

# PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

## Special Issues in Locally Advanced Breast Cancer (LABC): Medical Oncology Perspective

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# Outline

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- Staging for locally advanced breast cancer
- Inclusion of ipsilateral supraclavicular ( $N_{3c}$ ) involvement as LABC
- Systemic trials specific for LABC
- Role of radiation in LABC

# Goals of Primary Systemic Therapy for LABC

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- Recommendations of International Expert Panel on Use of Neoadjuvant Systemic Treatment Operable Breast Cancer
- In population of LABC:
  - 1° aim: Improve surgical options
  - 2° aims: Obtain freedom from disease  
Gain information on tumor response

# Natural History of LABC

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- LABC first recognized as disease not cured by surgery by Haagensen and Stout in 1943
- Retrospective study of 454 consecutive patients with  $T_{3-4}N_xM_0$  treated with RT from 1968-1972
  - No neo/adjuvant systemic therapy given
  - 133 selected patients underwent radical mastectomy
  - 72%  $T_4$  (15%  $T_{4d}$ )
  - 67%  $N_{1-3}$
  - Median survival 2.5 years

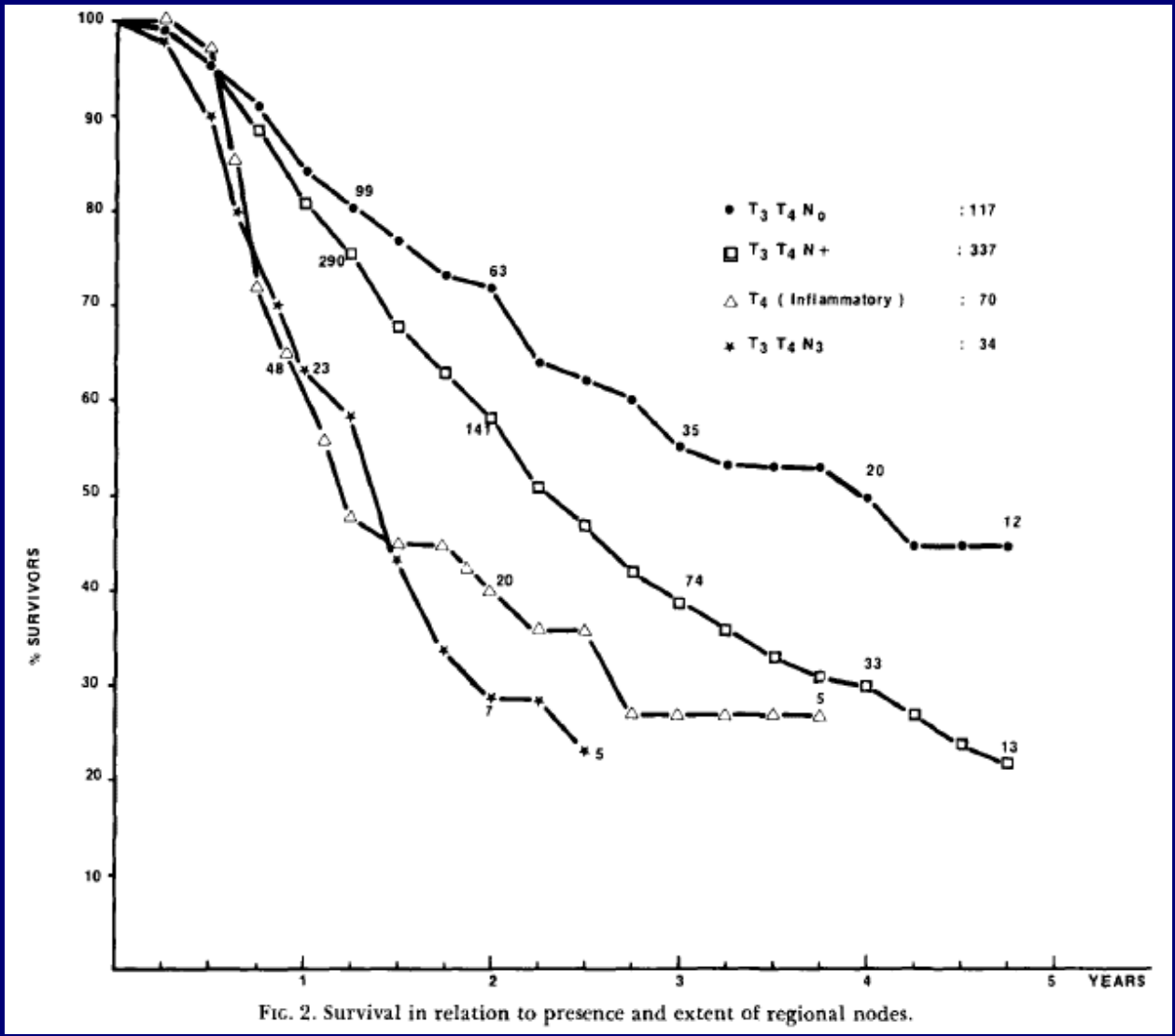


FIG. 2. Survival in relation to presence and extent of regional nodes.

Adapted from Zucali R, et al. Cancer 1976;37:1422-31

# Staging of LABC

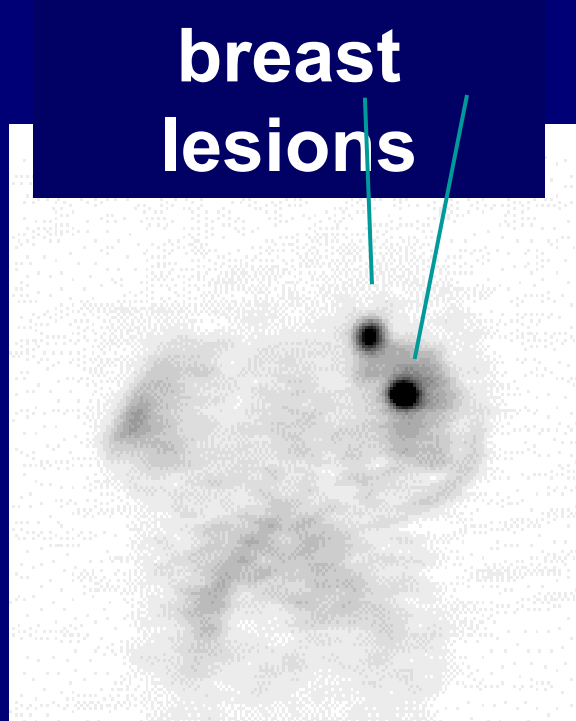
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- Systematic review of published literature 1966-1998
- In stage III breast cancer recommend chest imaging, liver imaging and bone scan
- Detection of distant metastases in stage III:
  - bone scan: 8.3%
  - liver U/S: 2.0%
  - CXR: 1.7%
- False(+) rates: 10-22% bone scan, 33-66% liver U/S and 0-23% CXR

# FDG PET - Left Breast Cancer

## Help Determine Extent of Advanced Axillary Disease

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(coronal slices)

**SUV<sub>Max</sub> = 11.1**



**SUV<sub>Max</sub> = 12.4**

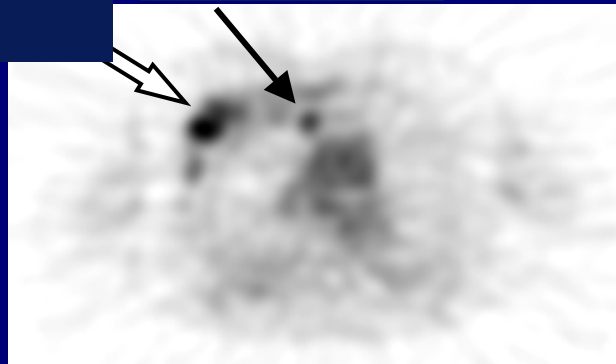
# Internal Mammary (IM) Node on FDG PET: Locally Advanced Breast Cancer Pre-Therapy Up to 20% IM nodal disease by FDG PET in LABC

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**Breast  
Tumor**

**IM Node**

**Emission**



**Transmissi  
on**



**IM uptake  
associated:**

- Non-OUQ location
- Inflammatory Br CA

**IM uptake predicted:**

- Likelihood of failure
- Pattern of failure



# Tumor Location and Risk of Relapse

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- Population based analysis of 6,781 women with early stage breast cancer from 1989-1995 comparing outcome of medial to lateral hemisphere tumors
- Despite medial based tumors:
  - smaller in size
  - less LVI
  - less nodal involvement
- Medial location tumors associated with worse outcome:
  - 5 year DDFS: 66.3% vs. 74.2% ( $p < 0.005$ )

# Ipsilateral Supraclavicular Node Involvement

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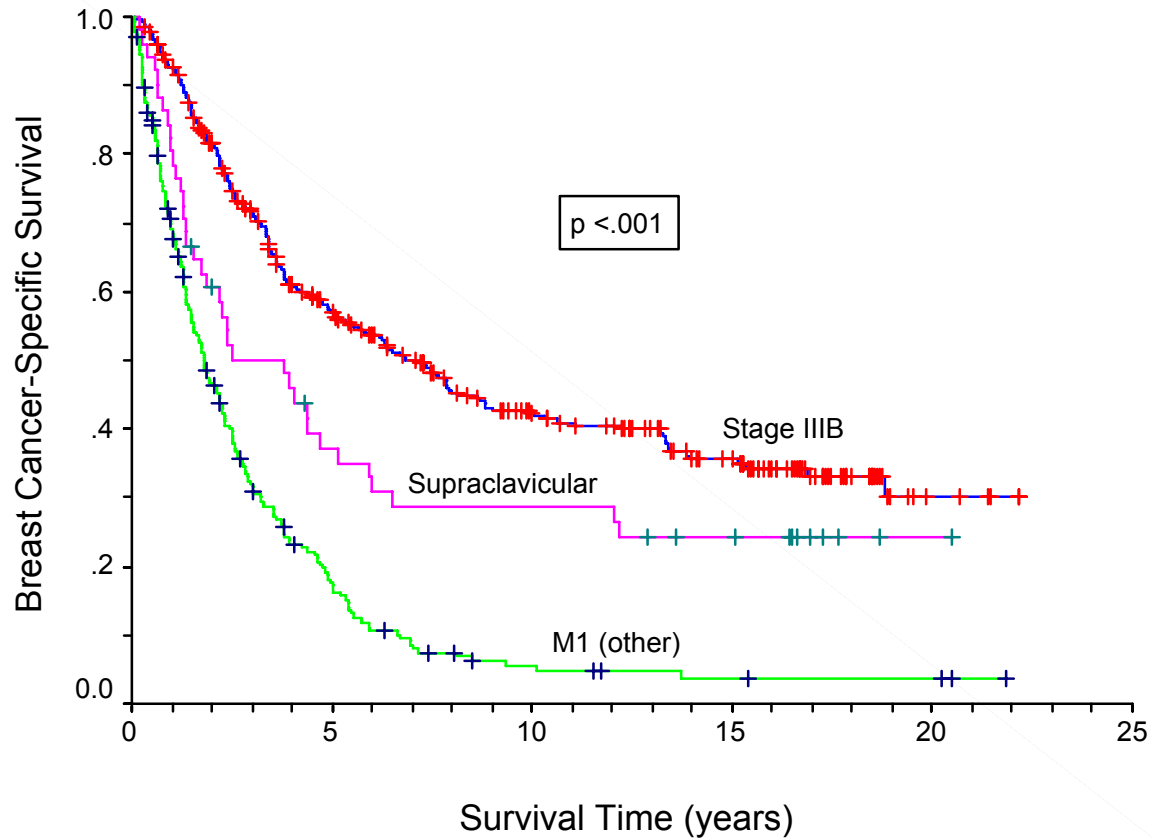
- 6<sup>th</sup> Edition AJCC Staging for breast cancer changed supraclavicular metastases from M<sub>1</sub> → N<sub>3C</sub>
- MD Anderson experience of n=70 with ipsilateral SCN treated with combined modality therapy (neoadjuvant anthracycline based chemotherapy) had 10 year DFS of 32%
- British Columbia cohort of ipsilateral SCN (n=51) had 10 year BCCS of 24%

Singletery SE, et al. J Clin Oncol 2002;20:3628-36

Brito RA, et al. J Clin Oncol 2001;19:628-33

Olivotto IA, et al. J Clin Oncol 2003;21:851-54

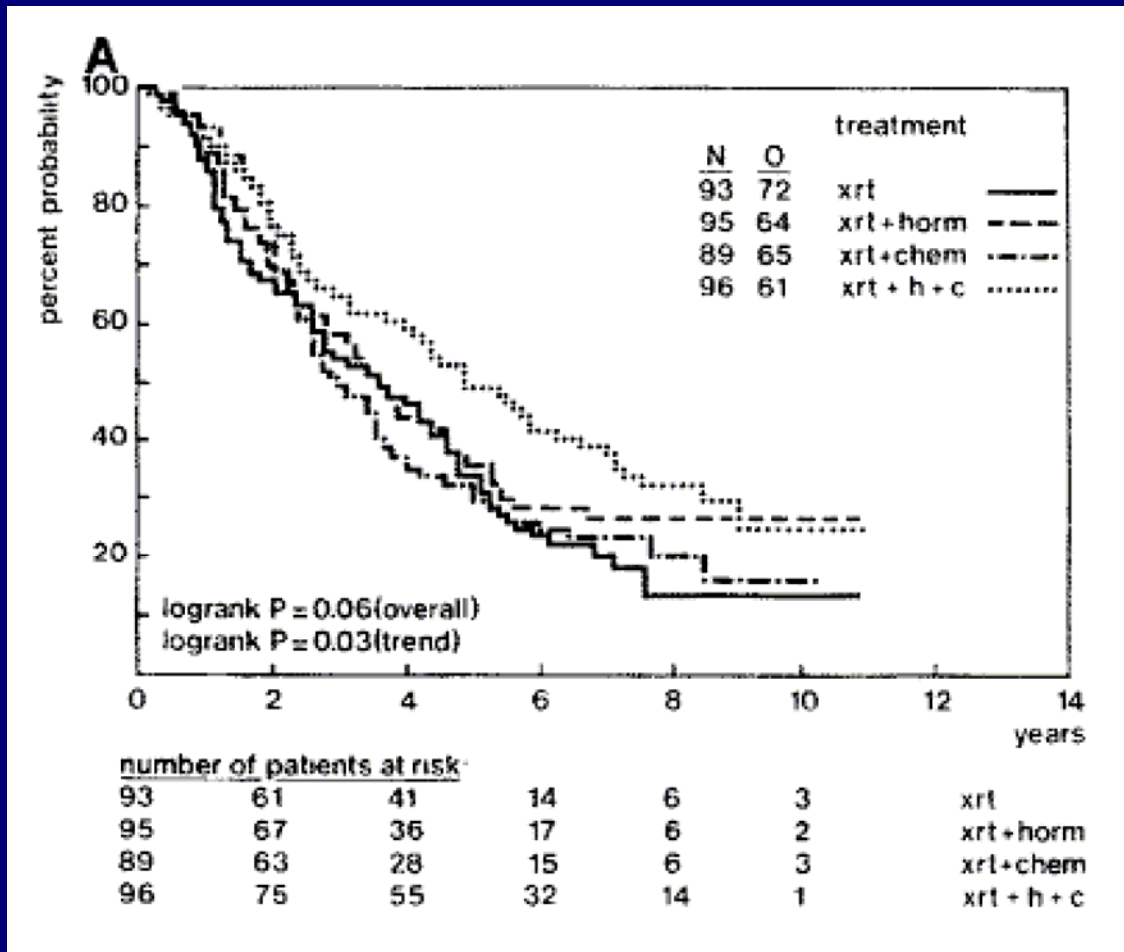
# Breast Cancer-Specific Survival



# Systemic Therapy Trials Specific for LABC

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- Initial largest RCT in LABC initiated in 1979 by EORTC assessed adjuvant chemotherapy, hormonal therapy or both in LABC
- N=410 with clinical LABC randomized to:
  - RT alone
  - hormonal therapy (Tamoxifen or OA)
  - CMF x 12
  - combination
- Mastectomy not part of treatment plan



Adapted from Bartelink H, et al. J Clin Oncol 1997;15:207-15

# Systemic Therapy Trials Specific for LABC

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- Other initial randomized phase III trials of chemotherapy in LABC failed to show OS improvement BUT:

small numbers (< 50/arm)

older chemotherapy regimens (CMF)

inconsistent staging

Schaake-Koning C, et al, et al. Int J Radiat Oncol Biol Phys 1985;11:1759-63

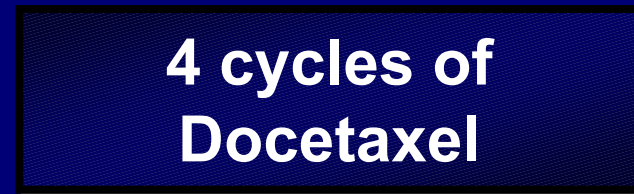
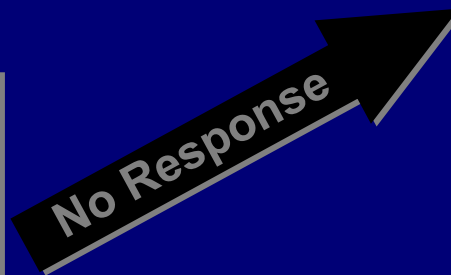
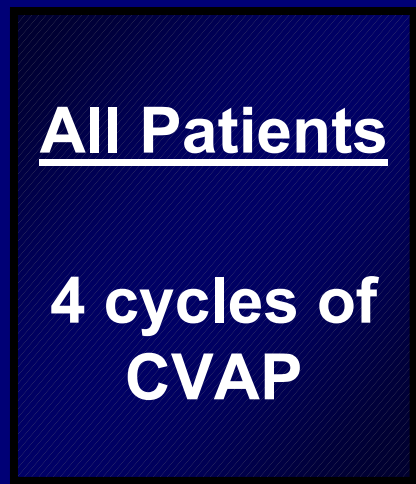
Derman DP, et al. Int J Radiat Oncol Biol Phys 1989;17:257-61

Rodger A, et al. Br J Cancer 1992;65:761-65

# The Aberdeen Breast Group Neoadjuvant Trial LABC

## First Phase

## Second Phase

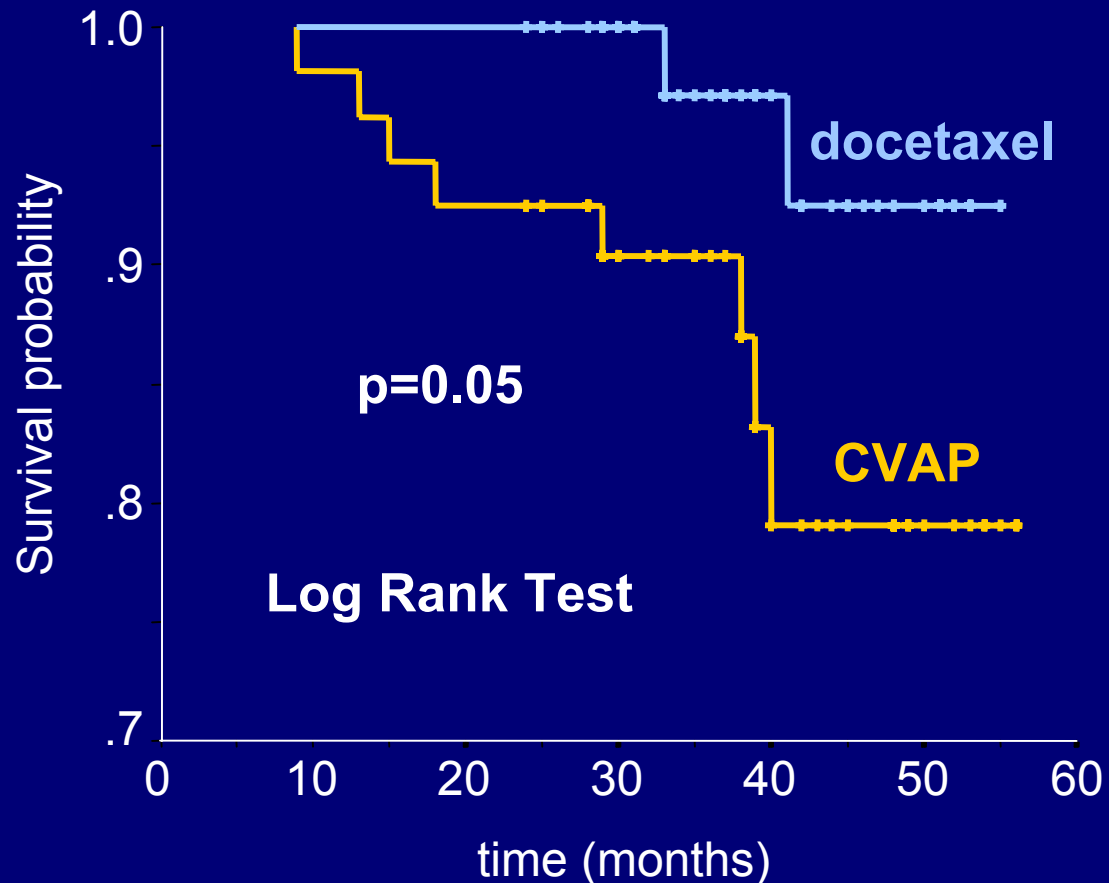


Final Assessment / Surgery

Large  $\geq 3$  cm tumors

T<sub>3</sub>, T<sub>4</sub>, T<sub>x</sub>N<sub>2</sub>

# Survival



- Patients who responded to CVAP
- Randomised to: *docetaxel* x4 or *CVAP* x 4
- Survival increased in docetaxel group



# EORTC-NCIC-SAKK Multi-centre Trial in LABC:

Patient Population  
(n = 448)

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- 40% T4a-c
- 45% T4d
- Locoregional treatment variable

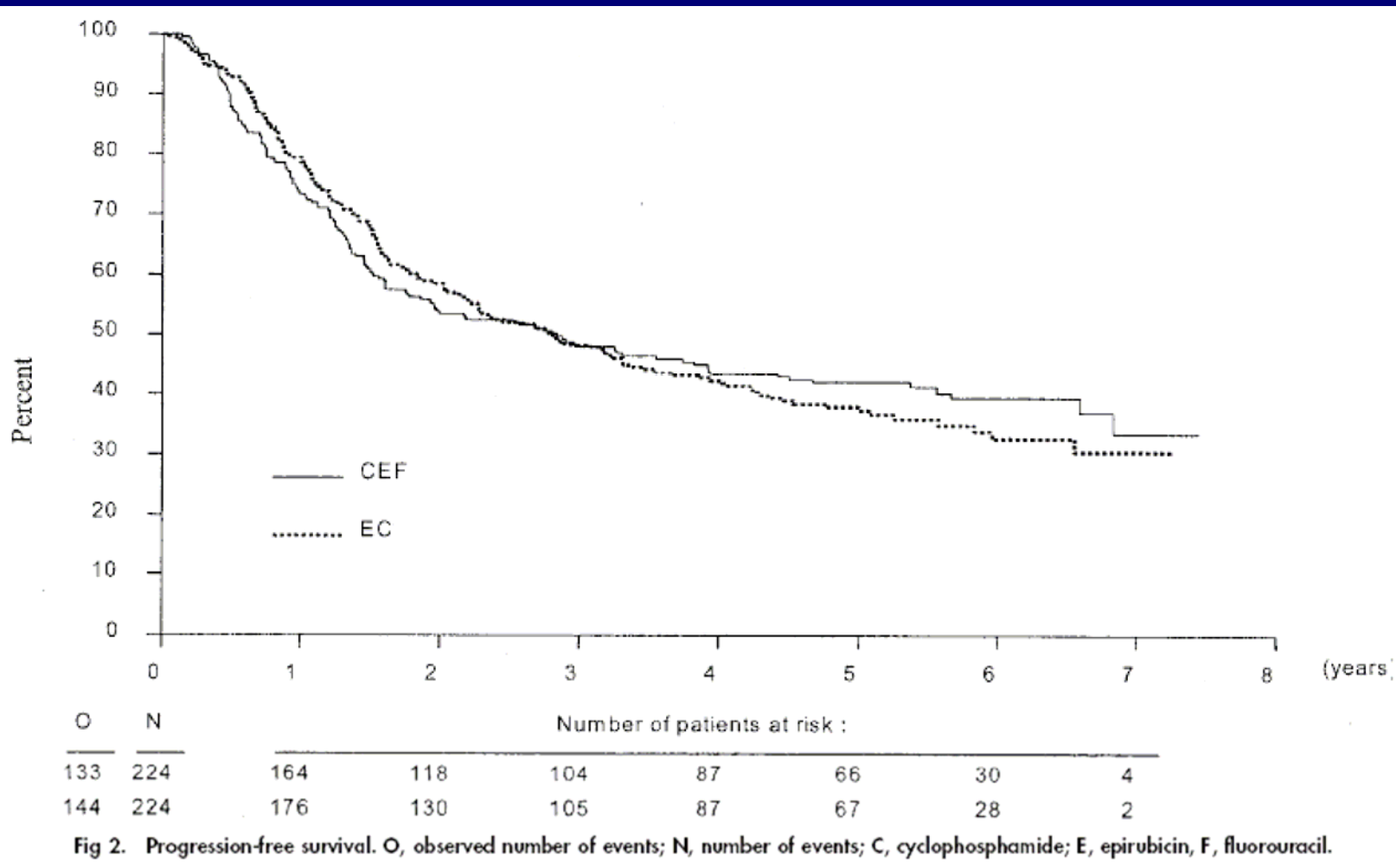
R  
A  
N  
D  
O  
M  
I  
Z  
A  
T  
I  
O  
N

C 75 mg/m<sup>2</sup> po q d days 1-14  
E 60 mg/m<sup>2</sup> IV days 1 and 8  
F 500 mg/m<sup>2</sup> IV days 1 and 8

**q 4 wk x 6**

E 120 mg/m<sup>2</sup> IV day 1  
C 830 mg/m<sup>2</sup> IV days 1  
with G-CSF day 2-13

**q 2 wk x 6**



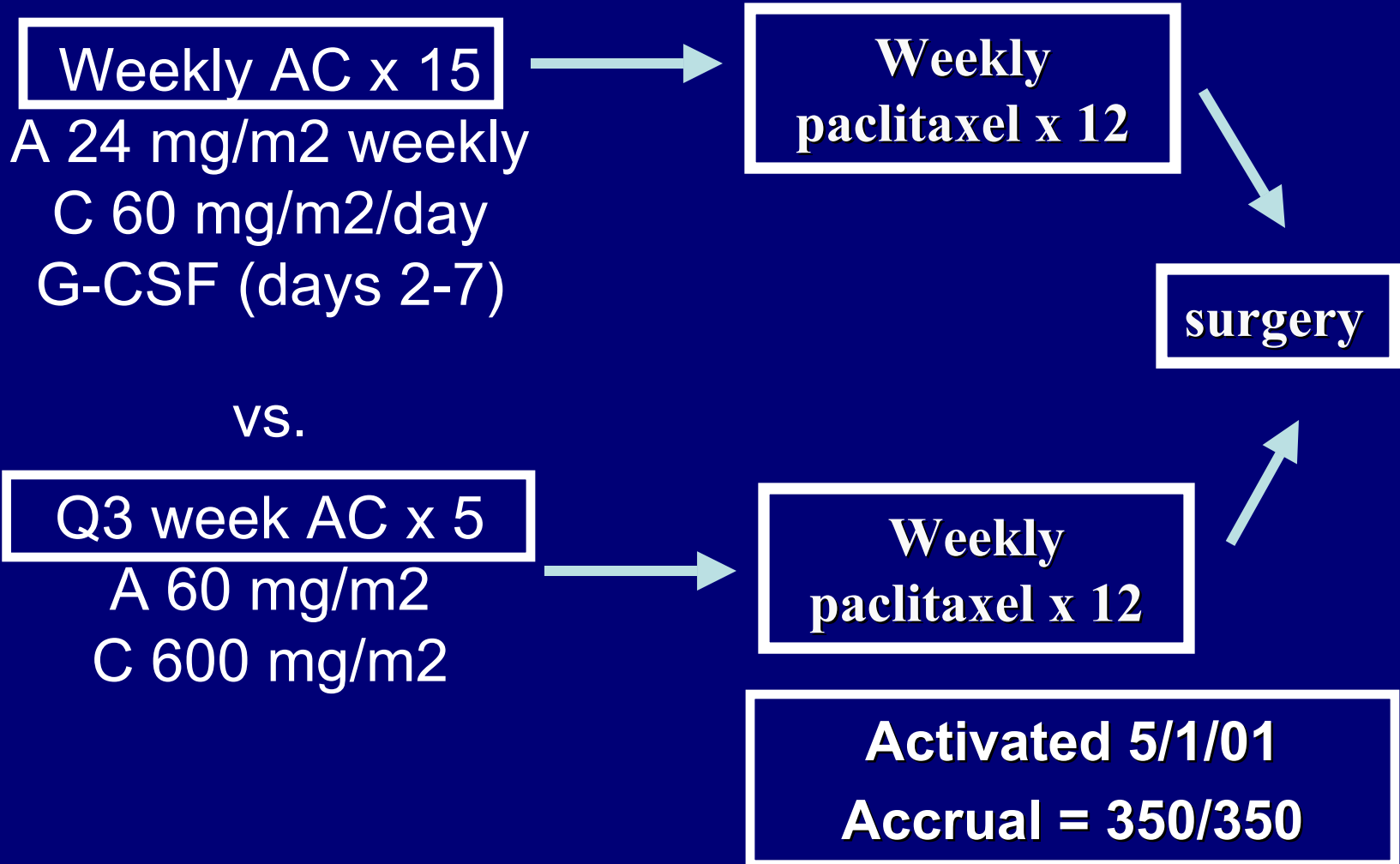
• In exploratory analysis: PFS worse in IBC (median 23.5 m) vs LABC (median 44 m)

Adapted from Therasse P, et al. J Clin Oncol 2003;21:843-50

# SWOG 0012/CTSU: Neoadjuvant Locally Advanced Breast Cancer Trial

PI: G. Ellis ASCO 2006

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# Anglo-Celtic Cooperative Oncology Group Study:

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Patient Population  
(n = 363)

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- T size  $\geq$  3 cm  
(operable)
- 15% T4d
- 8% LABC

R  
A  
N  
D  
O  
M  
I  
Z  
A  
T  
I  
O  
N

A 60 mg/m<sup>2</sup> IV days 1      **q 3 wk x 6**  
C 600 mg/m<sup>2</sup> IV days 1

A 60 mg/m<sup>2</sup> IV day 1      **q 3 wk x 6**  
T 75 mg/m<sup>2</sup> IV days 1

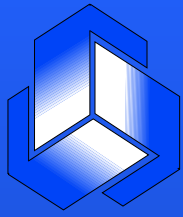
**Table 3.** Pathologic Response Rates in Patients Undergoing Surgery to the Breast (n = 342) After Primary Chemotherapy

Pathologic Response	AC (n = 172)			AD (n = 170)			All Patients (n = 342)			P
	No. of Patients	%	95% CI	No. of Patients	%	95% CI	No. of Patients	%	95% CI	
No residual disease	26	15	10 to 20	27	16	10 to 21	53	15	12 to 19	.86
No residual invasive disease (includes DCIS only)	41	24	17 to 30	36	21	15 to 27	77	23	18 to 27	.61
No residual invasive disease and negative axillary lymph nodes	27	16	10 to 21	20	12	7 to 17	47	14	10 to 18	.43

NOTE. The analyses do not include the 20 patients who did not have surgical intervention on completion of chemotherapy and do not include the one patient who had surgery to the axilla only.

Abbreviations: AC, doxorubicin and cyclophosphamide; AD, doxorubicin and docetaxel; DCIS, ductal carcinoma in situ.

- With 32 months median F/U no difference in RFS or OS



# EORTC 10994

**First prospective trial assessing the potential value of p53 in patients with locally advanced/inflammatory or large operable breast cancer prospectively randomized to a taxane vs a non taxane regimen (BIG 00-01)**

## Trial design

LABC or  
Large Operable Breast  
Cancer Pts

1850 pts

Randomized

Non Taxane Arm

Regimen x 6

LocoR

TRT

Taxane arm

3xT + 3xET

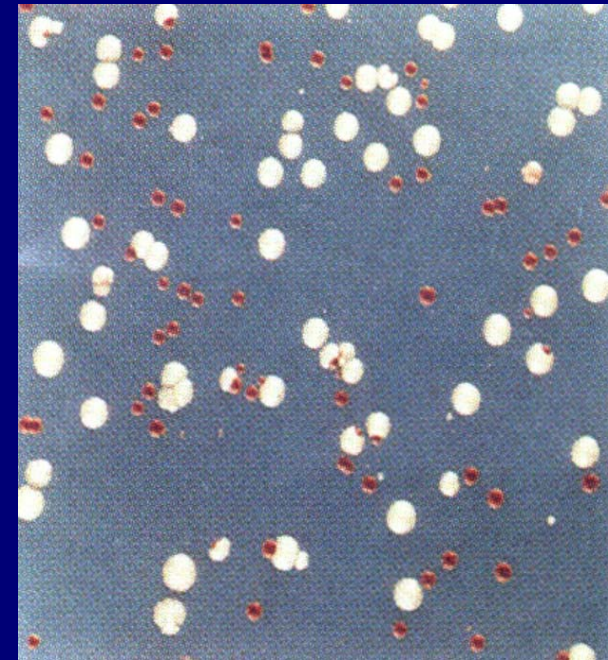
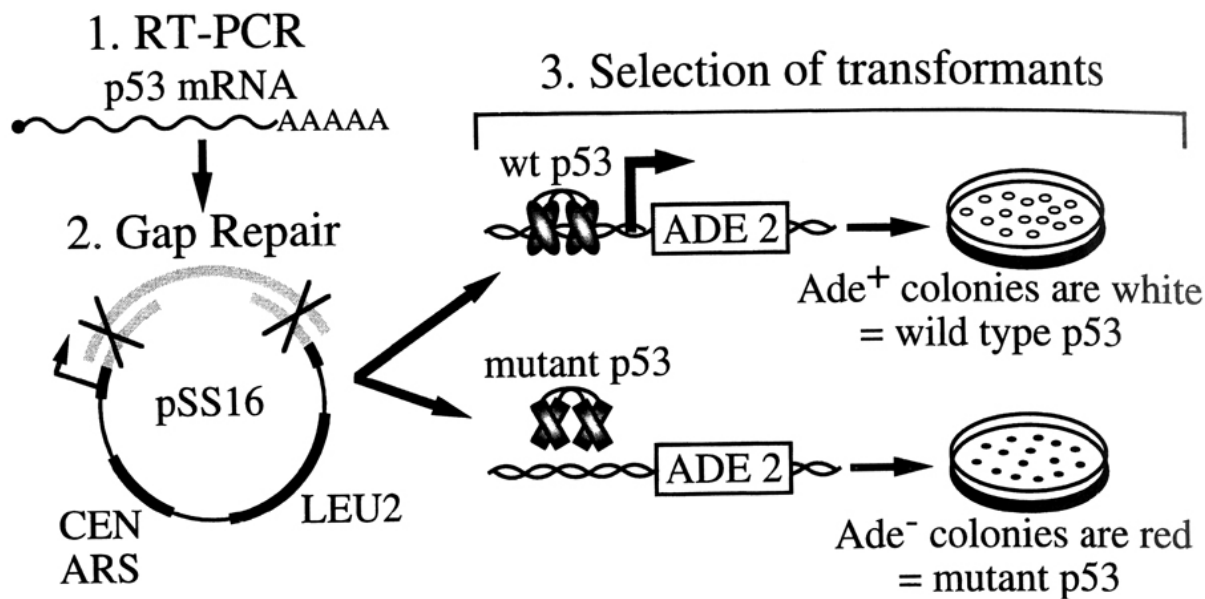
LocoR

TRT

Biopsies to be taken at baseline:

1. 1st sample: fixed for histopathological analysis
2. 2nd sample: snap frozen (2 trucut biopsies with 14G needle)

# Normal p53 Activates Transcription and Mutations Abolish Function



# Radiotherapy Trials Specific for LABC

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- Paucity of randomized trials investigating the role of RT in LABC
- To be reviewed by Dr. Buchholz Tues AM (8:00-8:20 AM)
- Data available for Stage III disease is following adjuvant systemic therapy
- Questions to be addressed:
  - timing (prior to or following surgery ?)
  - fields (include IMC ?)
  - sparing a cohort (pCR cohort ?)



# Conclusions

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- Complete staging in LABC is important with PET scanning potentially adding additional information
- Isolated SCN involvement (N3<sub>c</sub>) and inflammatory breast cancer (T4<sub>D</sub>) have different outcomes than LABC (separate trials or stratify)
- Limited number of trials specifically in LABC *appear* to show:
  - addition of taxane improves outcome
  - dose-intense anthracycline regimen does not improve outcome (but metronomic schedule may)
  - sequential taxane vs. concurrent taxane improves outcome
- Role of RT following neoadjuvant chemotherapy needs to be studied