National Cancer Institute

PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

Inflammatory Breast Cancer: A Unique Pathologic Entity ?

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

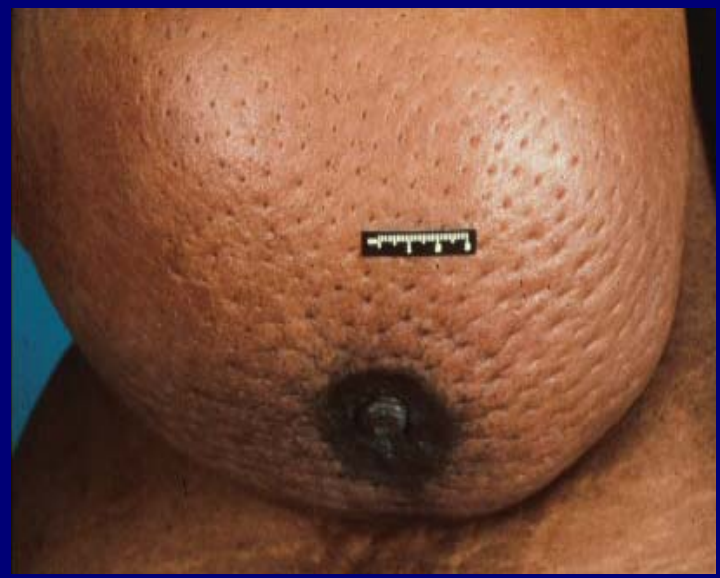
Outline

- Overview
- Therapy
  - High dose chemotherapy
  - NCI – 0173 bevacizumab study
  - Metronomic therapy
  - Lapatinib
- Future Directions

Inflammatory Breast Cancer

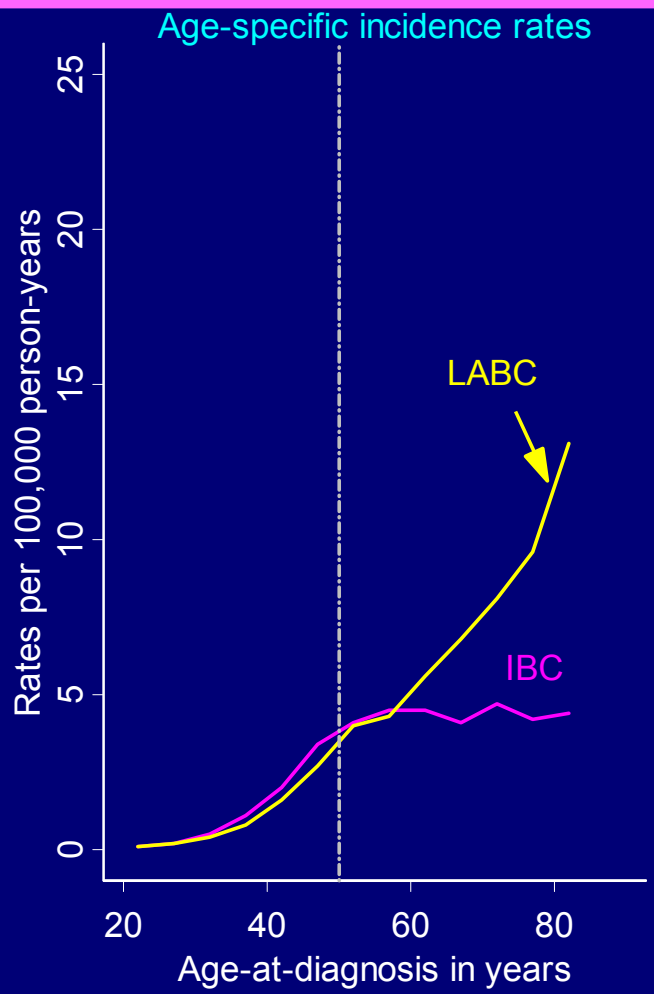
- Rare, 2% in U.S, higher in other countries
- Most aggressive form of breast cancer

- Clinical diagnosis
  - diffuse erythema
  - *peau d'orange*
  - often no palpable mass



Locally advanced breast carcinoma (IBC and LABC)

- There is a long-standing debate concerning whether *IBC* and *LABC* reflect an advanced breast cancer continuum or discrete clinicopathologic entities?



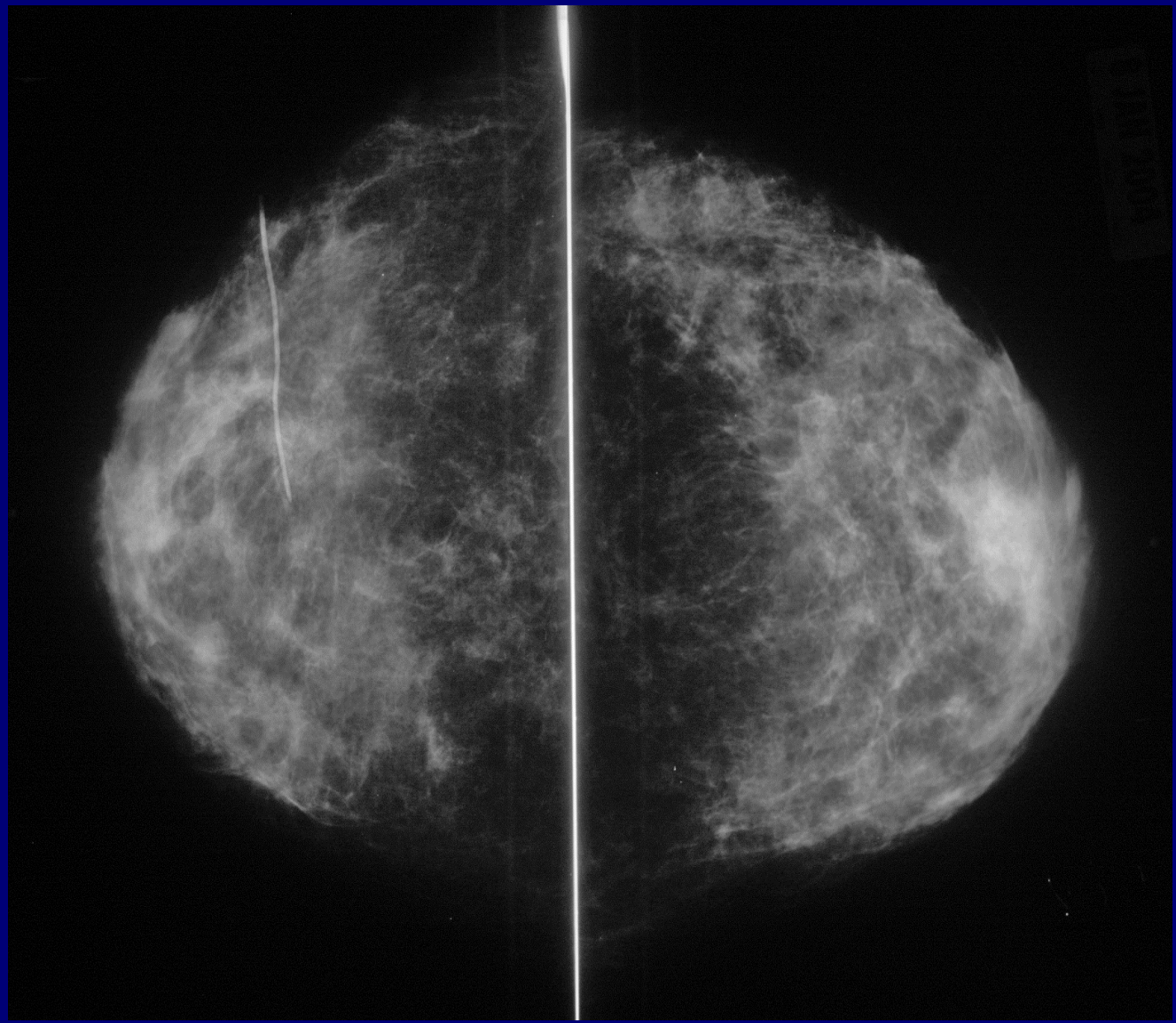
Anderson, et al, J Clin Oncol 21: 2254, 2003

Inflammatory Breast Cancer

- Small increased incidence in US over 30 years
- Higher incidence in Blacks than Whites
- Younger age than non-IBC
- Weak association with pregnancy/lactation, family history, and larger BMI
- Tunisian studies link increased incidence: rural residence, hyperimmune response, and MMTV

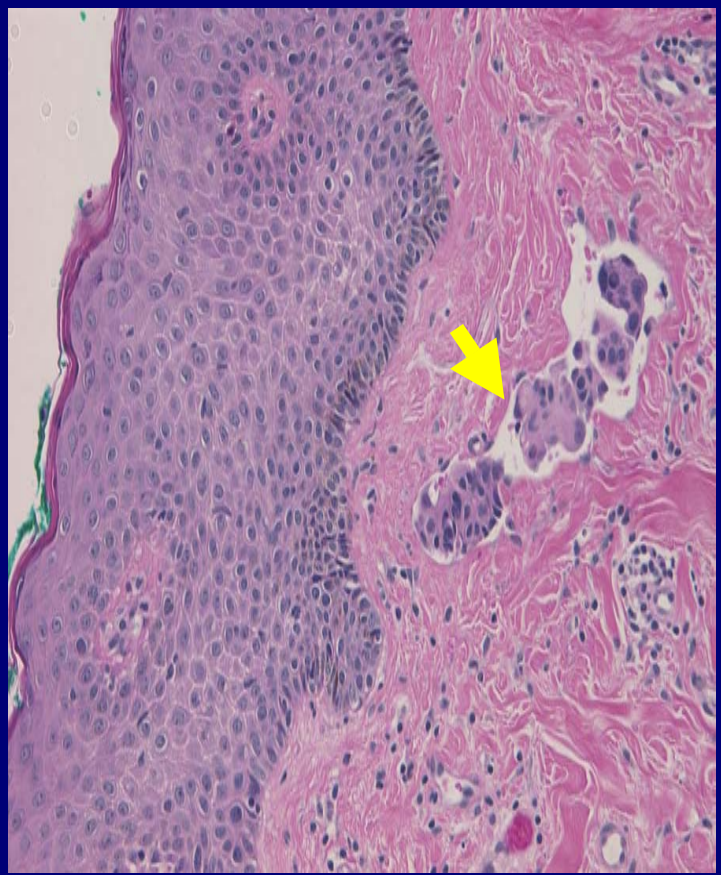
Anderson, et al Breast Disease;22:2005

Mammogram of patient with IBC

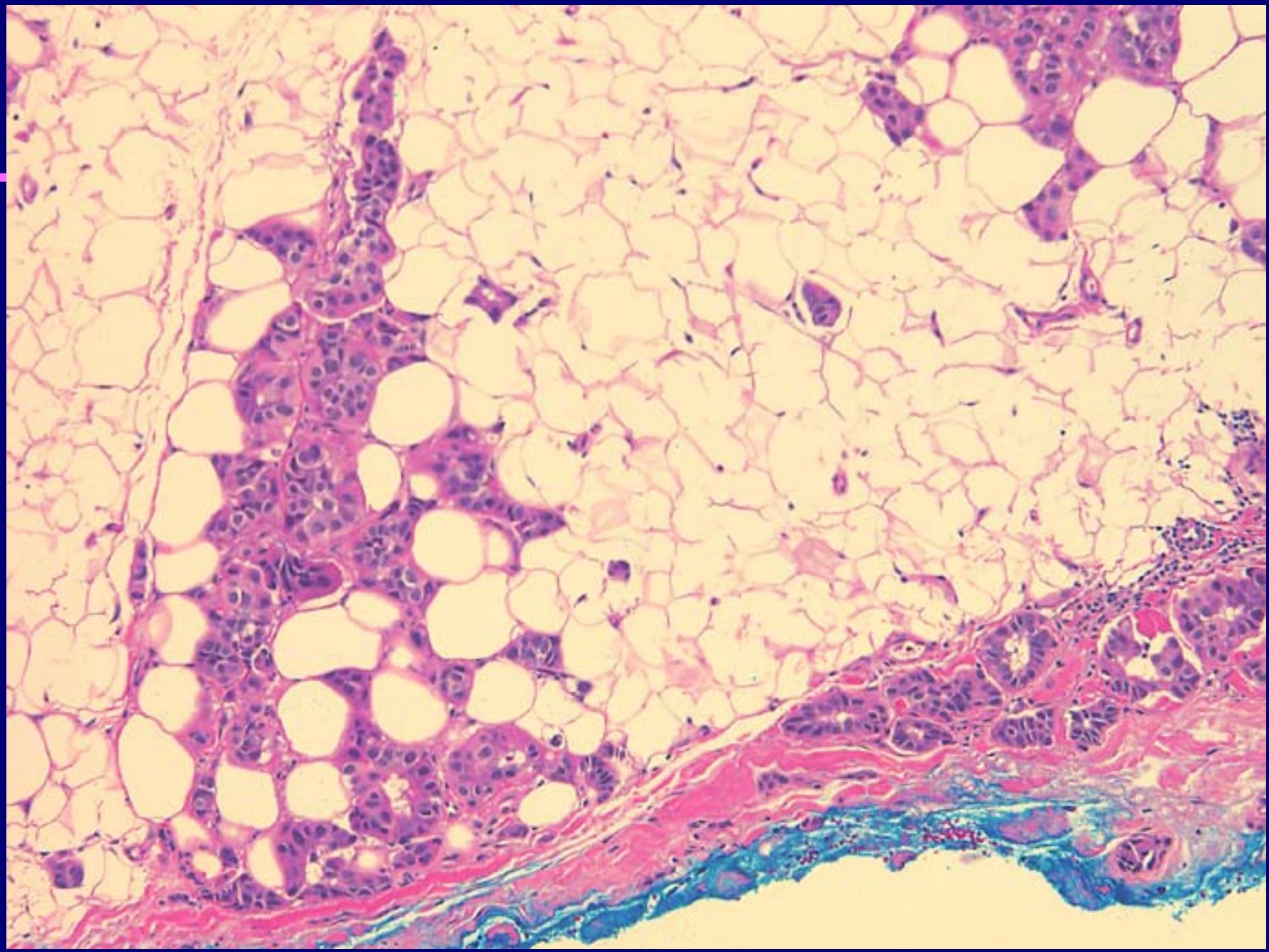


Courtesy of C. Chow

Inflammatory Breast Cancer



- Dermal lymphatic invasion (Not required)
- No increased inflammatory cells
- More frequently
  ER/PR negative
  Her-2/neu positive
- TNM - T4d - “majority of breast”



Inflammatory Breast Cancer Standard Treatment

Primary Chemotherapy*

↓

Mastectomy
With delayed reconstruction

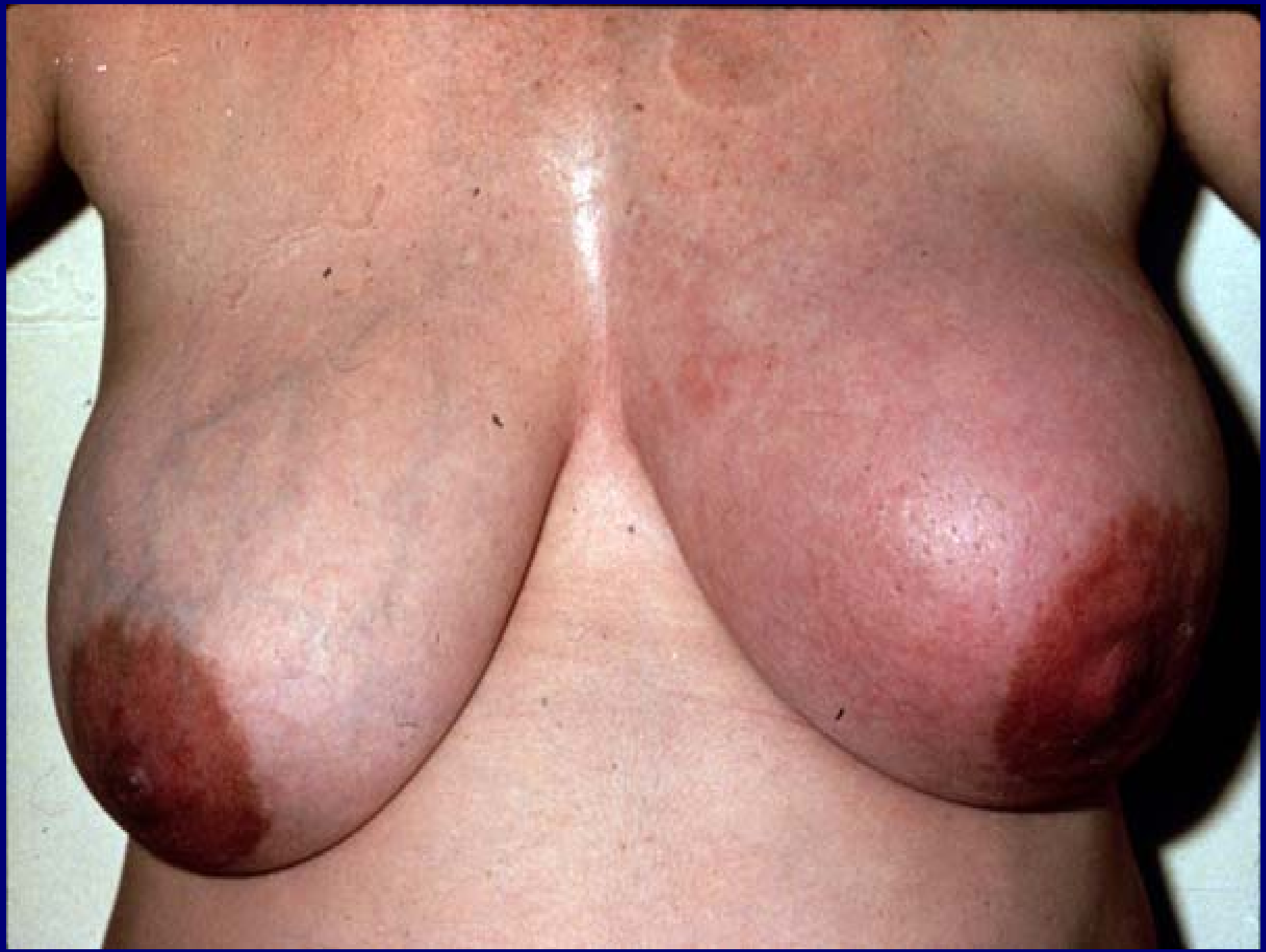
↓

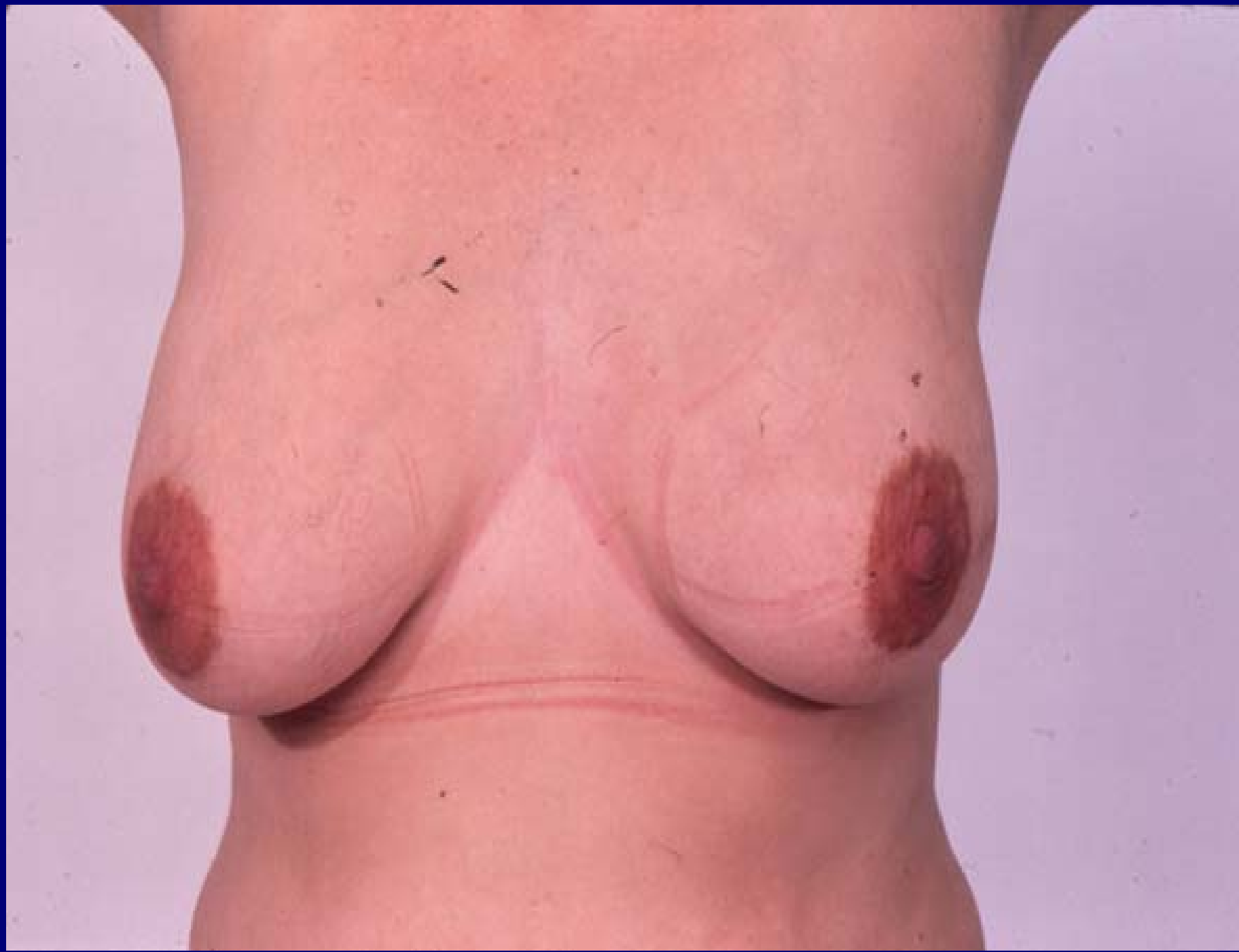
RT

↓

Hormonal Therapy

***Trastuzumab for HER2 positive tumors**

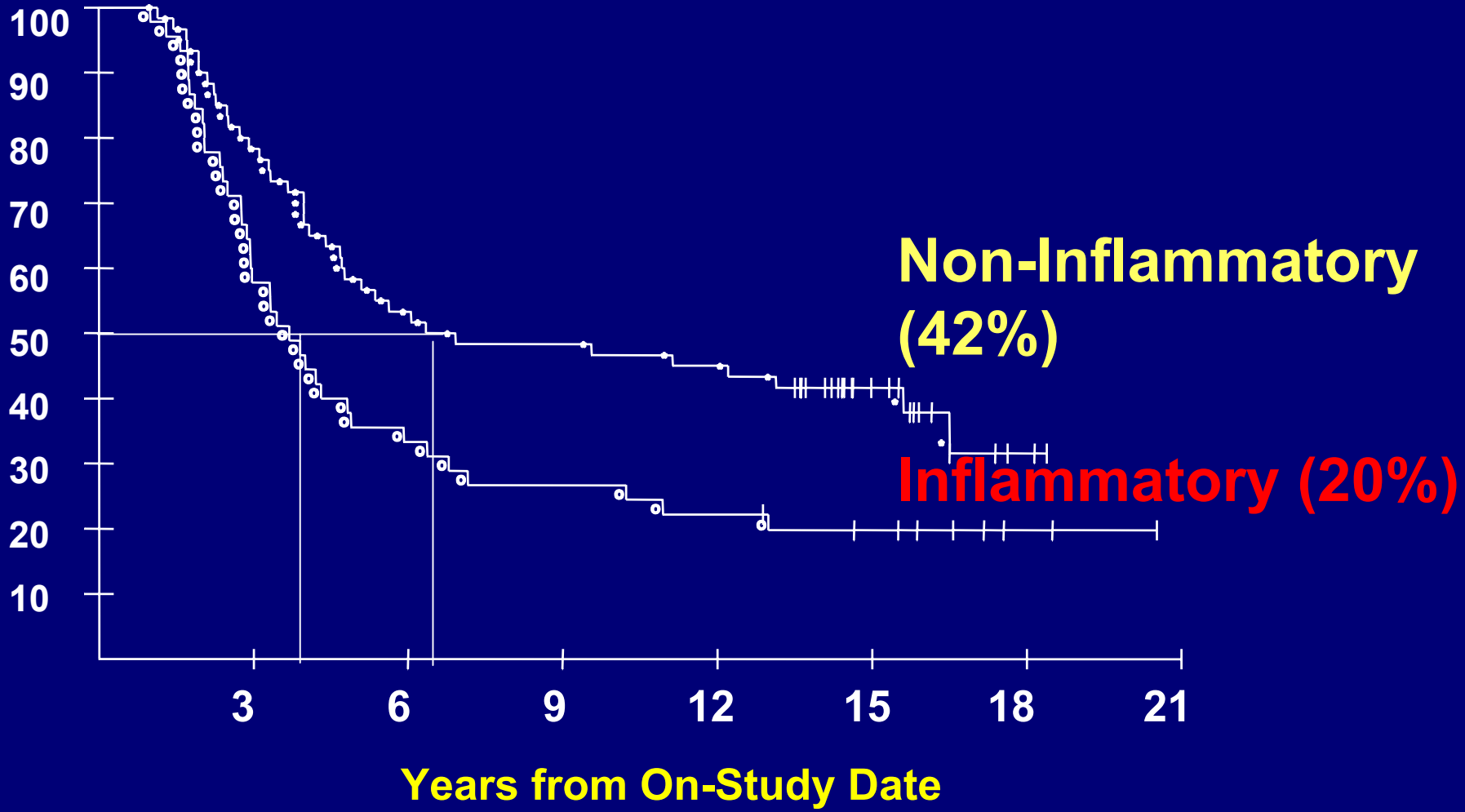




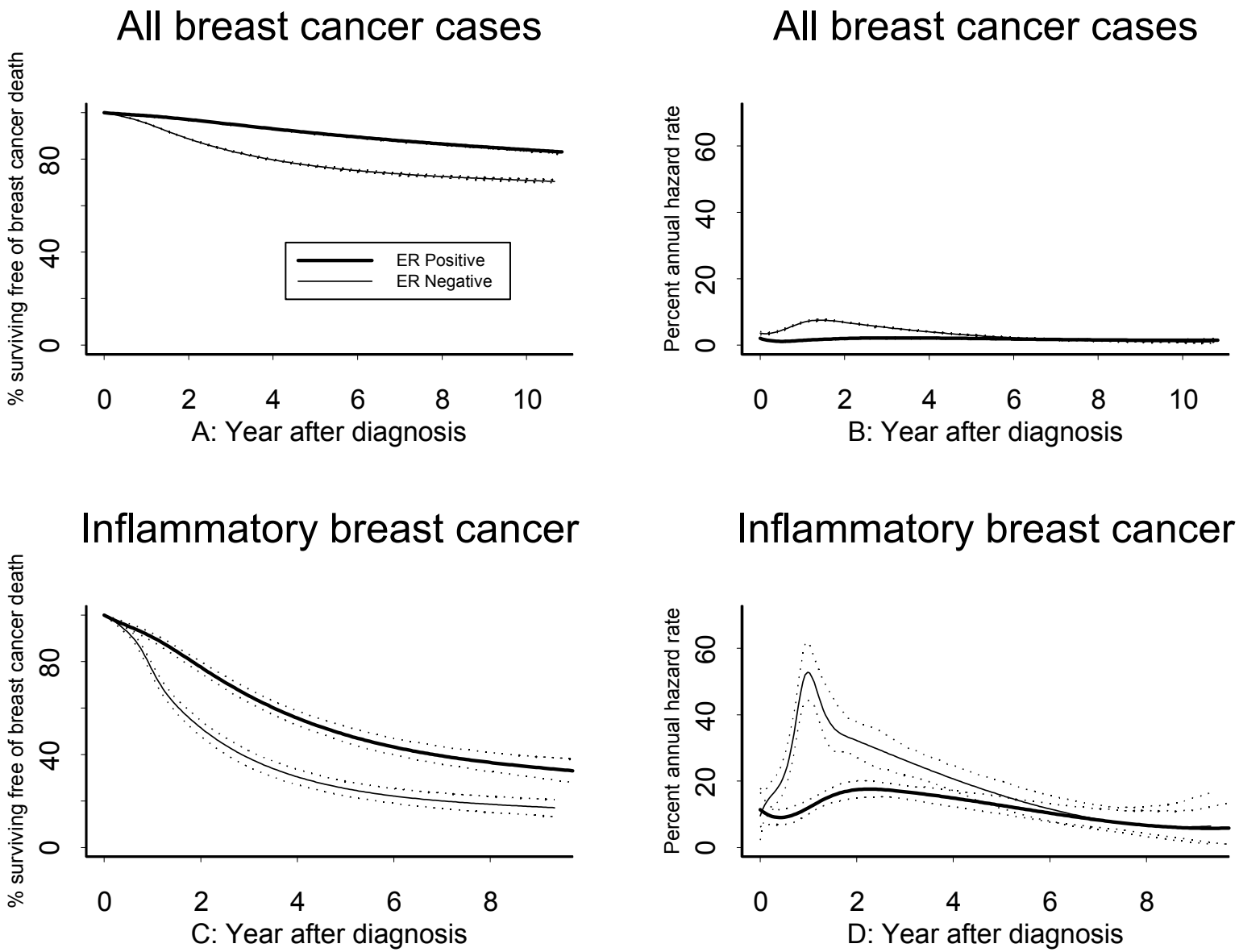
Survival and Prognosis of IBC: Single Institution Experiences

	N	Regimen	Median survival (months)	Overall survival	
				5 yr	10 yr
MD Anderson	178	FAC	37	40%	33%
Centre H. Becquerel	178	AVCF, FAC, FEC	37	32%	23%
Institut Gustav Roussy	230	RT +/- AVM/VCF, AVCMF	36	42-74% at 4 years	

IBC Survival: NCI MB 198



Low et al, J Clin Oncol 2004;22:4067



Anderson, et al Breast Disease;22:2005

British Columbia: Population-Based Survival Analysis

- Retrospective study from 1980-2000 of 485 IBC patients – 1/3 metastatic at diagnosis
- In 308 pts - more intensive chemo improved survival (data limited)
- Mastectomy improved local control: LRFS 59-63% with Mx and 34% without

Panades, J Clin Oncol 23:1941, 2005

High Dose Chemotherapy in IBC

	N	pCR(%)	OS(%)	yrs
Viens	100	32	70	3
Adkins	47	3	59	4
Bertucci	74	27	50	5
Somlo	120	NA	60	5
Ayash	50	14	64	2.3
Dazzi	21	21	52	4

Molecular characteristics of IBC

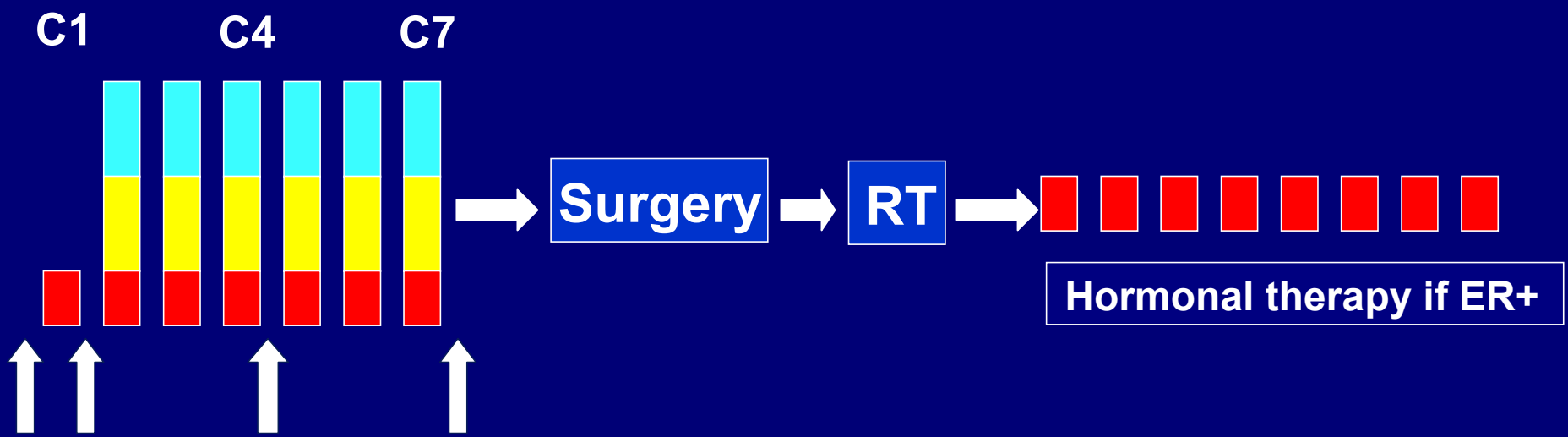
- Overexpression of E-Cadherin, MUC1, RhoC- GTPase, and p53
- Loss of LIBC/WISP3 or IGFBP-rp (tumor suppressor gene)
- Increase in angiogenic and lymphangiogenic (VEGFC and D) factors

Increased Microvessel Density in Inflammatory Breast Cancer

	N	MVD (Range)	p-value
IBC	45	25.5 (0-110.0)	0.009
Non-IBC	22	6.5 (0-92.5)	

McCarthy et al., Clin Cancer Res 2002; 8: 3857

NCI-0173 – IBC and LABC



Correlative studies

- Dynamic Contrast Enhanced MRI (DCE-MRI)
- Tumor Biopsies (mammotome)

Docetaxel 75 mg/m^2

Doxorubicin 50 mg/m^2

Bevacizumab 15 mg/kg

Wedam et al., J Clin Oncol 2006; 24:769

NCI-0173 Responses to Bevacizumab and Chemotherapy

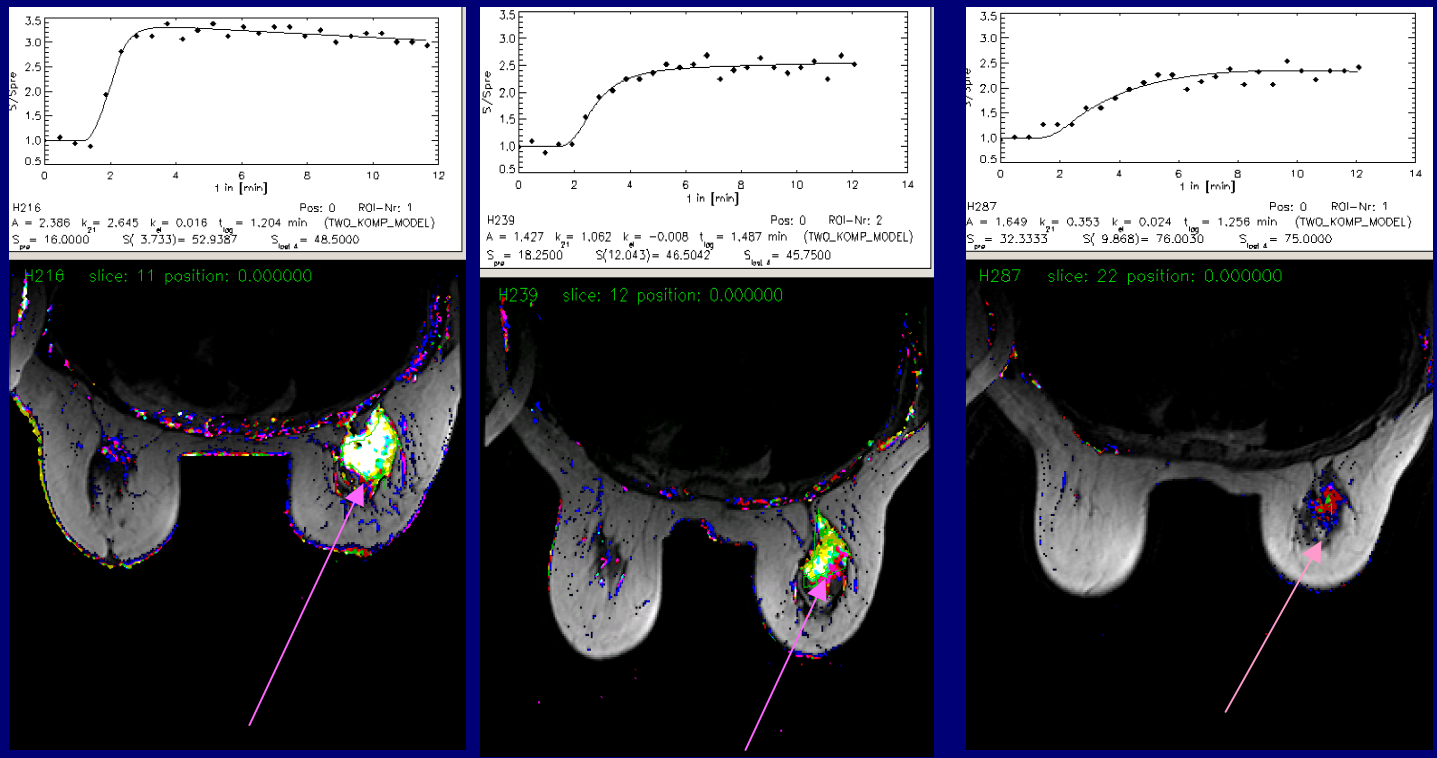
Total Patients	N= 21
• Partial Response	14 (67%)
– Pathologic CR	1
• Stable Disease	5 (24%)
• Progressive Disease	2 (9%)

Wedam et al., J Clin Oncol 2006; 24:769

Change in Molecular Markers from Baseline to C1 - 0173

- Ki67 + 2% (NS)
- MVD -15% (NS)
- VEGF-A - 50% (NS)
- VEGFR2 +70% (NS)
- pVEGFR2 (Y996) - 69% (0.024)
- pVEGFR2 (Y951) - 67% (0.004)
- TUNEL +129% (0.0008)

NCI-0173 DCE-MRI Time Intensity Comparisons



Baseline | **Post BV (cycle 1)** | **Post BV and chemo (cycle 4)**

Increased uptake of contrast in tumor reflecting permeability and flow

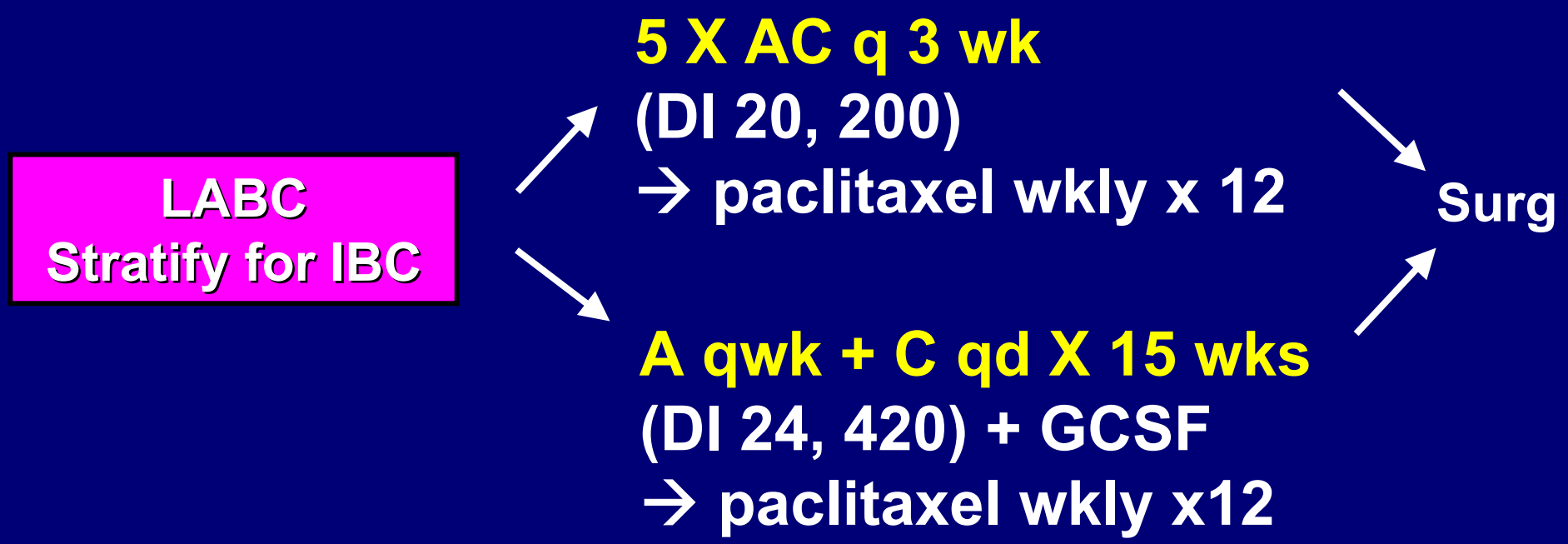
Wedam et al., J Clin Oncol 2006; 24:769

Summary NCI – 0173 Study

- Excellent clinical response to combined anti-angiogenic and chemotherapy
- Correlative studies after bevacizumab
  - Decrease in phospho-VEGFR2 (tumor cells)
  - Increase in tumor apoptosis (tumor cells)
  - Decrease in vascular permeability + flow on DCE-MRI
- Gene expression profiling in process for IBC signature

Wedam et al., J Clin Oncol 2006; 24:769

SWOG 0012
Conventional vs Metronomic Schedule



Ellis, et al ASCO 2006

SWOG 0012

- Accrual: 10/ 2002 – 12/2005
- Eligibility: locally advanced breast cancer, 372 patients randomized
- 265 evaluable for primary outcome, 132 arm 1, 133 arm 2, including those who did not proceed to surgery
  - 81 pts with IBC

SWOG 0012: Conclusions

	Arm 1 AC →P	Arm 2 AC+G →P
– pCR*	19%	31%
– pCR+N0	15%	26%

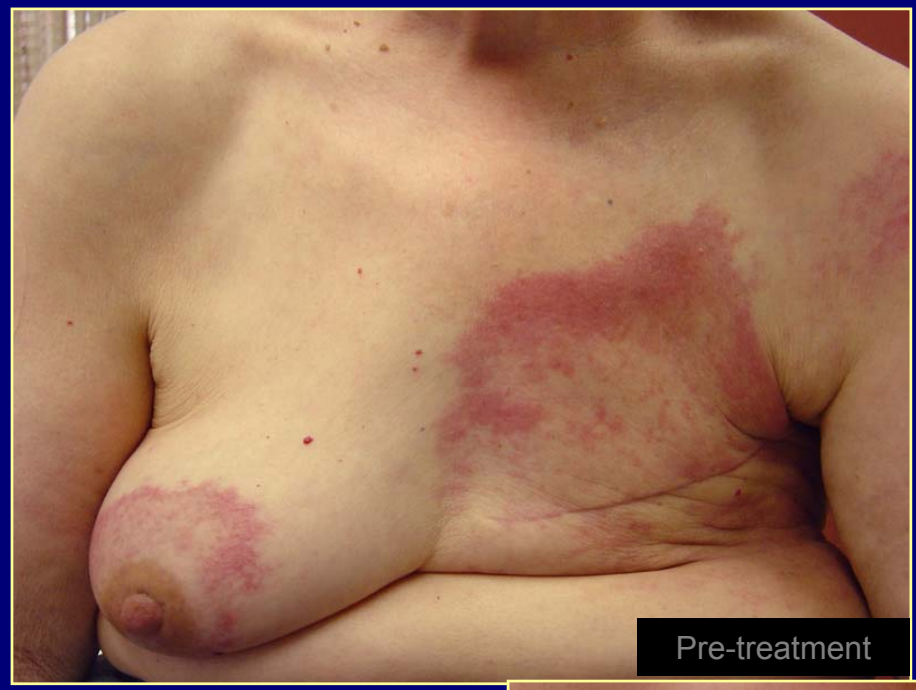
*OR = 2.11

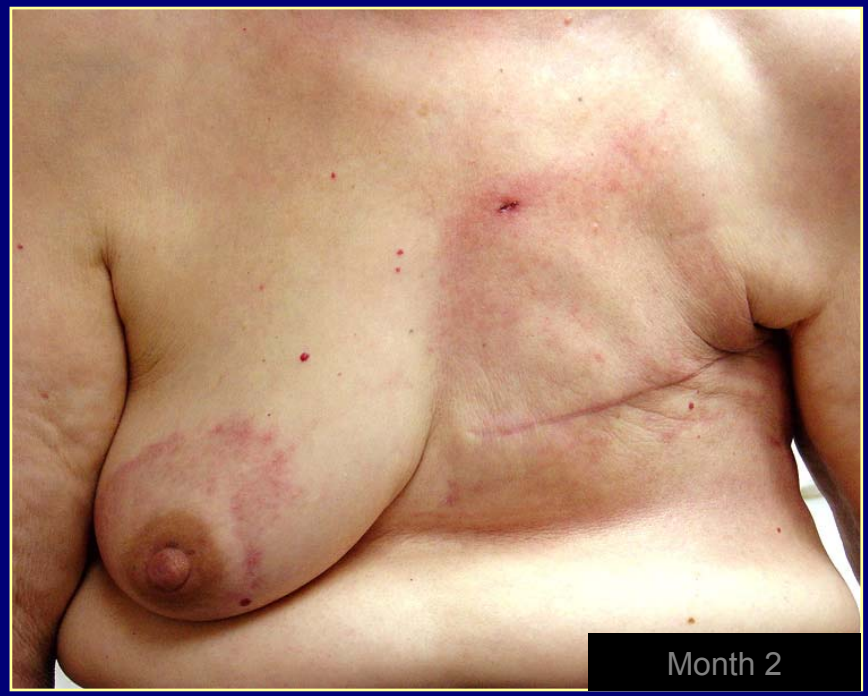
95% CI = 1.13 - 3.96, p = 0.020

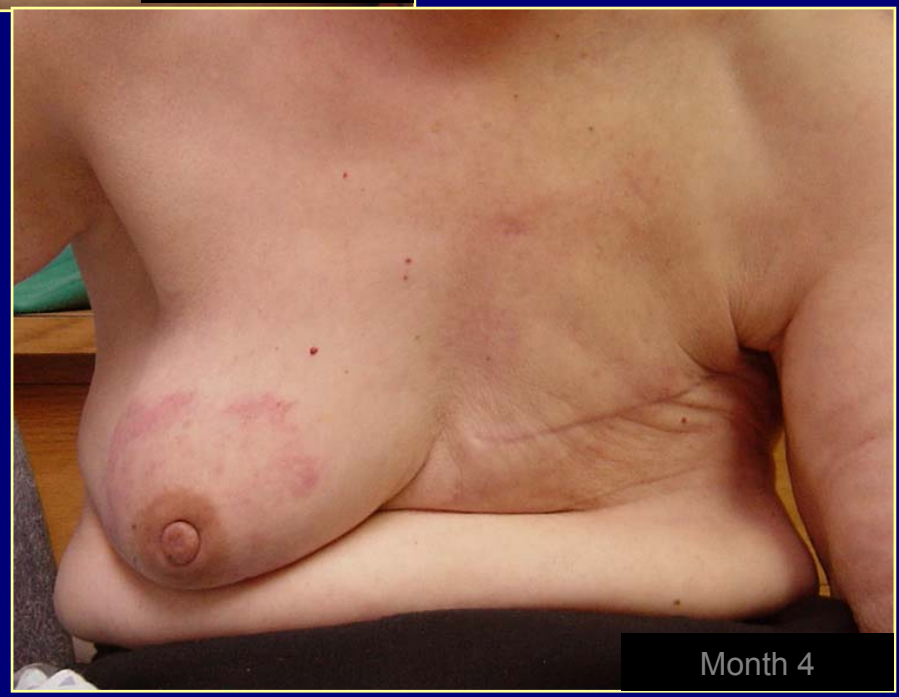
Inflammatory Breast Cancer

pCR	12%	32%

Responses seen in IBC Phase I lapatinib studies

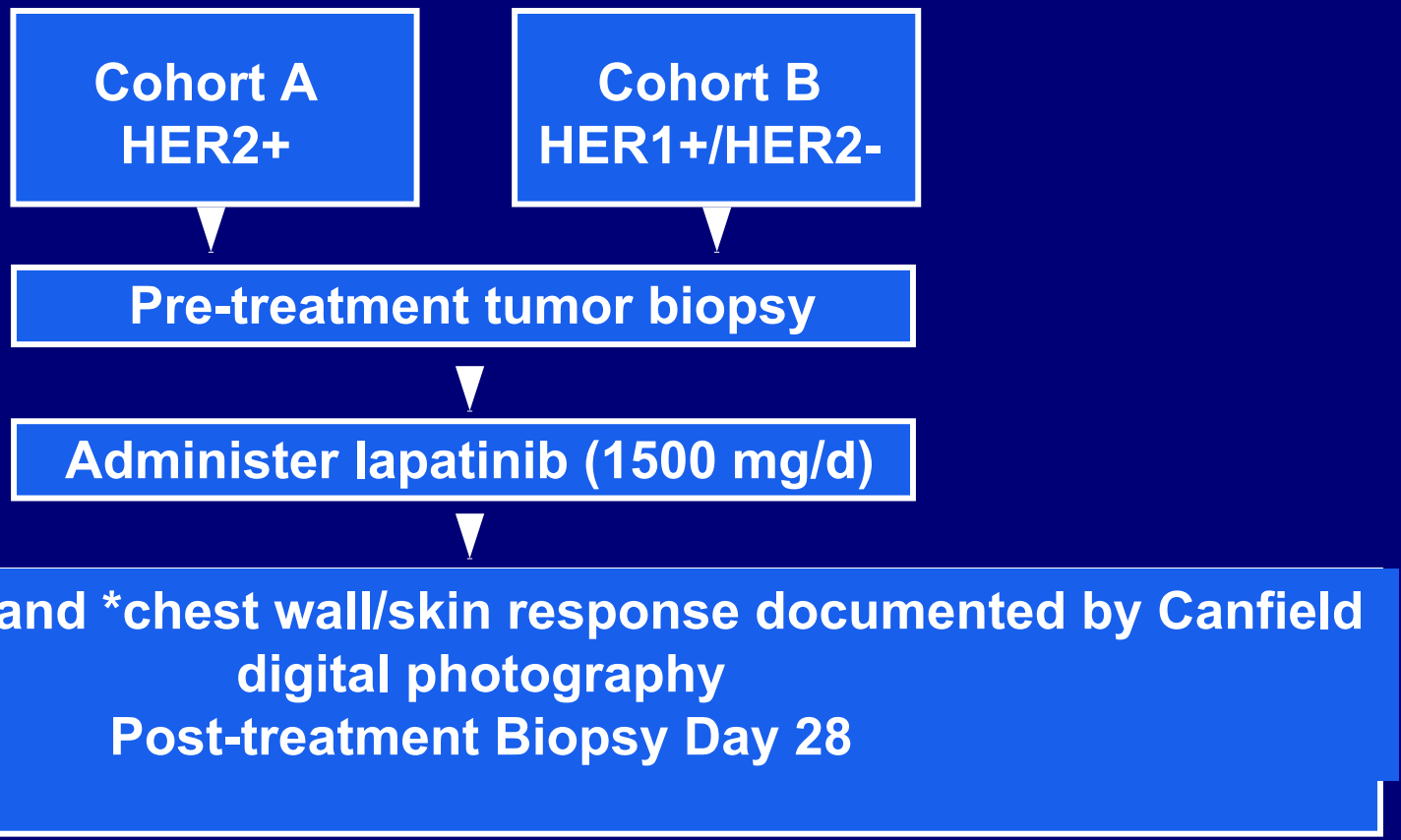






Spector et al

EGF103009 Lapatinib Refractory/Relapsed IBC Study Schema



Trudeau et al., ESMO 2006C

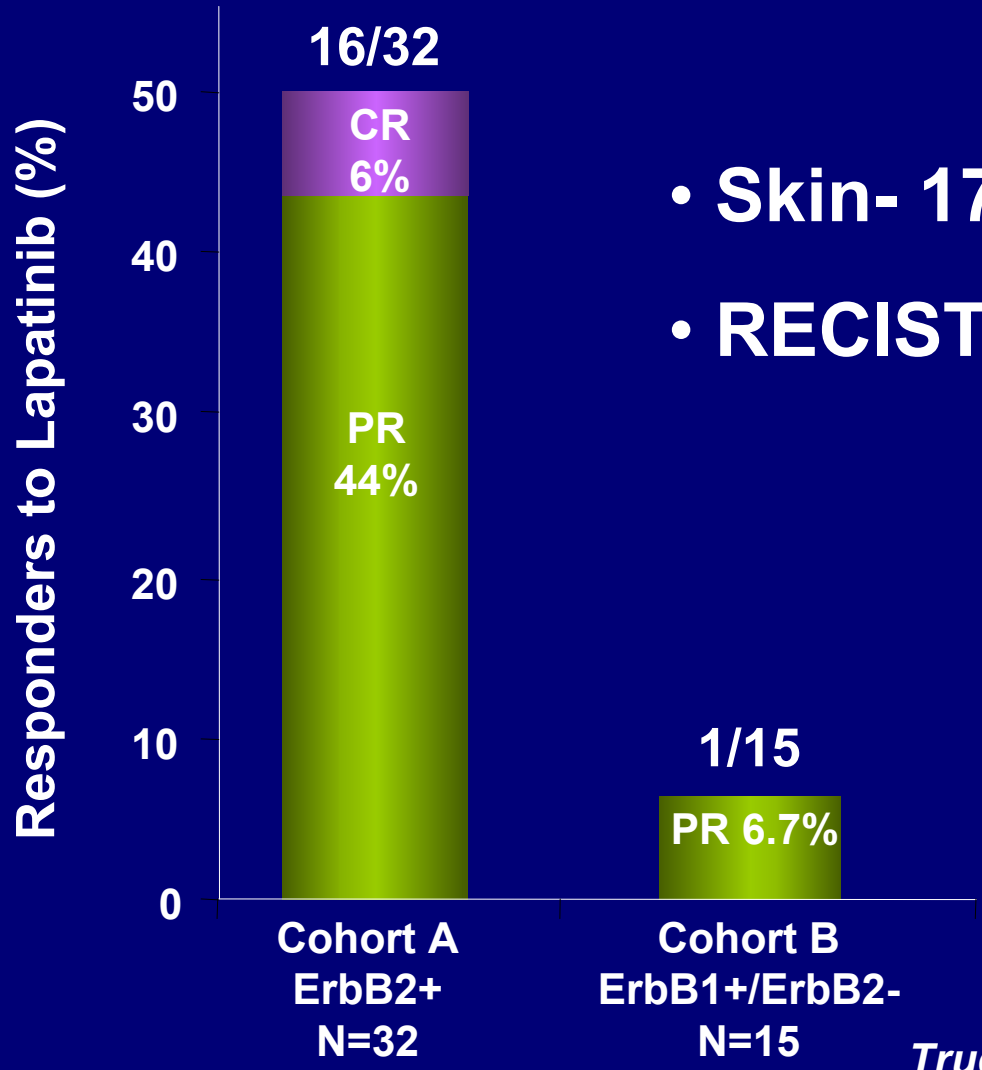
EGF103009 Baseline Characteristics

Median age	53 (32-79)
Dermal lymphatic invasion	75%
Stage	
III	21%
IV	79%
Median chemo regimens	4.5 (0-21)
Anthracycline	98%
Anthracycline/Taxane	78%
Trastuzumab	75% (Cohort A)
Sites	
North America/Israel/EU	71%
Tunisia	29%

*based on data from 49 patients; efficacy/safety data from 47 patients

Trudeau et al., ESMO 2006

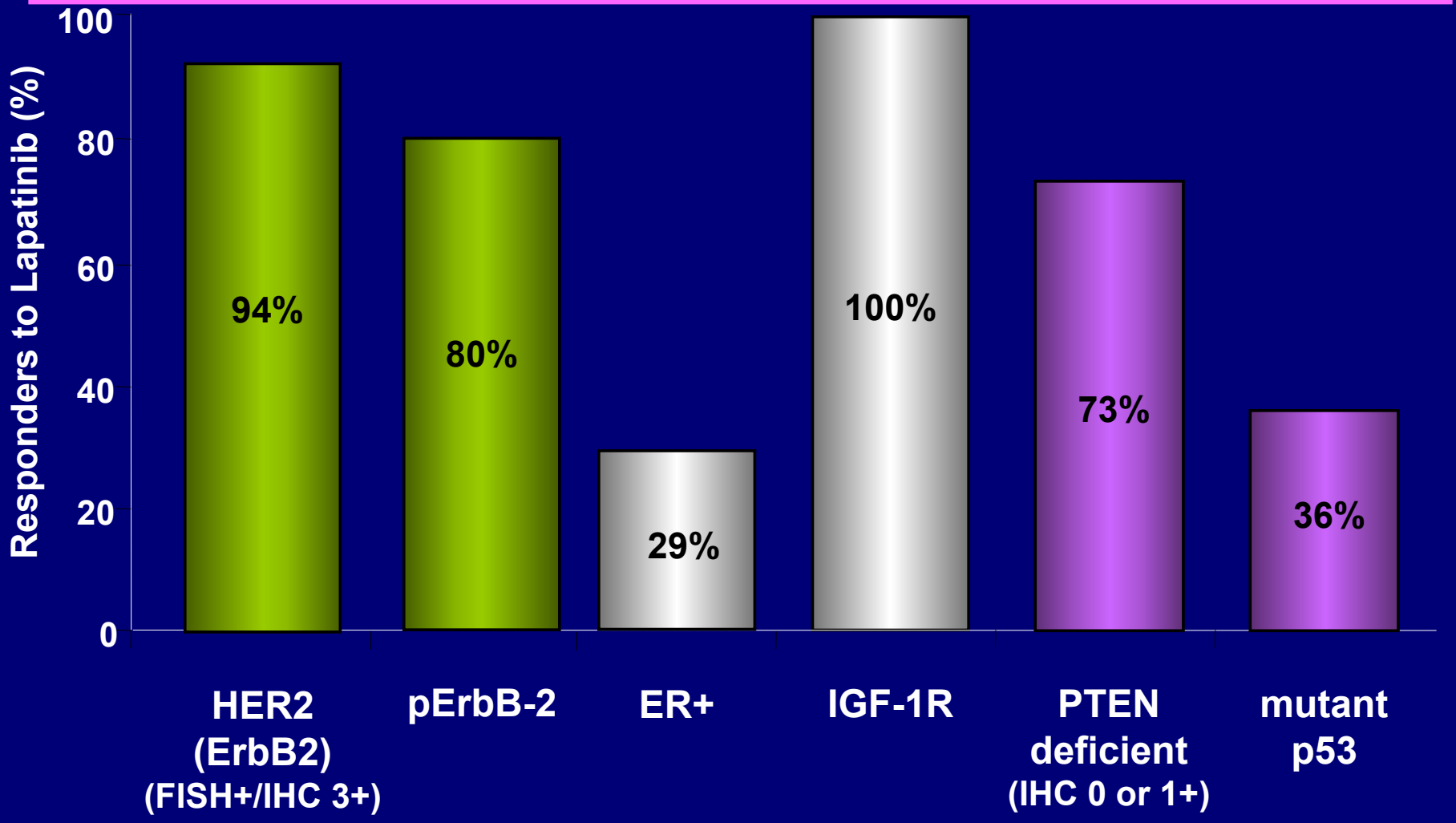
EGF103009 Response Rate to Lapatinib Monotherapy



- **Skin- 17 CR/PR**
- **RECIST- 9 PR**

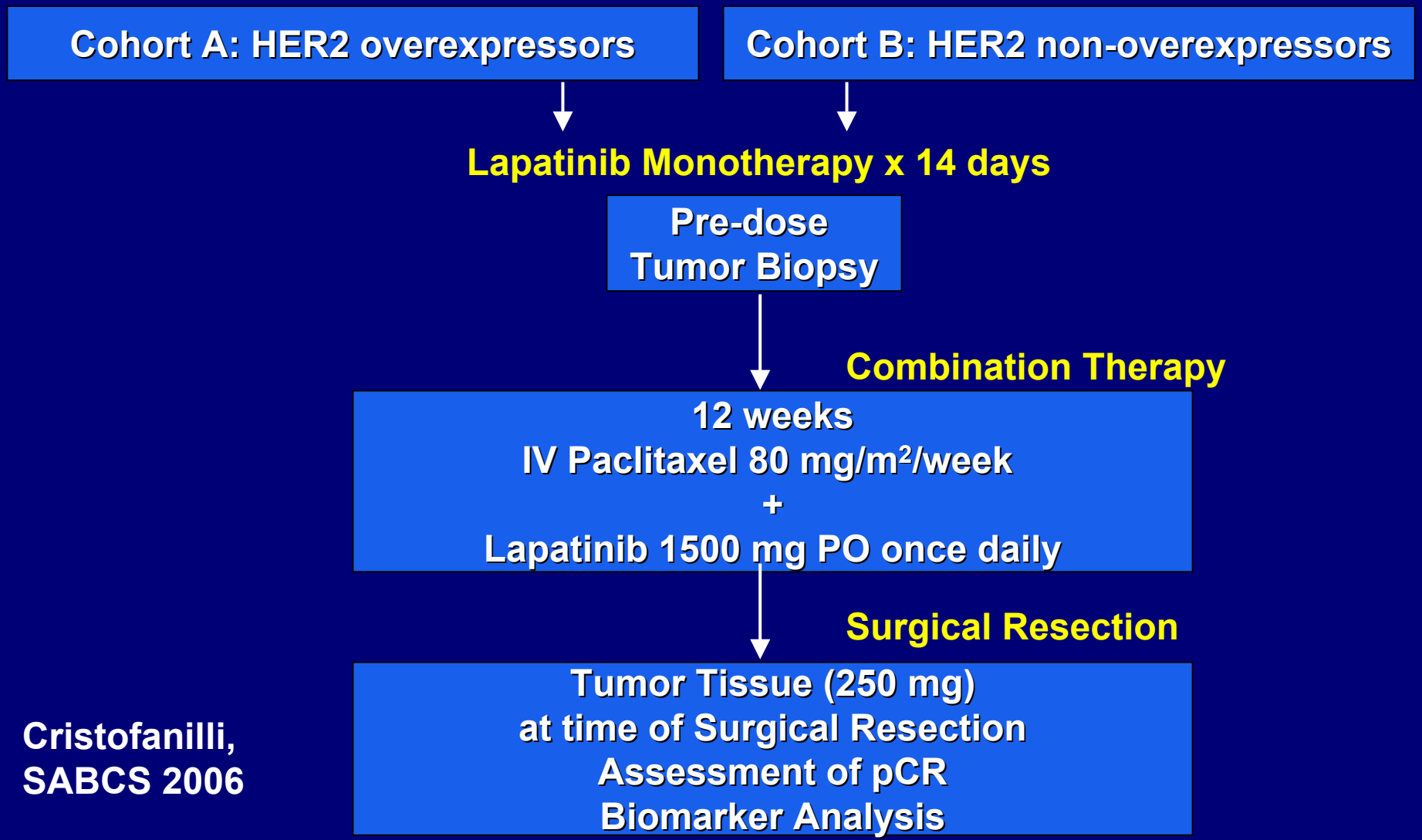
Trudeau et al., ESMO 2006

Biomarker Characterization of Responders



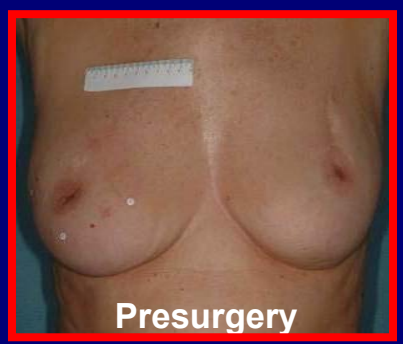
Trudeau et al., ESMO 2006

EGF102580 Lapatinib Plus Paclitaxel as Neoadjuvant Therapy in Newly-Diagnosed Inflammatory Breast Cancer



Cristofanilli,
SABCS 2006

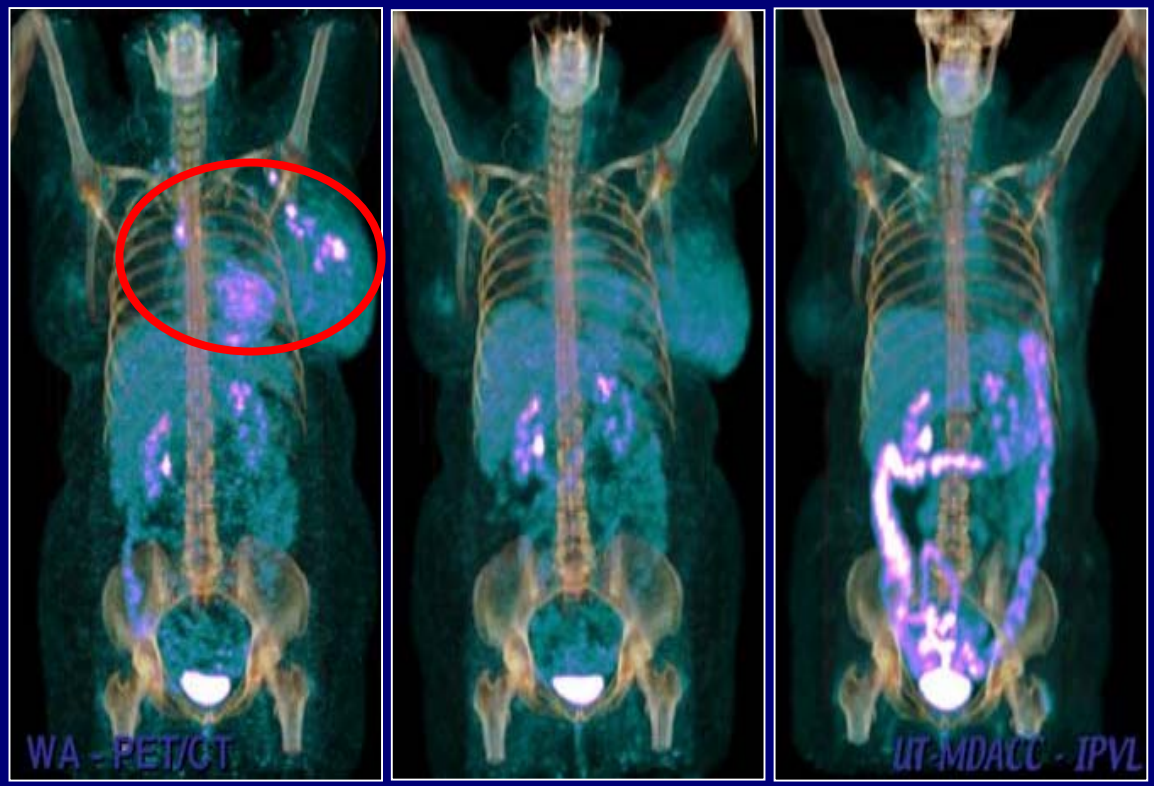
Objective Response Rates



	Cohort A (HER2+) N=30	Cohort B (HER2-) N=5
Clinical Skin/Chest Wall Responses		
Complete Response (CR)	3 (10%)	0
Partial Response (PR)	20 (67%)	4 (80%)
Stable Disease (SD)	3 (10%)	0
Progressive Disease (PD)	0	1 (20%)
Unknown	4 (13%)	0
Response Rate (CR or PR)	77%	80%
Clinical response to lapatinib monotherapy (d14)	10 (30%)	0
Pathological Complete Responses*		
Pathological CR*	3/18 (17%)	0/3

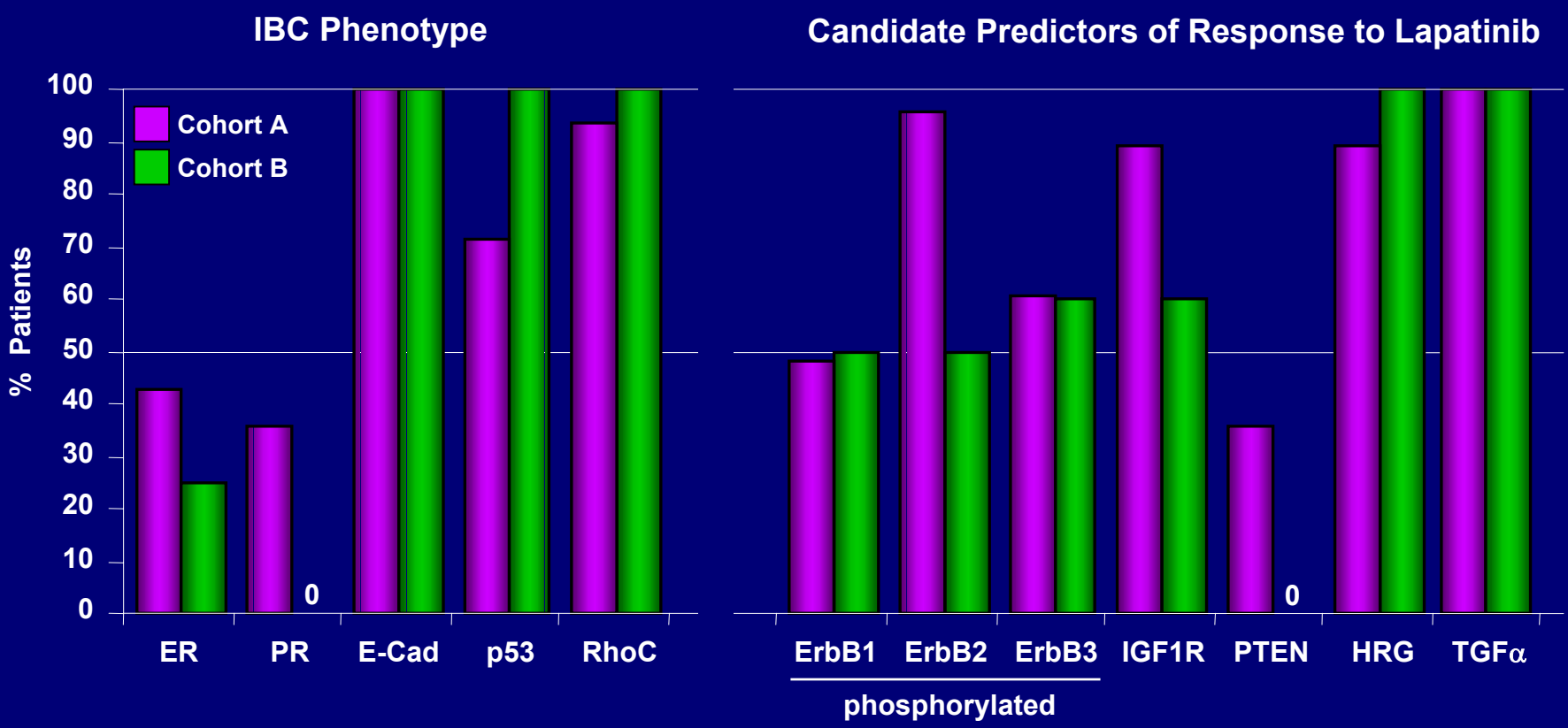
- Defined as no evidence of residual invasive tumor, including no residual tumor in the axillary lymph nodes

Functional Imaging to Evaluate Response to Lapatinib



Baseline | **Lapatinib Monotherapy** | **Before Surgery**

Biomarker Analyses



Lapatinib in IBC

- **Short course has 30% RR in previously untreated patients**
- **Monotherapy has 50% RR in heavily pretreated patients**
- **Activity almost exclusively in pts with HER2 positive disease**
- **Responses seen with PTEN deficiency or mutant p53**

Molecular Profiling of IBC

- 109 gene signature – over expression of basal phenotype
- NFκ-B overexpression
- Her-2/neu overexpression
- 16 pathways and 61 GO categories discriminate from non-IBC

RTPCR

- 27 upregulated genes
- Increased expression of angiogenesis and lymphangiogenesis related genes

- ***Bertucci et al. Cancer Res 2004 4:8558 and Cancer Res 2005 65:2170***
  Van Laere et al. Breast Cancer Res Treat 2005 Oct;93(3):237-46
  Bieche et al. Clin Cancer Res 2004 10:6789
  Ngyen, et al . Clin Cancer Res 2006
  Van der Auwera et al. Clin Cancer Res 2004 10:7965

Summary

- IBC is a rare disease with poor prognosis
- Anti-angiogenic therapy results in direct tumor effect
- Lapatinib effective in HER2 positive IBC
- Important to define molecular signature of IBC and predictors of response