Locally Advanced Breast Cancer: Systemic and Local Therapy

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Dana Farber Cancer Institute
SOBO 2012
What is the definition of LABC?

- **Stage III disease:**
  - Patients with large tumors or multiple positive lymph nodes but are “operable”
    - Can be treated similar to Stage II disease
    - Often receive “preoperative” systemic therapy with a goal of breast conservation
  - Patients with “inoperable” disease
    - Due to extent of disease – tumor size (T3, T4):
      - Skin involvement
      - Pectoralis involvement
      - Extensive lymph node involvement (N2, N3)
    - Requires preoperative systemic therapy in order to allow for definitive surgery (mastectomy)
What is the incidence / demographics of LABC in US?

- Approximately 33% of all BC diagnosed in 2001-7 were LABC

- Proportion of LABC is greater in younger women and racial-ethnic minorities

What is the variation in survival with LABC?

- Advances in therapy have improved the outcome
  - Understanding subtypes of BC
  - Development of targeted therapies
  - General acceptance of treatment scheme:

  **SEER 2001-7: 5-yr OS = 84%**

Siegel, CA Cancer J Clin 2012;62:10–29
IS THERE A DIFFERENCE BETWEEN INFLAMMATORY BREAST CANCER AND LABC?
LABC = \( f \) (biology • time)
IBC vs. LABC: Are they different entities?

• Younger age of diagnosis with IBC:
  • 45-57 yr

• Seer 2004-7: 2-yr BCS
  • IBC = 84%
  • LABC = 91%
  • $P < .0001$

• 43% higher risk of breast cancer death in IBC vs. LABC

Dawood S Cancer May 1, 2011; Anderson WF, JCO 21:2254, 2003
Diagnosis of Primary IBC vs. LABC

- 1-5% incidence in US
- **Clinical definition varies:**
  - Rapid onset – 3 mo
  - Erythema > 1/3 breast
  - Edema (peau d’orange)
  - Often warm breast, pain
  - Breast enlargement – often without a mass - “Ridge”
- Highly metastatic:
  - 35% metastasis at presentation
Pathologic Hallmark of IBC: Dermal Lymphatic Involvement
Intrinsic Subtypes of IBC: More Proliferative

Molecular Subtype of Cell of Origin Inherent in non-IBC Identical in IBC

Molecular Analysis: IBC vs. Non-IBC

<table>
<thead>
<tr>
<th></th>
<th>HER2 Positive</th>
<th>ER Negative</th>
<th>PR Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nguyen</td>
<td>26% v 17%</td>
<td>49% v 30%</td>
<td>68% v 43%</td>
</tr>
<tr>
<td>Charafe-Jaulfret</td>
<td>40% v 12%</td>
<td>54% v 24%</td>
<td>54% v 35%</td>
</tr>
<tr>
<td>Ben Hamida</td>
<td>33% v 14%</td>
<td>54% v 26%</td>
<td>53% v 35%</td>
</tr>
<tr>
<td>Zell (2014)</td>
<td>40% v 35%</td>
<td>44% v 33%</td>
<td>55% v 46%</td>
</tr>
<tr>
<td>Dawood (179)</td>
<td>62%</td>
<td>62%</td>
<td>70%</td>
</tr>
</tbody>
</table>

IBC: Rate of Relapse According to Breast Cancer Subtype

**OS**
- TNBC: 91, 48, 18, 10, 6, 5
- HER-2*: 83, 51, 23, 15, 6, 1
- ER*: 105, 84, 41, 26, 16, 4
- ER*/HER-2*: 37, 31, 17, 13, 10, 4
- Log-rank $p < .0001$
- 3.2 yr
- 2.0 yr

**DFS**
- Log-rank $p = .0007$
- 57%
- 29%

**LRR**
- Log-rank $p < .0001$
- 39%
- 8%

Li J et al. The Oncologist 2011;16:1675-1683
Tri-modality Therapy for IBC

- Prognosis is poor
- Incidence of metastatic disease at diagnosis = 20-40%
- Multidisciplinary management = Trimodality:
  - Pre-operative chemotherapy:
    - Most individuals die of systemic disease
    - Transform inoperable disease into operable disease
  - Modified Radical Mastectomy and radiation therapy
    - Optimal sequencing is not well defined, but both are necessary

University of Florida; N=84

Liauw, Cancer 2004; 100:920

5 yr = 47%
With trimodality rx

5 yr = 26%
Without trimodality rx
Benefit of Completing Tri-modality Therapy

<table>
<thead>
<tr>
<th></th>
<th>5 yr LRC</th>
<th>5 yr DMFS</th>
<th>5 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed</td>
<td>84%</td>
<td>47%</td>
<td>51%</td>
</tr>
<tr>
<td>Not completed</td>
<td>51%</td>
<td>20%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Bristol, Int j rad onc biol phys 2008;72:474
Inflammatory breast cancer-specific survival (IBCS) among women with de novo stage IV inflammatory breast cancer stratified by surgery to the primary.

![Graph showing survival distribution function with two survival curves. The upper curve indicates 57% 2-yr IBCS and the lower curve indicates 32% 2-yr IBCS.](image-url)
WHAT IS THE IMPORTANCE OF PATH-CR FOLLOWING PREOPERATIVE THERAPY?
Importance of Pathologic CR in IBC

Pathologic CR is a surrogate for improved long-term survival

5 yr OS
- MD Anderson; N=175
  - 83%
- British Columbia; N=148
  - 37%

5 yr RFS
- 79%
- 25%

BCSS
- 67%
- 23%

JCO 2005;23:1941  Cancer 2006;106:1000
The definition of pCR varies among studies

- No standard definition
- GBG has NO residual tumor, MDACC allows DCIS
  - MDACC study showed no impact – sample size may be too small
- NSABP & French allow even more residual tumor

<table>
<thead>
<tr>
<th>Group</th>
<th>GBG</th>
<th>MDACC</th>
<th>NSABP</th>
<th>French</th>
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<tbody>
<tr>
<td>ypT0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypTis</td>
<td></td>
<td></td>
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<tr>
<td>ypT&lt;1mic</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ypN0</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>ypN+</td>
<td></td>
<td></td>
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</tbody>
</table>

Slide Courtesy of F. Holmes  
What is the best predictor of DFS or OS?

\[pCR \ (ypT0 \ ypN0)\]
The importance of pCR in TN-LABC

- TNBC: If pCR achieved = outcome is similar to non-TNBC
- TNBC: If residual disease = poorer outcome c/w non-TNBC

MD Anderson – total = 255 TNBC v. 863 non-TNBC

JCO 2008;26:1275
Prognostic Impact of pCR on DFS According to Breast Cancer Intrinsic Subtype

von Minckwitz G et al. JCO 2012;30:1796-1804
HER2 positive disease

WHAT IS THE ROLE OF TARGETED THERAPY IN LABC?
NOAH Study

IBC=77
Total = 235 HER2+ (63 (27%) IBC)
Total = 99 HER- (14 IBC)

Doxorubicin 60mg/m2 → Paclitaxel
150mg/m2 q21d x 3

Paclitaxel 175mg/m2 q21d x 4

CMF x 3

Surgery + radiation therapy

• HER2+ : randomized to trastuzumab x 10 cycles with chemotherapy then to complete one year versus (N=117)
  • Chemotherapy alone (N=118)
  • HER2- : chemotherapy alone (N=99)

Gianni L. Lancet 2010;375:377
NOAH: Trastuzumab increases pCR rate

<table>
<thead>
<tr>
<th>Event-free Survival HER2+</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total series</td>
<td>0.59 (0.38-0.90)</td>
</tr>
<tr>
<td>Non-inflammatory</td>
<td>0.78 (0.47-1.30)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>0.27 (0.11-0.65)</td>
</tr>
<tr>
<td>ER and/or PR positive</td>
<td>0.87 (0.43-1.74)</td>
</tr>
<tr>
<td>ER and PR negative</td>
<td>0.46 (0.27-0.80)</td>
</tr>
<tr>
<td>cN=0</td>
<td>0.35 (0.09-1.29)</td>
</tr>
<tr>
<td>cN≥1</td>
<td>0.62 (0.39-0.98)</td>
</tr>
<tr>
<td>bpCR</td>
<td>0.48 (0.14-1.68)</td>
</tr>
<tr>
<td>No bpCR</td>
<td>0.78 (0.49-1.22)</td>
</tr>
</tbody>
</table>

- IBC Subset Analysis – ECCO 2007
- 61 / 228 pts with IBC, HER2+
- pCR = 48 % with trastuzumab
- 13% without trastuzumab

Gianni L. Lancet 2010;375:377; Baselga J. ECCO 2007, #2030
NOAH: trastuzumab adds to EFS

- 3 yr EFS HER2+: 71% v 56% (HR = 0.59)
- 3 yr OS HER2+: 87% v 79%
- 3 yr EFS HER2- : 67%
- 3 yr OS HER2-: 86%

Gianni L. Lancet 2010;375:377
GeparQuinto: is lapatinib better than trastuzumab?

ECH-TH (N=307)
- Epirubicin 90 mg/m² + cyclophosphamide 600 mg/m² q3w x 4 + trastuzumab 6 mg/kg
- Docetaxel 100 mg/m² q3w x 4 + trastuzumab 6 mg/kg
- Surgery
- Trastuzumab 6 mg/kg q3w x 12 mo

ECL-TL (N=308)
- Epirubicin 90 mg/m² + cyclophosphamide 600 mg/m² + lapatinib 1000 mg/day
- Docetaxel 100 mg/m² q3w x 4 + lapatinib 1000 mg/day
- Surgery
- Trastuzumab 6 mg/kg q3w x 12 mo

Untch Lancet Onc 2012;13:135
GeparQuinto: pCR rate

Untch Lancet Onc 2012;13:135
TRYPHAENA: what is the role of dual targeting agents?

HER2-positive EBC centrally confirmed (n = 225)

- All 3 arms were experimental
- Study dosing q3w:
  - FEC: 500 mg/m², 100 mg/m², 600 mg/m²
  - Carboplatin: AUC 6
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Pertuzumab: 840 mg loading dose, 420 mg maintenance
  - Docetaxel: 75 mg/m² (escalating to 100 mg/m² if tolerated, in Arms A and B only)

Schneeweiss A et al. Presented at SABC, 2011 (abstr S5-6).
# TRYPHAENA: Baseline Characteristics in the Safety Population

<table>
<thead>
<tr>
<th></th>
<th><strong>FEC+H+P x3</strong></th>
<th><strong>FEC x3</strong></th>
<th><strong>TCH+P x6</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 72</strong></td>
<td><strong>n = 75</strong></td>
<td><strong>n = 76</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>49.0 (27–77)</td>
<td>49.0 (24–75)</td>
<td>50.0 (30–81)</td>
</tr>
<tr>
<td><strong>ECOG PS 0, n (%)</strong></td>
<td>65 (91.5)</td>
<td>66 (88.0)</td>
<td>67 (88.2)</td>
</tr>
<tr>
<td><strong>1, n (%)</strong></td>
<td>6 (8.5)</td>
<td>9 (12.0)</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td><strong>ER- and/or PR-positive, n (%)</strong></td>
<td>39 (53.4)</td>
<td>35 (46.7)</td>
<td>40 (51.9)</td>
</tr>
<tr>
<td><strong>ER- and PR-negative, n (%)</strong></td>
<td>34 (46.6)</td>
<td>40 (53.3)</td>
<td>37 (48.1)</td>
</tr>
<tr>
<td><strong>Disease type, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Operable</strong></td>
<td>53 (72.6)</td>
<td>54 (72.0)</td>
<td>49 (63.6)</td>
</tr>
<tr>
<td><strong>Locally advanced</strong></td>
<td>15 (20.5)</td>
<td>17 (22.7)</td>
<td>24 (31.2)</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td>5 (6.8)</td>
<td>4 (5.3)</td>
<td>4 (5.2)</td>
</tr>
<tr>
<td><strong>HER2 IHC 0 and 1+, n (%)</strong></td>
<td>1 (1.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>2+, n (%)</strong></td>
<td>5 (6.8)</td>
<td>1 (1.3)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td><strong>3+, n (%)</strong></td>
<td>67 (91.8)</td>
<td>74 (98.7)</td>
<td>75 (97.4)</td>
</tr>
<tr>
<td><strong>HER2 FISH-positive, n (%)</strong></td>
<td>69 (94.5)</td>
<td>69 (92.0)</td>
<td>73 (94.8)</td>
</tr>
<tr>
<td><strong>FISH-negative, n (%)</strong></td>
<td>0 (0.0)</td>
<td>1 (1.3)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td><strong>Unknown, n (%)</strong></td>
<td>4 (5.5)</td>
<td>5 (6.7)</td>
<td>2 (2.6)</td>
</tr>
</tbody>
</table>

Schneeweiss A et al. Presented at SABC. 2011 (abstr S5-6).
TRYPHAENA: Pathologic Complete Response

ypT0/is

ypT0 ypN0

FEC+H+P x3 → T+H+P x3
(n = 73)

FEC x3 → T+H+P x3
(n = 75)

TCH+P x6
(n = 77)

50.7

45.3

61.6

66.2

57.3

51.9

Schneeweiss A et al. Presented at SABC. 2011 (abstr S5-6).
NeoSphere: what is the role of dual HER2 blockade? is there a population of patients who do not require chemotherapy?

HER2-positive EBC centrally confirmed (n = 417)

A

B

C

D

Docetaxel x 4
trastuzumab

Docetaxel x 4
Pertuzumab + trastuzumab

Pertuzumab + trastuzumab

Docetaxel x 4
Pertuzumab

Surgery

Trastuzumab to complete 1 year

### NeoSphere: pCR rate in ITT

<table>
<thead>
<tr>
<th></th>
<th>T+D (grp A=107) N (%)</th>
<th>P+T+D (grp B=107) N (%)</th>
<th>P+T (grp C=107) N (%)</th>
<th>P+D (grp D=96) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR ITT</td>
<td>31 (29%)</td>
<td>49 (46%)</td>
<td>18 (17%)</td>
<td>23 (24%)</td>
</tr>
<tr>
<td>pCR (N0)</td>
<td>23 (22%)</td>
<td>42 (39%)</td>
<td>12 (11%)</td>
<td>17 (18%)</td>
</tr>
<tr>
<td>pCR (N+)</td>
<td>8 (8%)</td>
<td>7 (7%)</td>
<td>6 (6%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>pCR (HR+)</td>
<td>10/50 (20%)</td>
<td>13/50 (26%)</td>
<td>3/51 (6%)</td>
<td>8/46 (17%)</td>
</tr>
<tr>
<td>pCR (HR-)</td>
<td>21/57 (37%)</td>
<td>36/57 (63%)</td>
<td>15/55 (27%)</td>
<td>15/50 (30%)</td>
</tr>
</tbody>
</table>

Triple Negative Breast Cancer

WHAT IS THE ROLE OF TARGETED THERAPY IN LABC?
BRCA1 Cell Lines Exhibit Differential Chemotherapy Sensitivity

- Increased sensitivity to DNA damaging agents like cisplatin

DF/HCC Preoperative Cisplatin in TNBC

> 2cm, Stage II/ III ER/PR/Her Neg Research Core Biopsy N=28

**Cisplatin**
75mg/m² q3wks x 4 cycles

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic CR</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>Clinical CR</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Clinical PR</td>
<td>10 (36%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>5 (17%)</td>
</tr>
</tbody>
</table>

Silver et al, JCO 2010

Standard Adjuvant Therapy per MD
Predictors of Response to Pre-operative Cisplatin in TNBC

Silver et al, JCO 2010
Is There a Role for Angiogenesis Inhibition in TN-LABC?
Pre-operative Cisplatin/Bevacizumab for TNBC

**Research bx**

**RESULTS**

Path CR (Miller-Payne 5)  
8/51 = 16%

Almost path CR (Miller-Payne 4)  
10/51 = 20%

18/51 = 36%

*Ryan et al, ASCO 2009*
German Breast Group: addition of bevacizumab to chemotherapy

ECT: 969

- Epirubicin 90 mg/m² IV + cyclophosphamide 600 mg/m² IV q3w x4
- Docetaxel 100 mg/m² IV q3w x4

ECT-B: 956

- Epirubicin 90 mg/m² IV + cyclophosphamide 600 mg/m² IV q3w x4
- Docetaxel 100 mg/m² IV q3w x4
- Bevacizumab 15 mg/kg IV q3w x8

Von Minckwitz NEJM 2012;366:4
Pathological Complete Response (pCR), According to Subgroup.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Odds Ratio (95% CI)</th>
<th>Test for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1925</td>
<td>1.29 (1.02–1.65)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 yr</td>
<td>304</td>
<td>1.71 (0.99–2.95)</td>
<td>0.26</td>
</tr>
<tr>
<td>≥40 yr</td>
<td>1621</td>
<td>1.20 (0.92–1.58)</td>
<td></td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>cT1–cT3</td>
<td>1690</td>
<td>1.30 (1.01–1.67)</td>
<td></td>
</tr>
<tr>
<td>cT4a–cT4d</td>
<td>235</td>
<td>1.23 (0.49–3.10)</td>
<td></td>
</tr>
<tr>
<td>Lymph-node stage</td>
<td></td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>cN0</td>
<td>767</td>
<td>1.20 (0.84–1.74)</td>
<td></td>
</tr>
<tr>
<td>cN1–cN3</td>
<td>1096</td>
<td>1.36 (0.98–1.89)</td>
<td></td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Operable</td>
<td>1702</td>
<td>1.23 (0.96–1.59)</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>223</td>
<td>2.43 (0.96–6.15)</td>
<td></td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Ductal or other</td>
<td>1713</td>
<td>1.31 (1.02–1.68)</td>
<td></td>
</tr>
<tr>
<td>Lobular</td>
<td>208</td>
<td>1.23 (0.40–3.79)</td>
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</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>1 or 2</td>
<td>1085</td>
<td>1.01 (0.66–1.53)</td>
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</tr>
<tr>
<td>3</td>
<td>829</td>
<td>1.48 (1.09–2.02)</td>
<td></td>
</tr>
<tr>
<td>Hormone-receptor status</td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>Negative</td>
<td>663</td>
<td>1.67 (1.21–2.31)</td>
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</tr>
<tr>
<td>Positive</td>
<td>1262</td>
<td>0.99 (0.66–1.50)</td>
<td></td>
</tr>
</tbody>
</table>

Intergroup: Triple Negative Pre-operative Trial (Sikov, PI)

N=400
ER/PR/HER2-
Stage II-IIIB

Breast imaging
Blood
MUGA
Tumor Biopsy*

Bevacizumab

Paclitaxel
Carboplatin
No carboplatin

Dose-dense
AC

Surgery

RT prn

Breast imaging
Blood
MUGA

Breast imaging
Blood

Breast imaging
Blood
WHAT IS THE ROLE OF TARGETED THERAPY IN LABC?
ER-positive disease: Can preoperative endocrine therapy be enough?
Preoperative Endocrine Therapy

- Preoperative endocrine therapy is a relatively nontoxic alternative to chemotherapy
  - Reduces tumor burden
  - Reduces risk of chemotherapy-prohibiting co-morbidities
  - Allows for determination of tumor’s susceptibility to surgery
  - Makes breast conservation surgery feasible
Is There a ‘Best’ Neoadjuvant Endocrine Therapy?

**Letrozole v Tam**

- Letrozole (L): 56% (90/162)
- Tamoxifen (T): 36% (58/162)

*P = 0.004*

P-24 Eiermann et al. 2001

**Anastrozole v Tam**

- Anastrozole (A): 45% (123/276)
- Tamoxifen (T): 36% (94/259)

*P = 0.05*

IMPACT and PROACT Smith et al. 2004
Anastrozole v Tamoxifen v Combination
No Correlation between Clinical Response (IMPACT) and long term outcome (ATAC)

**IMPACT (Neoadj)**

- Anastrozole: 37%
- Tamoxifen: 36%
- Combination: 39%

**ATAC (Adjuvant)**

- Anastrozole
- Tamoxifen
- Combination

Proportion event-free (%)

<table>
<thead>
<tr>
<th>Time to event (mo)</th>
<th>Anastrozole</th>
<th>Tamoxifen</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>95</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>18</td>
<td>90</td>
<td>90</td>
<td>90</td>
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<tr>
<td>24</td>
<td>85</td>
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<tr>
<td>30</td>
<td>80</td>
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**Smith et al JCO 2005**
How can we predict outcome with neoadjuvant endocrine therapy?

**Preoperative Endocrine Prognostic Index (PEPI)**

- Pathologic tumor size
  - T1/2 (0)
  - T3/4 (3)
- Nodal status
  - N0 (0)
  - N positive (3)
- Ki67 level
  - Range
- ER status (Allred score)
  - 0-2 (3)
  - 3-8 (0)

- Based upon post-NE therapy
- Developed from P-024 (n=228)
- Validated in IMPACT (n=203)
- Separation of 3 PEPI risk groups
- Risk score 0, 1-3, >4

Ellis JNCI 2008;100:1380
Development and validation of the Preoperative Endocrine Prognostic Index (PEPI).

NEOADJUVANT THERAPY FOR OPERABLE DISEASE
Treatment Goals of Neoadjuvant Therapy

- **Goals**
  - Improved tumor downstaging
    - Inoperable → Operable
    - Mastectomy → BCT
      - Improves the rate of breast conservation surgery
  - Reduce risk of recurrence
    - Provides *in vivo* assessment of anti-tumor effects

- **Appropriate patient population:**
  - Inoperable disease
  - Desiring breast conservation
  - Access to a clinical trial with novel therapy
Operable Breast Cancer

Stratification
- Age
- Clinical Tumor Size
- Clinical Nodal Status

Operation
- AC x 4
  - + TAM if ≥50 yrs.

AC x 4
- + TAM if ≥50 yrs.

Operation
B-27 Schema

Operable Breast Cancer

Randomization

I
AC x 4
Tam X 5 Yrs
Surgery

II
AC x 4
Tam X 5 Yrs
Docetaxel x 4
Surgery

III
AC x 4
Tam X 5 Yrs
Surgery
Docetaxel x 4
B-18 16 year f/u and B-27 9 year f/u
Meta-analysis of neo-adjuvant therapy vs. adjuvant therapy

LRF Update: NSABP B-18/B-27
8-YR Cum. Incidence of LRF by Path Nodal Status and pCR

Rastogi JCO 2008;26:778
B-18: Down-staging and BCS

P < 0.01

- BCS NC = 68%
- BCS AC = 60%

Bar chart showing:
- Post-op Chemo: 58%
- Pre-op Chemo: 40%
NSABP B-27
Disease-free Survival

Would more Rx be better?
Yes: tumor really sensitive to chemo
No: pt doing well already

Would more Rx be better?
Yes: high risk warrants therapy
No: tumor resistant already

GeparTrio trial

2 cycles TAC → Sonographic Evaluation
→ No Change 1/3
→ Complete or Partial Remission 2/3

Randomization
→ 4 cycles TAC
→ 4 cycles NX

Randomization
→ 4 cycles TAC
→ 6 cycles TAC

Surgery

RR pCR
51% 5%
51% 5%
75% 21%
75% 24%

Conclusions

- NC is an option for all patients who are candidates for systemic therapy
  - NC should be tailored to the biological profile of the primary tumor
- The prognostic value of pCR is more conclusive in TNBC and HER2+ disease
- NE is appropriate for HR+ LABC
  - Uncertain significance of pCR and other indicators of prognosis
- Neoadjuvant therapy can be used for down-staging, improving BCS rates, and access to novel therapies