Neoadjuvant Treatment of Breast Cancer

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Conflicts or Am I a Pharmaceutical Company Slut?

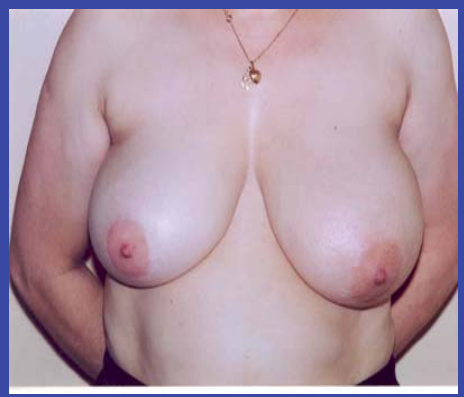
- Advisory Boards
  - Roche, GSK, sanofi aventis, Genetech, Array, Lilly, Novartis, AstraZeneca, Pfizer,
- Research Funding
  - Roche, GSK, AstraZeneca

Neoadjuvant Chemotherapy

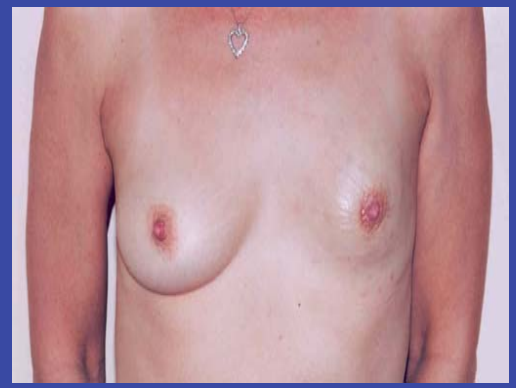
- Systemic therapy given prior to surgery
  - Operable
  - Locally Advanced Breast Cancer (LABC)
  - Medically unstable patients
- Cytotoxic chemotherapy
- Hormonal therapy
  - Studies of AI vs Tamoxifen
- Presurgical/window studies
  - New agents, end point of tissue analysis

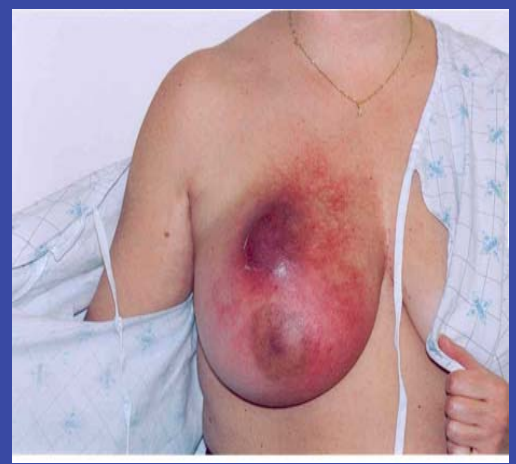
What are the indications for Neoadjuvant therapy?

Operable **Goal** Inoperable



- **Improve surgical options**
- **Deliver adequate "adjuvant" chemotherapy**
- **Provide in vivo anti-tumour assessment**
- **Assess surrogate biologic endpoints for response & survival**





Evolution of Modern Adjuvant Chemotherapy – 1975 -2009

1970s

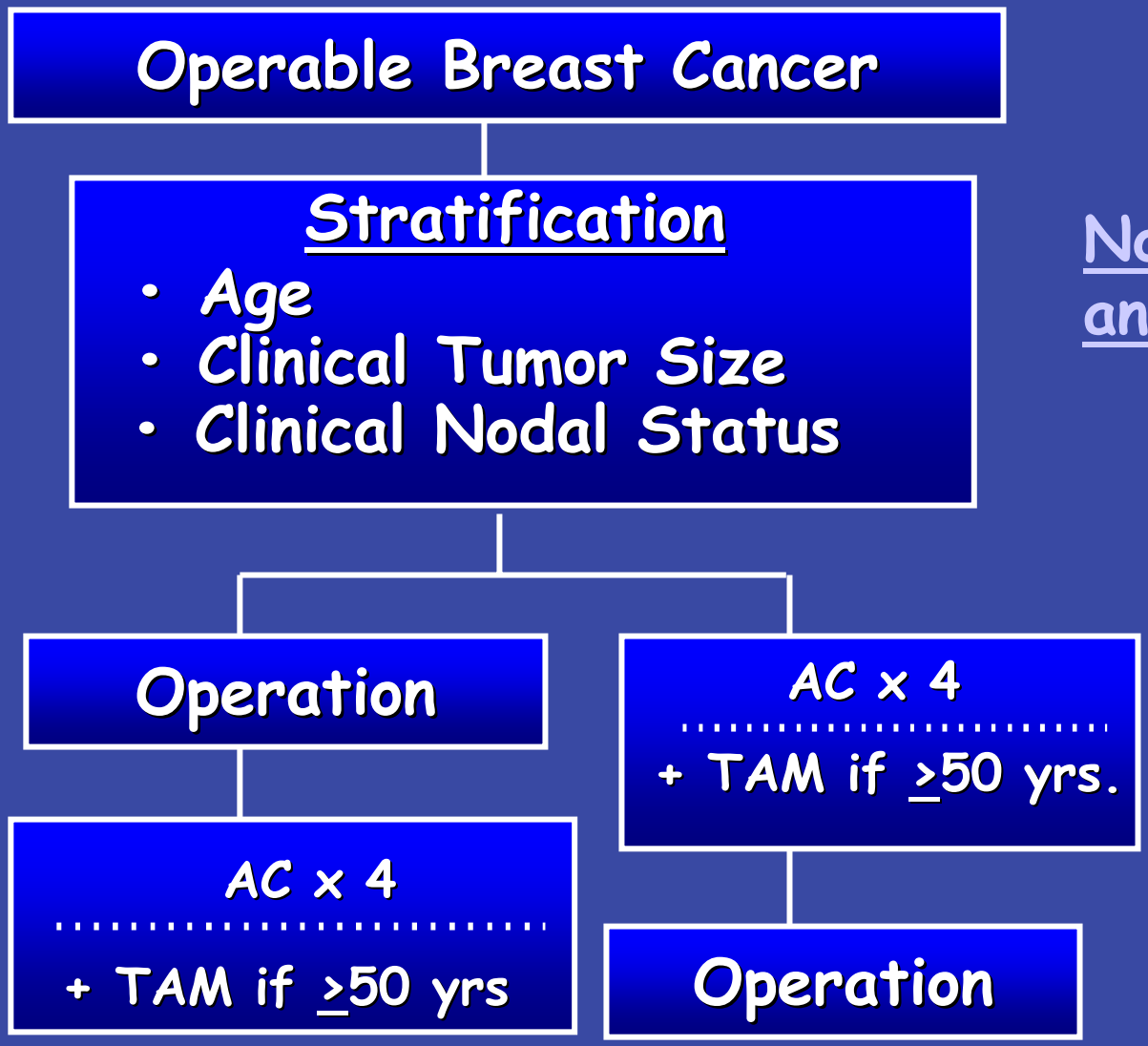
1980s

1990s

2000s

- **Seminal First Step 1975**
  - CMF p.o.
- **Transition Era 1980 -1990**
  - AC, FAC
- **3rd Generation Regimens 1990 -2000**
  - Epirubicin Combinations: CEF/FEC
  - Questions of Dose
  - Sequential taxanes: AC→ T
  - Combinations taxane: TAC
  - Which Taxane and Which Schedule
- **Predictive Era 2000 +**
  - Addition of Trastuzumab
  - Do ER+ tumors benefit from chemo
  - Are Anthracyclines Necessary?
  - Who benefits from Taxanes
  - Other biologics – antiangiogenics etc

Operable Breast Cancer: NSABP B-18



No difference in DFS and OS

Lumpectomy Rates

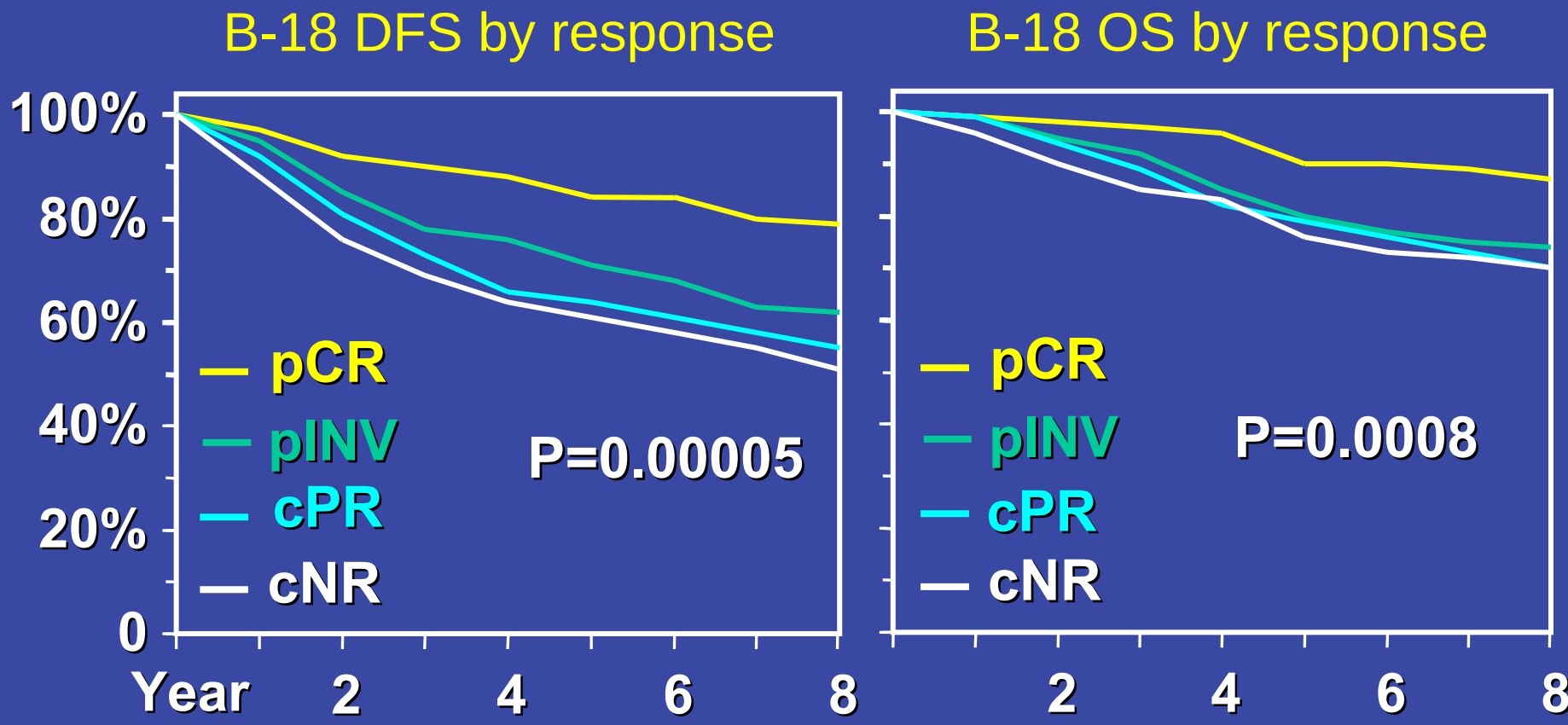
60% vs 68%

Preop AC

cCR	pCR
36%	13%

Neoadjuvant therapy - Operable Breast Cancer

- Clinical response predicts overall survival
- Pathologic response predicts overall survival



Wolmark N: CDC, 2000

Neoadjuvant Chemo – NON LABC

- Benefits
  - Assessment of response to chemo
  - Time for consideration of surgical options - ?BRCA+ etc
  - BCS in borderline situations
  - No delay in chemo
- Risks
  - Lack of knowledge of axilla unless SNLD is done prior
  - Delays surgery which in many cases may be the most important treatment
  - Clinical CR not usually a Pathological CR
  - Will the patient have the surgery?

Reminder of LABC

- **LABC**
  - 10 -15% of all new Breast Cancers
  - Higher incidence of HER2 +, young women, PABC
  - LABC, Inflammatory BC
  - Sometimes neglected, sometimes just aggressive
- **Prognosis is poor**
  - local recurrence
  - systemic relapse
  - overall survival
  - **15 yr OS**
    - **20% IBC, 40% NIBC**

Challenges/Objectives in the Neoadjuvantly treated Breast Cancer

- Surgical oncology
- Who to send for preoperative therapy?
- Role of breast conservation
- Role of SLN surgery
- Surgery on relapse

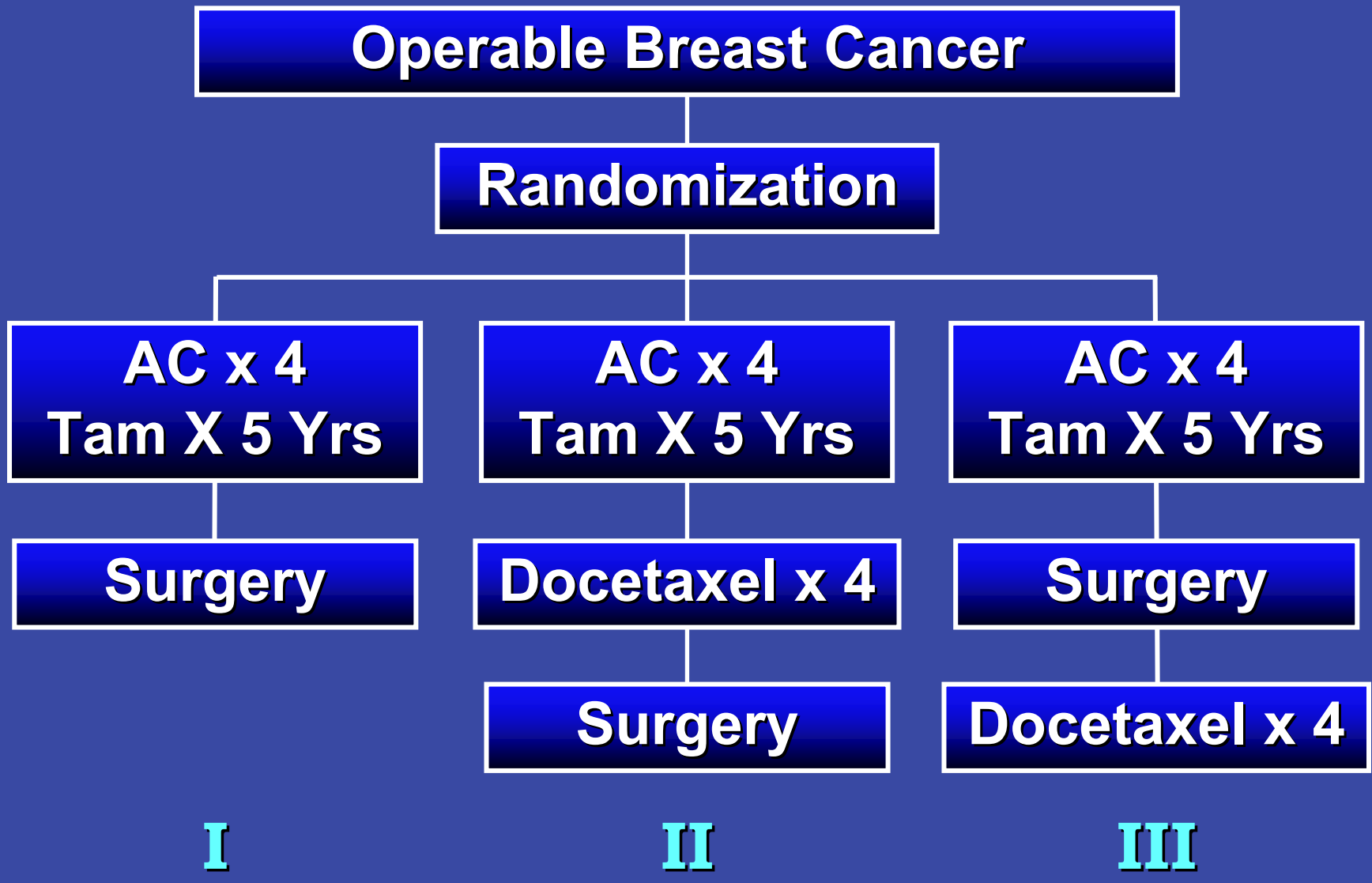
- Medical oncology
- What drugs to give for preoperative therapy?
- How can we improve response rates?
- What to give on relapse?

- Radiation oncology
- Combined chemo-rads?
- Role of breast conservation
- Radiotherapy for inoperable/progressive disease despite NAT
- Radiotherapy on relapse

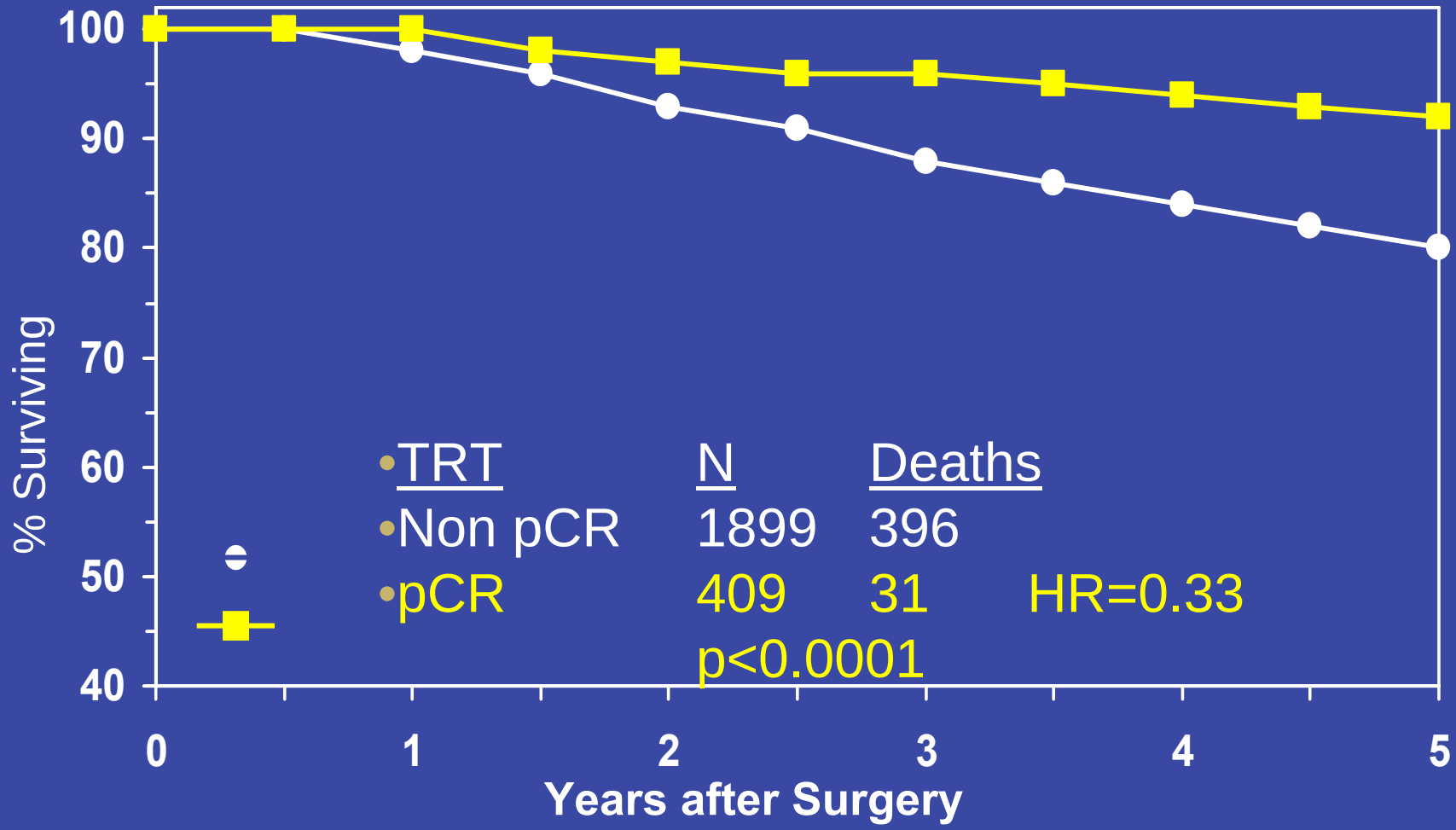
Measuring Benefit from Neoadjuvant therapy

- Does response predict for overall survival?
- What is clinical CR?
- What is pathological CR?
- Does it affect surgical outcomes?

B-27 Schema (n=2,411)

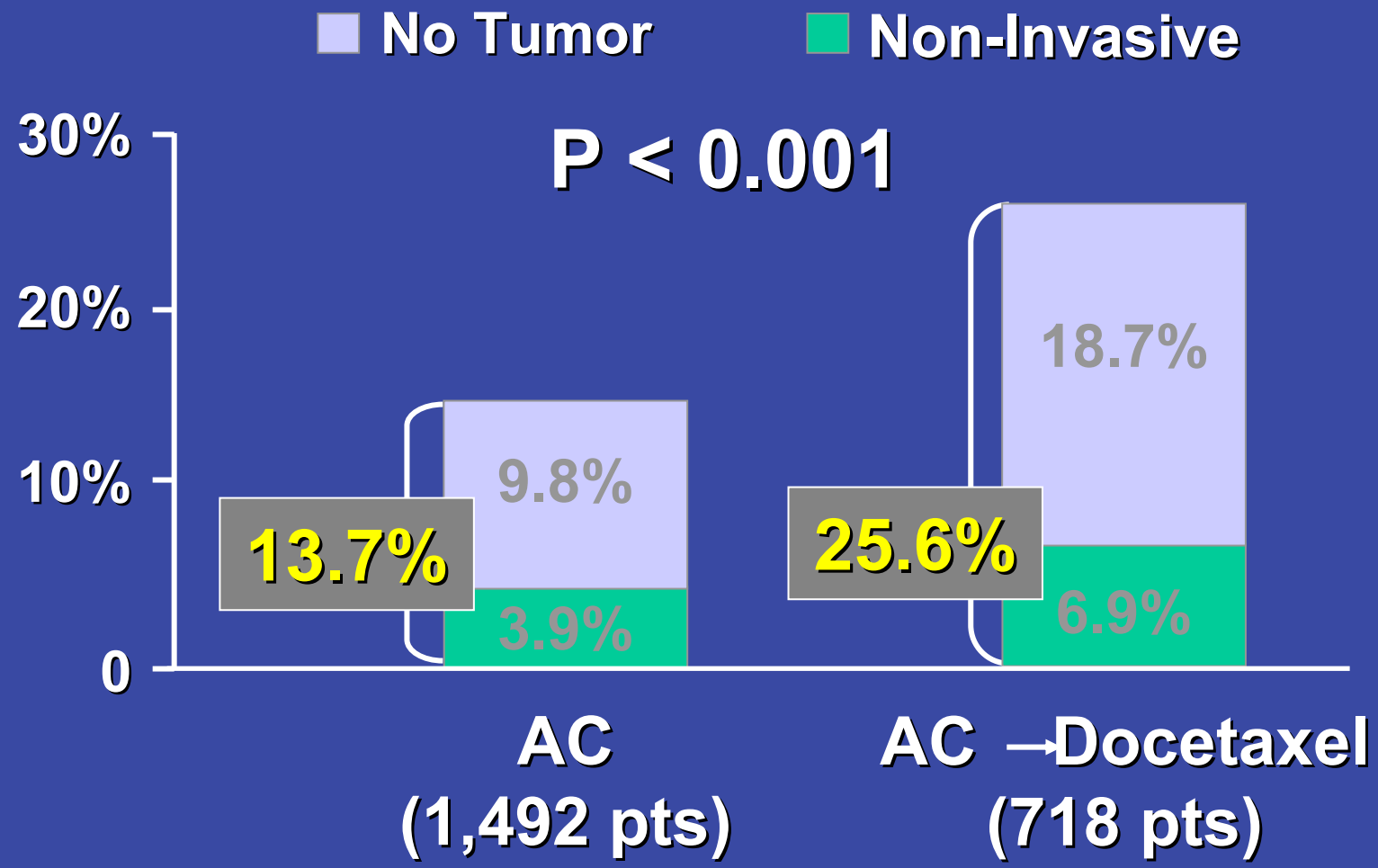


Clinical response and pathologic response are currently used as a surrogate of survival and as a tool to compare chemotherapy regimens

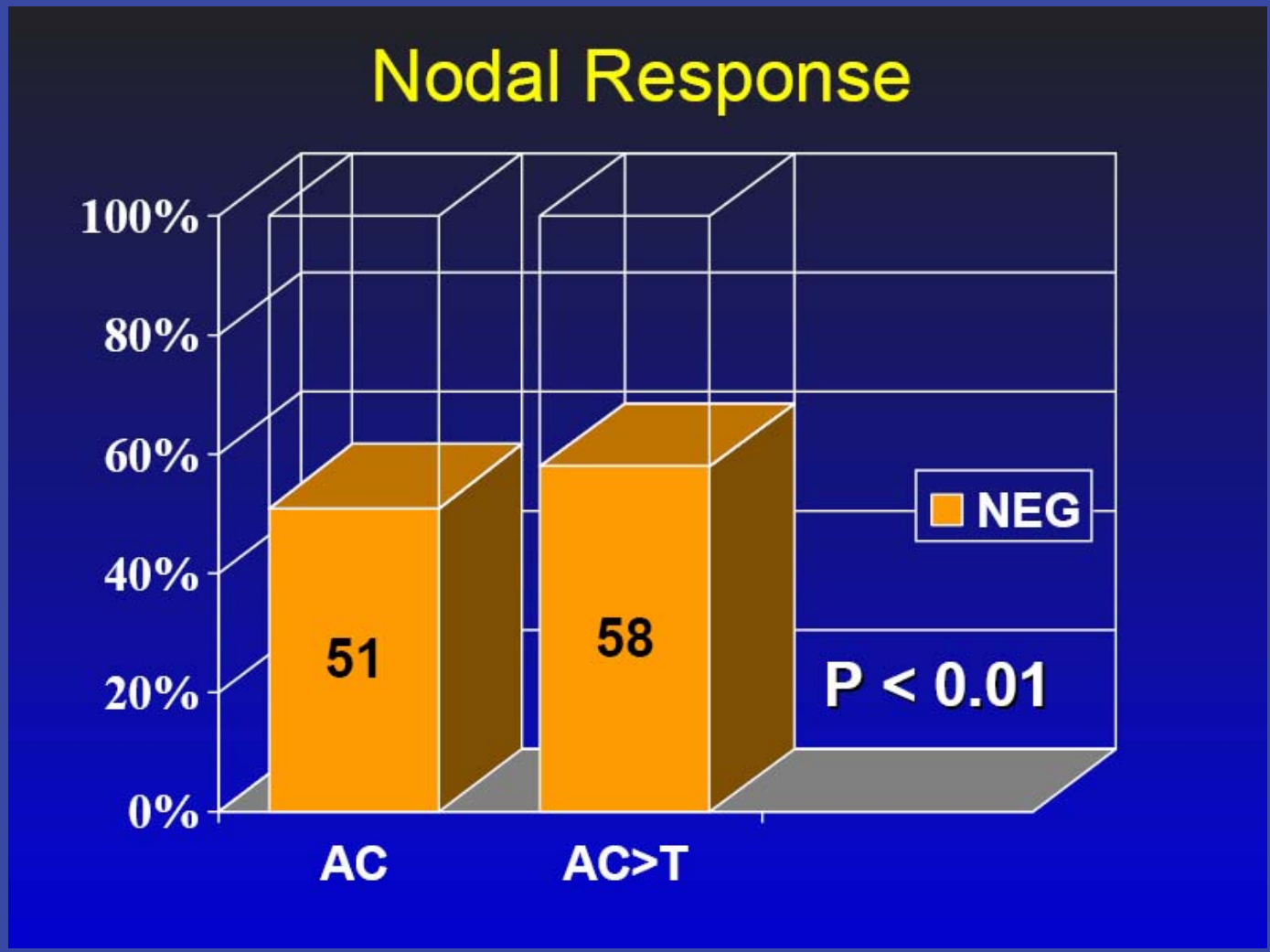


NSABP B-27: Overall Survival - pCR vs. non-pCR patients (Bear JCO 2003)

B-27
Pathologic Response (pCR) in Breast



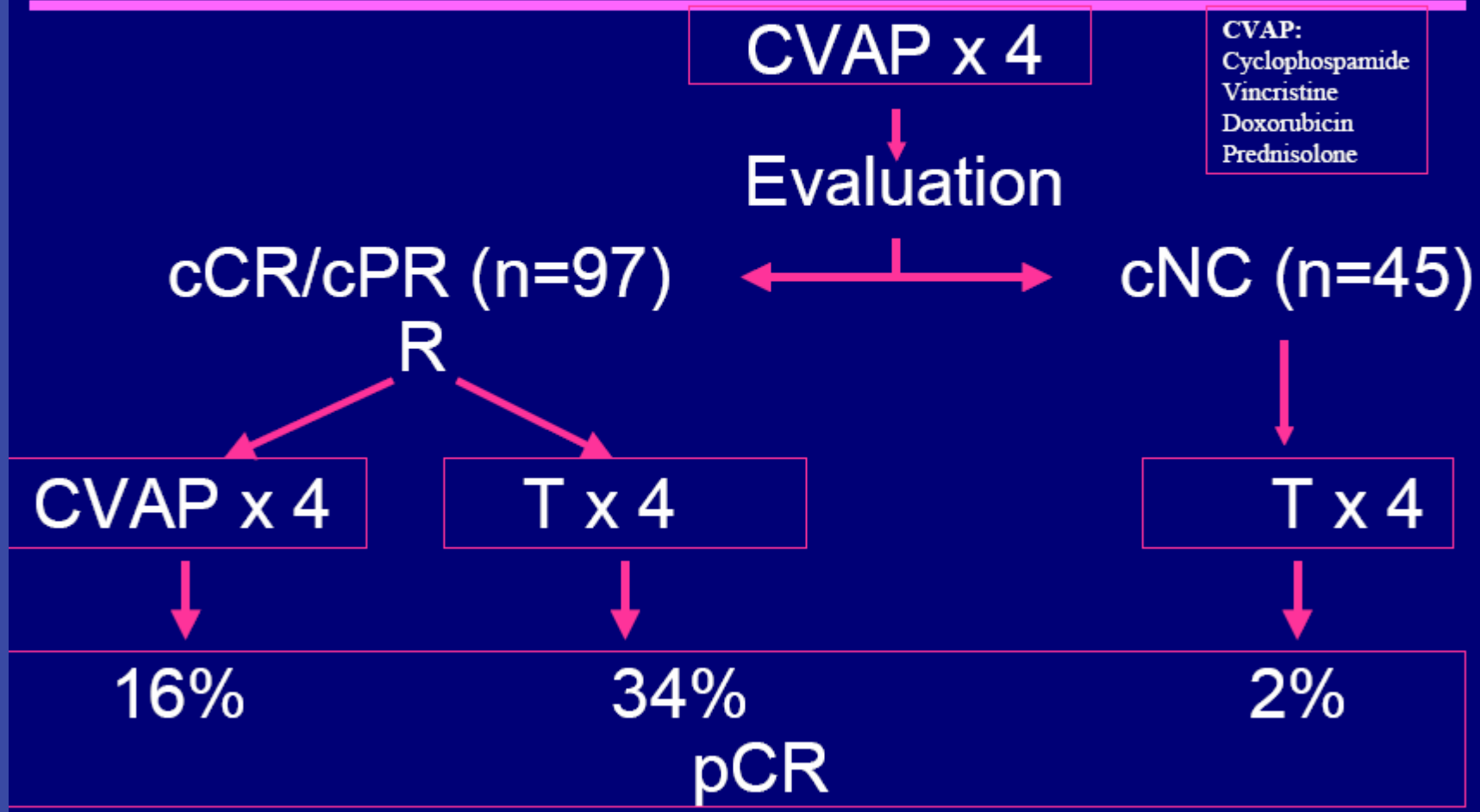
B-27: Nodal Down-staging



Rastogi P, et al. J Clin Oncol 2008;26:778-85

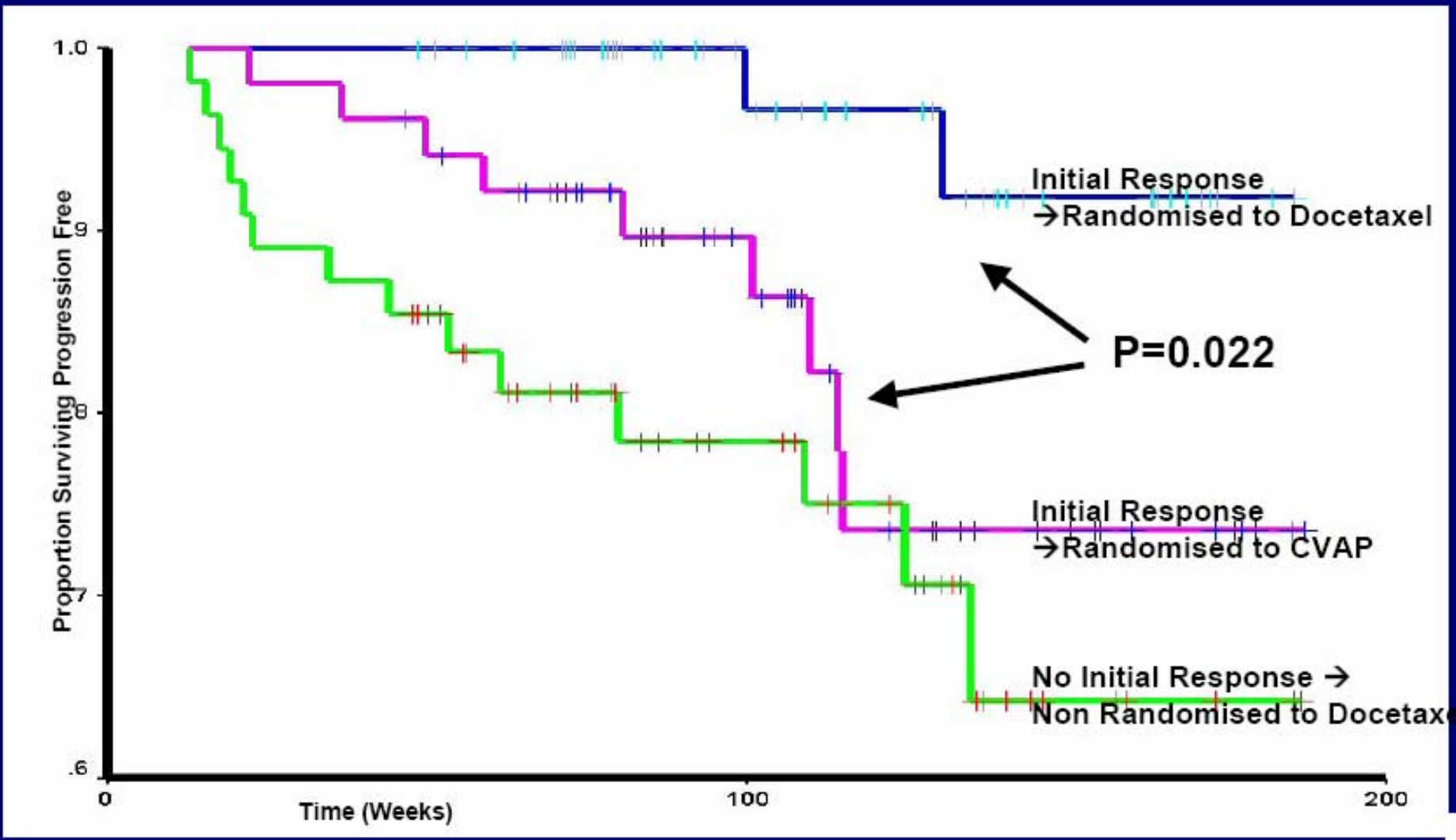
Aberdeen Trial

n = 133 Patients T>3cm or IIIB



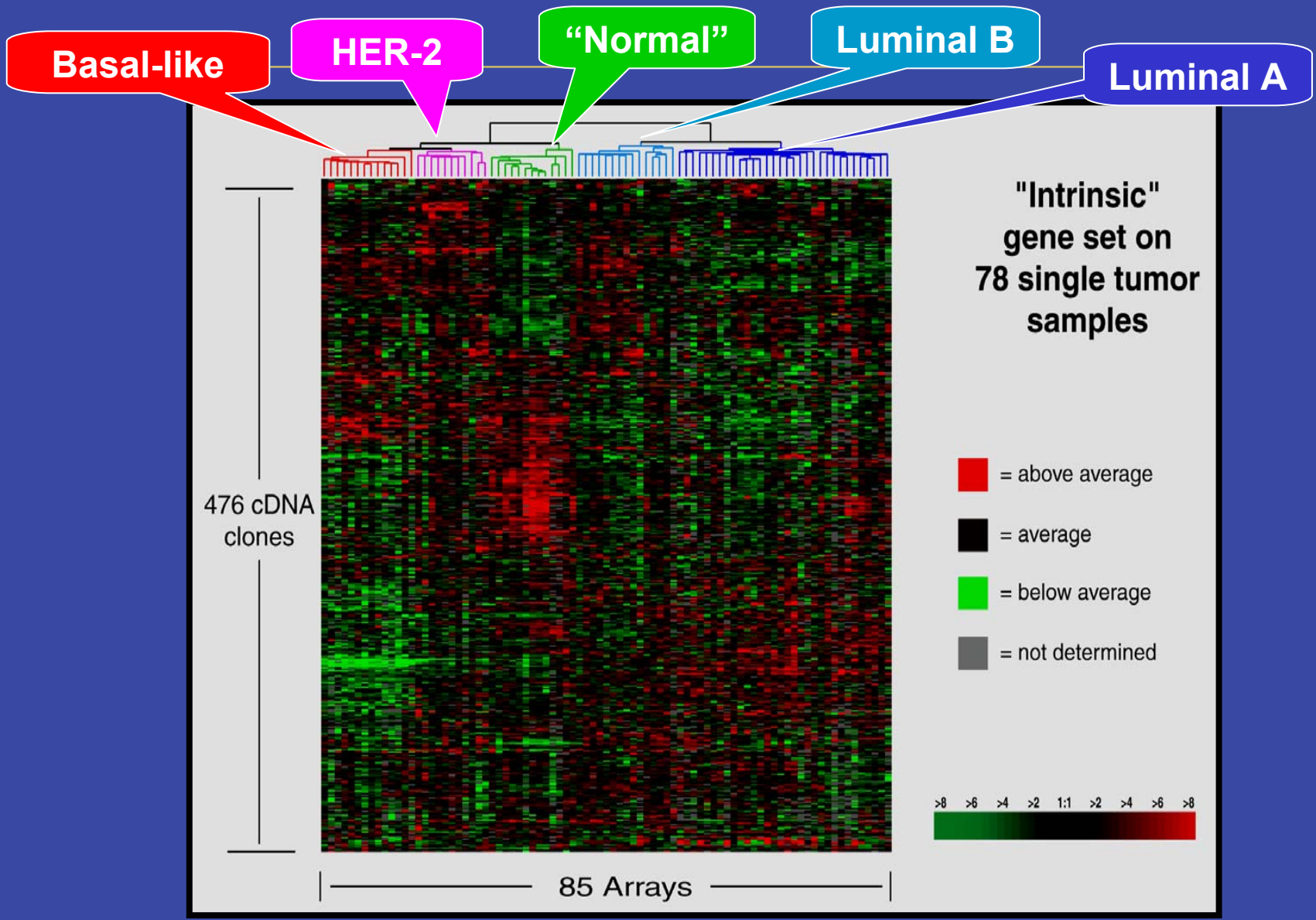
Eremin O et al. Breast Cancer Res Treat 57:29 1999

Progression-free Survival in the Aberdeen-Study (median F-up: 104 wks)



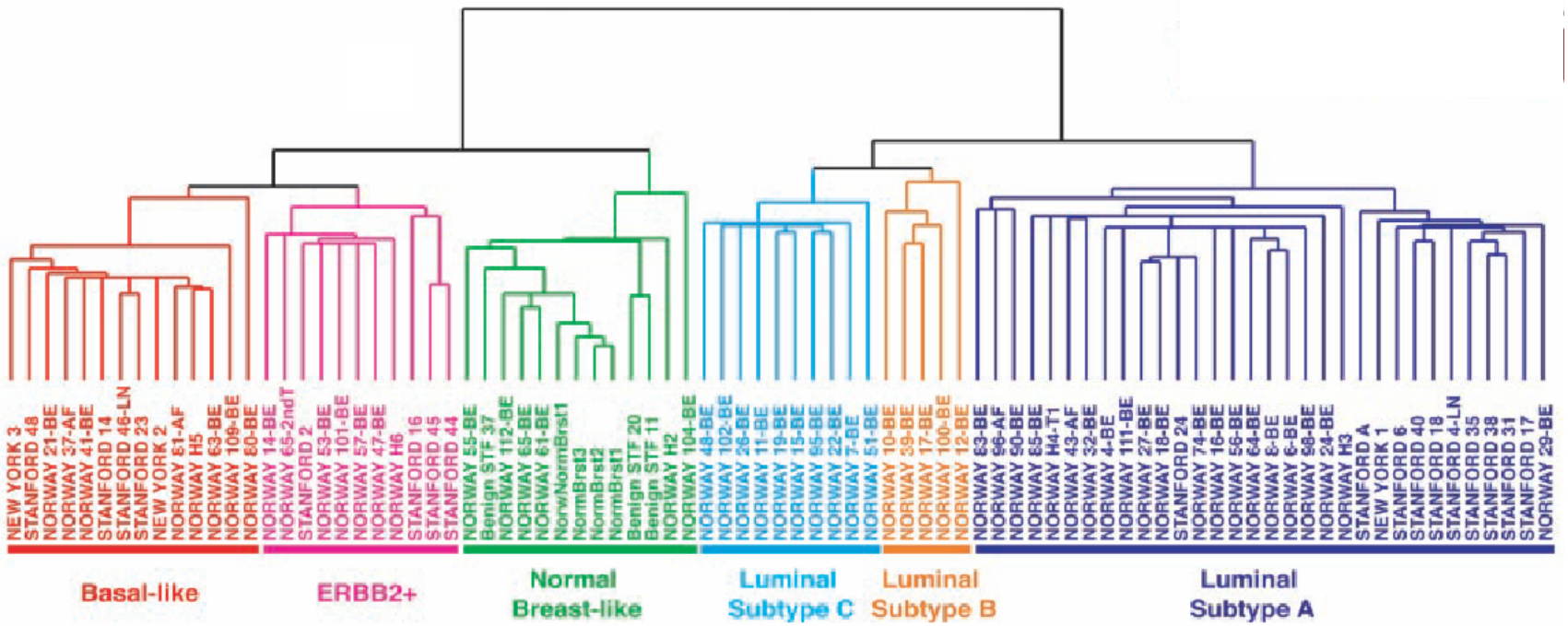
Heys SD, Clin Breast Cancer 2002

Breast Cancer is not ONE Disease

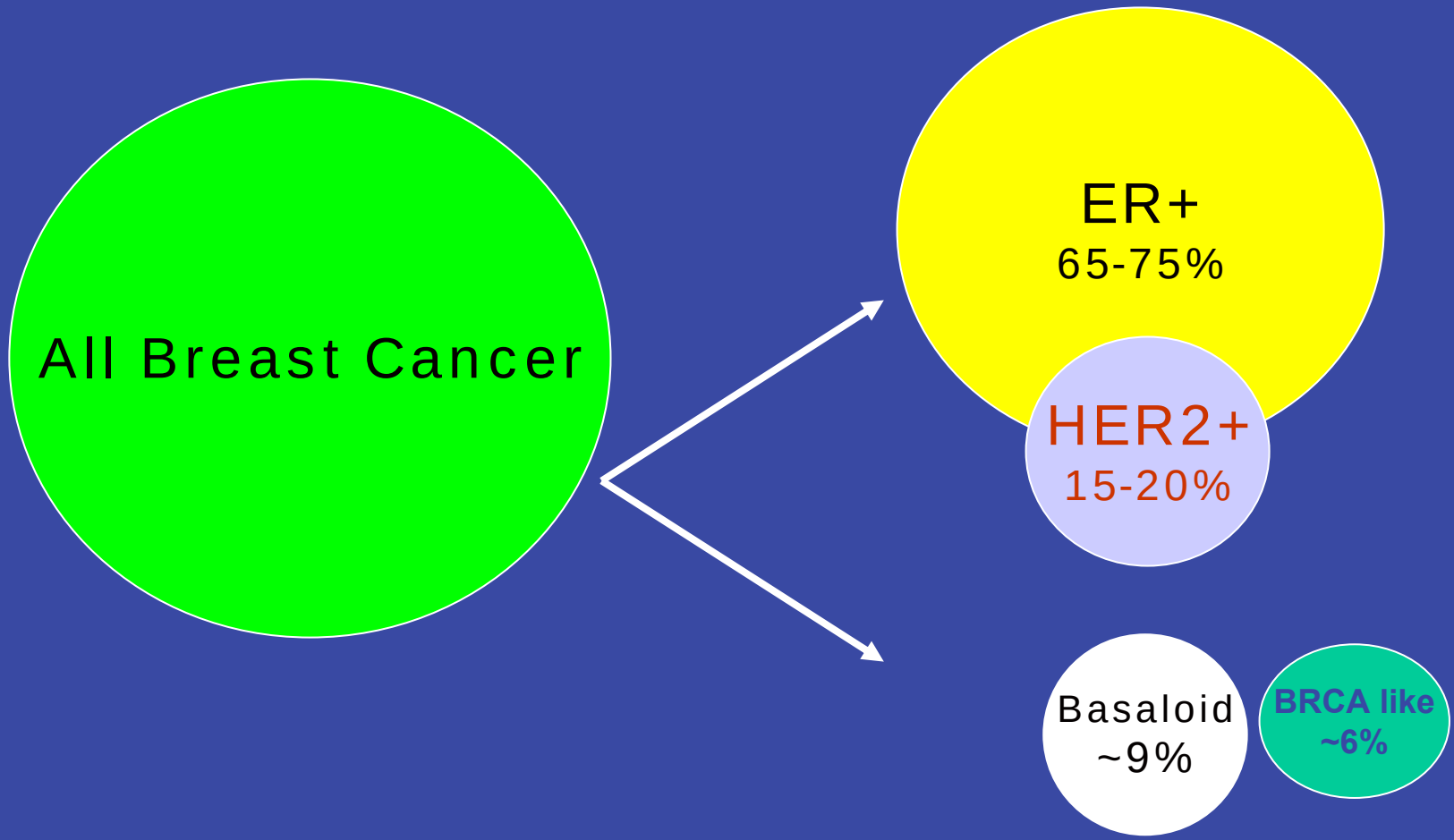


Sorlie T et al, PNAS 2001

Gene expression patterns of breast carcinomas distinguish tumour subclasses with clinical implications



Therese Sørlie [a,b,c], Charles M. Perou [a,d], Robert Tibshirani [e], Turid Aas [f], Stephanie Geisler [g], Hilde Johnsen [b], Trevor Hastie [e], Michael B. Eisen [h], Matt van de Rijn [i], Stefanie S, Jeffrey [j], Thor Thorsen [k], Hanne Quist [l], John C. Matese [c], Patrick O. Brown [m], David Botstein [c], Per Eystein Lønning [g], and Anne-Lise Børresen-Dale [b,n]


All Breast Cancer
ER+
65-75%
HER2+
15-20%
Basaloid
~9%
BRCA like
~6%

What is the "standard" for Her2- breast cancer in BC?

- Neoadjuvant
  - Any of our current adjuvant protocols
  - Dose dense AC-Paclitaxel
  - FEC – Doc
  - TAC
  - TC
  - AC
  - CMF
  - Hormones -AI
- LABC
  - AC- Docetaxel
  - FEC-DOC
  - TAC
  - Dose dense AC-Paclitaxel
  - Hormones - AI

Choosing Therapy by Responsiveness not just Risk

Targeted therapy

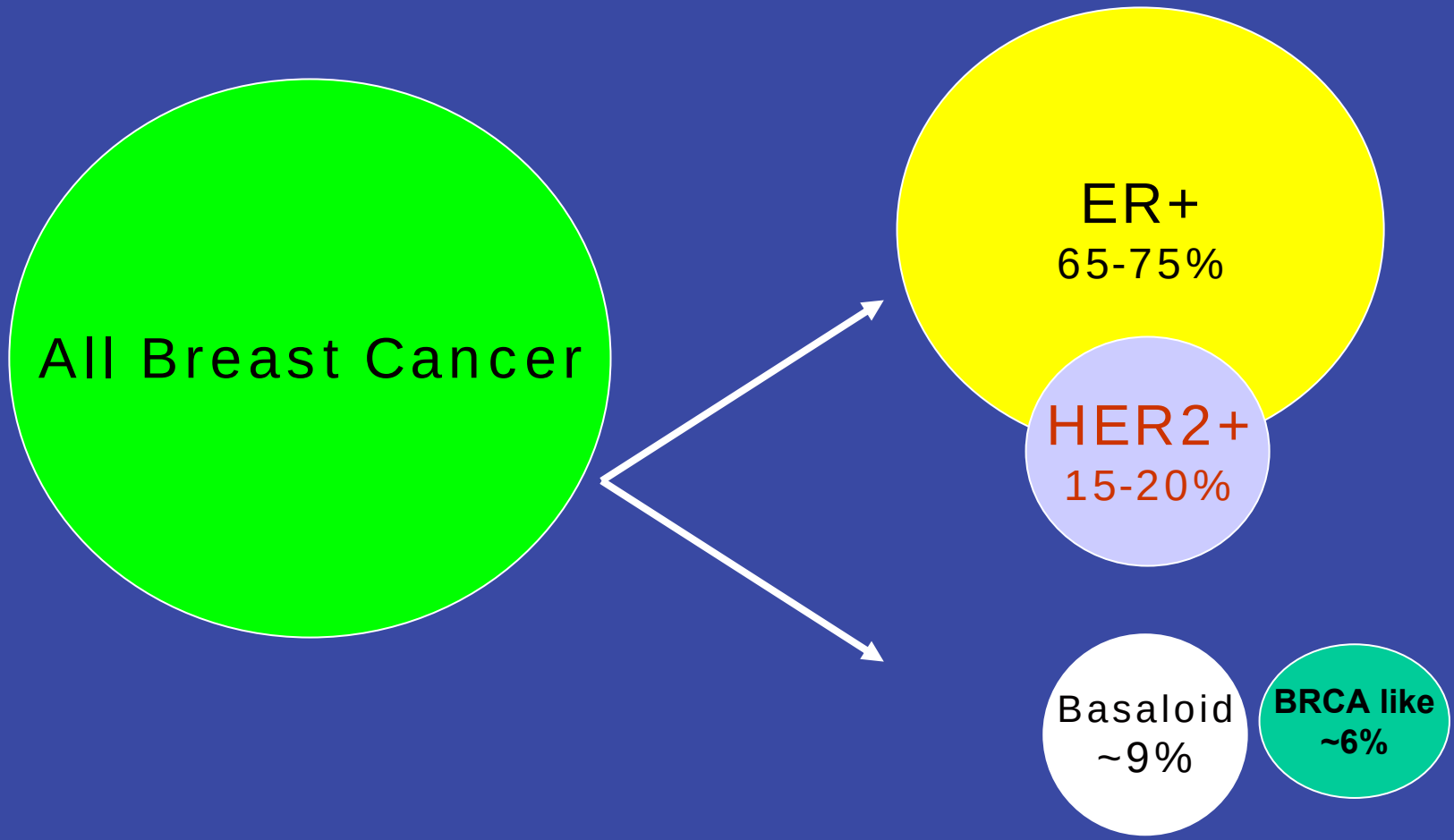
Understanding Response - Predictors

Individualizing Therapy

Understanding the Pharmacogenomics

Case Example

- 66 year old woman presents with a right breast mass, 3.5 cm in lower inner quadrant tethered to chest wall
- VERY anxious
- Treated with Letrozole 2.5 mg daily
- RT to breast and nodal area
- Mastectomy – after 4 months
- 1.4 cm residual disease resected
- Continued on letrozole with plans x 5 years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ER+
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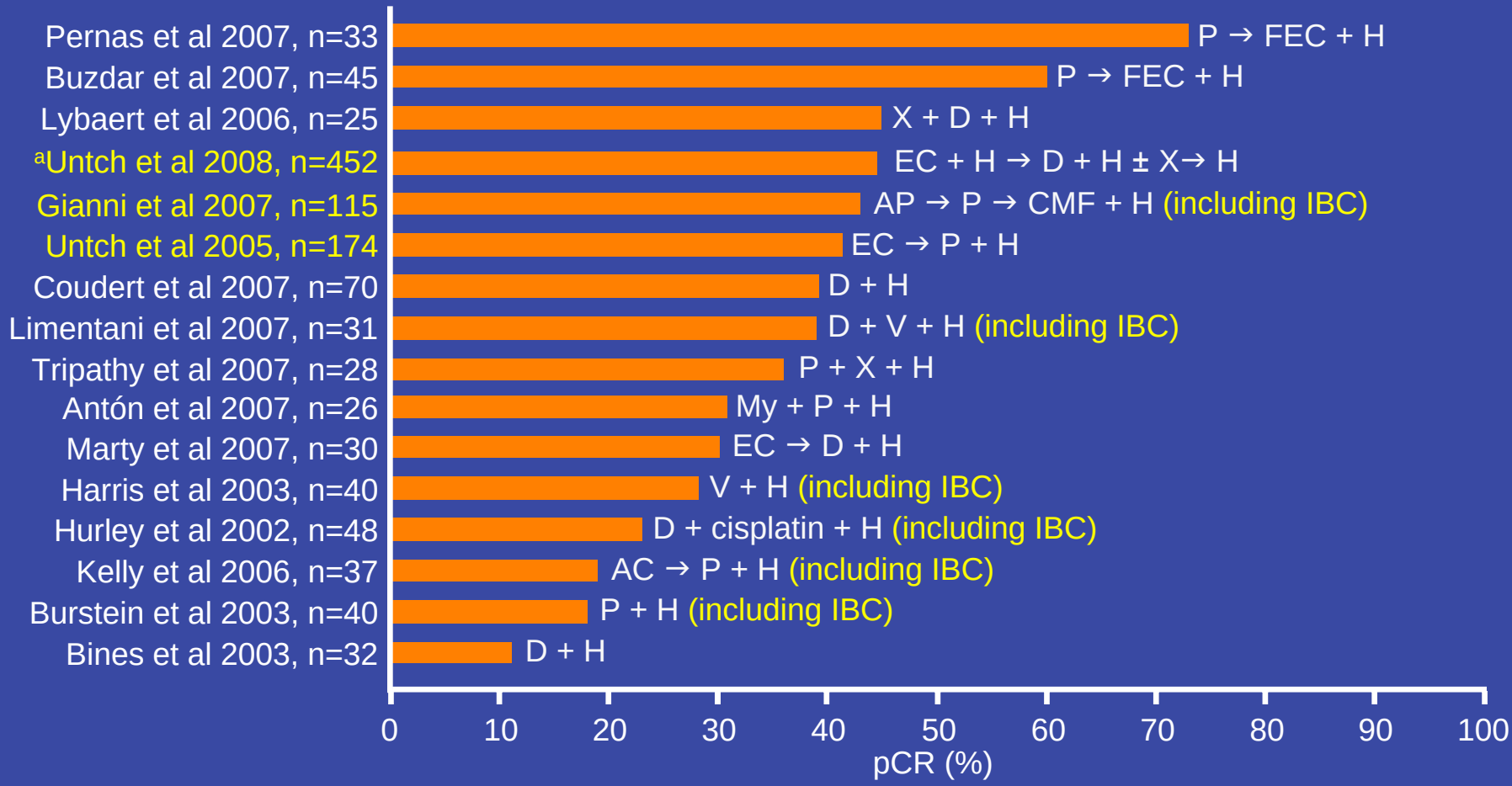
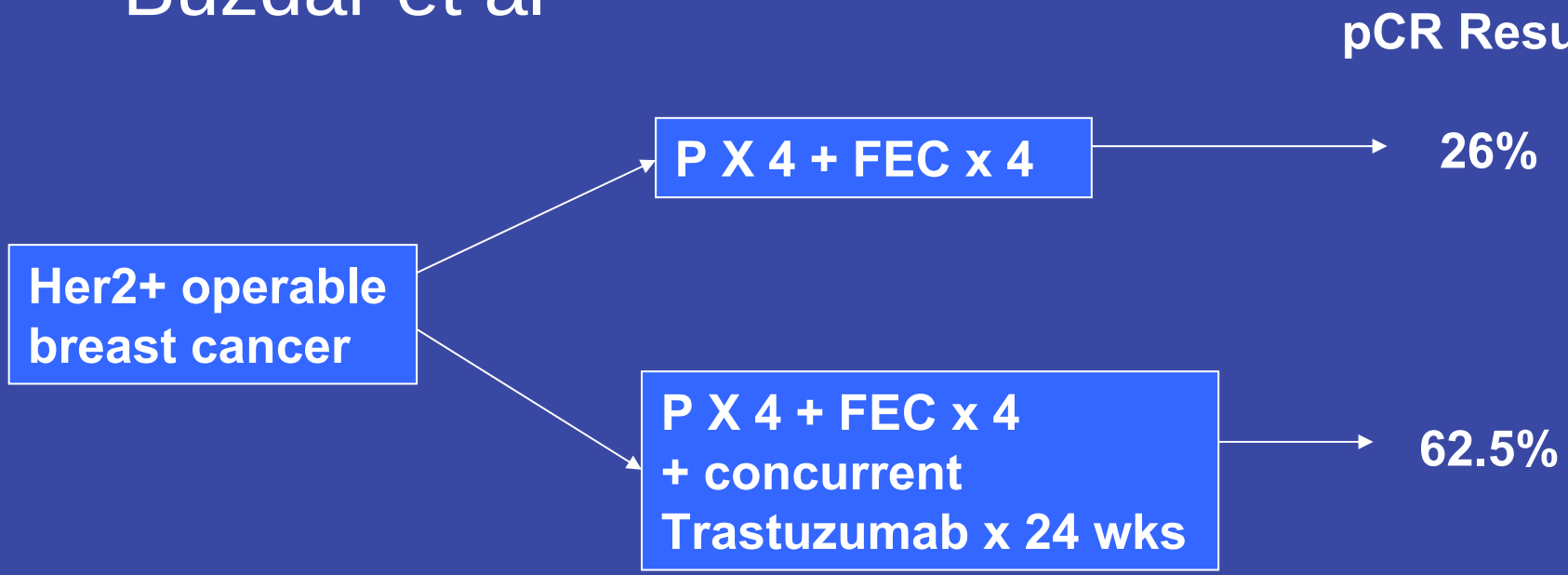
Neoadjuvant Herceptin regimens exhibit high pCR rates (16 studies, 1,226 patients)



[a]X was given either concurrently or sequentially with D + H
EC, epirubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide
My, Myocet; X, Xeloda

Neoadjuvant Trastuzumab

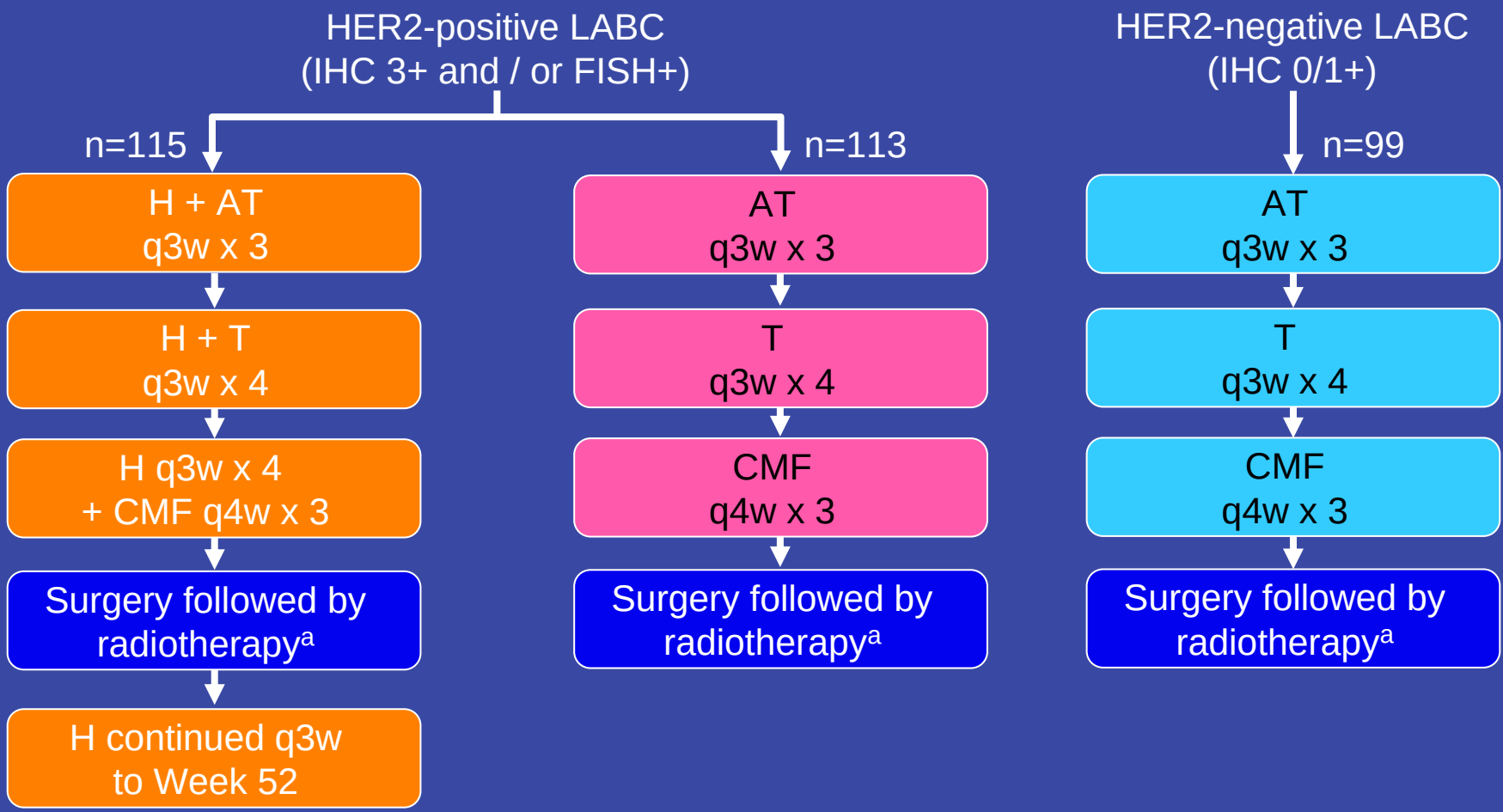
- Buzdar et al



Planned sample size 164

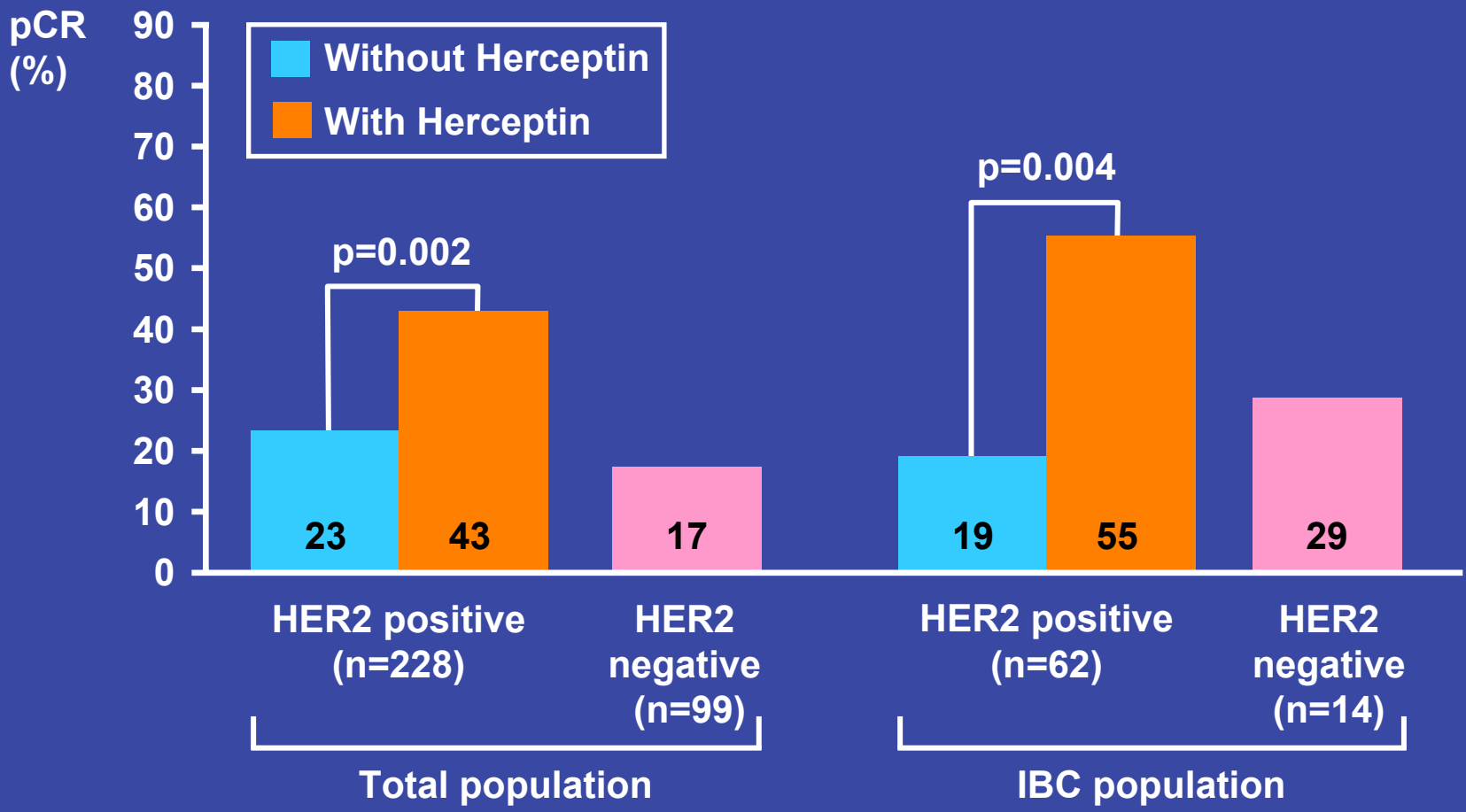
Study closed after 42 pts accrued due to better than expected results

NOAH: the largest neoadjuvant trial in HER2-positive breast cancer



[a]Hormone receptor-positive patients receive adjuvant tamoxifen; LABC, locally advanced breast cancer; H, trastuzumab (8 mg/kg loading then 6 mg/kg); AT, doxorubicin (60 mg/m^2), paclitaxel (150 mg/m^2); T, paclitaxel (175 mg/m^2); CMF, cyclophosphamide, methotrexate, fluorouracil

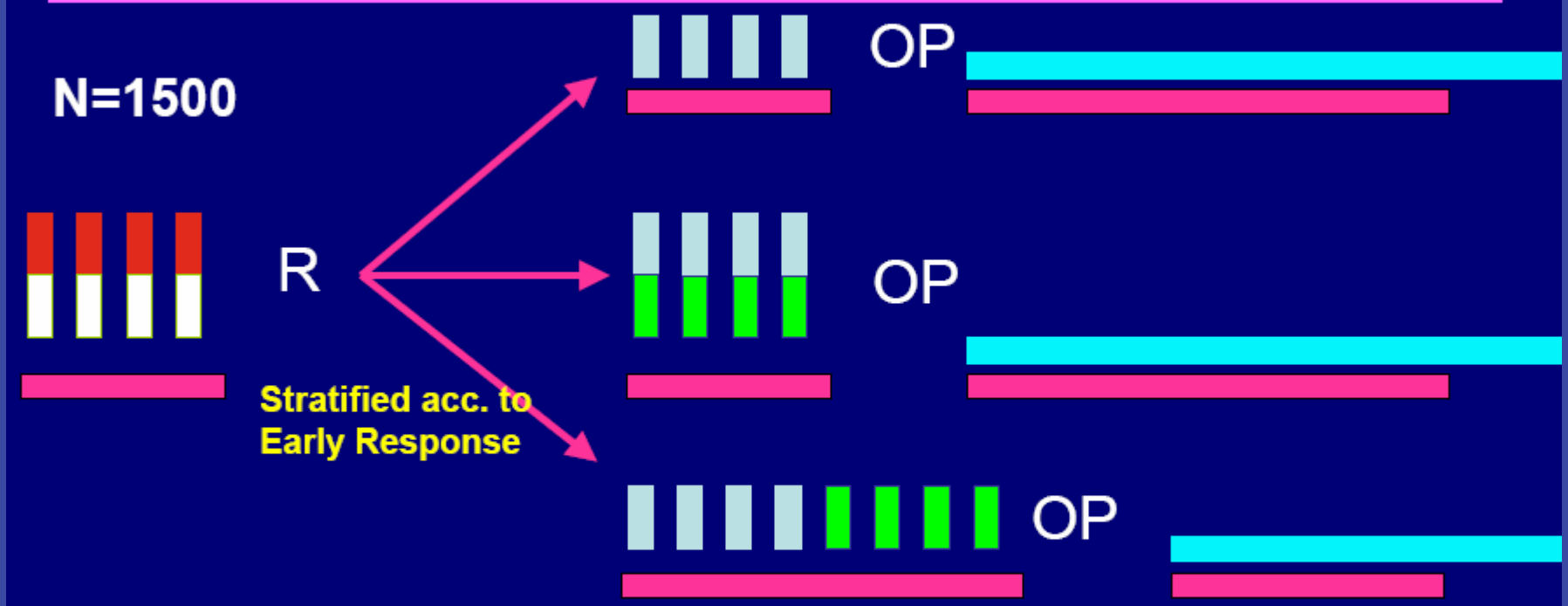
Neoadjuvant Herceptin significantly improves pCR rates in the NOAH trial



pCR, pathological complete response in the breast
IBC, inflammatory breast cancer

Baselga et al 2007; Gianni et al 2007

GeparQuattro

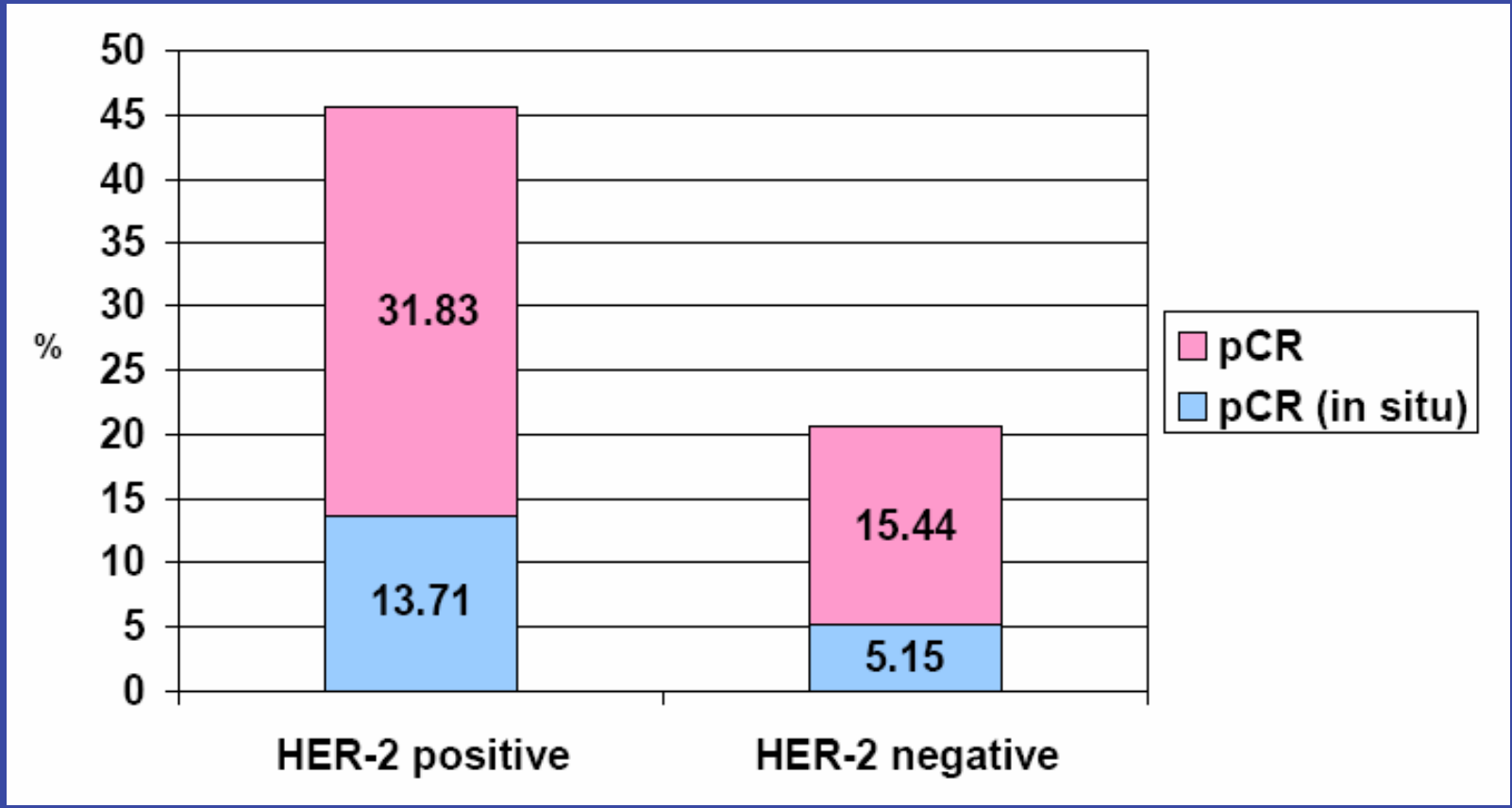


Epirubicin 90 mg/m²
Cyclophosphamide 600 mg/m²
Docetaxel 100 mg/m² (A) 75 mg/m² (B,C)
Capecitabine 1800 mg/m²
If Her2 pos: Trastuzumab 6 mg/kg q3w 1y
If endocrine responsive Tam/AIs

AGO

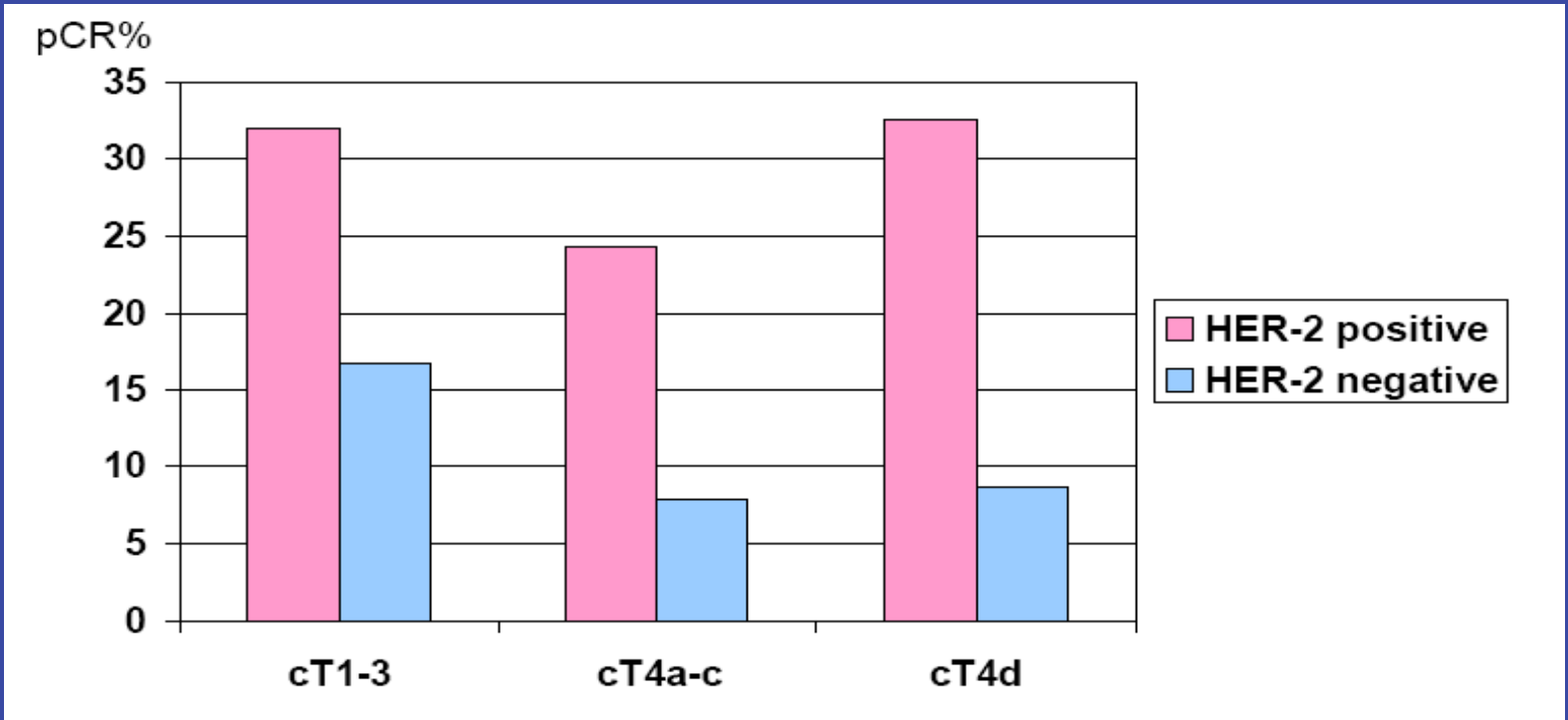
GBG GERMAN BREAST GROUP

Pathologic Complete Response (pCR)



Untch M et al. EBCC 2008

pCR According to Tumour Stage*



*Predefined and stratified
pCR, pathological complete response

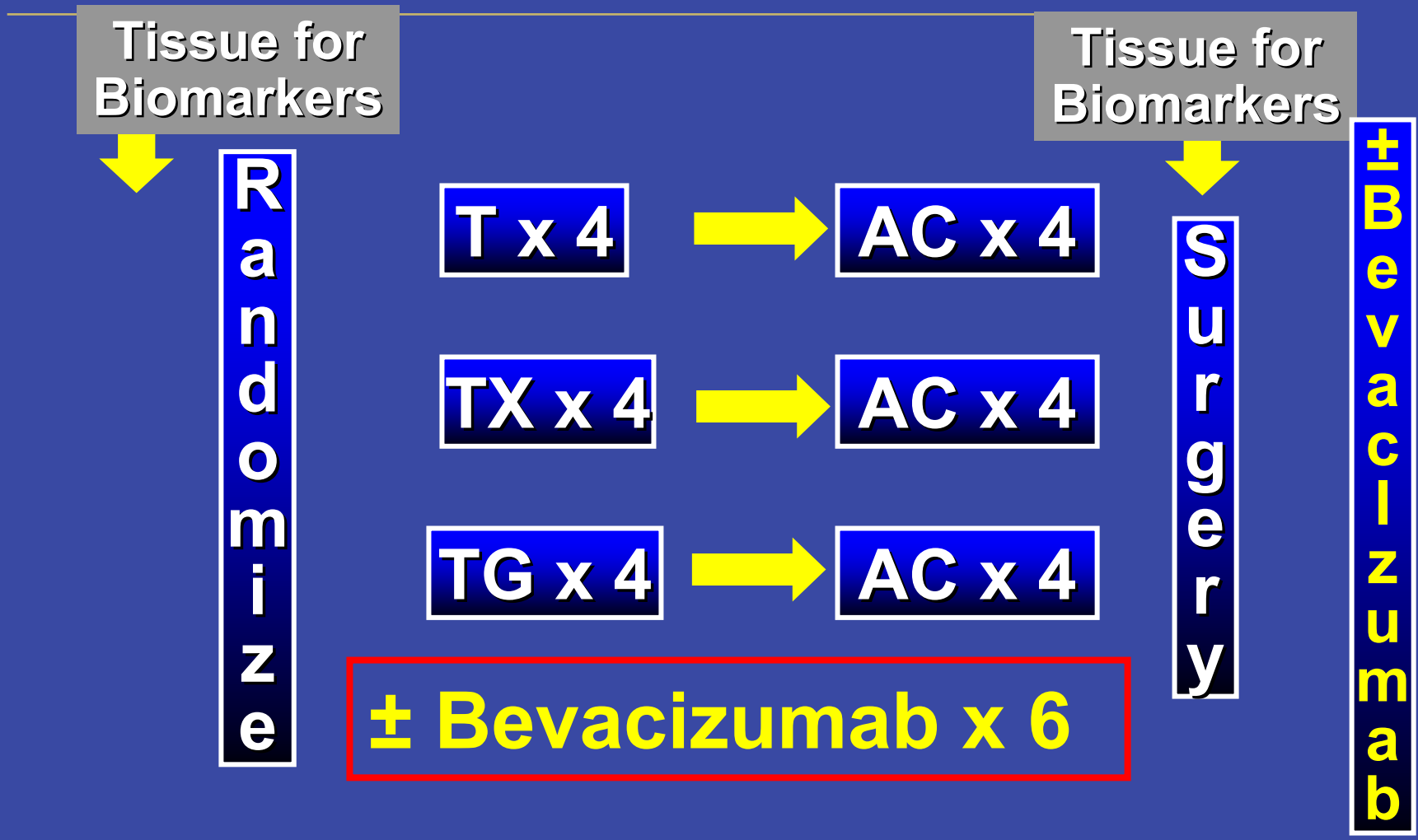
Untch M et al. EBCC 2008

What is the “standard” Her2+ in BC?

- Staging with MUGA or Echo
- Initiation of chemotherapy with
  - AC – dose dense or three weekly followed by Docetaxel /or paclitaxel and Herceptin x 4
  - FEC – followed by Docetaxel and Herceptin x 3
  - TCH – docetaxel/carbo/herceptin x 6
  - Herceptin continuing for a year
- Radiation and Surgery
- Hormonal therapy if ER/PR positive

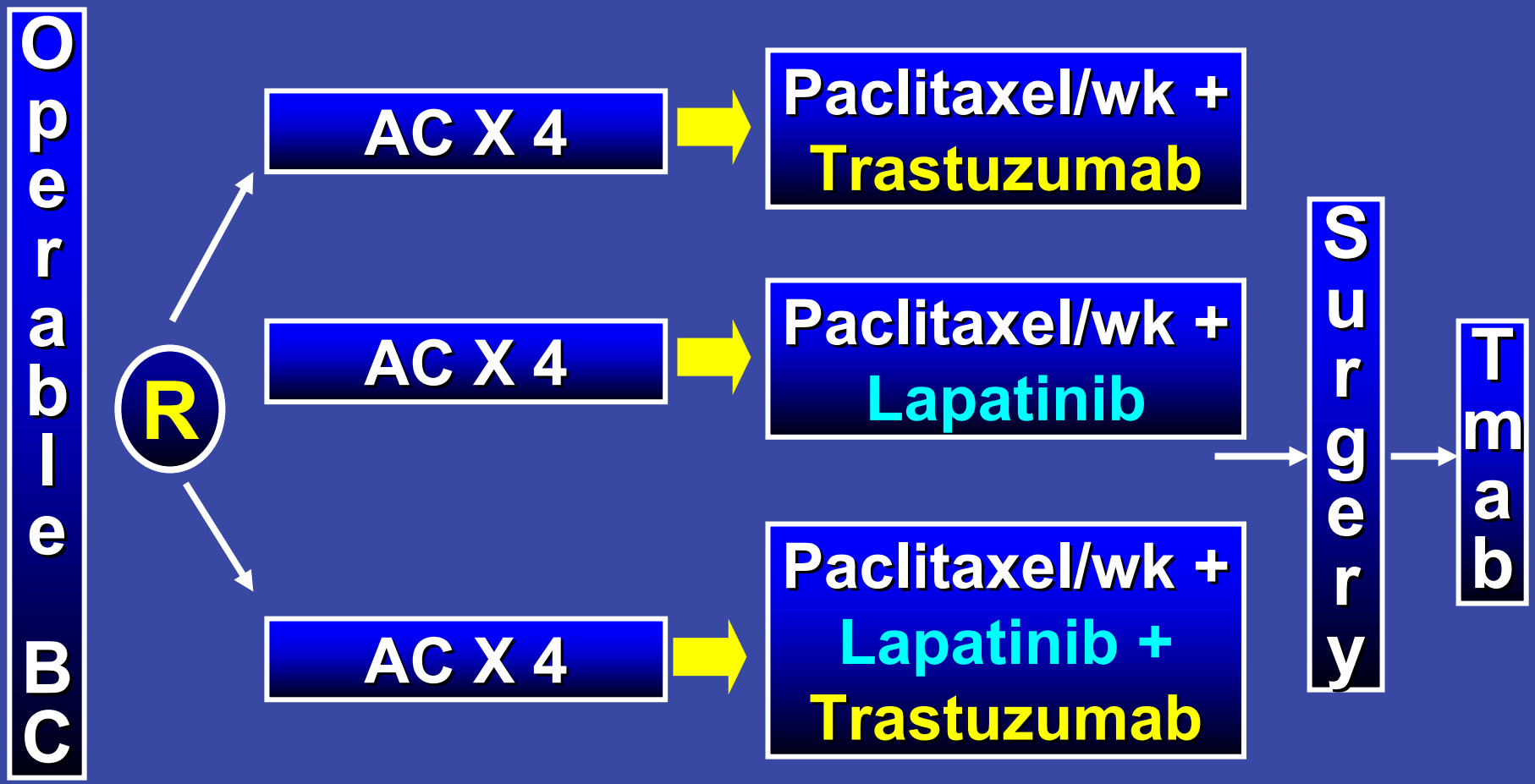
Trials that are pending

NSABP B-40
Her2 Neg ≥2cm



Endpoints: pCR; 2⁰ endpoint: pCR Δ (29→38%)
DFS N=1200 Started: 11-07

NSABP B-41
Her2 Pos



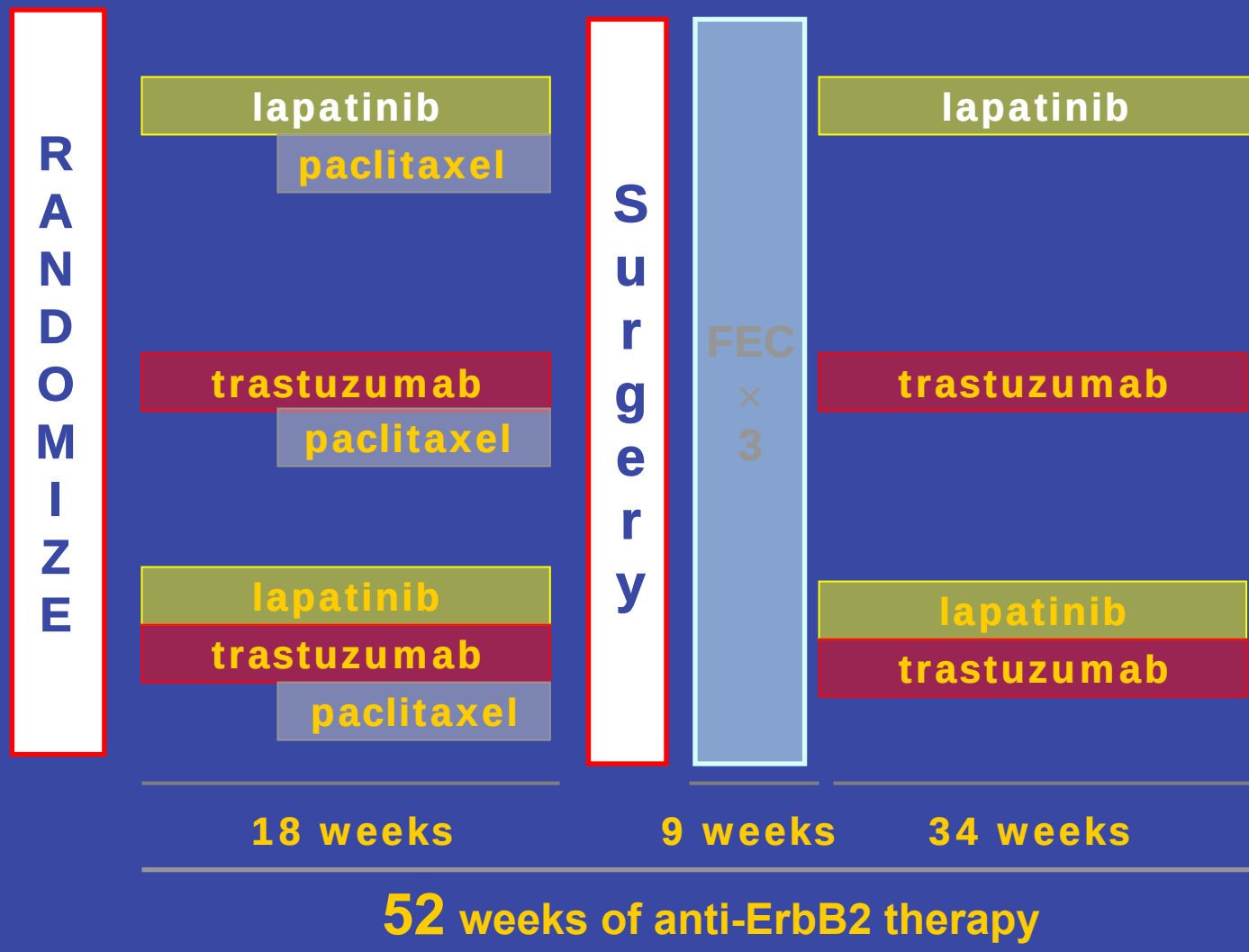
N=522; pCR Δ 22% (42→64%)

NEO-ALTTO (EGF106903)

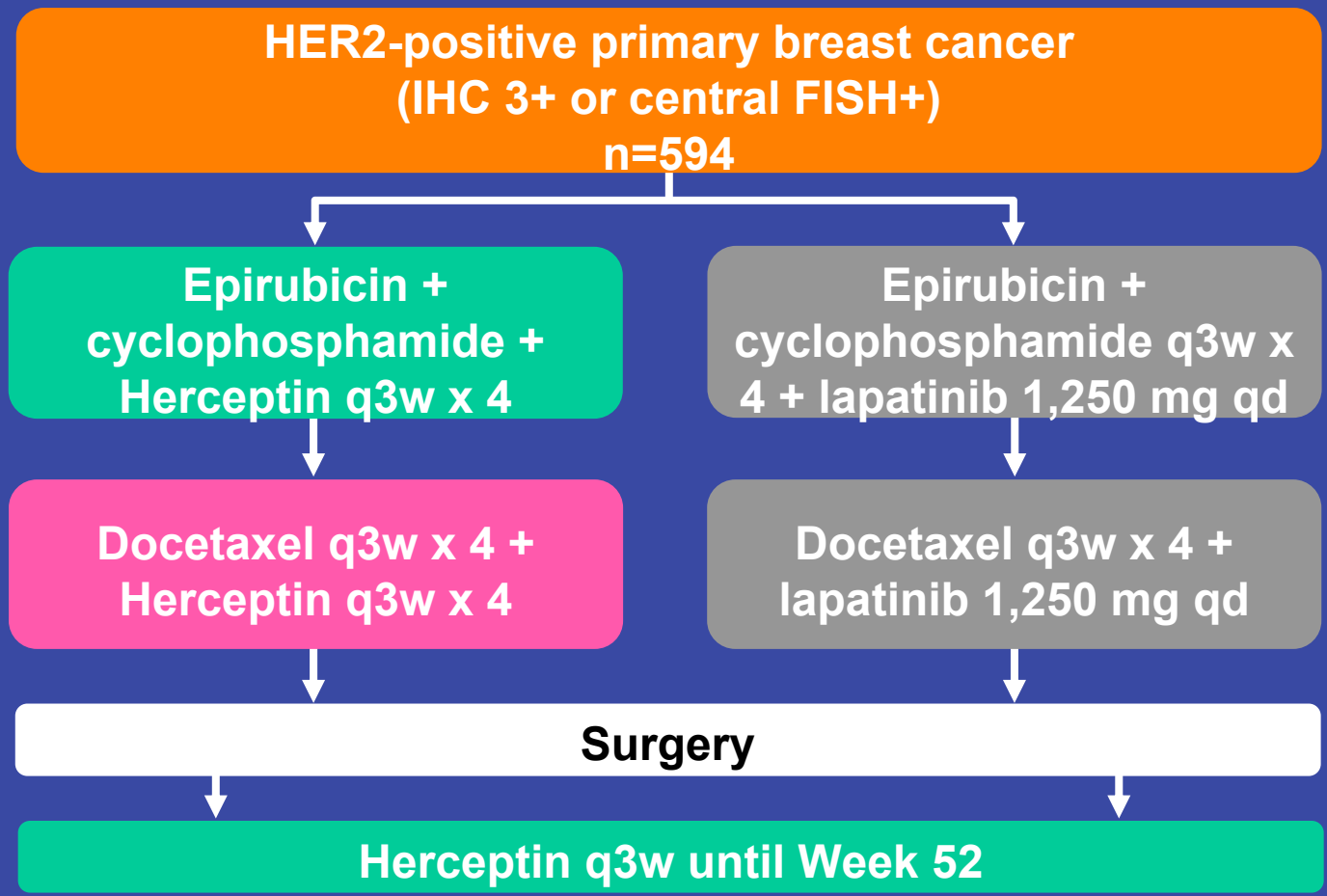
Invasive breast cancer
HER2+
T>2 cm
(inflammatory BC excluded)
LVEF ≥ 50%

N=450

Stratification:
—T< 5 cm versus T> 5 cm
—ER or PgR + versus both ER and PgR –
—N0-1 versus N ≥2
—Conservative surgery or not

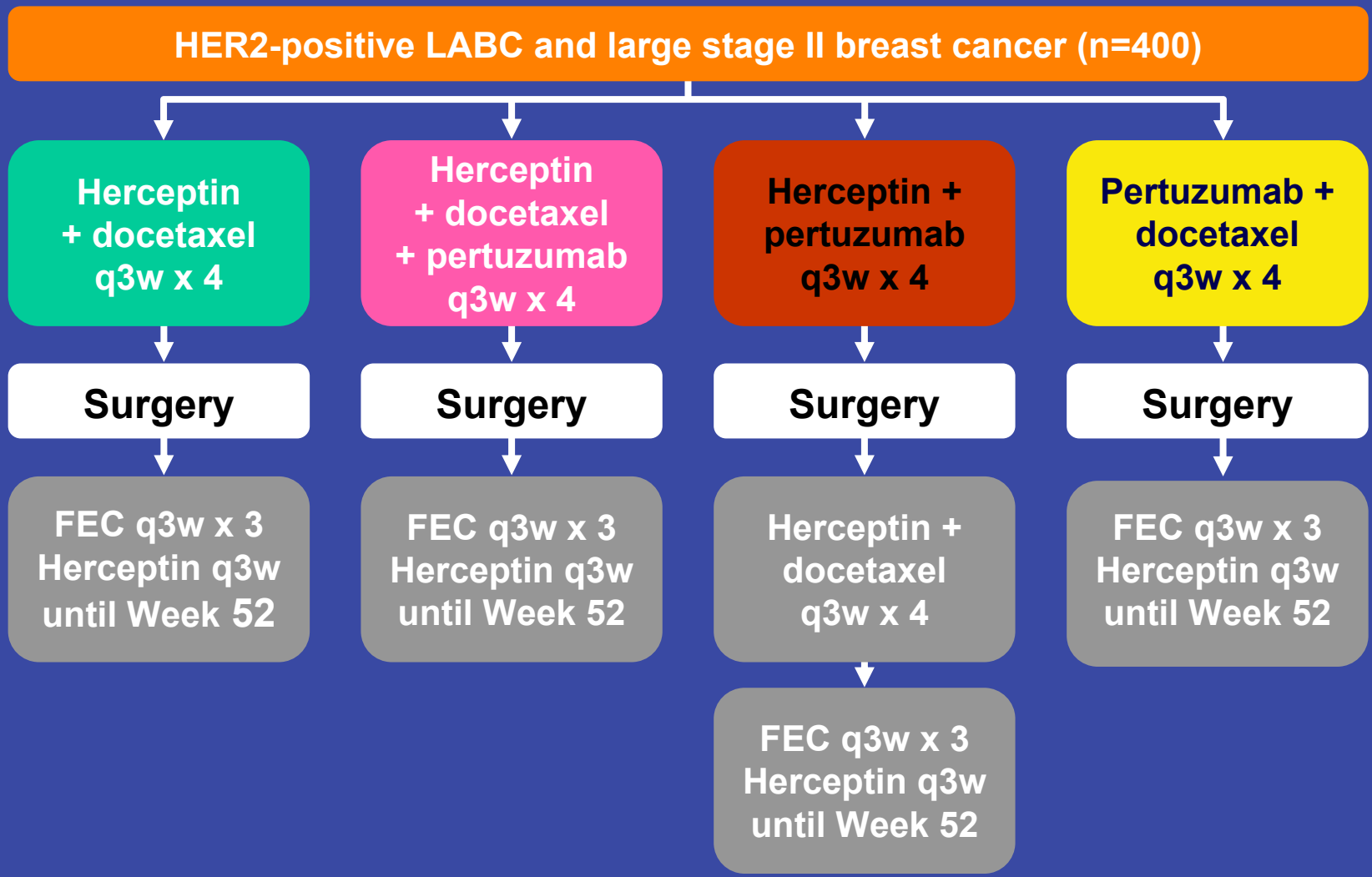


GeparQuinto study: neoadjuvant Herceptin vs lapatinib



Docetaxel 75 mg/m^2 q3w x 4; epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 q3w x 4; Herceptin 8 mg/kg loading dose followed by 6 mg/kg q3w for 12 months; lapatinib 1,250 mg/day for 24 weeks

Neosphere study: neoadjuvant Herceptin + pertuzumab



But is chemotherapy the answer to all the questions in LABC?

Our most successful therapies target self-sufficiency in growth signals

Growth Factor	Therapy
• Estrogen/ER	• SERMs, AIs, oophorectomy, fulvestrant
• HER2	• Trastuzumab – Lapatinib

How effective is Neoadjuvant Chemotherapy in ER+ Breast Cancer

- Chemotherapy is less effective in ER+ disease vs ER- disease (but doesn't mean some patients don't benefit)
- Doe Luminal A benefit vs luminal B or others?
- Other predictive markers needed for taxane sensitivity? Other new agents?

Phase III SWOG 8814 (TBCI 0100)
Postmenopausal, N+, ER+

RANDOMIZE

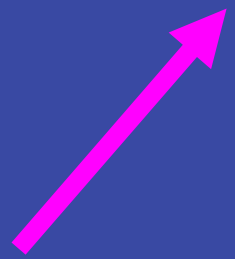
n = 1477

tamoxifen x 5 yrs
(n = 361)

CAF x 6, with concurrent tam
(n = 550)

CAF x 6, then tamoxifen
(n = 566)

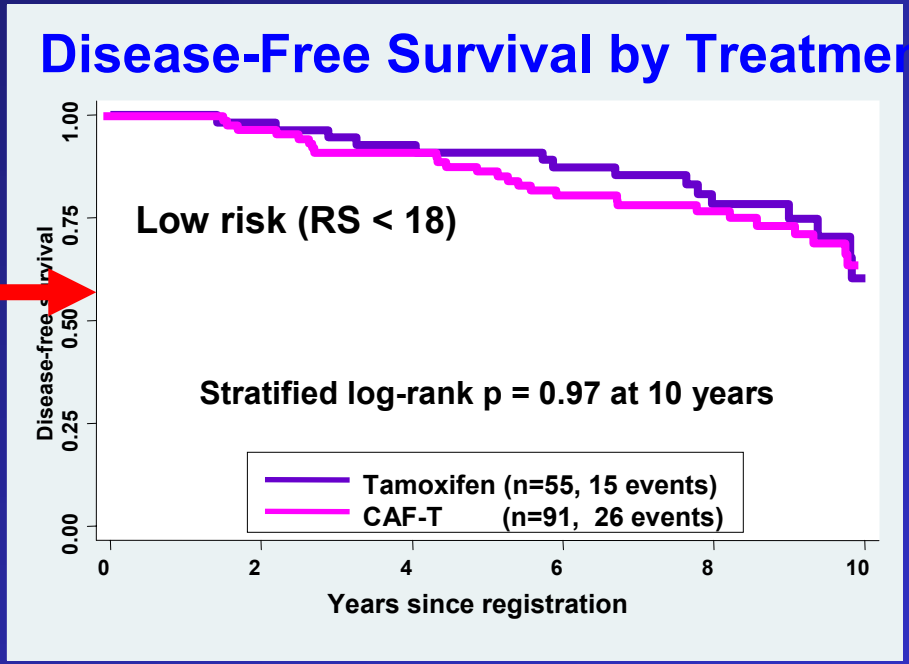
Superior Disease-Free Survival (DFS) and Overall Survival (OS) over 10 Years

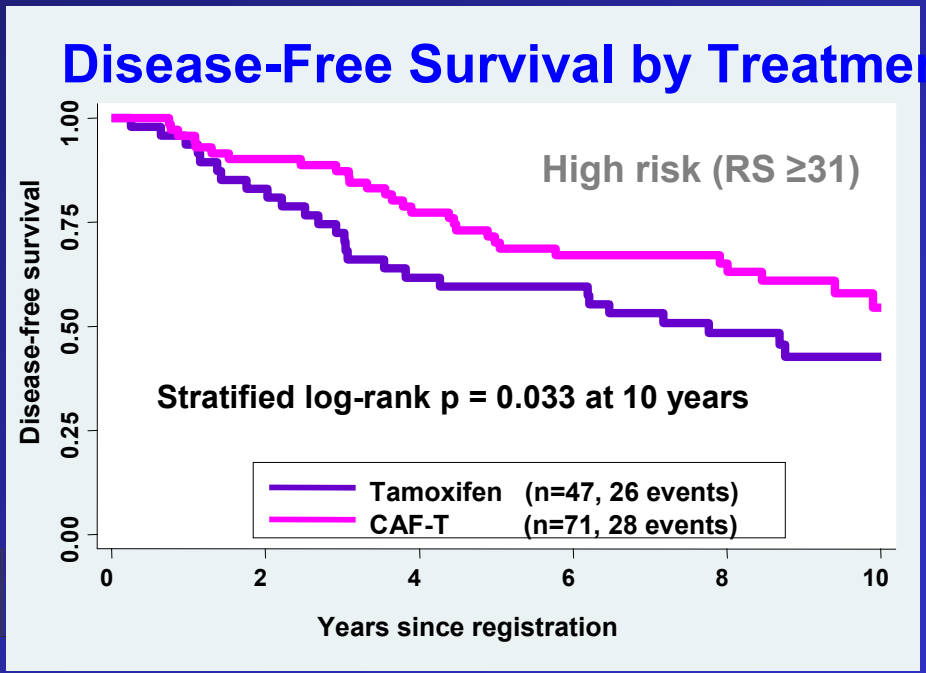


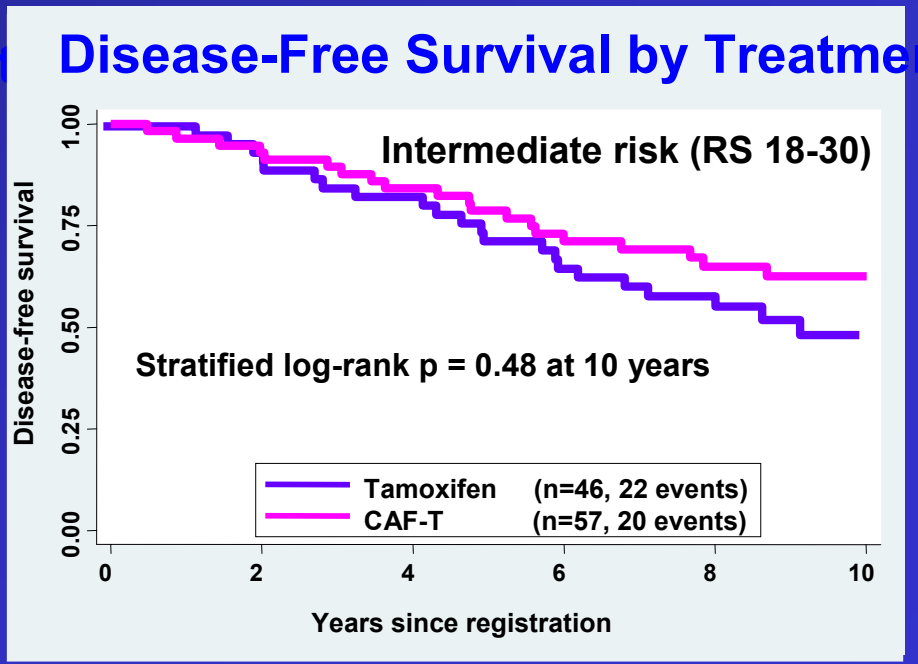
Albain, et al. Breast Cancer Res Treat 2007

No benefit to CAF over time if low RS (n=146)

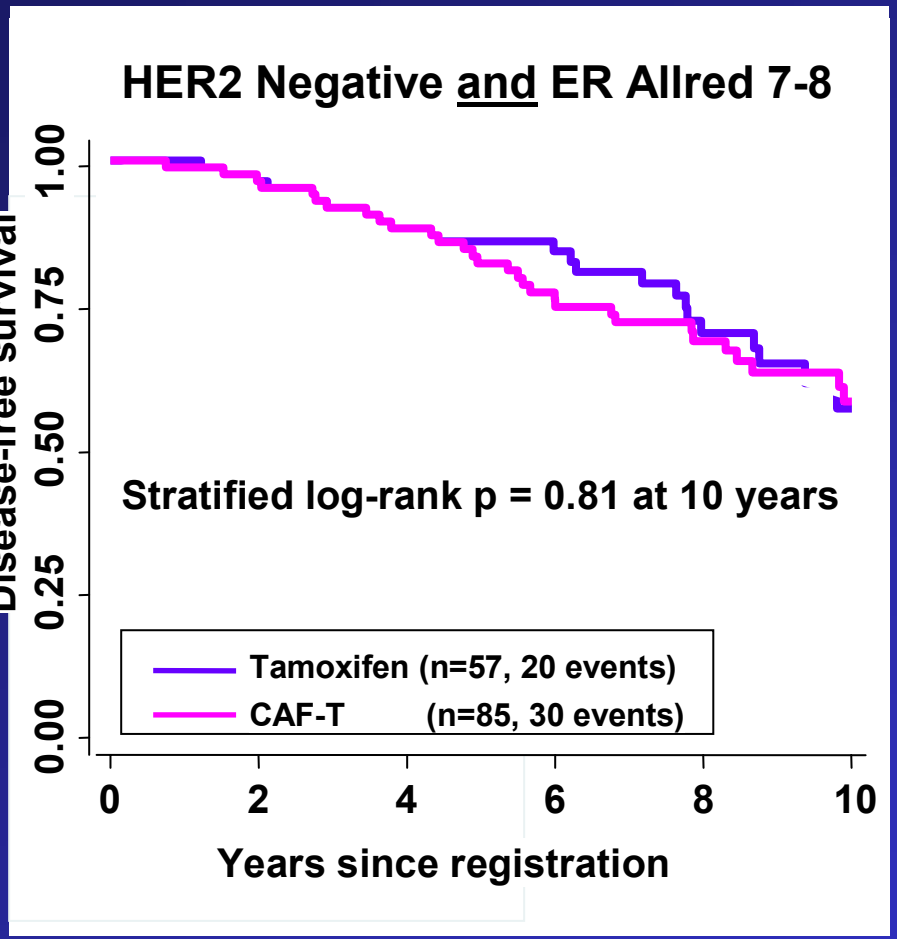
Strong benefit if high RS

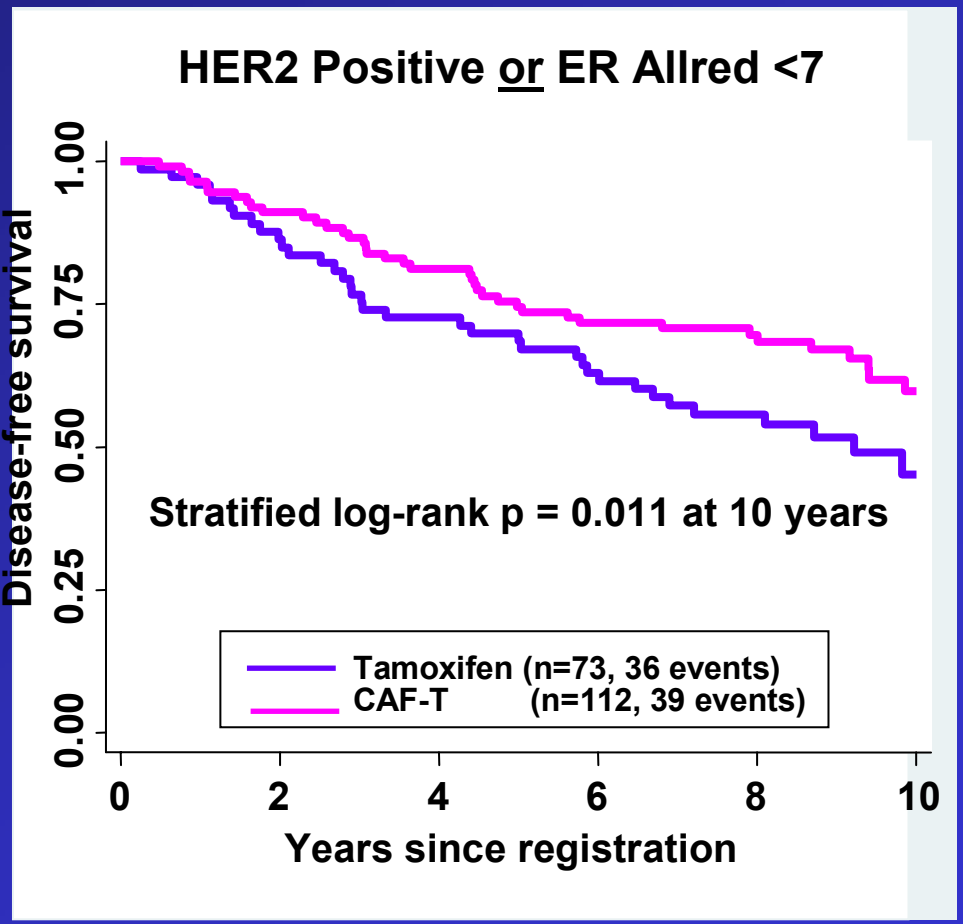






No DFS Benefit from CAF if Central IHC is Both HER2 Negative and ER Level High* (n=142)





*Test for Interaction p=0.052

BC Cancer Agency
CARE & RESEARCH

Surely neoadjuvant chemotherapy is the best?

- Semiglazov et al. PASCO 2004
  - neoadjuvant treatment in women aged >70 with ER + breast cancer
    - Doxorubicin and Paclitaxel (q3 weeks, 4 cycles) (n=60)
    - 3 months treatment with anastrozole or exemestane (n=59)

- There was a trend towards more breast conservation in the AI arms.

	chemotherapy	anastrozole	exemestane
pathological CRs	7.4%	3.3%	6.8%
overall clinical RRs	76%	75%	81%

Challenges in the Management of LABC

What are the response rates like in the real world?

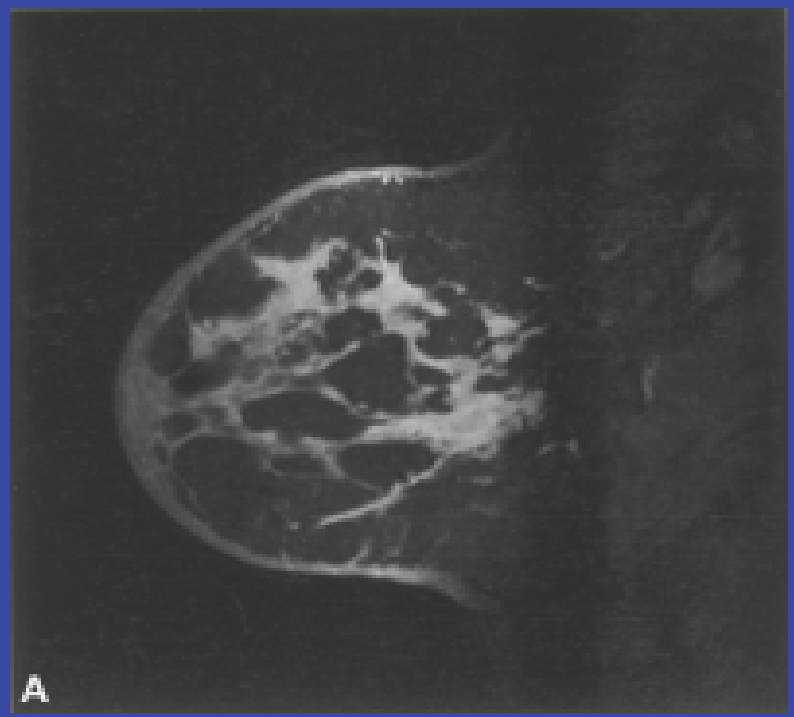
Clinical
Pathological

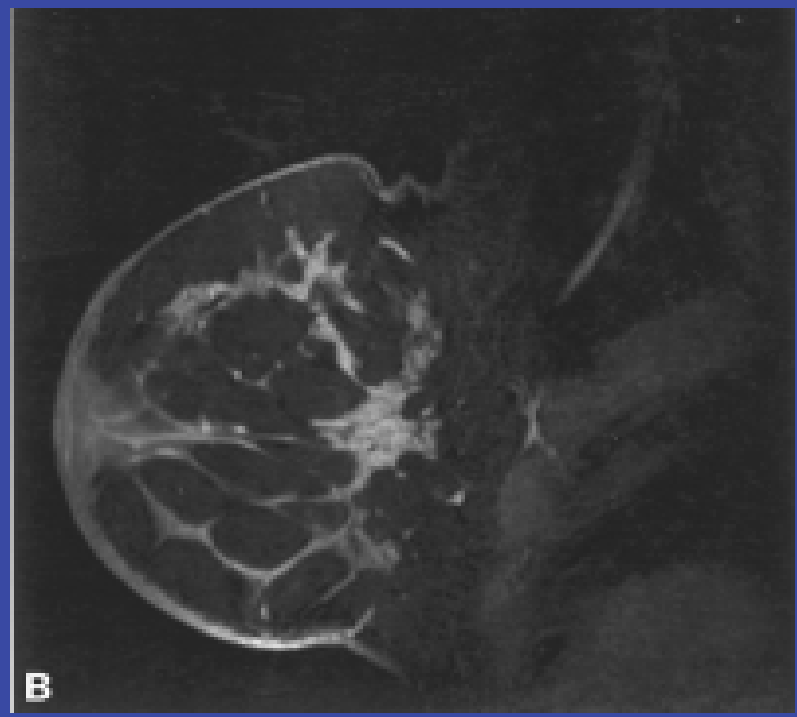
Challenges in the Management of LABC

Should patients with LABC have a lumpectomy if good response to chemotherapy?

Pre-Treatment MRI of Breast Cancer with Septal Spread

After Neo-Adjuvant Chemotherapy
Tumour shrunk to lesser volume along septa





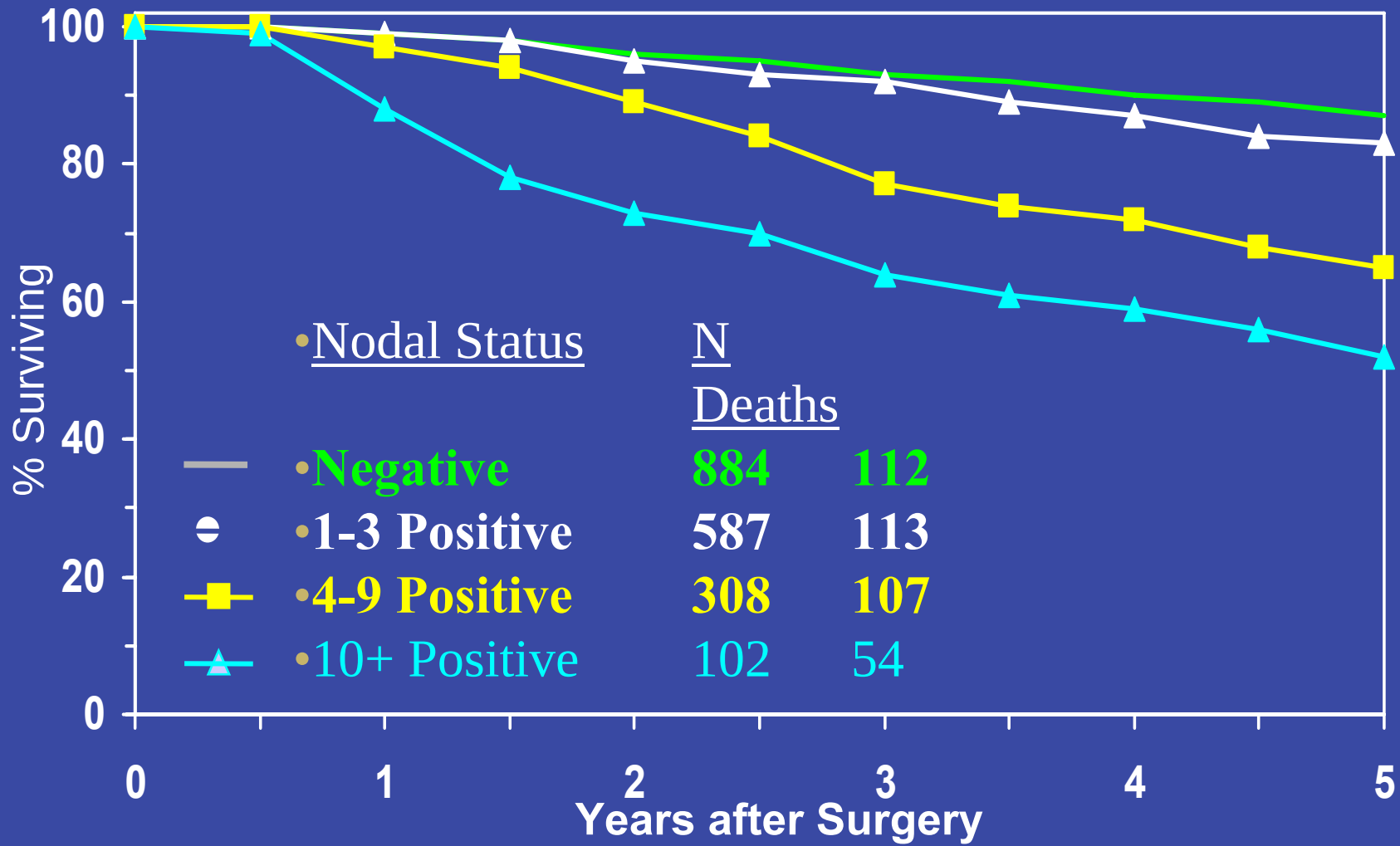
Pathologic Response to Neoadjuvant Chemotherapy (TSRCC)

Study	Definition	pCR rate (n=117) (%)
NSABP	pCR in breast only No microinvasive disease Can have DCIS	10.3
Aberdeen	pCR in breast/axilla No microinvasive disease Can have DCIS	8.6
TSRCC	pCR in breast and axilla No microinvasive disease Can have DCIS	8.6
Chevallier	pCR in breast and axilla No microinvasive isease No DCIS	4.3

Challenges in the Management of LABC

Should we treat patients with residual lymph node involvement after neoadjuvant chemotherapy with further adjuvant chemotherapy?

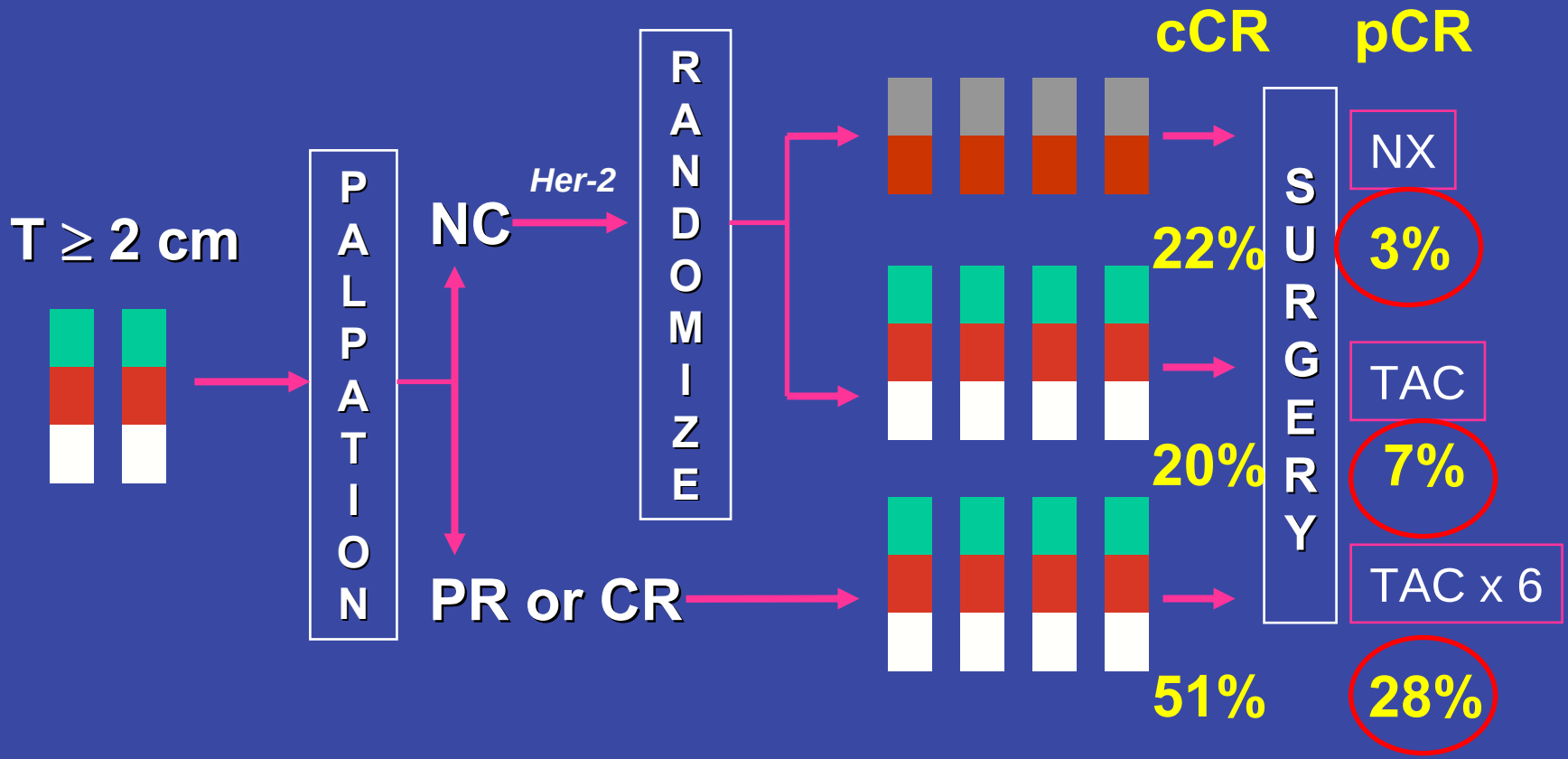
Should we treat patients with residual lymph node involvement after neoadjuvant chemotherapy with further adjuvant chemotherapy?



NSABP B-27: Overall Survival nodal Status; Patients without **pCR**

(Bear JCO 2003)

Gepartrio Pilot



TAC
Docetaxel 75 mg/m²
Doxorubicin 50 mg/m²
Cyclophosphamide 500 mg/m²

NX
Vinorelbine 25 mg/m², Days 1 and 8
Capecitabine 2000 mg/m², Days 1–14

G von Minckwitz ASCO Abstract #85

Systemic therapy – when more is less!

- LABC or neoadjuvant patients not responding to chemotherapy
  - More or different chemo is not always the answer
  - Chemo is toxic
  - Importance of multidisciplinary team
  - Unique area for further study:
    - Role of RT
    - Role of biologics
    - Understanding chemo-resistance
    - Response predictors
    - Response Assessment Tools

Challenges

Surgical oncology

- Who to send for preoperative therapy?
  - In the setting of LABC – we are hoping to make surgery feasible
  - This is different from using NAT as the standard for ALL patients
- Role of breast conservation
  - Not common for LABC population
  - Can be done when feasible
- Role of SLN surgery
  - Very high rate of nodal involvement
- Surgery on relapse
  - Palliation in the setting of very poor prognosis

Summary

Preoperative vs. Postoperative
- OS = DFS = ↑BCS

Clinical and pathologic response predicts overall survival

Standard chemo is an anthracycline & taxane regimen for HER2 negative with the addition of herceptin for HER2 positive

For older HR+ pts consider endocrine therapy

Currently no role for more chemo for patients with residual disease after preoperative therapy

"Og discovered fire, and Thorak invented the wheel. There's nothing left for us."