Neoadjuvanta translationella studier

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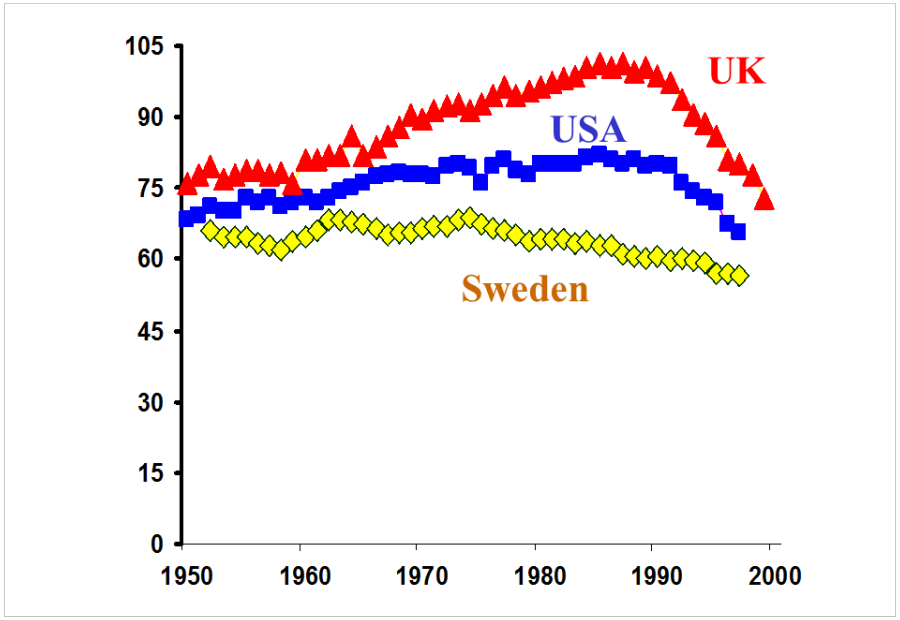
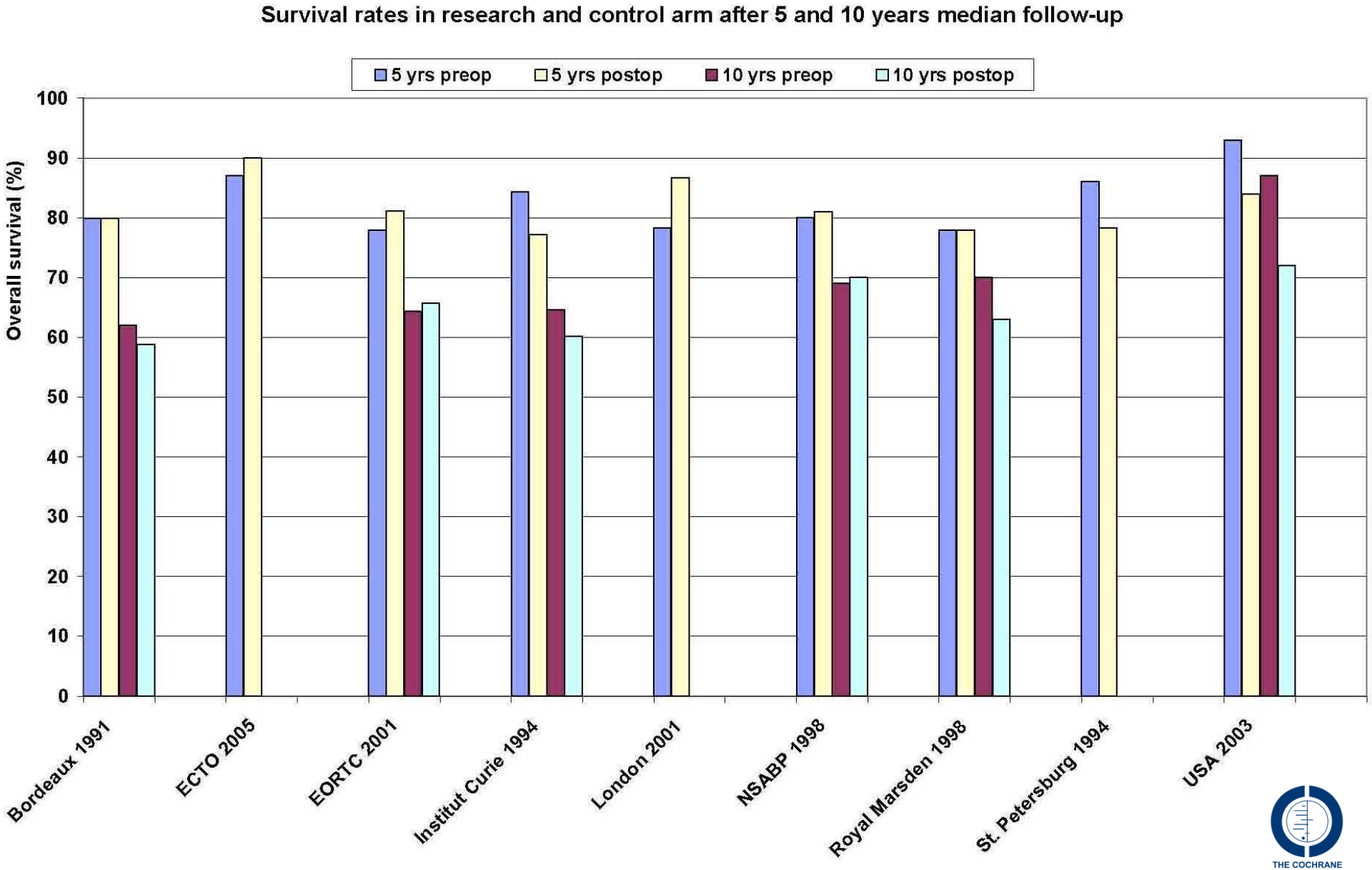
- Bröstcancer är potentiellt en generaliserad sjukdom – redan vid diagnosen
- Kirurgi är en viktig del av behandlingen - men inte nödvändigtvis som primär åtgärd



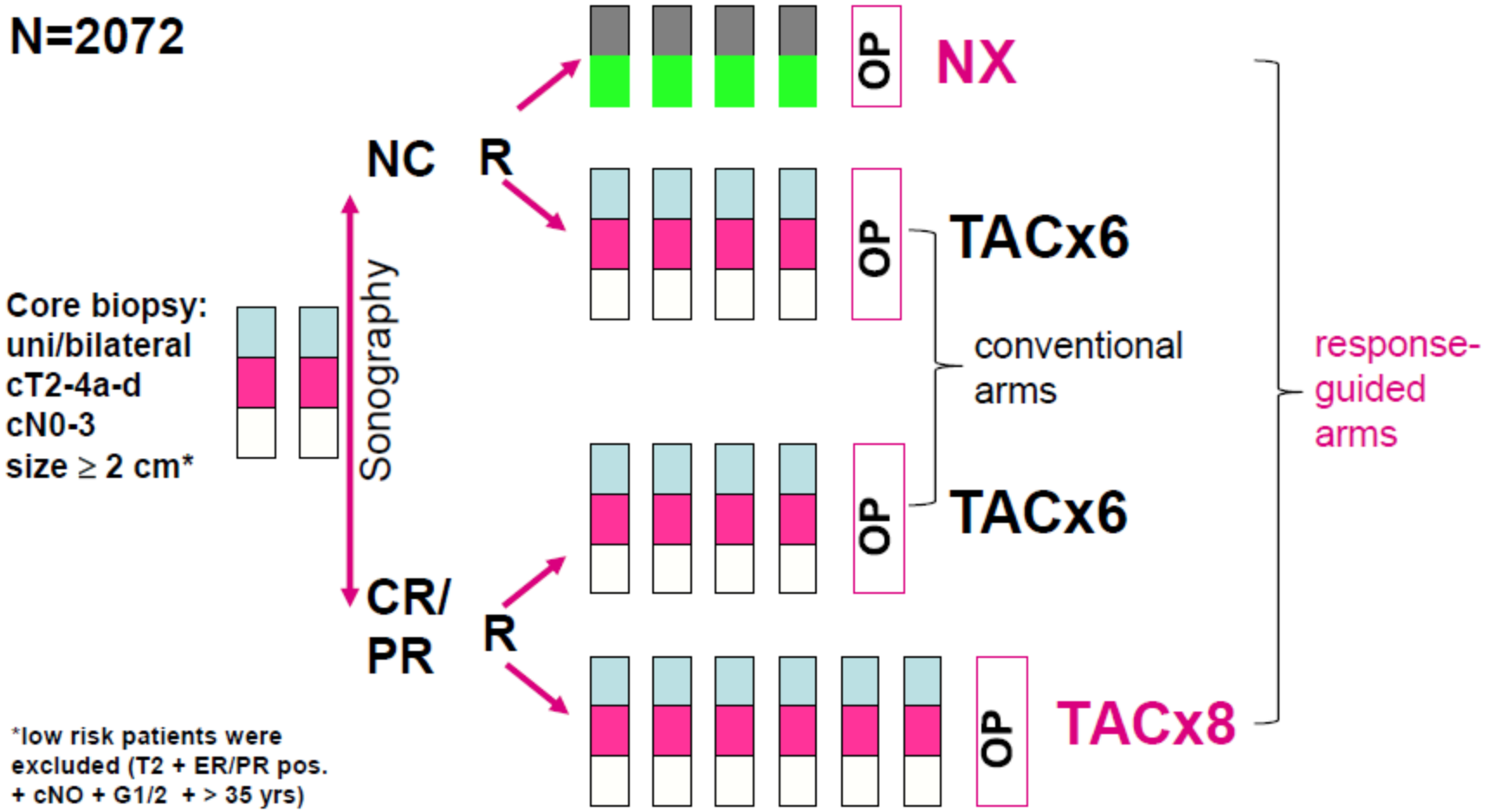
Summary of findings

Outcome	No of Participants (No of trials)	Control group risk	Relative effect (95% CI)	Absolute effect	Quality	Comments
death	4621 (10)	(24.9%)	RR 0.98 (0.87 to 1.09)	fewer/1 000	⊕⊕⊕⊕ High	Hazard ratios were used.
loco regional recurrence (excluding trials with no surgery)	4198 (8)	(8.5%)	RR 1.12 (0.92 to 1.37)	26 more/1 000	⊕⊕⊕◯ Moderate	
loco regional recurrence (studies with exclusive radiotherapy)	843 (3)	(15.9%)	RR 1.45 (1.06 to 1.97)	67 more/1 000	⊕⊕⊕◯ Moderate	
mastectomy	5292 (10)	(52.9%)	RR 0.71 (0.67 to 0.75)	166 fewer/1 000	⊕⊕⊕◯ Moderate	Substantial heterogeneity
mastectomy (excluding 2 studies)	3709 (8)	(43.1%)	RR 0.82 (0.76 to 0.89)	80 fewer/1 000	⊕⊕⊕⊕ High	Excluding two studies: one with intensive chemotherapy and one with no breast conservation in control arm in protocol.
Infectious complications	2799 (4)	(13.8%)	RR 0.69 (0.56 to 0.84)	42 fewer/1 000	⊕⊕⊕⊕ High	



THE COCHRANE COLLABORATION®

GeparTrio Trial Design



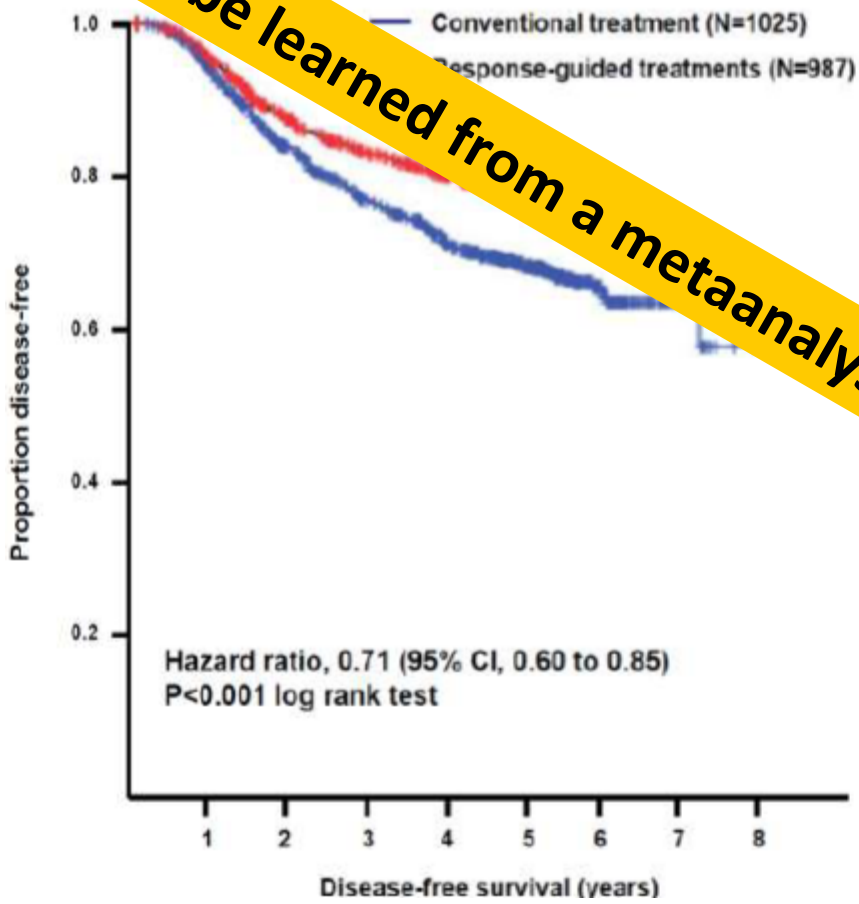
Aims

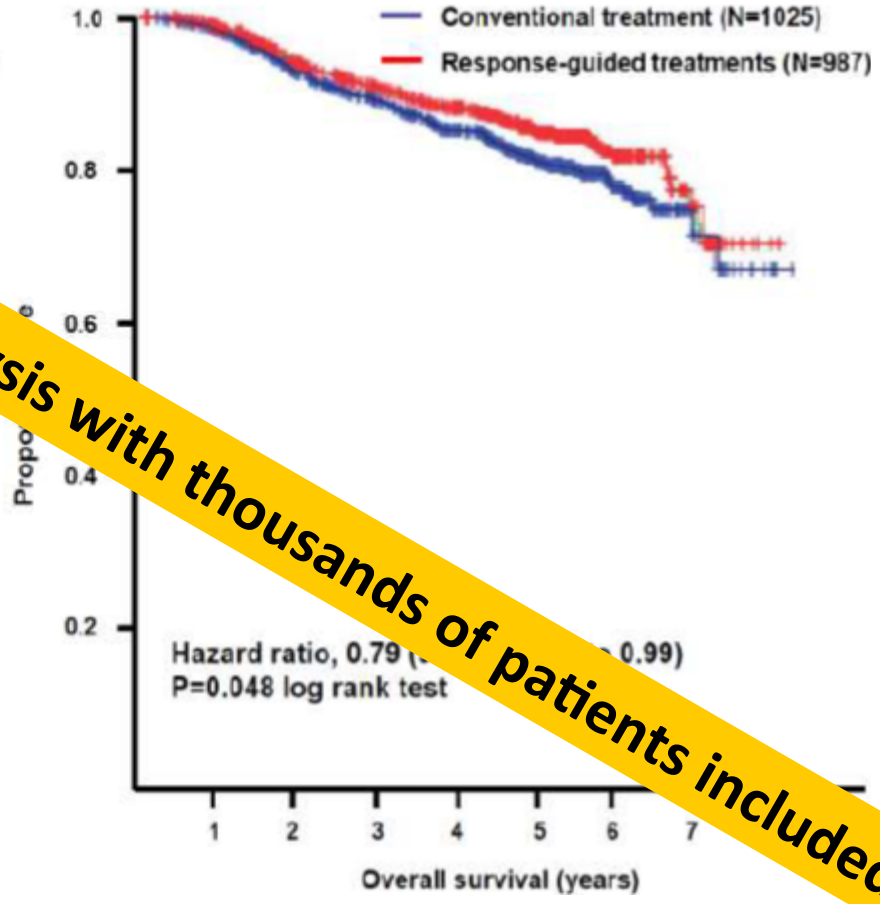
- To take advantage from the *in vivo* chemo-sensitivity test situation of neoadjuvant treatment
- To develop specific treatment strategies for patients with or without response to 2 cycles TAC
  - Responding patients:

    → treatment intensification by increased cycle number
  - Non-responding patients:

    → switch to non-cross resistant treatment

DFS and OS after
nventional (TACx6) vs. response-guided (TACx8/TAC-NX) treatment





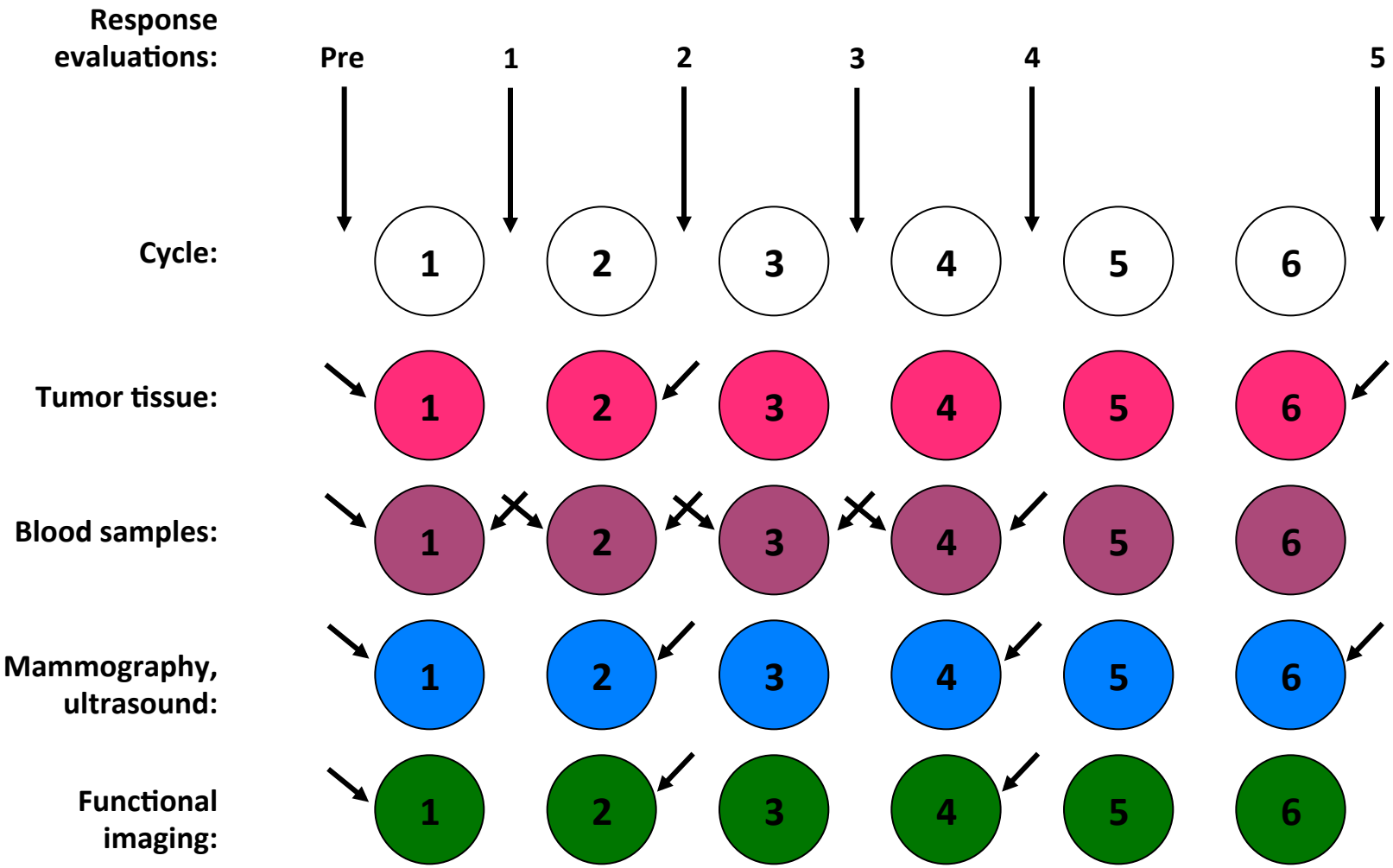
Could that be learned from a metaanalysis with thousands of patients included?

Adjuvant Systemic Therapy is a "blind" procedure: It is administered after the only opportunity for monitoring for effectiveness has been eliminated

Gabriel Hortobagyi, SA 2012

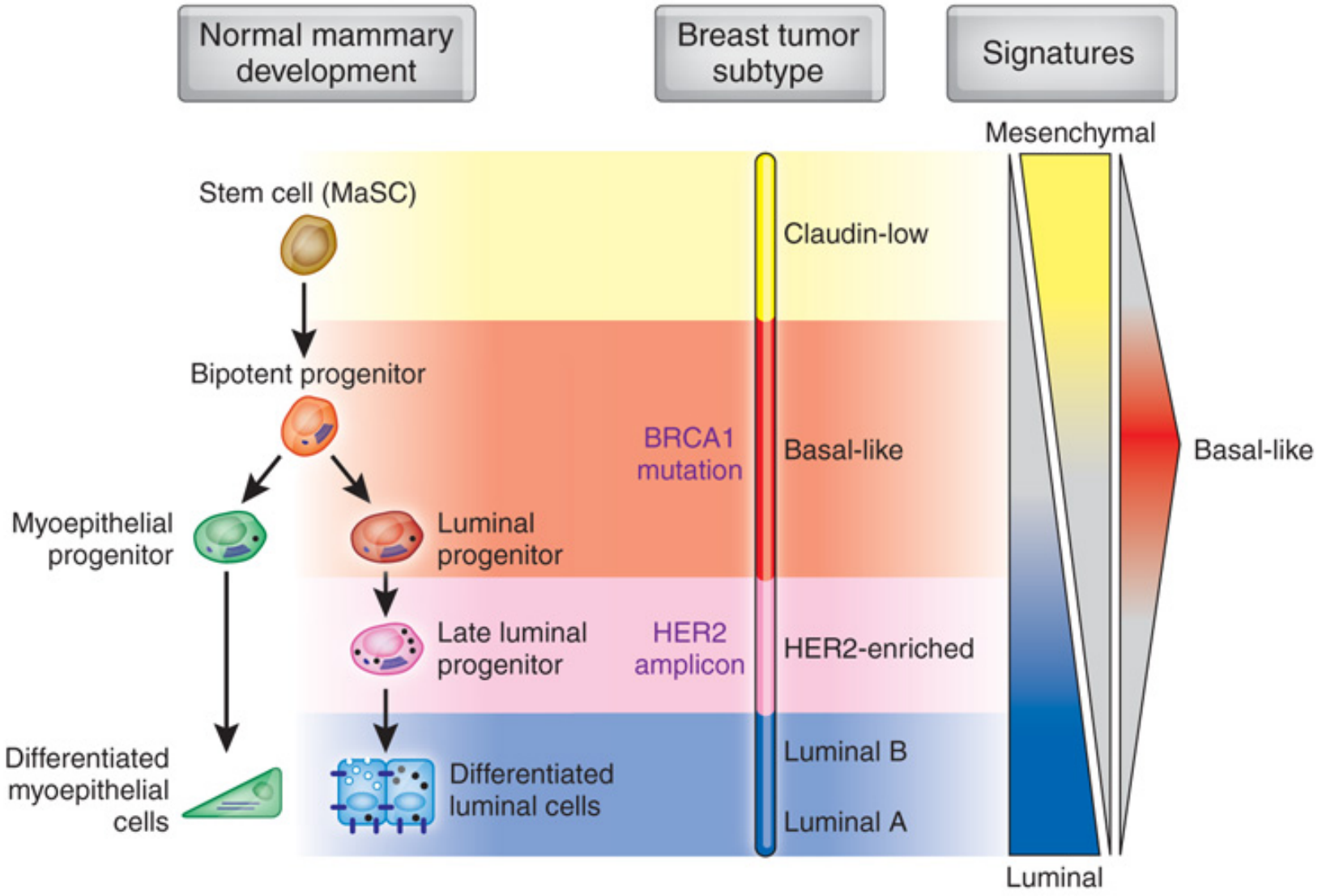
PROMIX - Preoperative treatment of breast cancer with a combination of epirubicin, docetaxel and bevacizumab

A translational trial on molecular markers and functional imaging to predict response early



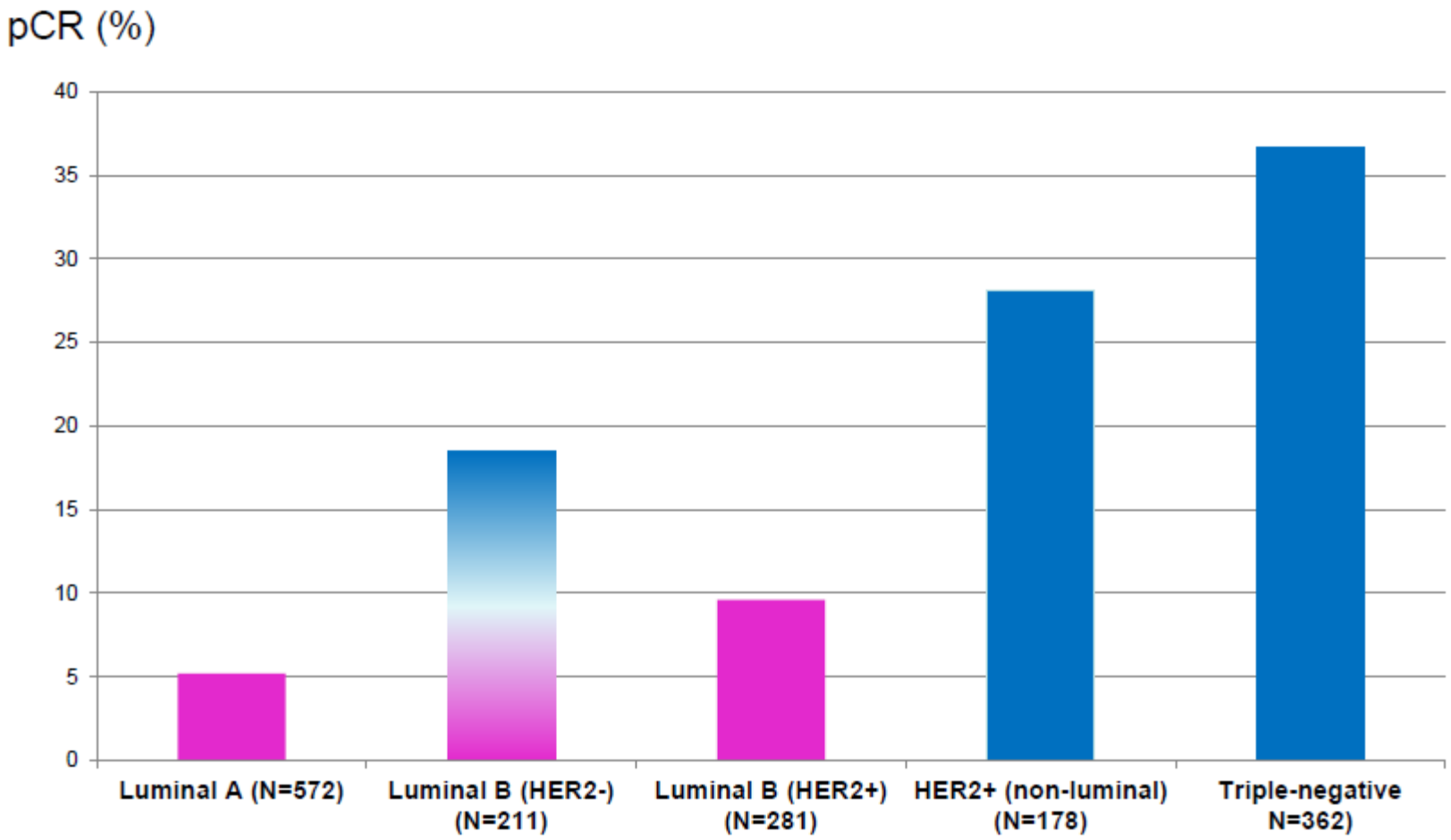
Patient and tumor characteristics		
Patients (n)		151
Age at registration (yr)		
Mean		50 (27.8-70.6)
Median		47,6
Menopausal status		
Premenopausal	90	60%
0-5 years postmenopausal	16	11%
More than 5 years postmenopausal	43	28%
Unknown	2	1%
Tumour size (mm)		
Mean		58
Median		52
≤20	4	3%
>20	138	91%
Unknown	9	6%
Lymph node metastasis (axilla)		
Positive	81	54%
None/Not known	70	46%

Patient and tumor characteristics		
Histological grade acc. to Elston & Ellis		
Grade I	4	3%
Grade II	47	31%
Grade III	33	22%
Unknown	67	44%
Hormone receptor status		
ERα positive (%)		
<10	107	71%
>10	41	27%
Unknown	3	2%
PR positive (%)		
<10	65	43%
>10	83	55%
Unknown	3	2%
ER and/or PR positive		
Positive	111	74%
Negative	37	25%
Unclassified	3	2%



Prat & Perou Nat Med 2009

pCR Rates by Subtype



Pathological response stratified by subtype

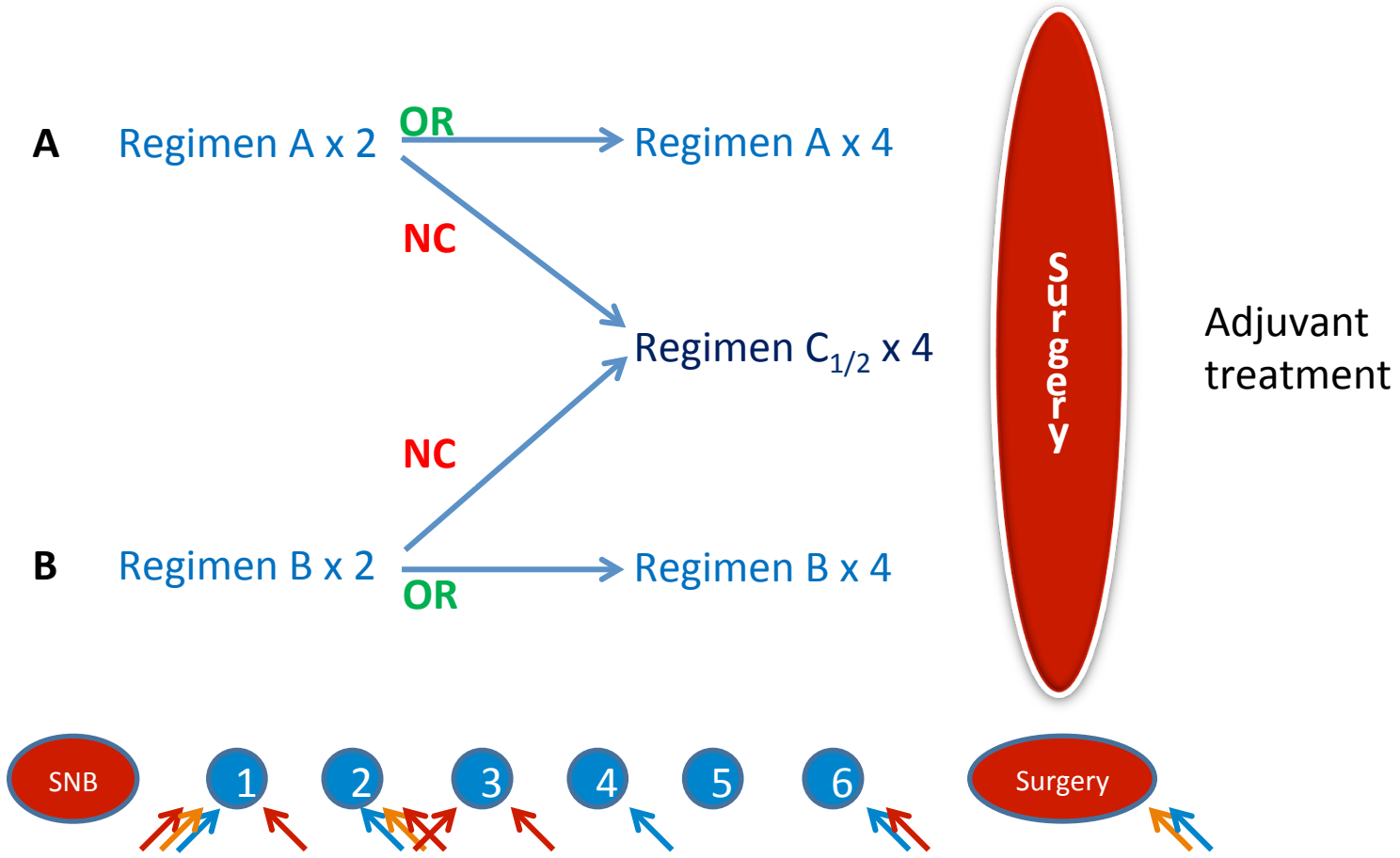
	pCR	pPR/NC	PD	Unknown	Total
Subtype					
Luminal A	0 (0%)	23 (21%)	0 (0%)	3 (33%)	26 (17%)
Luminal B	10 (50%)	55 (50%)	2 (100%)	4 (44%)	75 (50%)
TNBC	10 (50%)	24 (22%)	0 (0%)	2 (22%)	37 (25%)
Unclassified	0 (0%)	8 (7%)	0 (0%)	0 (0%)	13 (9%)

Förutsättning för translationell forskning

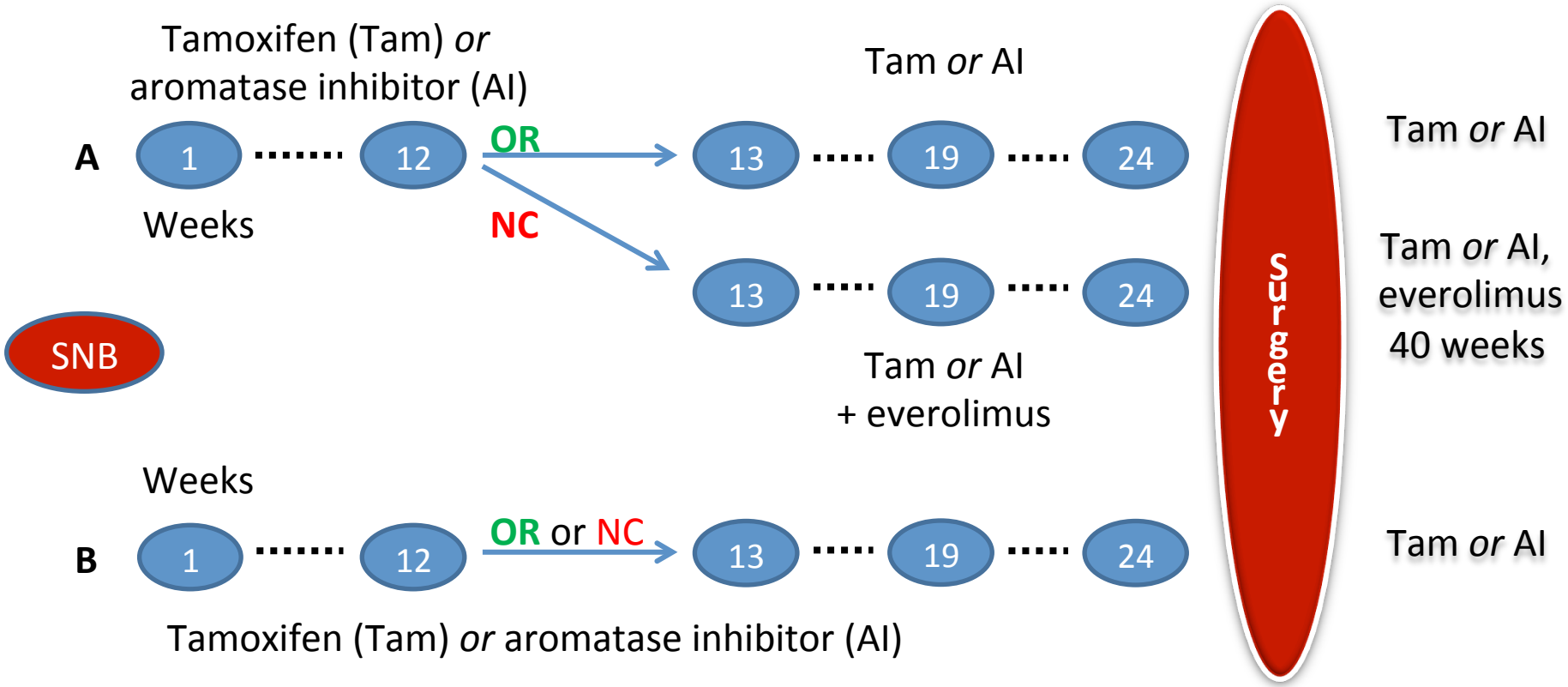
- Snabb utveckling av tumörbiologisk kunskap med avancerad teknologi
- Functional imaging ökar kunskapen om ”vad som händer” i tumören under behandling
- ”*in vivo*” tillåter test av nya målriktade droger i tidigare obehandlad tumör
- Seriella tumörbiopsier och blodprovtagningar
- Nära samarbete mellan radiolog, patolog, labforskare, kirurg och onkolog

Neoadjuvant response-guided treatment of breast cancer based on molecular subtypes.

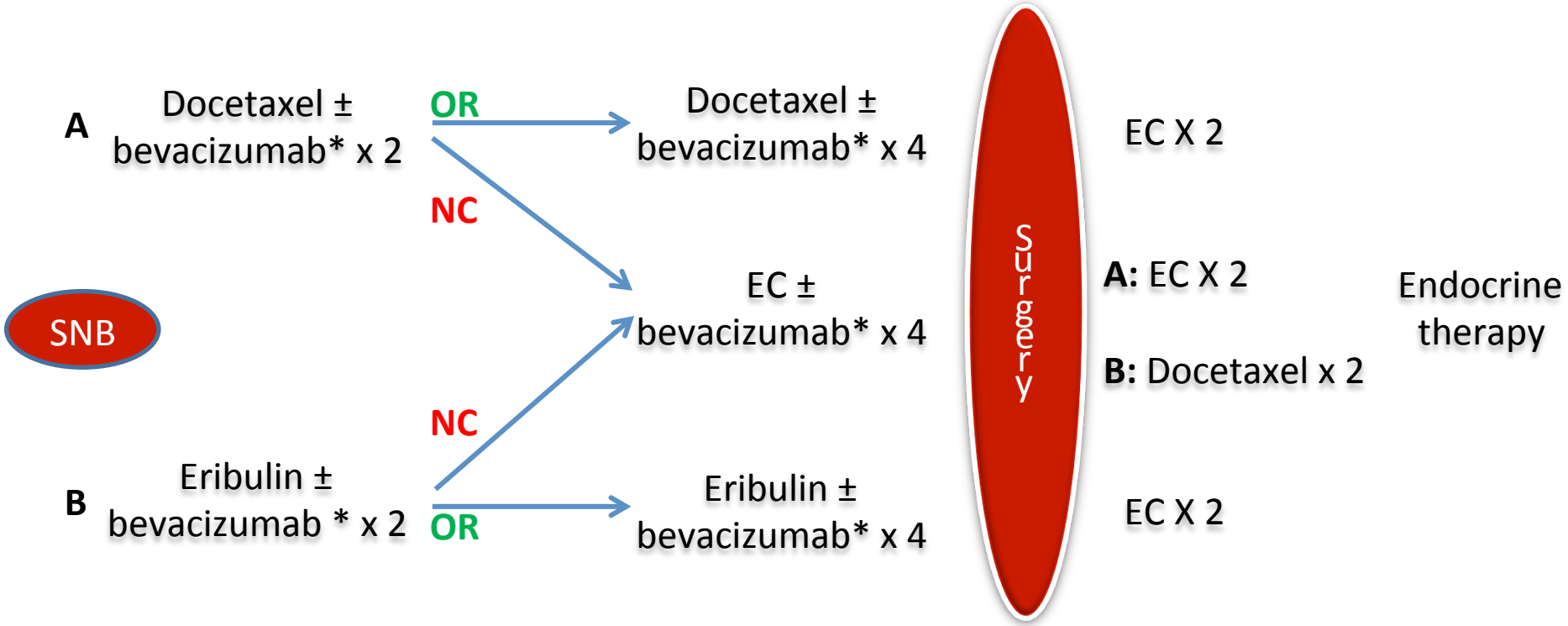
A set of exploratory translational trials


A
Regimen A x 2
OR
Regimen A x 4
NC
Regimen C1/2 x 4
NC
B
Regimen B x 2
OR
Regimen B x 4
Surgery
Adjuvant treatment
SNB
1
2
3
4
5
6
Surgery
Biopsy:
Blood:
Radiology/funct. imaging:
OR: objective response; NC: no change

Luminal A

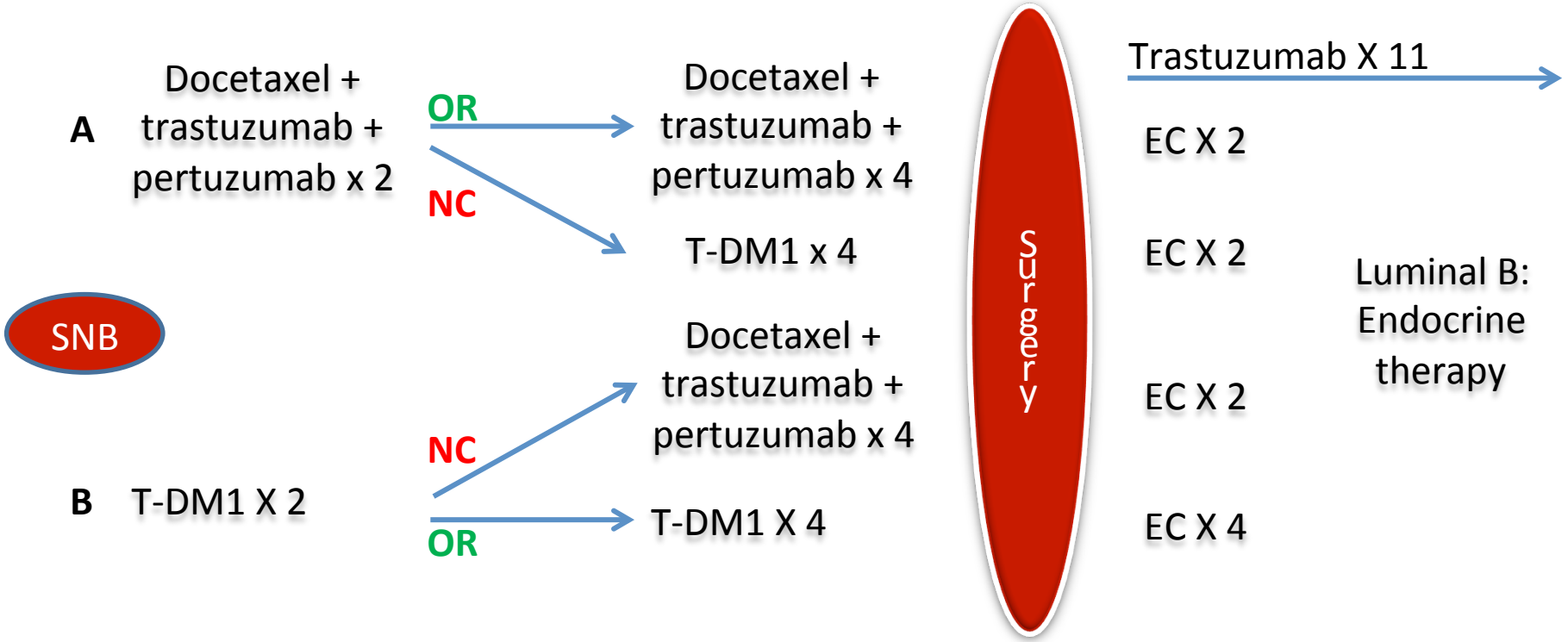

Tamoxifen (Tam) *or* aromatase inhibitor (AI)
A
1
12
Weeks
OR
NC
13
19
24
Tam *or* AI
Tam *or* AI
Tam *or* AI, everolimus 40 weeks
SNB
Tam *or* AI + everolimus
Surgery
Weeks
B
1
12
OR or NC
13
19
24
Tam *or* AI
Tamoxifen (Tam) *or* aromatase inhibitor (AI)

Luminal A $_{N+}$, Luminal B

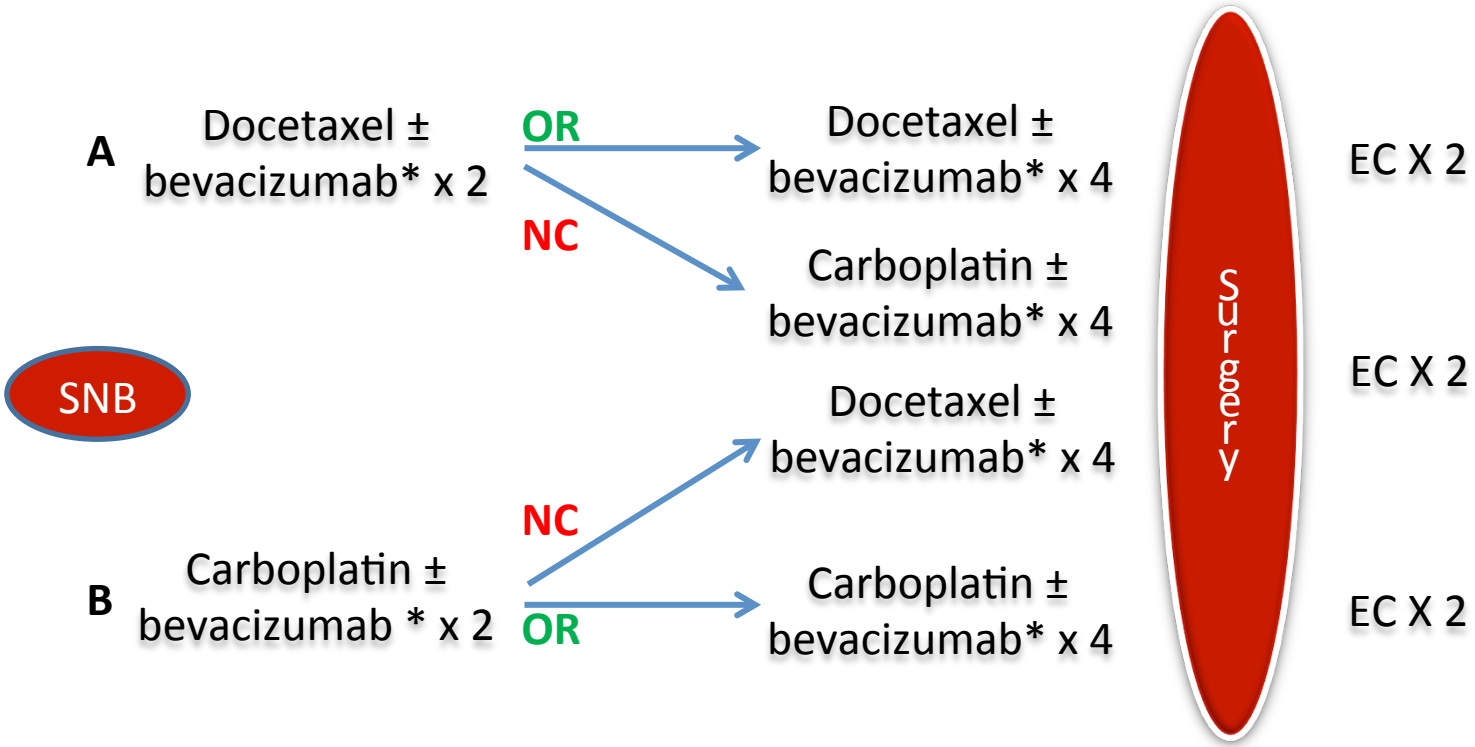


*: biomarker-guided randomization

HER2+ (ER-/PR- *or* luminal B)



Triple-negative breast cancer



*: biomarker-guided randomization

PROMIX - Preoperative treatment of breast cancer with a combination of epirubicin, docetaxel and bevacizumab

A translational trial on molecular markers and functional imaging to predict response early

Epirubicin +
docetaxel (Taxotere ®) } x 2

CR*

SD,PR*

PD*

Epirubicin +
docetaxel (Taxotere®) } x 4

Epirubicin +
docetaxel (Taxotere ®) +
bevacizumab (Avastin ®) } x 4

Individualized
treatment

*: OR = Objective response; SD = Stable disease, PD = Progressive disease

Breast Cancer Includes Several Distinct Molecularly Defined Subtypes

Molecular subtype[1,2]	Characteristic biomarkers	Prevalence[3]
Luminal A	ER+, PgR+, HER2–	28–31%
Luminal B	ER+, PgR+, HER2+	19–23%
HER2-enriched	ER–, PgR–, HER2+	12–21%
Basal-like	ER–, PgR–, HER2– Cytokeratins EGFR	11–23%
Claudin-low[3]	ER–, PgR–, HER2– Low/absent expression of luminal differentiation markers High enrichment for EMT markers, immune response genes and cancer stem cell-like features	7–14%

EGFR = epidermal growth factor receptor; EMT = epithelial-to-mesenchymal transition; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; PgR = progesterone receptor; TNBC = triple-negative breast cancer; 1. Sørlie et al. PNAS 2001; 2. Nguyen et al. J Clin Oncol 2008; 3. Prat et al. Breast Cancer Res 2010

Intrinsic subtype	Clinico-pathologic surrogate definition	Notes
Luminal A	**'Luminal A-like'** *all of:* ER and PgR positive HER2 negative Ki-67 'low'[a] Recurrence risk 'low' based on multi-gene-expression assay (if available)[b]	The cut-point between 'high' and 'low' values for Ki-67 varies between laboratories.[a] A level of <14% best correlated with the gene-expression definition of Luminal A based on the results in a single reference laboratory [23]. Similarly, the added value of PgR in distinguishing between 'luminal A-like' and 'luminal B-like' subtypes derives from the work of Prat et al. which used a PgR cut-point of ≥20% to best correspond to Luminal A subtype [24]. Quality assurance programmes are essential for laboratories reporting these results.
Luminal B	**'Luminal B-like (HER2 negative)'** ER positive HER2 negative and *at least one of:* Ki-67 'high' PgR 'negative or low' Recurrence risk 'high' based on multi-gene-expression assay (if available)[b]	'Luminal B-like' disease comprises those luminal cases which lack the characteristics noted above for 'Luminal A-like' disease. Thus, either a high Ki-67[a] value or a low PgR value (see above) may be used to distinguish between 'luminal A-like' and 'luminal B-like (HER2 negative)'.
	'Luminal B-like (HER2 positive)' ER positive HER2 over-expressed or amplified Any Ki-67 Any PgR	
Erb-B2 overexpression	**'HER2 positive (non-luminal)'** HER2 over-expressed or amplified ER and PgR absent	
'Basal-like'	**'Triple negative (ductal)'** ER and PgR absent HER2 negative	There is an 80% overlap between 'triple-negative' and intrinsic 'basal-like' subtype. Some cases with low-positive ER staining may cluster with non-luminal subtypes on gene-expression analysis. 'Triple negative' also includes some special histological types such as adenoid cystic carcinoma.

Translational network

- Rapid development of tumor biology
- Functional imaging adds to ”anatomical” imaging
- Trend to replace adjuvant by neoadjuvant *”in vivo”* treatment
- Early testing of new targeted drugs
- Serial biopsies and blood samples
- Close cooperation between radiologist, pathologist, laboratory scientists, surgeons and oncologists