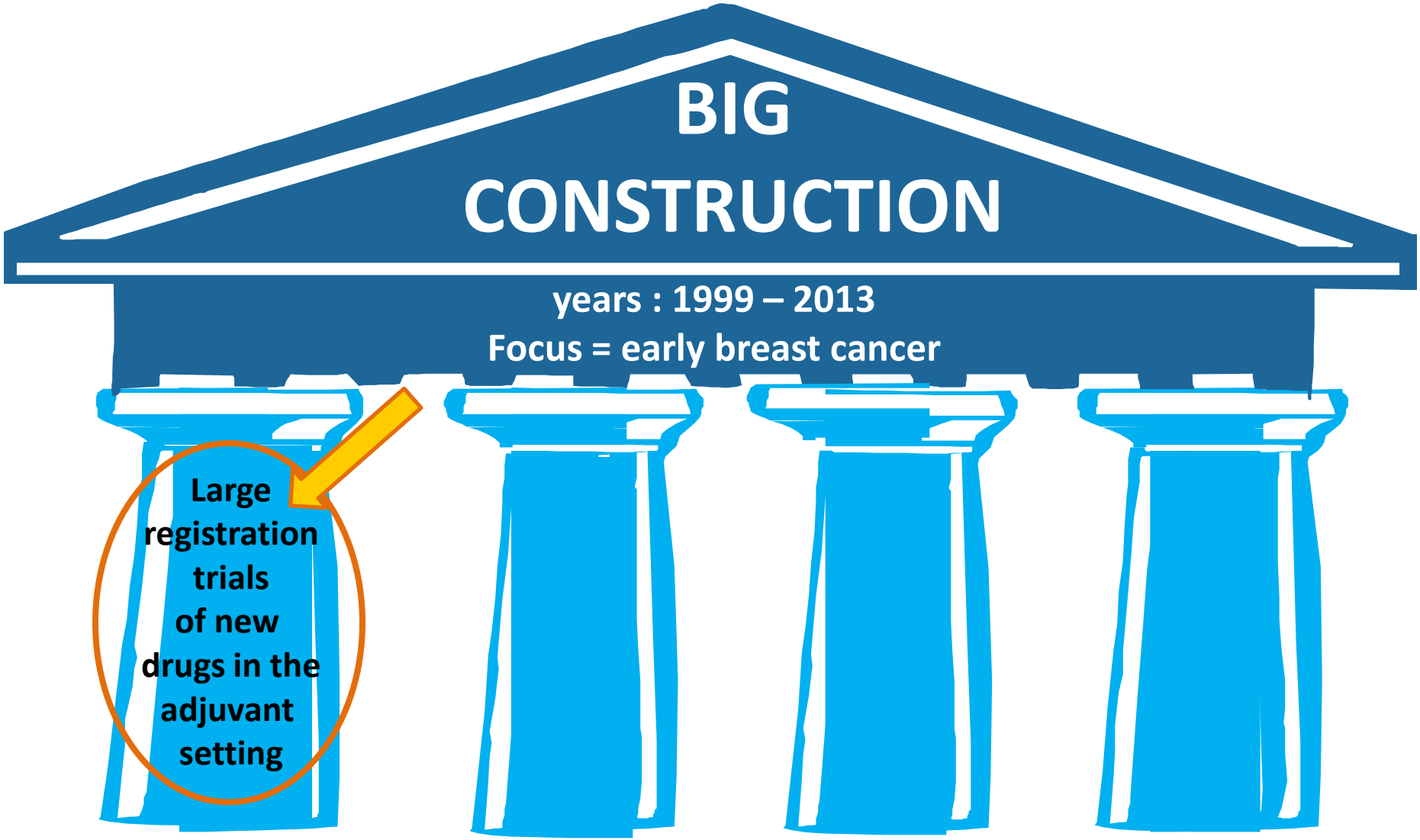
BIG in 2015 : 55 BIG member groups worldwide



National GROUPS or
International GROUPS / centres

→ Large multinational trials
e.g. HERA, ALTTO, (NEO)ALTTO, APHINITY, MINDACT

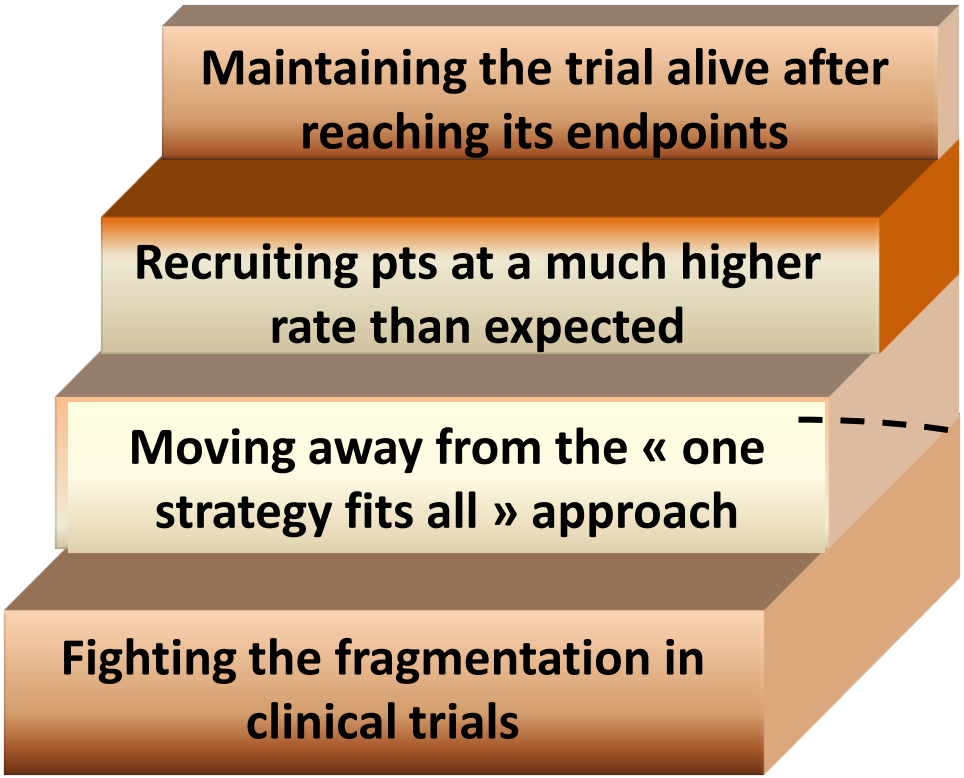
BIG
BREAST INTERNATIONAL GROUP


BIG
CONSTRUCTION
years : 1999 – 2013
Focus = early breast cancer
Large registration trials of new drugs in the adjuvant setting

Successes and failures in designing, setting up and conducting international pivotal clinical trials

The BIG experience

« SUCCESSES »



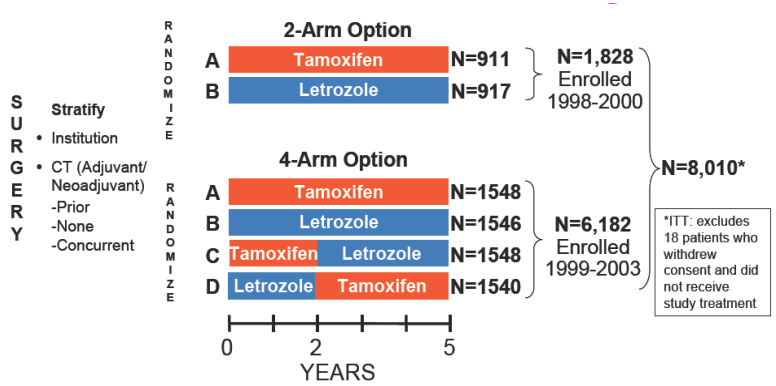
« FAILURES »

Successes and failures in designing, setting up and conducting international pivotal clinical trials

The BIG experience

Moving away from the "one strategy fits all approach"

BIG 1-98 Overall Design



Pharma Interest

Academia Interest

Previous Analyses:

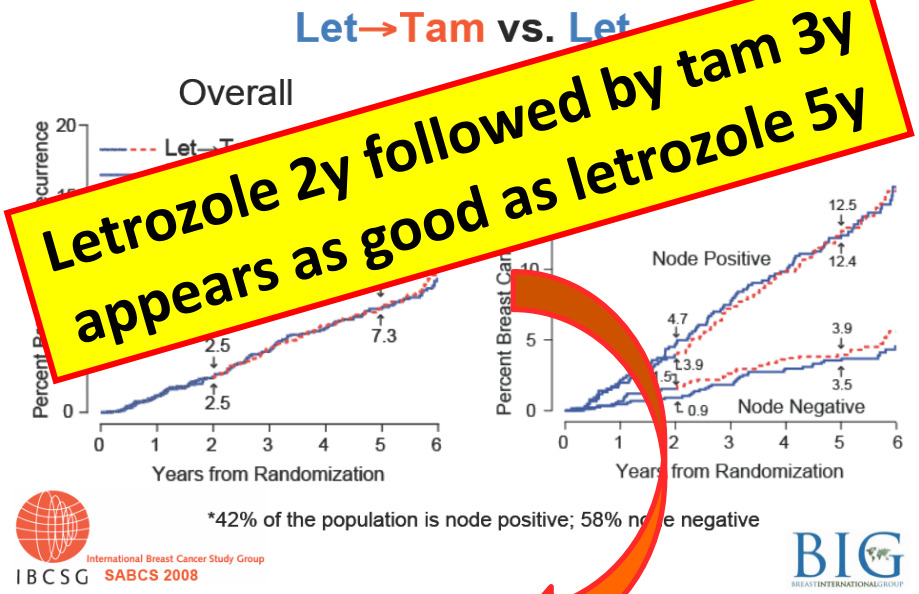
Is 5 years Let superior to 5 years Tam as initial therapy?

- Primary Core Analysis (PCA), Median follow-up 26 months
- Monotherapy Arm Analysis, Median follow-up 51 months

IBCSG International Breast Cancer Study Group SABCS 2008

BIG

Breast Cancer Events



Letrozole 2y followed by tam 3y appears as good as letrozole 5y

*42% of the population is node positive; 58% node negative

IBCSG International Breast Cancer Study Group SABCS 2008

BIG

This matters for patients!

Successes and failures in designing, setting up and conducting international pivotal clinical trials

The BIG experience

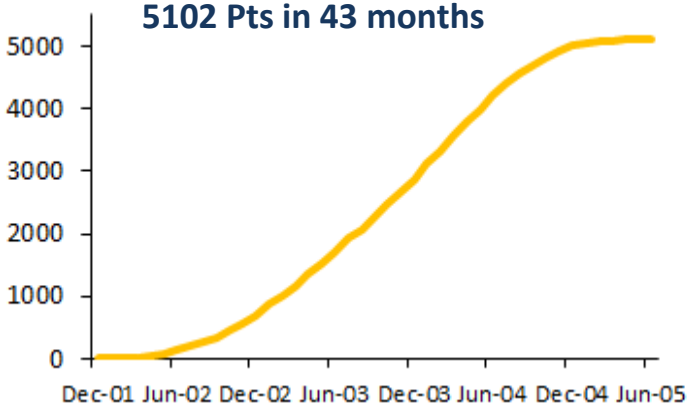
Activating trials across continents and recruiting at high speed

Single HER2 blockade vs observation

Trastuzumab

HERA

5102 Pts in 43 months

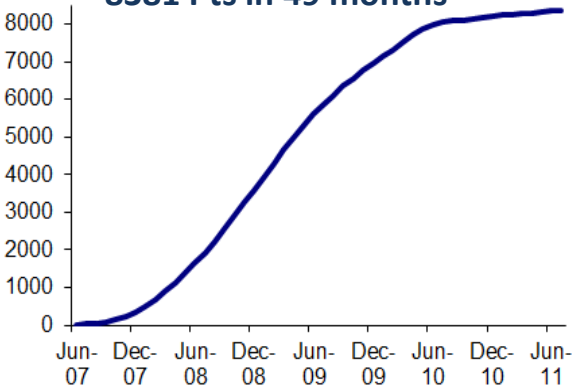


Dual HER2 blockade vs single HER2 blockade

Trastuzumab ± Lapatinib

ALTTO

8381 Pts in 49 months



Trastuzumab ± Pertuzumab

APHINITY

4223 Pts in 18 months (still recruiting pts)

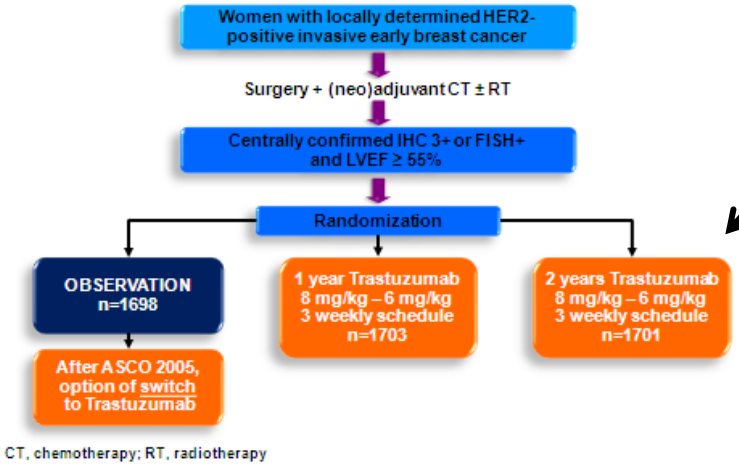
Europe	3850 (75%)	4470 (54%)	2450 (58%)
North America	160 (3%)	959 (11%)	614 (14%)
South America	284 (6%)	444 (5%)	119 (3%)
Australasia	808 (16%)	2508 (30%)	1040 (25%)

Successes and failures in designing, setting up and conducting international pivotal clinical trials

The BIG experience

Moving away from the "one strategy fits all approach"

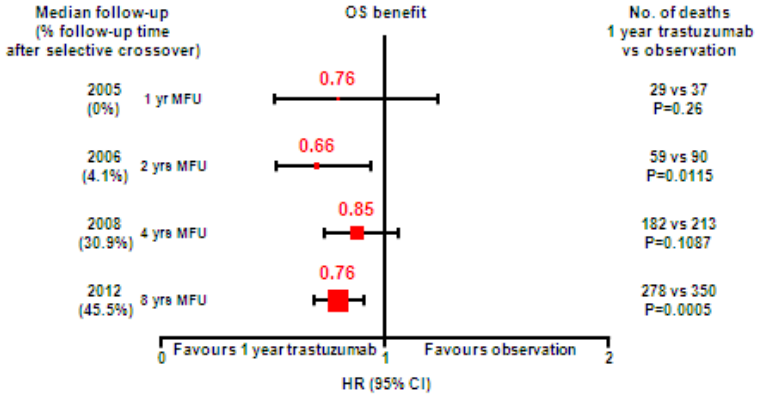
HERA TRIAL DESIGN
Accrual 2001 – 2005 (n=5102)



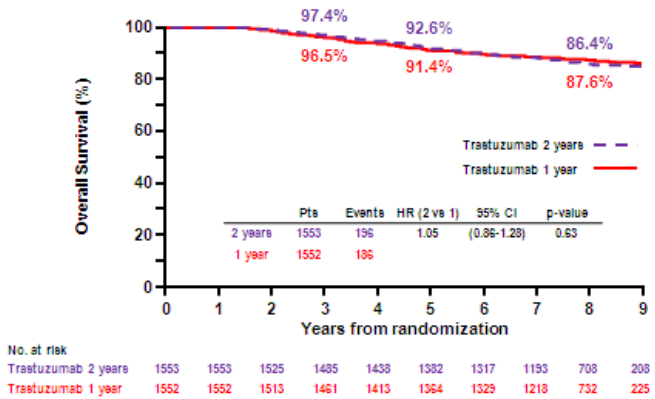
CT, chemotherapy; RT, radiotherapy

This arm was inserted by Academia

O.S. is improved with 1y trastuzumab



Trastuzumab (T) for 2y is not better than T for 1y



Successes and failures in designs…
The BIG experience
What about translational research ?

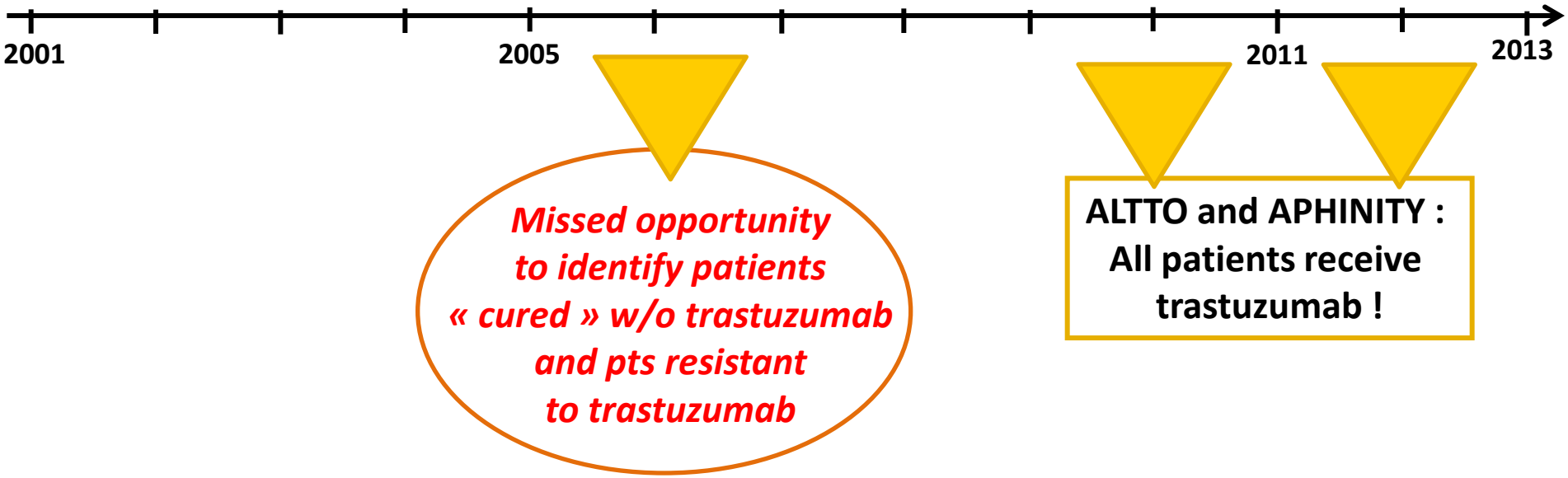
VERY SLOW and INEFFICIENT biomarker discovery process

Trastuzumab Yes or No
N > 10.000

Hera + NSABP B3 + NCCTG 9381…

Trastuzumab ±
Lapatinib
(ALTTO)

Trastuzumab ±
Pertuzumab
(APHINITY)

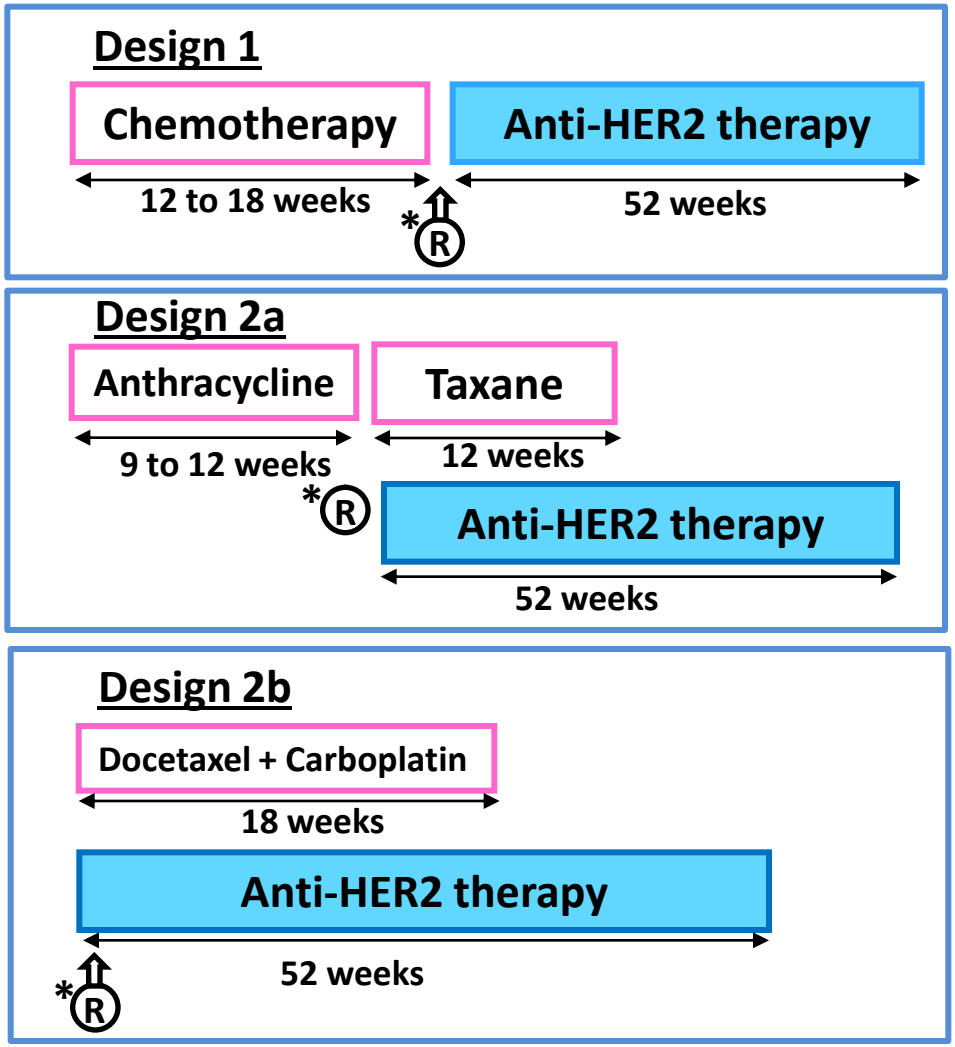


ALTTO STUDY DESIGN

Anti-HER2 therapy: 4 groups assigned by randomization

- Trastuzumab (T) x 52 weeks
- Lapatinib (L) x 52 weeks
- T x 12 wks ⟷ L x 34 weeks (6 weeks)
- Trastuzumab x 52 weeks and Lapatinib x 52 weeks

3 modalities of adjuvant CT administration per physician's choice



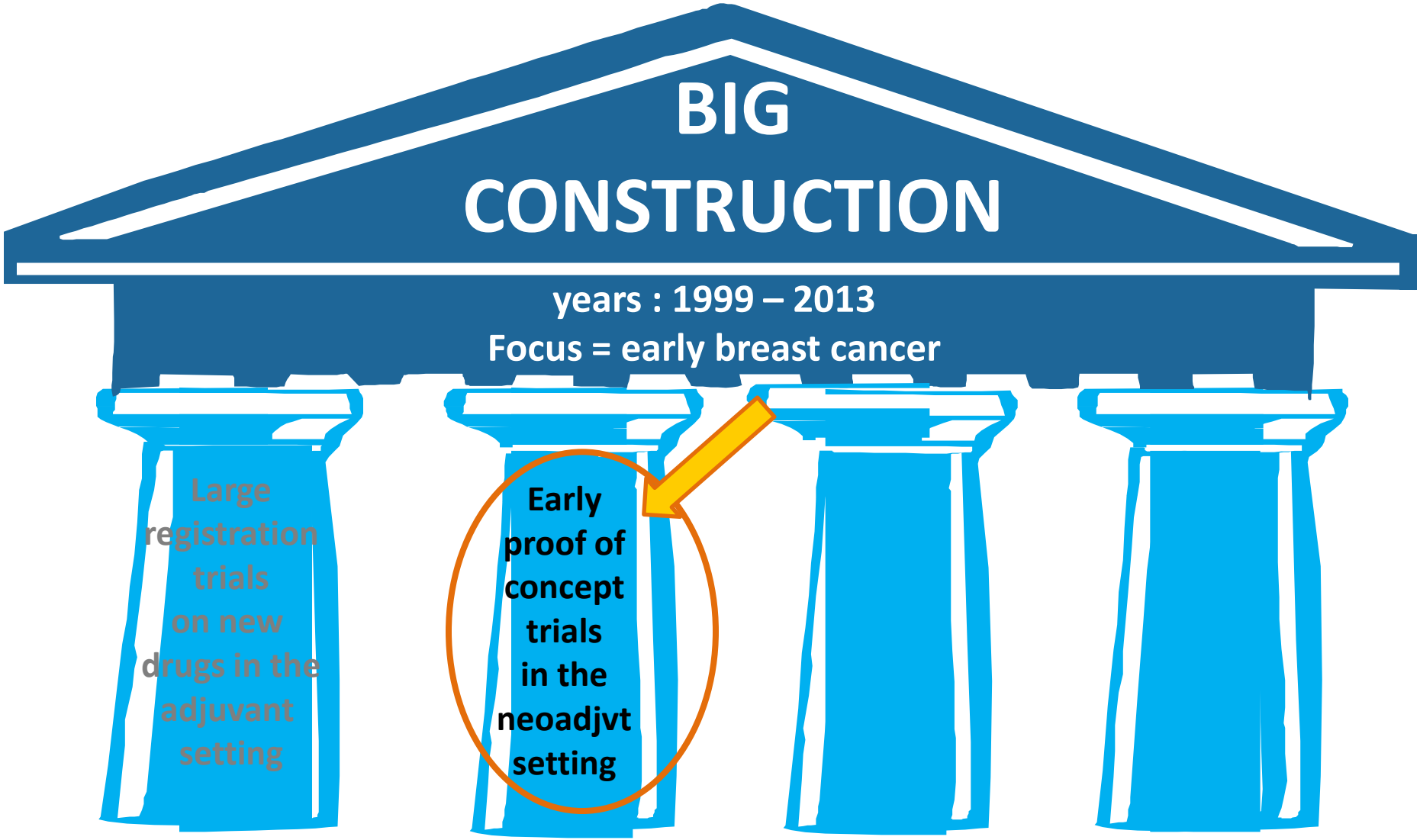
* R: refers to the timing of randomization

2011: Closure of L alone arm

2014: ASCO presentation

Comparison	Assumptions	Result (HR, 97.5% CI, P-value)
L + T vs. T	Test superiority in intention-to-treat (ITT) population at alpha = **0.025**	0.84 (0.70, 1.02), p = **0.048**
T→ L vs. T	Test non-inferiority in per protocol population (PPP) at alpha = **0.025**	0.93 (0.76, 1.13), p = **0.044**

Protocol amendment after the closure of the lapatinib alone arm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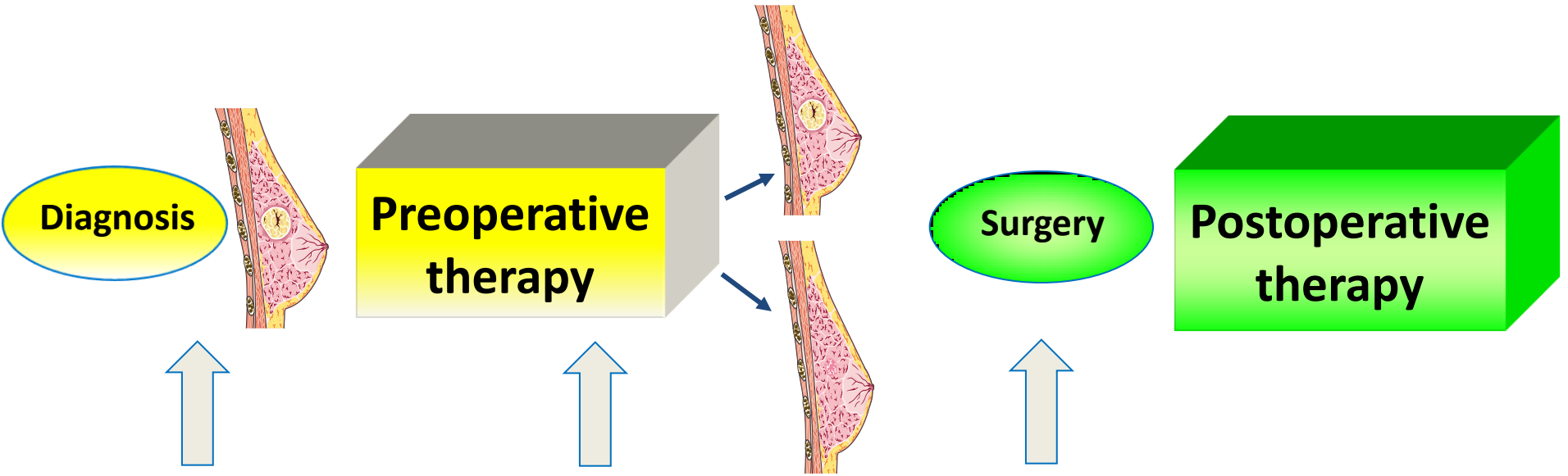
NEOADJUVANT SETTING : AN ATTRACTIVE MODEL FOR CLINICAL / TRANSLATIONAL RESEARCH



Biopsy
Fine molecular characterization

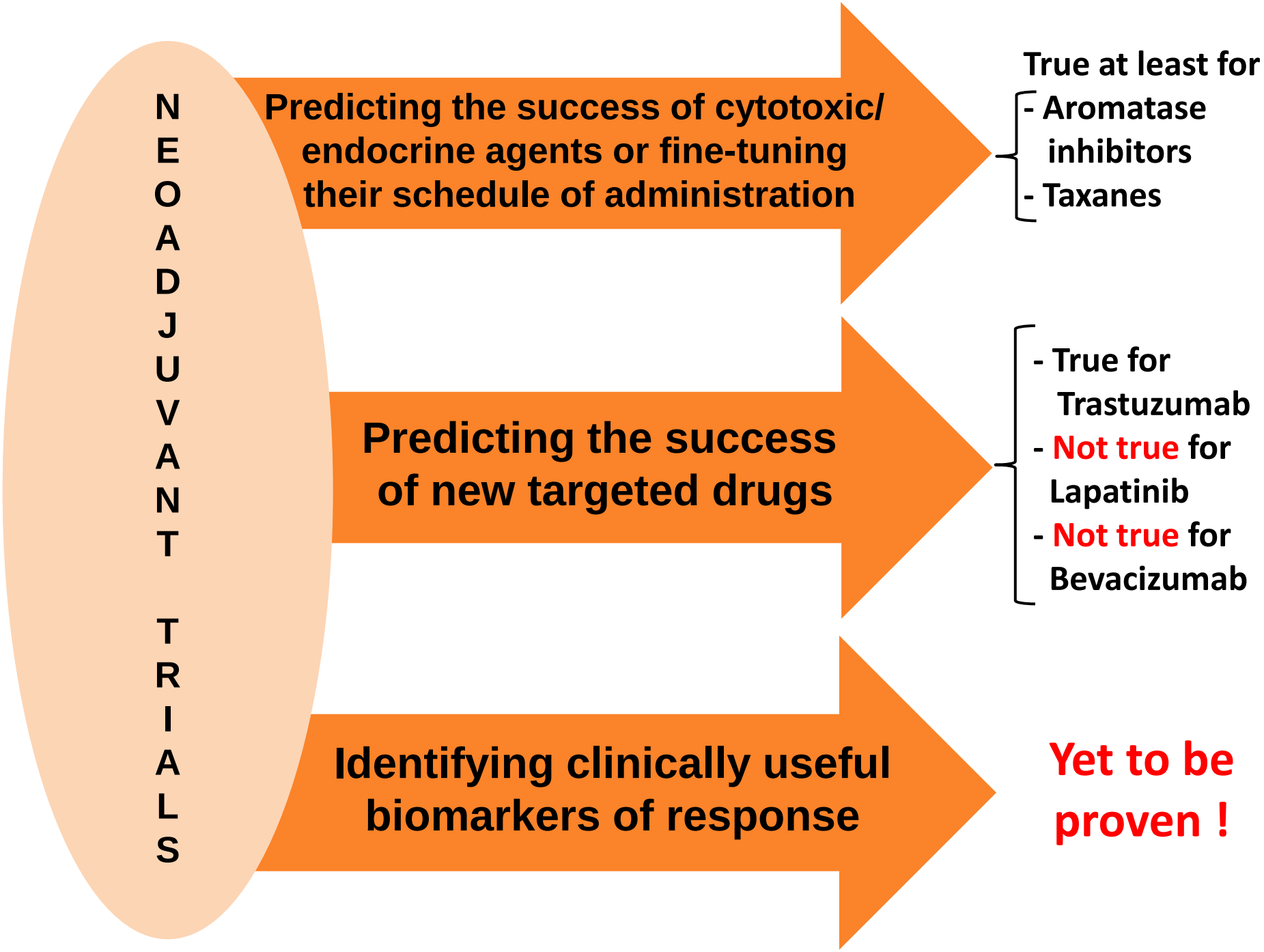
+ Molecular imaging
+ Blood

Intermediate by Early read-out of efficacy

+ Molecular imaging
+ Blood

Pathology at Sx
Mid-term read-out of efficacy

In vivo assessment of response +
Easy access to tissue +
Short-term surrogate endpoints !

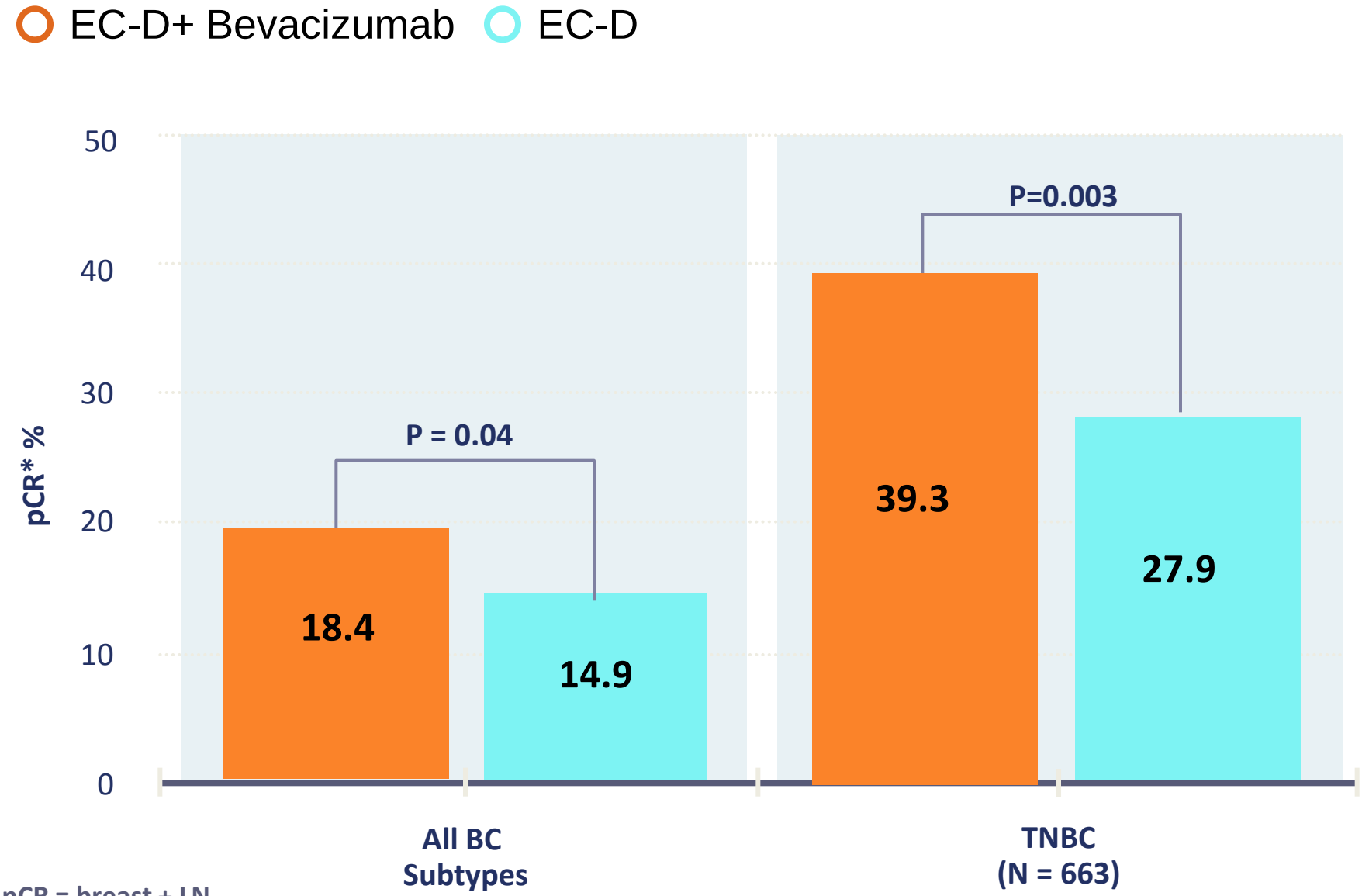

NEOADJUVANT TRIALS
Predicting the success of cytotoxic/ endocrine agents or fine-tuning their schedule of administration
True at least for
- Aromatase inhibitors
- Taxanes
Predicting the success of new targeted drugs
- True for Trastuzumab
- Not true for Lapatinib
- Not true for Bevacizumab
Identifying clinically useful biomarkers of response
Yet to be proven !

Key questions	Preoperative trials	Postoperative trials
• Docetaxel in sequence with anthracycline or anthracycline ?	Aberdeen N=162	Many adjuvant trials N ~ 44,000
• Paclitaxel q3wks or weekly ?	MD Anderson N=258	ECOG 1199 trial N=5,000
• Aromatase inhibitor or tamoxifen ?	M. Ellis / M. Dowsett N=324 / N=330	Many adjuvant trials N>40,000

Predicting the success of new targeted agents Using the neoadjuvant model

Key questions	Preoperative trials	Postoperative trials
• **Trastuzumab** combined or not with chemo in HER2+ BC ?	**NOAH trial :** Strong positive signal in terms of pCR, DFS, OS for trastuzumab arm	Almost **all adjuvant trials** « positive » **:** (B31, Hera, NCCTG-9831, BCRIG006) N>13000
• **Lapatinib** alone… comparable to trastuzumab in HER2+ BC ?	**NeoALTTO trial :** pCR lapatinib arm close to pCR trastuzumab arm	**ALTTO trial :** (N=8381) Lapatinib alone arm closed by IDMC !
• **Bevacizumab** combined or not with chemo in HER2- BC ?	**Geparquinto trial :** N=1948 with strongest Signal in triple – BC (pCR 32 → 39%)	**Beatrice trial :** N = 2591 … negative at 32 months fup

Early signal in TNBC

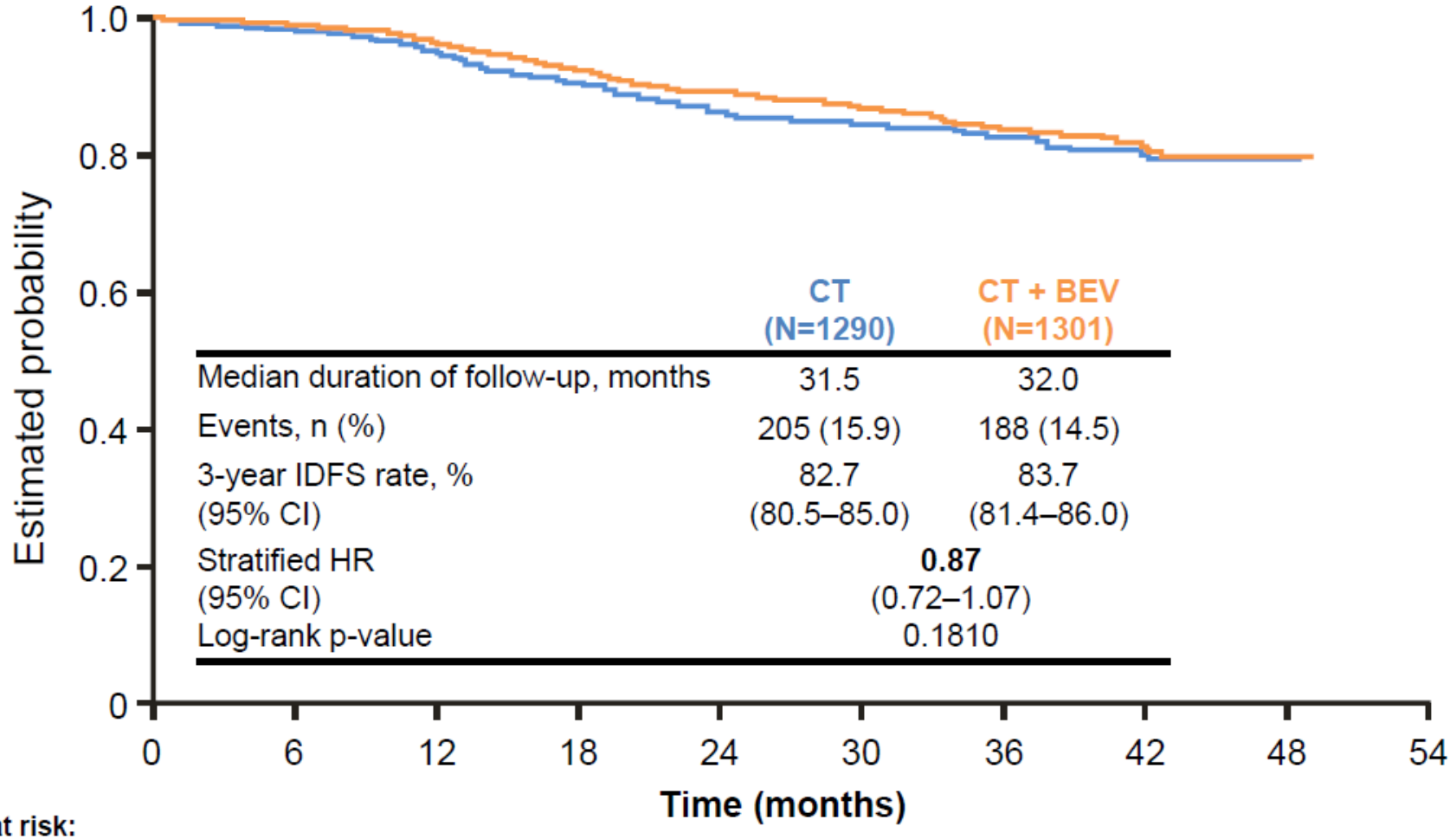


*pCR = breast + LN

Von Minckwitz, G, Eidtmann H, Rezai M et al, NEJM 2012; 366:299-309

The BEATRICE trial in triple negative BC

Primary endpoint: IDFS[a]



	CT (N=1290)	CT + BEV (N=1301)
Median duration of follow-up, months	31.5	32.0
Events, n (%)	205 (15.9)	188 (14.5)
3-year IDFS rate, % (95% CI)	82.7 (80.5–85.0)	83.7 (81.4–86.0)
Stratified HR (95% CI)	**0.87** (0.72–1.07)	
Log-rank p-value	0.1810	

No. at risk:

CT + BEV	1301	1244	1193	1129	1058	814	409	122	4	0
CT	1290	1221	1151	1086	994	772	383	105	2	0

[a]Intent to treat, not censored for non-protocol therapy

D. Cameron – SABCS 2012

BIOMARKER RESEARCH:
Disappointing stories in early breast cancer

	Biomarker of benefit in the neoadjuvant setting	? Validated in the adjuvant setting
Aromatase inhibitor « tailoring »	HER2+++	NO !
Taxane « tailoring »	Low tau mRNA	NO !
Trastuzumab a/o pertuzumab « tailoring »	No biomarker found beyond HER2 in an hypothesis driven approach examining isolated biomarkers	?

Tumor infiltrating lymphocytes (TILs)

↗ TILs

↗ Immune gene expression signatures

→

Present mostly in HER2+ and TNBC

+

Good prognosis TNBC and HER2+

+

Higher pCR rates to neoadjuvant chemotherapy in TNBC and HER2+ breast cancer

Desmedt et al. CCR 2008; Finak et al. Nat Med 2008; Schmidt M et al., Cancer Res 2008;Teschendorff AE et al., Breast Cancer Res 2008; Rody A et al., BCR 2009; Farmer et al. Nat Med 2009; Denkert et al. JCO 2010; Desmedt et al. JCO 2011;Ignatiadis et al. JCO 2012;

FinHER:

Only *LPBC* benefit from addition of trastuzumab

↑

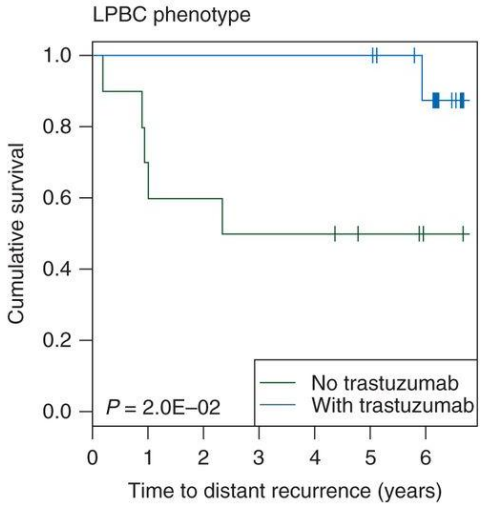
Conflicting results

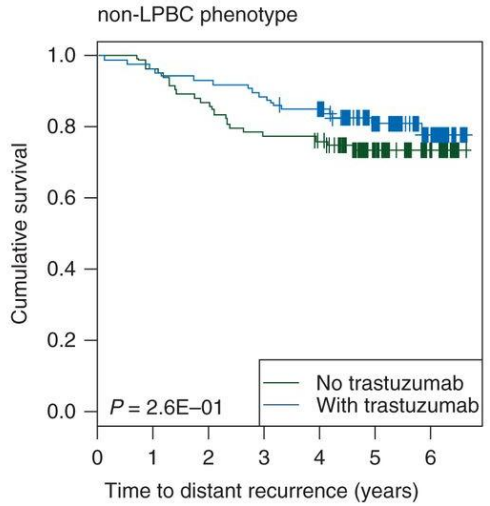
↓

N9831:

Only *non-LPBC* benefit from addition of trastuzumab

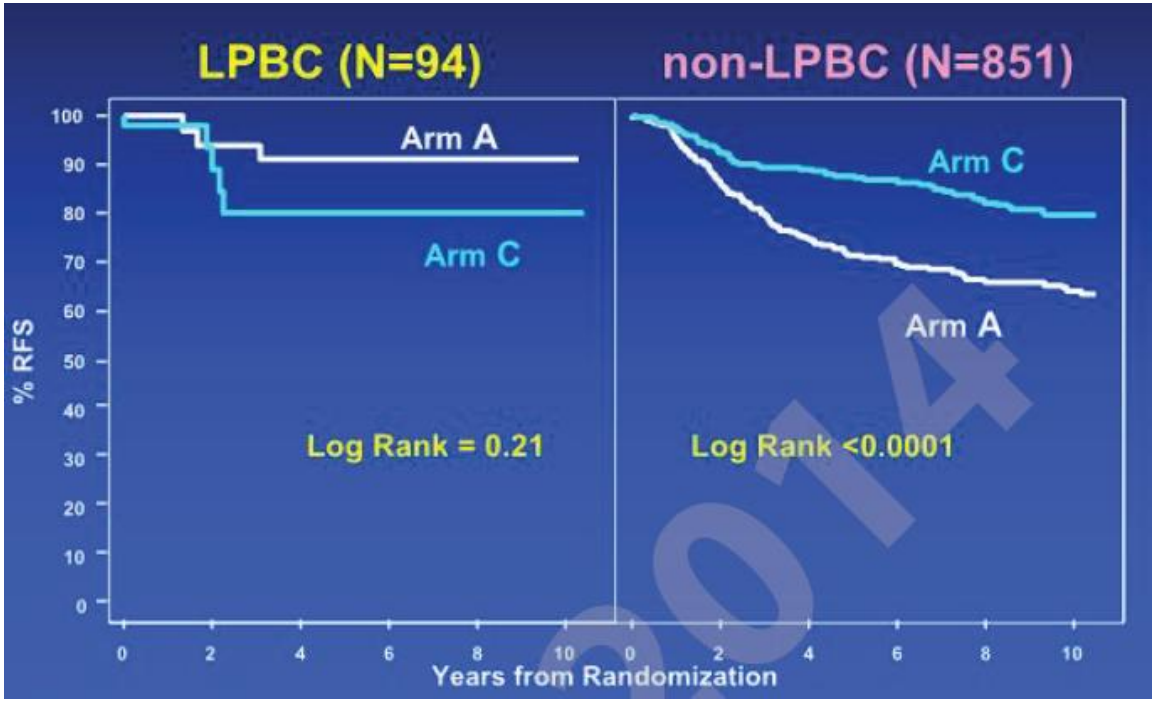
B



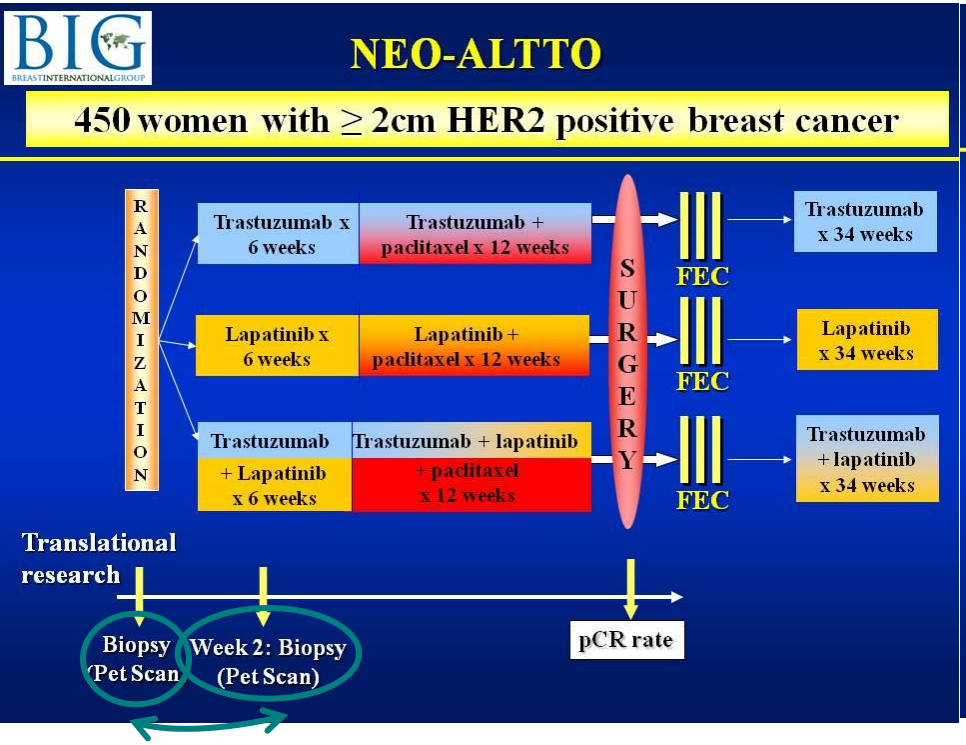


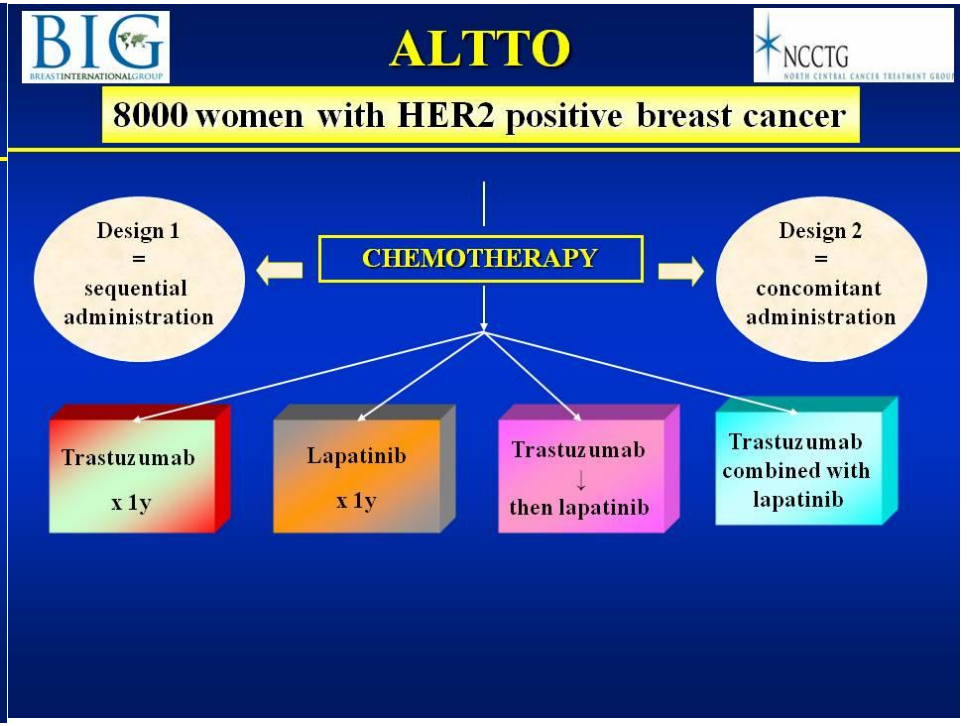
Number at risk							
No trastuzumab	10	7	6	5	5	3	1
With trastuzumab	11	11	11	11	11	11	7

Number at risk							
No trastuzumab	84	81	73	66	63	40	19
With trastuzumab	87	84	81	77	73	50	18



TWO SISTER TRIALS





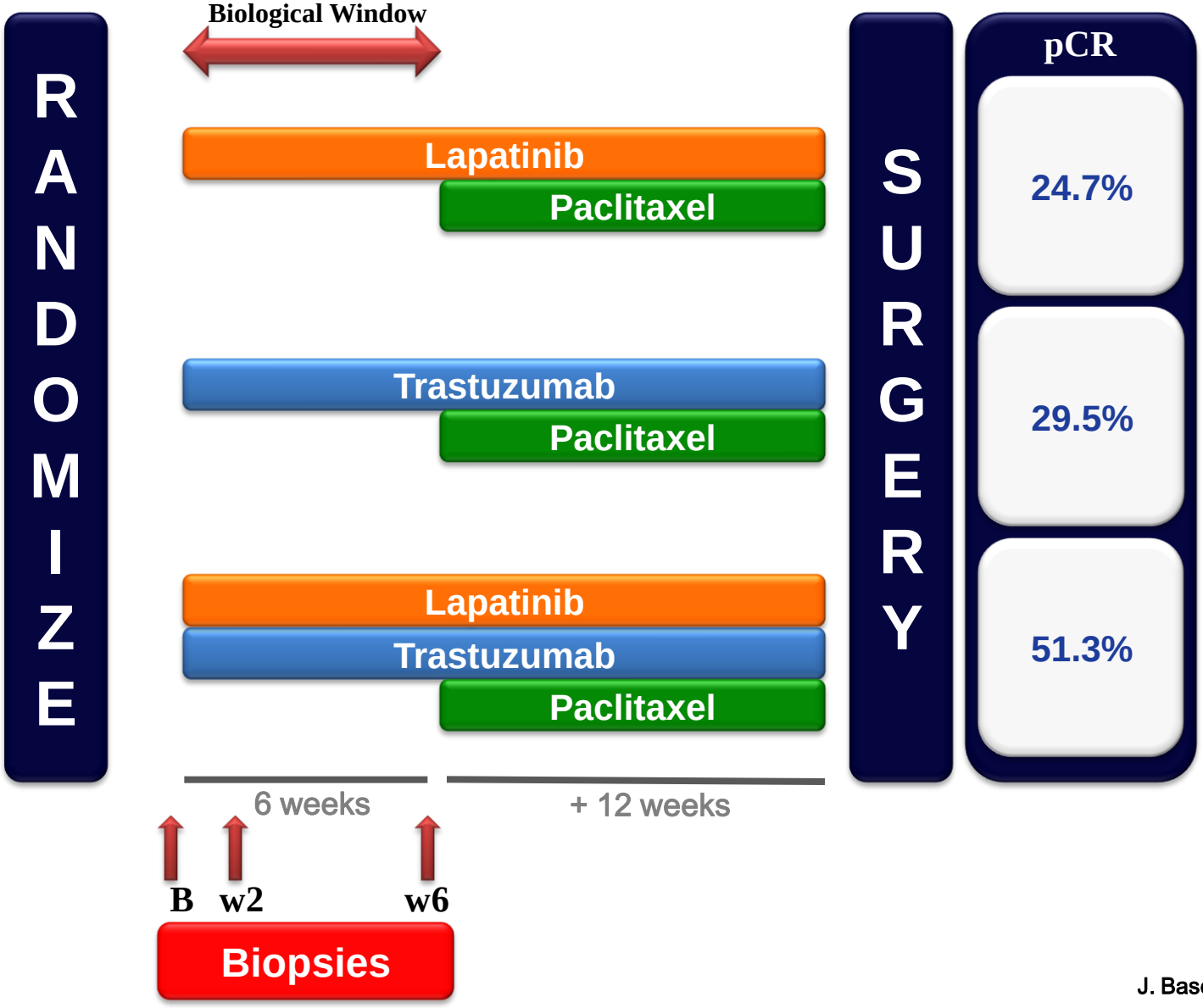
pCR x 2 with dual HER2 blockade

Negative DFS results in early 2014

Biomarker discovery… ?

Biomarker validation…?

Neo-ALTTO Study (N = 455 women)



J. Baselga, SABCS 2010

Neoadjuvant trials testing dual HER2 blockade

Trials	N° pts	chemo	Single blockade pCR (trastuzumab)	Dual blockade pCR	pvalue
NeoSphere	417	Docetaxel	29%	46%	0.0141
NeoAltto	455	Paclitaxel	29%	51%	0.0001
CALGB 40601	305	Paclitaxel	46%	56%	0.12 (NS)
NSABP-B41	529	AC/paclitaxel	52%	62%	0.095

The doubling in pCR observed with L + T in NeoALTTO did not translate into improved survival outcomes in ALTTO!

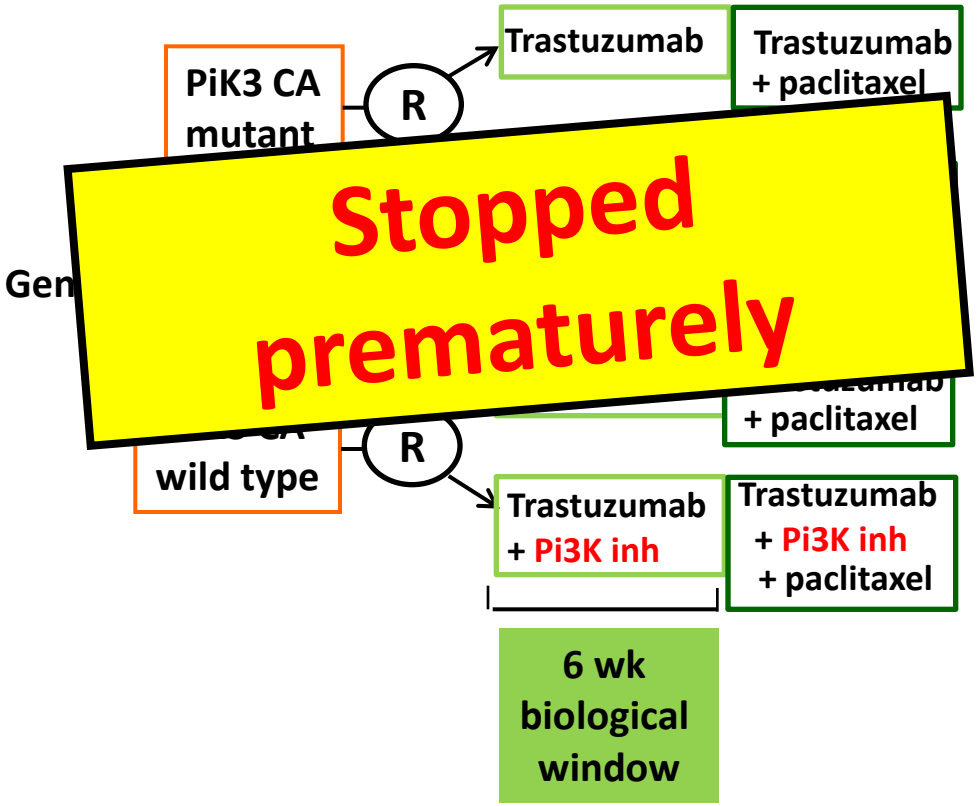
LESSONS LEARNED from the ALTTO TRIAL RESULTS

- ✓ **A substantial proportion of women with HER2+ BC are cured by today's adjuvant chemotherapy and trastuzumab**
- ✓ **Moving a new drug (eg: lapatinib) too quickly to the adjuvant setting carries significant risks**
- ✓ **For the neoadjuvant model to have a chance to predict outcome in the adjuvant setting, most « key players » must be given prior to surgery (in NeoALTTO, anthracyclines were given postoperatively)**
- ✓ **The best use of dual HER2 blockade might be in the context of adjuvant chemotherapy de-escalation**

Can neoadjuvant trials provide reassuring « proof of concept » prior to the launch of large, pivotal adjuvant trials?

BIG's neoadjuvant program of Pi3K inhibitors

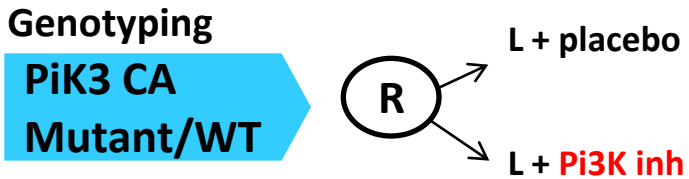
HER2-positive BC



« Success » = Increase in pCR by 18% in either subgroup

N = 220

Luminal BC



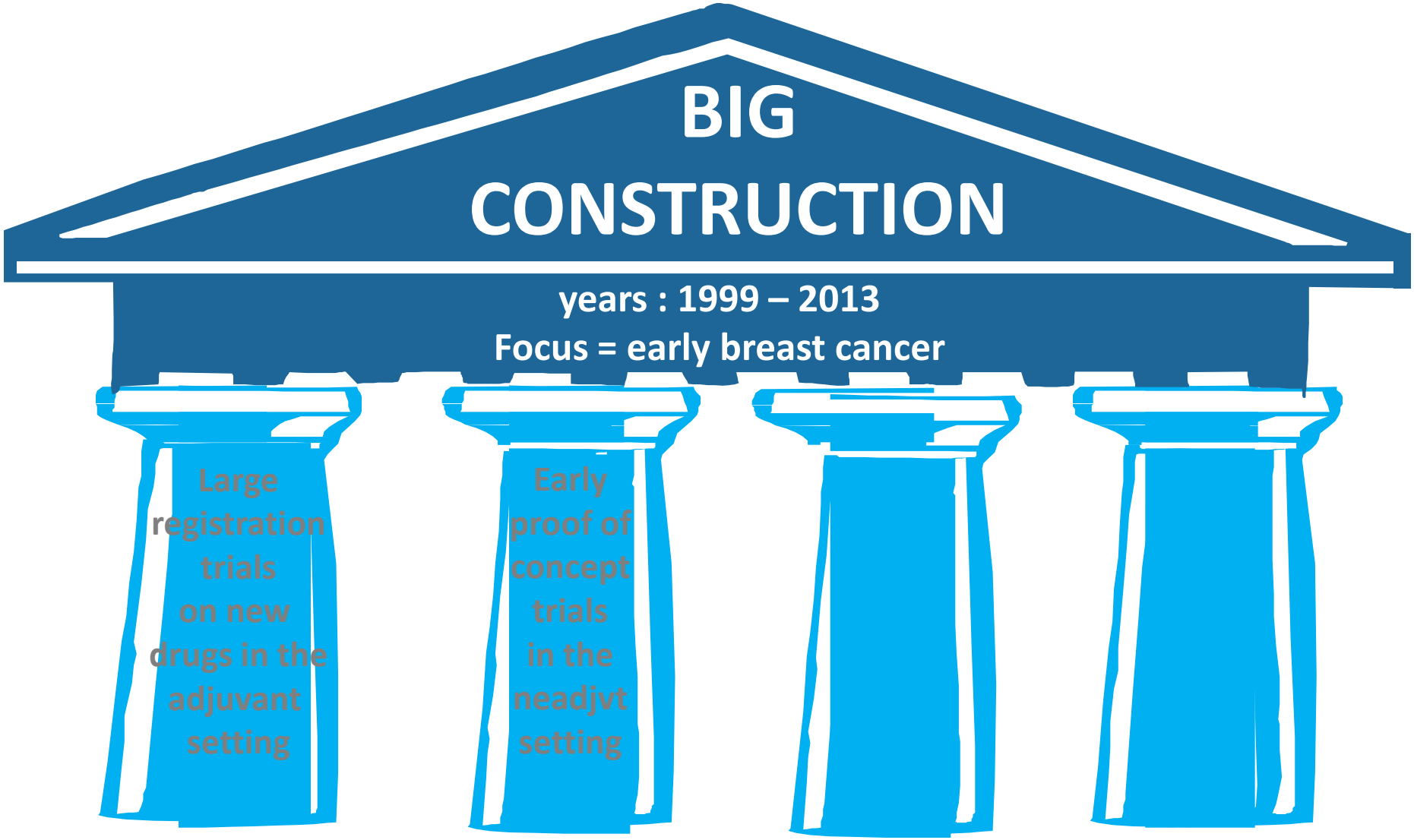
« Success » = Increase in RR (MRI) by 21% and/or Increase in pCR by 13%

N ≈ 330

BIG : lessons learned from the setting-up of an ambitious neoadjuvant program

Although the model generates considerable enthusiasm on both sides (Academia & Pharma)

1. Optimal design and statistical considerations require lengthy discussions
2. Safety issues for truly « early » compounds need to be adequately addressed
3. The trial may be « killed in utero » if, meanwhile, the new drug performs poorly in other solid tumors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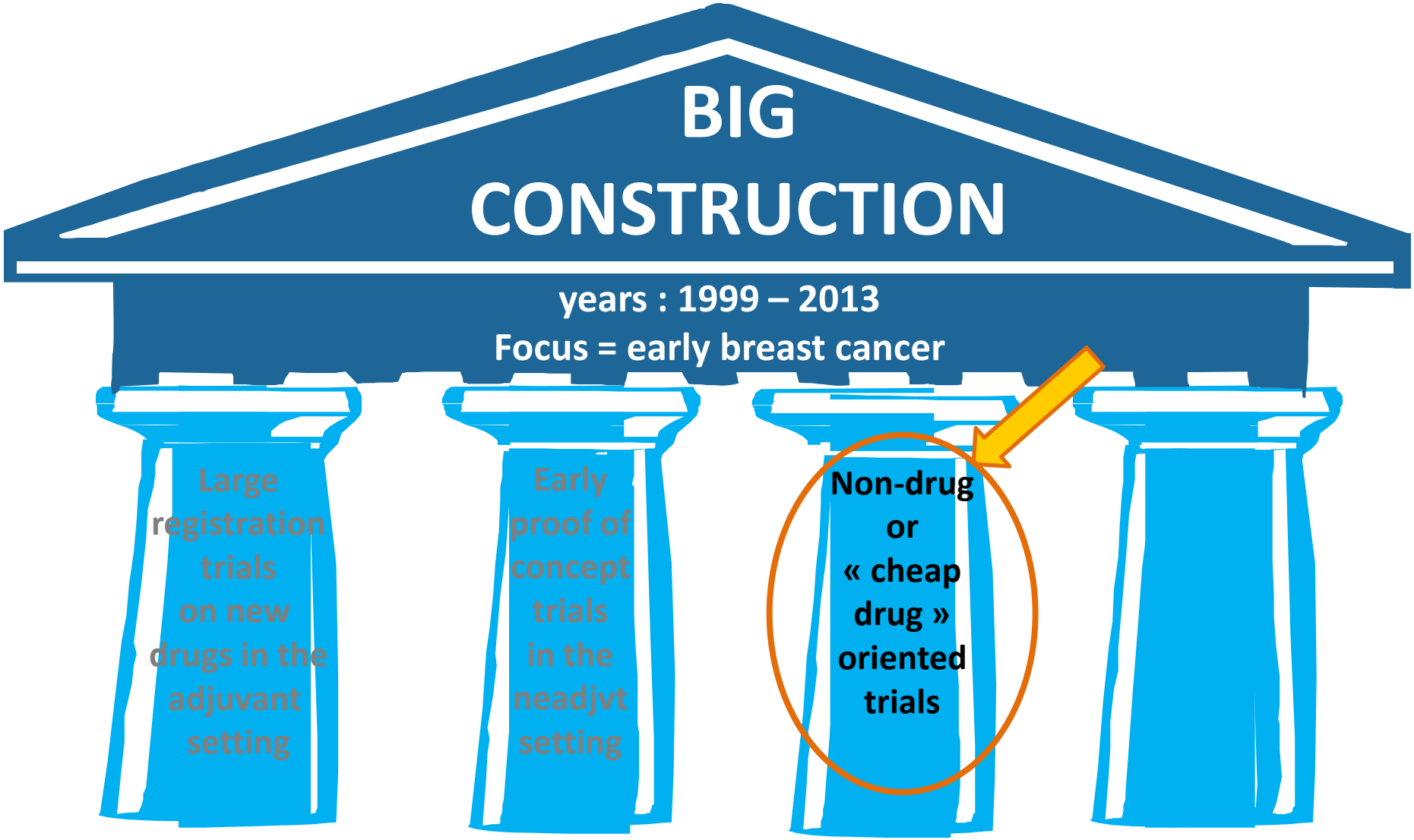
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Non-drug or « cheap drug » oriented trials

Successes and failures in designing, setting up and conducting international pivotal clinical trials

The BIG experience

Non drug or "cheap" drug oriented trials

BIG 02-05
« ACTION »
UK led trial

CT or NoCT in older ER- pts

Expected accrual : 1000
Actual accrual : 4

↓

Stopped permanently

BIG 01-05
« CASA »
IBCSG led trial

PLD or metronomic « CM » or observation in older pts

Expected accrual : 1296
Actual accrual : 77

↓

Stopped permanently

BIG
« SUPREMO»
UK led trial

Chest wall irradiation in intermed risk post mastectomy

Expected accrual : 1600
Actual accrual : 1688

↓

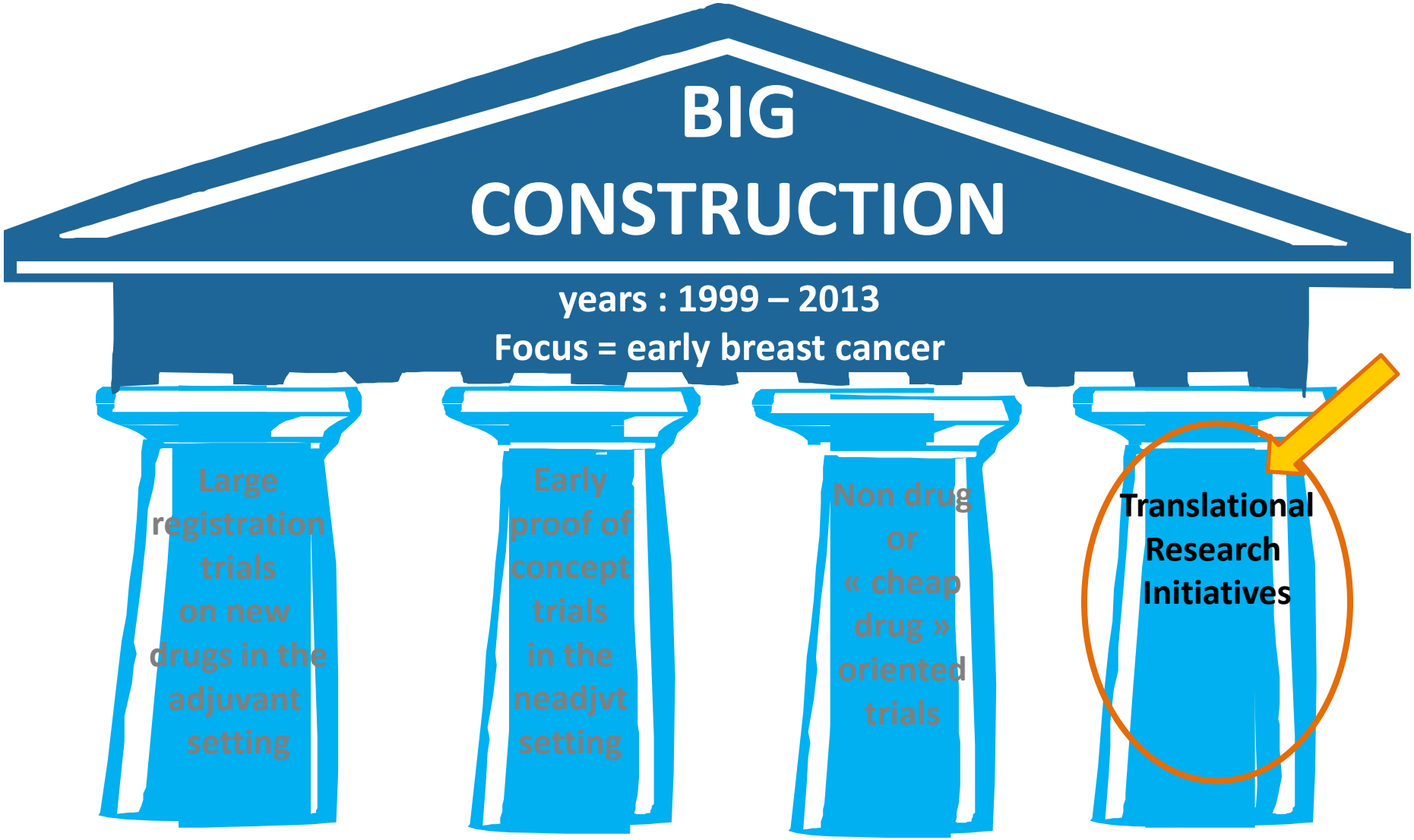
BIG
« DCIS»
TROG led trial

DCIS : radiation doses & fractionation schedules

Expected accrual : 1600
Actual accrual : 1060

↓

« Success » : only thanks to huge academic efforts to obtain multiple grants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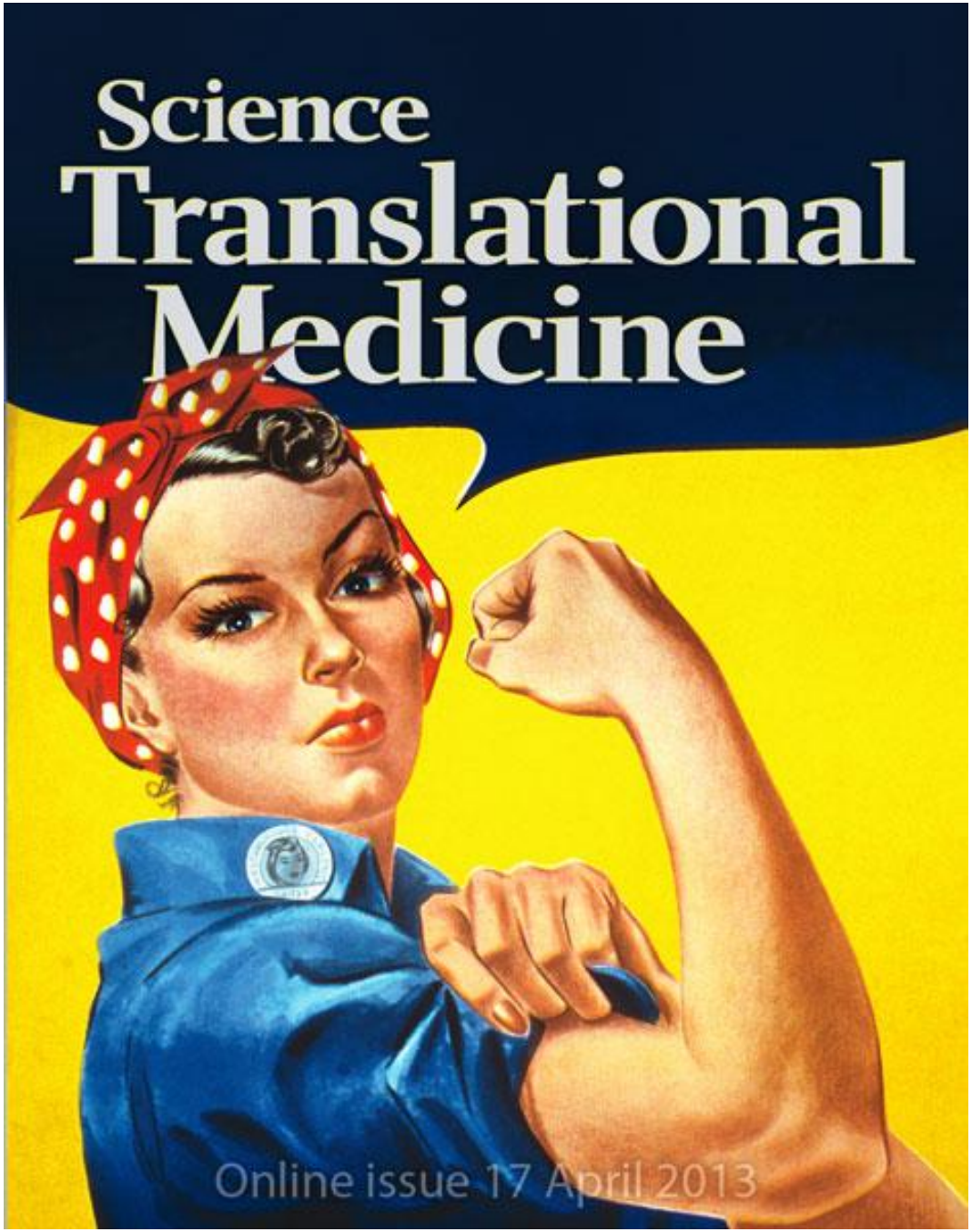
Translational Research Initiatives


Science
Translational
Medicine
Online issue 17 April 2013

Translational Research in Breast Cancer

- Small, ”proof of concept” studies

- Large, clinical-practice changing studies
  - MINDACT
  - AURORA

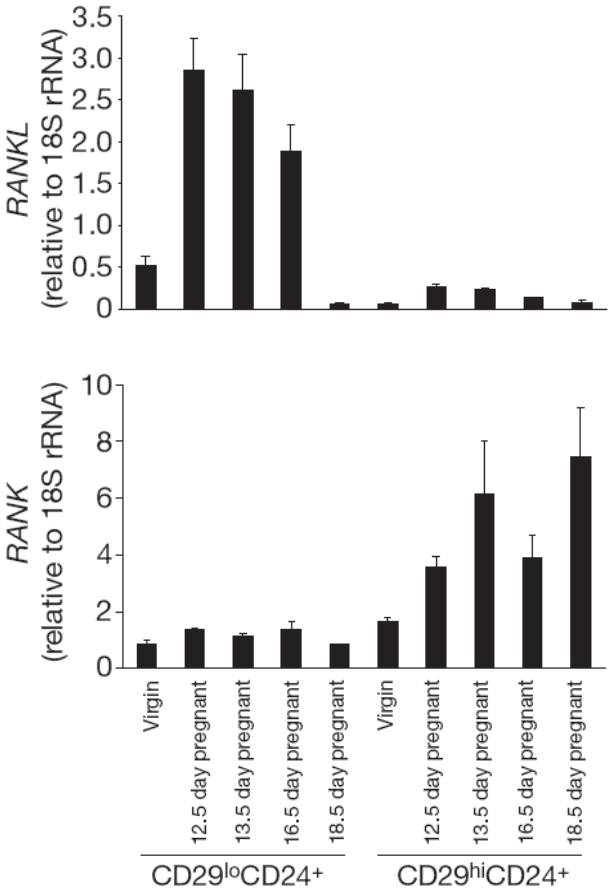
↓↓ age is associated with ↑↑ in RANKL expression independent of BC subtype and stage

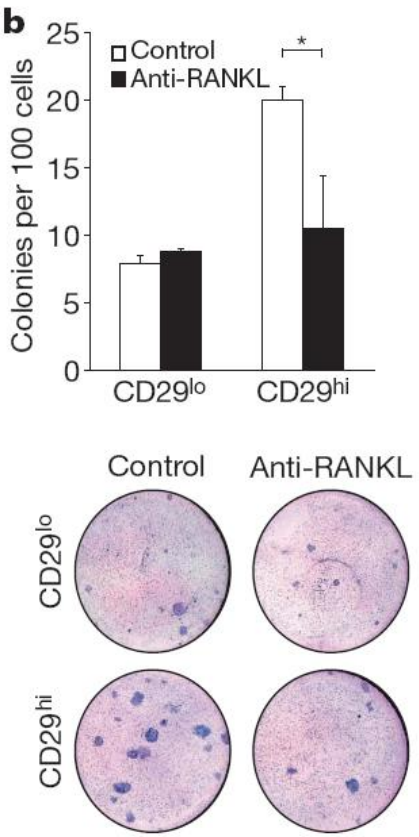
Function			Untreated cohort (cohort 1, n = 1,188)			Treated cohort (cohort 2, n = 2,334)			Expression in young BC
	Genes	Gene sets	Effect of age adjusted for data set	Effect of age adjusted for all covariates	FDR of 2nd adjustment	Effect of age adjusted for data set	Effect of age adjusted for all covariates	FDR of 2nd adjustment	Up- or downregulated
Apoptosis related	FAS		1.7E-04	6.6E-03	0.03	7.5E-04	3.9E-03	0.008	down
	CASP3		2.2E-03	2.2E-02	0.08	3.3E-03	2.5E-02	0.04	
	BAD		3.8E-03	3.2E-02	0.11	4.0E-03	1.7E-02	0.03	
MAP kinase related		MAPK	1.2E-13	5.8E-07	<0.0001	1.6E-08	5.9E-05	0.0002	up
mTOR/PI3K related	PDPK1		3.3E-03	2.1E-02	0.08	2.3E-05	7.6E-04	0.002	up
		PIK3CA-GS	1.4E-12	6.7E-09	<0.0001	1.7E-11	5.0E-11	<0.0001	
BRCA related	BRCA1		3.3E-04	3.8E-04	0.003	2.4E-02	4.4E-02	0.06	down
		BRCA1 mutant	5.4E-09	4.5E-03	0.02	5.6E-06	2.5E-03	0.006	up
Stem cell related	RANKL		5.8E-08	1.8E-10	<0.0001	1.3E-06	1.6E-06	<0.0001	up
		MaSC	8.0E-11	1.5E-09	<0.0001	3.5E-18	3.2E-15	<0.0001	up
Luminal progenitor	c-kit		5.8E-12	3.3E-13	<0.0001	7.9E-08	1.3E-07	<0.0001	up
		Luminal progenitor	1.7E-09	1.1E-03	0.007	2.4E-05	1.9E-02	0.04	up

Azim HA Jr et al., Clin Cancer Research 2012

RANKL beyond Bone Metastases

RANKL mediates the effect of hormone signaling on Mammary stem cell function





Asselin-Labat M et al; Nature 2010

RANKL inhibition
Anti-tumoral effect?

- Collectively this data suggest that the effect on RANKL inhibition may go far beyond its osteoclastic actions.

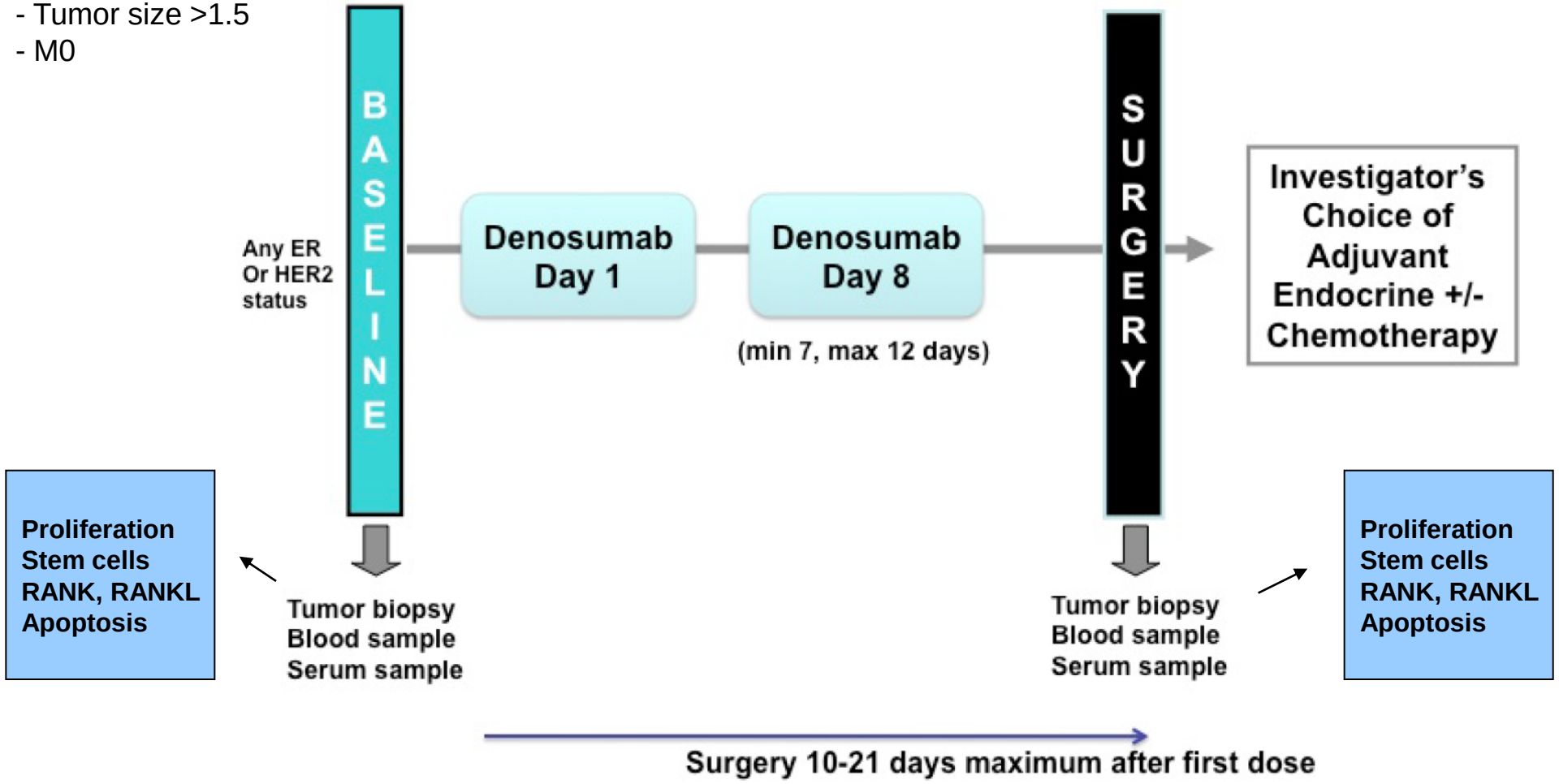
- Development of a window study to evaluate the role of RANKL on newly diagnosed breast cancer patients

D-BEYOND

Denosumab Biological Effects in Young Women Diagnosed with Breast Cancer

Key eligibility
- Pre-menopausal
- Tumor size >1.5
- M0

PI [S. Loi, M. Piccart, C. Sotiriou, H. Azim]

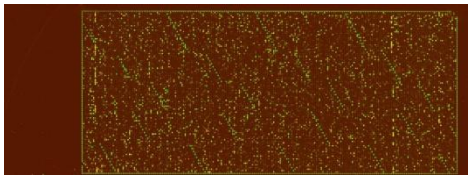


(Erasmus, IJB, Leuven, Mons, Namur + Melbourne)

EudraCT number 2011-006224-21

DEVELOPMENT OF A PROGNOSTIC SIGNATURE

tumour samples of known clinical outcome

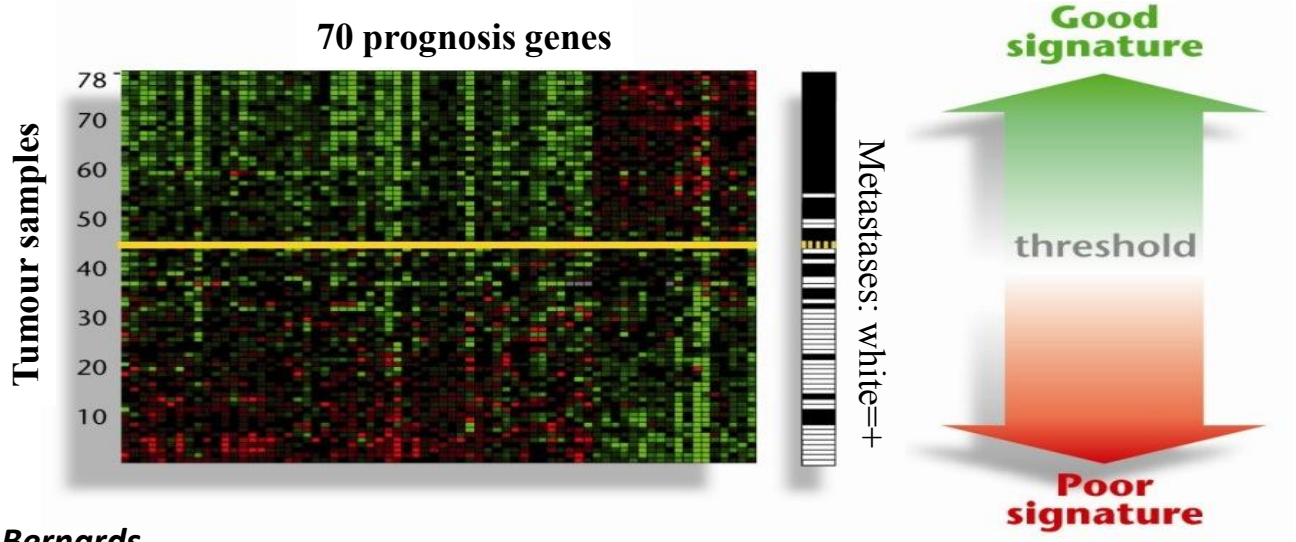


Unbiased full genome gene expression analysis

Prognosis reporter genes

distant metastases group

no distant metastases group



Courtesy of R. Bernards

MINDACT : CURRENT STATUS

Enrolled :
6694 women,
all evaluated according to clinical-pathological risk (adjvt on line) and the 70gene signature

High risk by both methods	Discordant risk	Low risk by both methods
N = 1873 (28,0%)	N = 2187 (32,7%)	N = 2634 (39,3%)

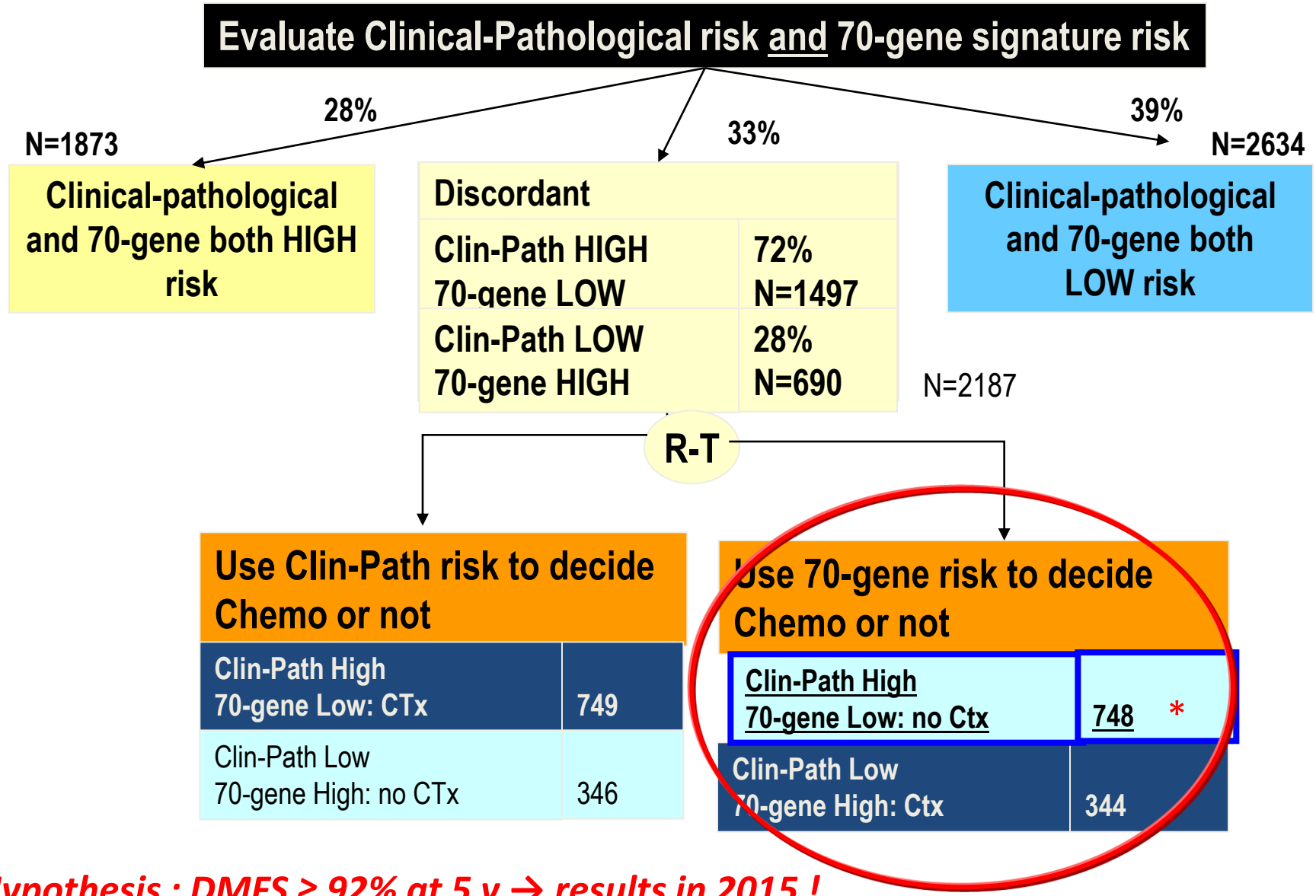
[Predicted 30%]

Supported by EU 6th framework program

EORTC-BIG MINDACT TRIAL DESIGN

6,000 Node - & 1-3 N+ women

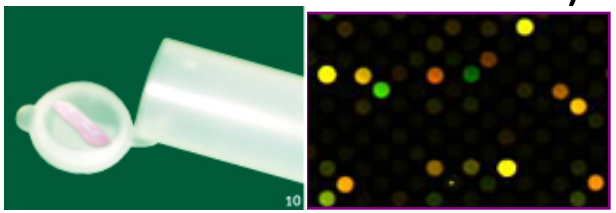
numbers as enrolled (as randomized)



** Hypothesis : DMFS ≥ 92% at 5 y → results in 2015 !*

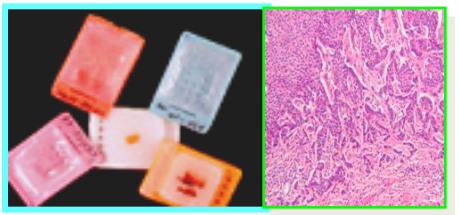
MINDACT : A GOLDMINE FOR FUTURE RESEARCH !!!

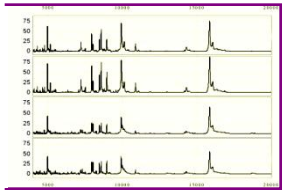
FROZEN TUMOR SAMPLES (remaining after RNA extraction for MINDACT)



PARAFFIN-EMBEDDED TUMOR SAMPLES (after TMA construction)

SERUM & BLOOD SAMPLES





Independent biological materials bank
Policy for access to samples and/or data

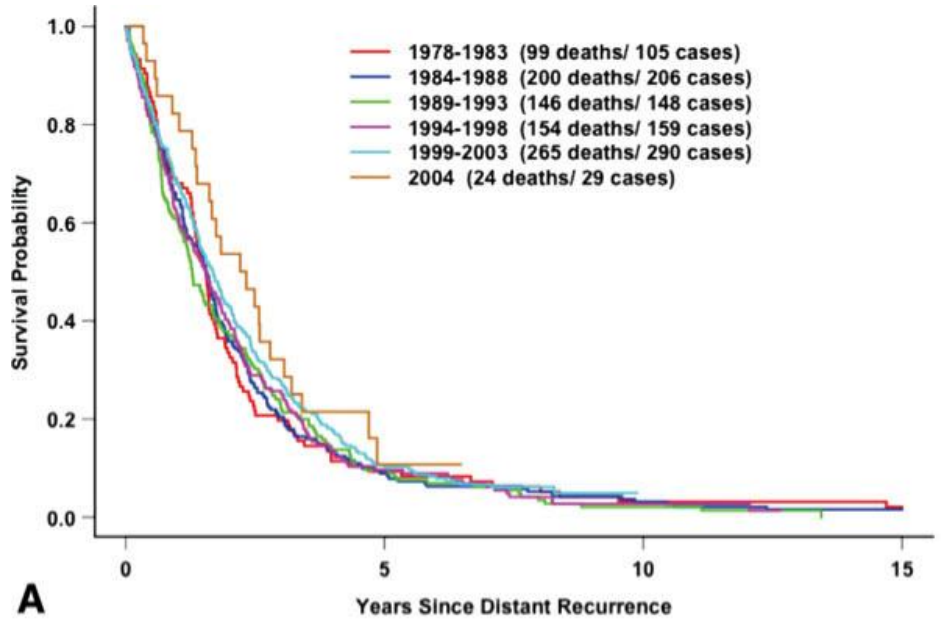
Metastatic BC by year of diagnosis

Survival in Patients With Metastatic Recurrent Breast Cancer After Adjuvant Chemotherapy

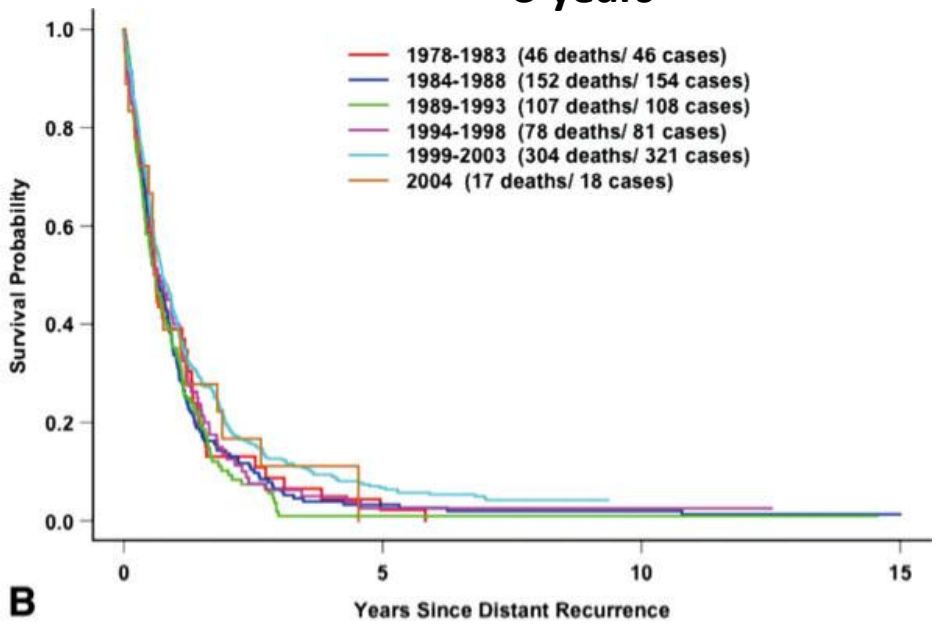
Little Evidence of Improvement Over the Past 30 Years

Distant recurrence from interval

ANY



< 3 years



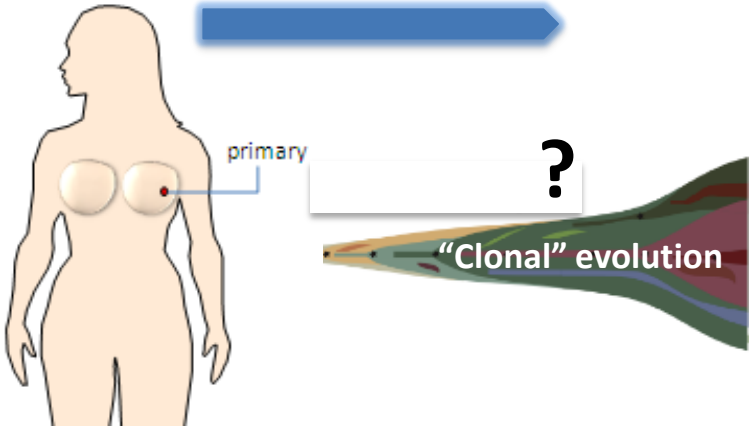
Amye J. Tevaarwerk et al, Cancer 2013;119:1140-8
ECOG data base (N = 13785 pts entered in adjt trials between 1978-2002 of whom 3447 (25%) became metastatic

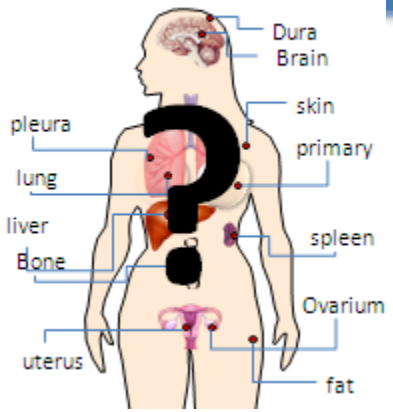
The landscape of genomic alterations in metastatic Breast Cancer

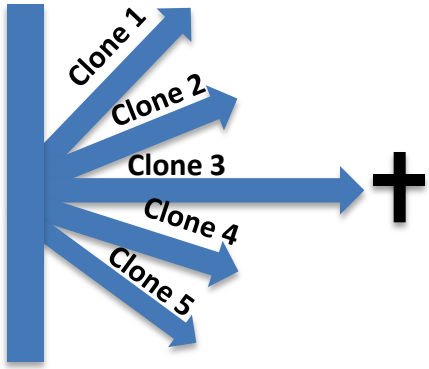
"Early" Breast Cancer → Metastatic relapse +

Adjuvant therapy

Sequential systemic therapies







? **Dynamics of the subdonal tumor architecture over time**

? **Relative importance of "driver" mutations in the "trunk" or in the branches**

? **Can "driver" mutations be captured by plasma tumour DNA**

? **Which clones are going to play a major role in the lethal evolution of the disease**

TGS RNA seq → Primary tumor

TGS RNA seq → Metastatic lesions

Plasma ctDNA

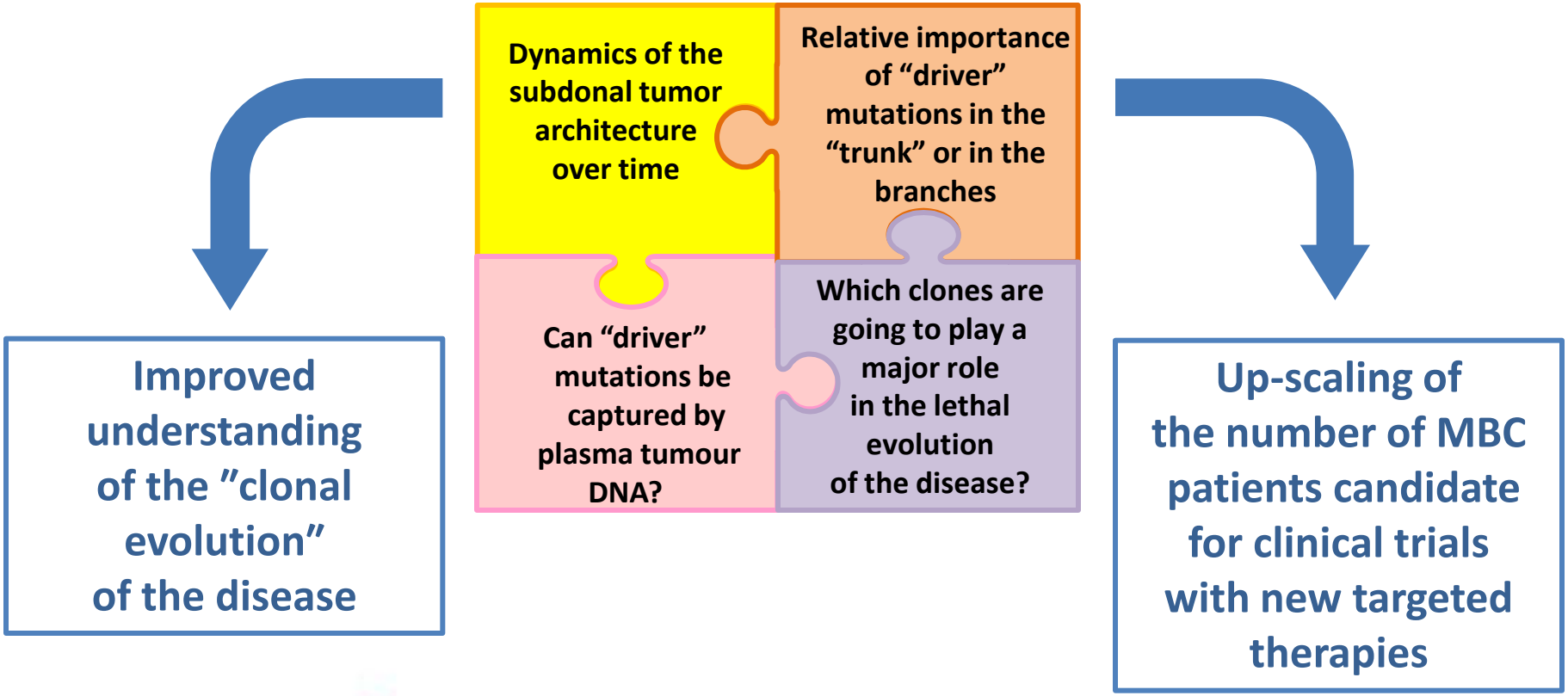
Plasma ctDNA

Plasma ctDNA

Plasma ctDNA

The AURORA Program

A prospective, longitudinal study of 1,300 women with Metastatic Breast Cancer recruited at 81 centers across 15 European countries
Secured budget as of 2014: 11 million euros



BCRF BREAST CANCER RESEARCH FOUNDATION

Fondation Cancer

NIF Trust

BIG against breast cancer

AURORA
Metastatic Breast Cancer - molecular aberrations

Newly diagnosed or 1st Line MBC Patients

N=1,300

Screening Failure n=300

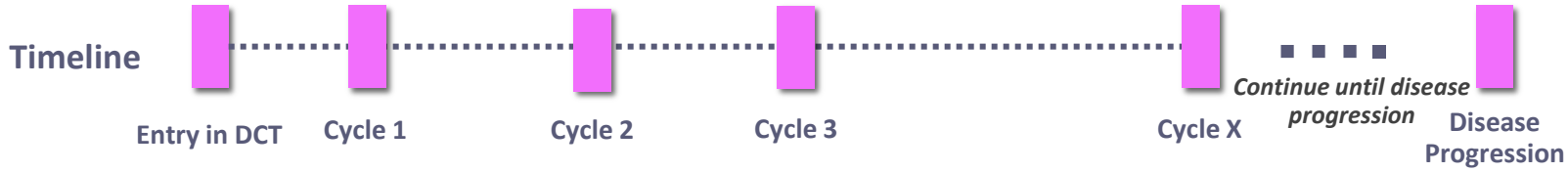
'Actionable' Mutation(s) (n~300)

Downstream Targeted Clinical Trials as first or second line

'Non-Actionable' Mutations (n~700)

Standard of Care

Clinical Outliers (Exceptional Responders and Rapid Progressors) to be subjected to WES



Metastatic Lesion	Biopsy – TGS (real time) and RNAseq (on batches)
Primary Tumour	Archival – TGS (real time) and RNAseq (on batches)
Blood	TGS (real time)
Plasma/Serum	Collection every 6 months – up to 10 years
Clinical Outcome Information	Collection every 6 months – up to 10 years


PINK for OCTOBER
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