Locally Advanced Breast Cancer: Systemic and Local Therapy

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Albert Einstein College of Medicine
Associate Chairman, Department of Oncology
Montefiore Medical Center
Bronx, New York
Overview

• Definition & Presentation
  – Non-inflammatory vs. Inflammatory

• Neoadjuvant Systemic Chemotherapy
  – Therapeutic Goals
  – Cytotoxic Drug Sequence
  – pCR as Regulatory Endpoint
  – Variable Outcomes in Residual Disease
  – Anti-HER2 Therapy Cytotoxic Therapy
  – Role of Platinums in TNBC (other talk)

• Neoadjuvant Endocrine Therapy
  – Therapeutic Goals

• Local Therapy
  – Clinical trials
What is the definition of LABC?

- **Clearly inoperable – clinical stage IIIB-C**
  - T4d - Inflammatory carcinoma (Stage IIIB)
  - T4a (chest wall), b (skin), c (both)
  - N3c (ipsilateral suprclavicular)
  - N3b (internal mammary)
  - N3a (infraclavicular)

- **Potentially operable but regionally advanced and may benefit from downstaging – clinical stage IIB-III A**
  - T3 - tumor > 5 cm
  - N2a - palpable adenopathy fixed/matted
  - N2b – internal mammary nodes (no axillary nodes)
Inflammatory Breast Cancer

• **Clinical presentation**
  – 1% of all breast cancers in U.S. – associated with younger age and black race
  – Rapid development of breast erythema, warmth, and/or peau d’orange
  – Associated with breast mass in approximately one-half of cases
  – Up to 1/3 may have distant metastases at presentation

• **Pathologic findings**
  – Invasive ductal carcinoma, usually high grade and with dermal lymphatic invasion (usually present, not required for diagnosis)

• **Workup and staging evaluation**
  – Bilateral diagnostic mammogram, breast and axillary ultrasound or MRI, if indicated, to identify breast mass and/or axillary nodes, contralateral disease
  – CT scan of chest/abdomen/pelvis and bone scan, or diagnostic PET/CT scan

• **Management**
  – Neoadjuvant chemotherapy, including an anthracycline and taxane, plus trastuzumab/pertuzumab if HER2/neu-positive, concurrent with taxane, followed by continued trastuzumab postoperatively for a total of 1 year
  – Modified radical mastectomy (no sentinel node biopsy alone)
  – Chest wall and regional lymph node radiotherapy after surgery
  – Hormonal therapy for at least 5 years if tumor is ER-positive
Molecular Characteristics of IBC vs. Non-IBC

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>
</tr>
</thead>
<tbody>
<tr>
<td>Nguyen</td>
<td>26% v 17%</td>
<td>49% v 30%</td>
</tr>
<tr>
<td>Charafe-Jaulfret</td>
<td>40% v 12%</td>
<td>54% v 24%</td>
</tr>
<tr>
<td>Ben Hamida</td>
<td>33% v 14%</td>
<td>54% v 26%</td>
</tr>
<tr>
<td>Zell</td>
<td>40% v 35%</td>
<td>44% v 33%</td>
</tr>
</tbody>
</table>

Relation Between Clinical Presentation and Outcomes: LABC, IBC, and Non-LABC/IBC

A. Breast Cancer Specific Survival by Breast Cancer Group

- Cumulative Proportion Surviving
- Survival in Years
- Non-T4 Patients (m.s.t. >10 yrs.)
- LABC Patients (m.s.t. = 6.4 yrs.)
- IBC Patients (m.s.t. = 2.9 yrs.)

B. Breast Cancer Specific Survival by IBC Definition

- Cumulative Proportion Surviving
- Survival in Years
- ClinOnly IBC (m.s.t. = 3.0 yrs.)
- ClinPath IBC (m.s.t. = 2.9 yrs.)
- PathOnly IBC (m.s.t. = 2.3 yrs.)

Hance et al. JNCI 2005; 97: 966
Neoadjuvant Chemotherapy
Metaanalysis of Randomized Trials Comparing Pre vs. Postoperative Systemic Chemotherapy
(9 trials, 3046 patients)

Mauri et al. JNCI 2005; 97: 188-194
Neoadjuvant Systemic Therapy: Therapeutic Goals

• Cytotoxic (+/- biologics) - same as adjuvant therapy plus
  – Downstaging
  – Facilitate breast conservation
  – Additional prognostic information
  – *Screen for active agents (clinical trials)*

• Endocrine therapy
  – Primary therapy (in lieu of surgery)
  – Defer primary surgical therapy
  – *Identify highly estrogen-dependent tumors where cytotoxics may be spared (clinical trials)*
NSABP B-18
Neoadjuvant vs Adjuvant AC

Operable Breast Cancer

Stratification
- Age
- Clinical Tumor Size
- Clinical Nodal Status

Operation
AC x 4

- Clinical Response: 79%
- cCR: 36%  cPR: 43%
- pCR: 13%
- Increase in lumpectomy rate: 68% vs 60%
- Downstaging of (+) axillary nodes: 58% vs 40%
- No difference in DFS and S
- Significant correlation between pCR and outcome
Operable Breast Cancer

Stratification
- Age
- Clinical Tumor Size
- Clinical Nodal Status

Operation
AC x 4

NSABP B-18
Neoadjuvant vs. Adjuvant AC

Disease-Free Survival

Wolmark N: JNCI Monogr, 2001
NSABP B-27 Schema

Operable Breast Cancer (2411 pts)

Randomization

AC x 4 Tam X 5 Yrs

Surgery

AC x 4 Tam X 5 Yrs

Docetaxel x 4

Surgery

AC x 4 Tam X 5 Yrs

Surgery

Docetaxel x 4
B-27

Response in the Breast

Clinical Response

Pathologic Response

\[
\begin{array}{c|c|c|c}
\text{Clinical Response} & \text{AC (1502 pts)} & \text{AC \rightarrow Docetaxel (687 pts)} \\
\hline
\text{cCR} & 40\% & 65\% \\
\text{cPR} & 45\% & 26\% \\
\text{cNR} & 14\% & 9\% \\
\end{array}
\]

\[P < 0.001\]

\[
\begin{array}{c|c|c|c}
\text{Pathologic Response} & \text{AC (1,492 pts)} & \text{AC \rightarrow Docetaxel (718 pts)} \\
\hline
\text{No Tumor} & 85\% & 18.7\% \\
\text{Non-Invasive} & 13.7\% & 9.8\% \\
\text{Invasive} & 9.8\% & 25.6\% \\
\end{array}
\]

\[P < 0.001\]

Breast pCR in B27: Effect of ER Status on Response

Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer

Cornelia Liedtke, Chafika Mazouni, Kenneth R. Hess, Fabrice André, Attila Tordai, Jaime A. Mejia, W. Fraser Symmans, Ana M. Gonzalez-Angulo, Bryan Hennessy, Marjorie Green, Massimo Cristofanilli, Gabriel N. Hortobagyi, and Lajos Pusztai

Treatment

Single agent taxane: 166, 12% for TNBC, 2% for Non-TNBC

FAC/FAC/AC: 308, 20% for TNBC, 5% for Non-TNBC

T-FAC/T-FEC: 588, 28% for TNBC, 17% for Non-TNBC
Weekly Paclitaxel Improves Pathologic Complete Remission In Operable Breast Cancer when Compared with Paclitaxel Given Every 3 Weeks

*J Clin Oncol 2005: 23; 5983-5992*

<table>
<thead>
<tr>
<th>Pathologic CR</th>
<th>Weekly</th>
<th>Every 3 Weeks</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=131</td>
<td>N=127</td>
<td></td>
</tr>
<tr>
<td>Breast Alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>31%</td>
<td>21%</td>
<td>P=0.2</td>
</tr>
<tr>
<td>Breast &amp; Axillary Nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>27%</td>
<td>15%</td>
<td>P=0.02</td>
</tr>
<tr>
<td>ER-negative</td>
<td>48%</td>
<td>23%</td>
<td>P=0.007</td>
</tr>
<tr>
<td>ER-positive</td>
<td>22%</td>
<td>11%</td>
<td>P=0.007</td>
</tr>
</tbody>
</table>
Chemotherapy Induced Senescence as a Mechanism of Drug Resistance

DNA Damage Is Able to Induce Senescence in Tumor Cells *in Vitro* and *in Vivo*\(^1\)

Robert H. te Poele,\(^2\) Andrei L. Okorokov, Lesley Jardine, Jeffrey Cummings, and Simon P. Joel\(^3\)

Department of Medical Oncology, St. Bartholomew’s Hospital, London EC1A 7BE [R. H. t. P., S. P. J.]; YCR P53 Research Group, Department of Biology, University of York, York YO10 5DD [A. L. O.]; and Imperial Cancer Research Fund, Medical Oncology Unit, Western General Hospital, Edinburgh EH4 2XU [L. J., J. C.], United Kingdom

<table>
<thead>
<tr>
<th></th>
<th>SA-β-gal positive, n (%)</th>
<th>SA-β-gal negative, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated tumor</td>
<td>15 (41)</td>
<td>21 (59)</td>
</tr>
<tr>
<td>p53 +++/++++</td>
<td>3 (20)</td>
<td>13 (61)</td>
</tr>
<tr>
<td>p16 +++/++++</td>
<td>13 (87)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Untreated tumor</td>
<td>2 (10)</td>
<td>18 (90)</td>
</tr>
</tbody>
</table>

Tumor tissue SA-β-Gal positive

Tumour tissue p53

Positive p16 staining
Rationale for Taxane $\Rightarrow$ AC Sequence:
Paclitaxel Decreases the Interstitial Fluid Pressure and Improves Oxygenation in Breast Cancers in Patients Treated With Neoadjuvant Chemotherapy: Clinical Implications

Overall change and 95% CI in tumor (A) interstitial fluid pressure (IFP) and (B) oxygen pressure (pO2) in breast cancer patients who had both pre- and post-first chemotherapy measurements available.
Neo-tAnGo Treatment Schema

2 x 2 factorial design

Epirubicin 90mg/m²
Cyclophosphamide 600mg/m²
Q 21 days

Paclitaxel 175mg/m²
Gemcitabine 2000mg/m²
Q 14 days

ASCO 2009, abstract 522
Primary endpoint: pCR rates

- A 2-reader review of pathology reports, blinded to treatment, was undertaken (812 pts)
- pCR defined as
  - pCR in all breast tumours AND
  - absence of disease in AxLNs in all breast tumours

<table>
<thead>
<tr>
<th>Component qn</th>
<th>EC &amp; T (n=404)</th>
<th>EC &amp; TG (n=408)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR rate (95% CI)</td>
<td>17% (14-21)</td>
<td>17% (14-21)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sequencing qn</th>
<th>EC$\rightarrow$T$\pm$G (n=406)</th>
<th>T$\pm$G$\rightarrow$EC (n=406)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR rate (95% CI)</td>
<td>15% (11-18)</td>
<td>20% (16-24)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Adjustment for stratification variables does not alter results (Age, ER status, Tumour size, Nodal status, Inflammatory / Locally advanced disease)
### pCR rate (95%CI), split by HER2 & ER

<table>
<thead>
<tr>
<th>Component qn</th>
<th>EC &amp; T</th>
<th>EC &amp; TG</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 neg (n=506)</td>
<td>14% (10-19)</td>
<td>16% (12-21)</td>
<td>0.44</td>
</tr>
<tr>
<td>HER2 pos (n=186)</td>
<td>21% (13-30)</td>
<td>22% (14-32)</td>
<td></td>
</tr>
<tr>
<td>ER neg (n=270)</td>
<td>32% (24-40)</td>
<td>31% (23-40)</td>
<td>0.96</td>
</tr>
<tr>
<td>ER pos (n=542)</td>
<td>10% (7-14)</td>
<td>11% (7-15)</td>
<td></td>
</tr>
</tbody>
</table>

#### Sequencing qn

<table>
<thead>
<tr>
<th>Sequencing qn</th>
<th>EC→T±G</th>
<th>T±G→EC</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 neg (n=506)</td>
<td>12% (9-17)</td>
<td>18% (13-23)</td>
<td>0.03</td>
</tr>
<tr>
<td>HER2 pos (n=186)</td>
<td>17% (10-26)</td>
<td>26% (17-36)</td>
<td></td>
</tr>
<tr>
<td>ER neg (n=270)</td>
<td>30% (22-38)</td>
<td>33% (25-42)</td>
<td>0.02</td>
</tr>
<tr>
<td>ER pos (n=542)</td>
<td>7% (4-10)</td>
<td>14% (10-19)</td>
<td></td>
</tr>
</tbody>
</table>

*p*-value for pCR rates across randomised groups, adjusted for characteristic
pCR as Regulatory Endpoint

Pathological Complete Response and Accelerated Drug Approval in Early Breast Cancer

Tatiana M. Prowell, M.D., and Richard Pazdur, M.D.
CTNeoBC Selected Trials

- 12 neoadjuvant randomized controlled trials
- pCR clearly defined with all necessary data collected
- Long-term follow-up EFS and OS data collected

<table>
<thead>
<tr>
<th>TRIALS</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBG/AGO: 7</td>
<td>6377</td>
</tr>
<tr>
<td>NSABP: 2</td>
<td>3171</td>
</tr>
<tr>
<td>EORTC/BIG: 1</td>
<td>1856</td>
</tr>
<tr>
<td>ITA: 2</td>
<td>1589</td>
</tr>
<tr>
<td>Total # patients</td>
<td>12993</td>
</tr>
</tbody>
</table>
1. Is pCR associated with long term outcomes (EFS and OS)?

**Event-free Survival**

- HR = 0.48, \( P^* < 0.001 \)
- Green line: pCR (n = 2131)
- Red line: no pCR (n = 9824)

**Overall Survival**

- HR = 0.36, \( P^* < 0.001 \)
- Green line: pCR (n = 2131)
- Red line: no pCR (n = 9824)

pCR = ypT0/is ypN0  
* Nominal p-value
2. Which pCR definition is best associated with long term outcome?

<table>
<thead>
<tr>
<th></th>
<th>ypT0 ypN0 n (%)</th>
<th>ypT0/is ypN0 n (%)</th>
<th>ypT0/is n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>1554 (13%)</td>
<td>2131 (18%)</td>
<td>2599 (22%)</td>
</tr>
<tr>
<td>No pCR</td>
<td>10401 (87%)</td>
<td>9824 (82%)</td>
<td>9356 (78%)</td>
</tr>
</tbody>
</table>
Association of pCR Definitions on EFS and OS

Event-free Survival

Overall Survival

Event-free Probability

Survival Probability

- ypT0 ypN0 (n = 1554)
- ypT0/is ypN0 (n = 2131)
- ypT0/is (n = 2598)

pCR vs. no pCR HR: 0.44
pCR vs. no pCR HR: 0.48
pCR vs. no pCR HR: 0.60

pCR vs. no pCR HR: 0.36
pCR vs. no pCR HR: 0.36
pCR vs. no pCR HR: 0.51

Months since Randomization

Months since Randomization

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3. In which breast cancer subtypes does pCR associate with long term outcome?
Association of pCR with EFS in HR+ HER2- Subtype

HR+:
- HR=0.49, P* < 0.001

HR+, Grade 1 or 2:
- HR=0.63, P* = 0.07

HR+, Grade 3:
- HR=0.27, P* < 0.001

pCR=ypT0/is ypN0

* Nominal p-value
Association of pCR with EFS in Triple Negative Subtype

Triple Negative

Event-Free Survival Probability

HR = 0.24, P* < 0.001

- pCR (n = 389)
- no pCR (n = 768)

* Nominal p-value

pCR = ypT0/is ypN0
4. What magnitude of pCR improvement in a randomized trial will predict long term clinical benefit (EFS and OS improvement)?
Subgroup analysis

Excluding patients with HR+ Grade 1 or 2

Triple negative subgroup

Her2+ subgroup
Summary

1. pCR association with long term outcomes (EFS and OS):
   - Individual patients who attain a pCR have a more favorable long-term outcome.

2. Best pCR definition associated with long term outcome:
   - Data show comparable EFS or OS regardless of the presence or absence of DCIS.
   - For consistency, a standard pCR definition (ypT0ypN0 or ypT0/isypN0) should be used in future trials.
Summary

3. Association of pCR with EFS by breast cancer subtype:
   - Larger Association in patients with aggressive breast cancer tumor subtypes
   - Smaller Association in patients with less aggressive tumors
4. Magnitude of pCR improvement that predicts long-term clinical benefit (EFS and OS improvement):

- Could not be established possibly due to:
  - low pCR rates
  - heterogeneous population
  - lack of targeted therapies (except NOAH trial)

- Larger pCR differences between treatment arms are needed to translate into long-term outcome and may vary according to breast cancer subtype.
FDA Public Breast Cancer Workshop

Innovations in Breast Cancer Drug Development
NEOADJUVANT BREAST CANCER WORKSHOP

March 22, 2013
8:00 a.m. to 5:00 p.m.
Federal Research Center

CO-SPONSORED BY THE:
U.S. Food & Drug Administration (FDA) &
American Society of Clinical Oncology (ASCO)
with support from the American Association for Cancer Research (AACR)
CO-CHAIRS: DR. SANDRA SWAIN AND DR. PATRICIA CORTAZAR
Where do we stand?

- We need a validated endpoint for regular approval
- pCR is not yet an established surrogate endpoint and we do not have sufficient experience to validate it
- Uncertainty regarding the ultimate outcome:
  - Long-term efficacy (EFS and OS)
  - Long-term safety

We will need long term follow-up and confirmation of ultimate outcome

The Neoadjuvant Regulatory Path could be opened through Accelerated Approval
How should the surgical management of the axilla be standardized?
- Need for standardized upfront ultrasound + core Bx
- Post chemotherapy SLNBx is generally accepted approach in USA.
- The need for at least 2 SLN removals for SLNBx to ↓ false rate

Need to standardize management of surgical specimen and preliminary recommendations
- Pre treatment placement of marker (clip), precision of assessment is critical
- Centralized pathology review not feasible
- Pre-specified standardized management of surgical specimen and pathology reporting
**NOAH Study: Addition of Neoadjuvant Trastuzumab to Chemotherapy Improves Pathologic CR Rate & Clinical Outcomes**

<table>
<thead>
<tr>
<th>HER2-positive disease</th>
<th>p value*</th>
<th>HER2-negative disease</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>With trastuzumab (n=117)</td>
<td>Without trastuzumab (n=118)</td>
<td></td>
<td>Without trastuzumab (n=99)</td>
</tr>
<tr>
<td>bpCR</td>
<td>50 (43%)</td>
<td>26 (22%)</td>
<td>0.0007</td>
</tr>
<tr>
<td>tpCR</td>
<td>45 (38%)</td>
<td>23 (19%)</td>
<td>0.001</td>
</tr>
<tr>
<td>OR†</td>
<td>102 (87%)</td>
<td>87 (74%)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Data are n (%). bpCR= pathological complete response in breast tissue. tpCR= total pathological complete response (in breast and axillary nodes). OR= overall response. *For comparison of HER2-positive disease groups. †For comparison of without trastuzumab groups. ‡Complete and partial clinical responses.

### Event-Free Survival

Chemotherapy: APx3 ➔ Px4 ➔ CMFx3
A- Doxorubicin 60 mg/m2, P-paclitaxel 175 mg/m2

### Overall Survival

Gianni et al. Lancet 2010; 375: 377
# Neoadjuvant Trials of HER2-Directed Therapy

- Lapatinib Less Effective than Trastuzumab
- Dual HER2 Therapy More Effective

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy</th>
<th>Anti-HER2</th>
<th>pCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeparQuinto¹</td>
<td>EC-Docetaxel</td>
<td>T</td>
<td>45.0</td>
</tr>
<tr>
<td></td>
<td>“</td>
<td>L</td>
<td>29.9</td>
</tr>
<tr>
<td>NSABP-41²</td>
<td>AC - Paclitaxel</td>
<td>T</td>
<td>49.4</td>
</tr>
<tr>
<td></td>
<td>“</td>
<td>L</td>
<td>47.4</td>
</tr>
<tr>
<td></td>
<td>“</td>
<td>T+L</td>
<td>60.2</td>
</tr>
<tr>
<td>NeoSphere³</td>
<td>None</td>
<td>T+P</td>
<td>16.8</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td>T</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td>“</td>
<td>P</td>
<td>24.0</td>
</tr>
<tr>
<td></td>
<td>“</td>
<td>T+P</td>
<td>45.8</td>
</tr>
<tr>
<td>NeoALTTO⁴</td>
<td>Paclitaxel</td>
<td>T</td>
<td>29.5</td>
</tr>
<tr>
<td></td>
<td>“</td>
<td>L</td>
<td>24.7</td>
</tr>
<tr>
<td></td>
<td>“</td>
<td>T+L</td>
<td>51.3</td>
</tr>
</tbody>
</table>

P = pertuzumab, T = trastuzumab, L = lapatinib

Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial

Luca Gianni, Tadeusz Pienkowski, Young-Hyuck Im, Laslo Roman, Ling-Ming Tseng, Mei-Ching Liu, Ana Lluch, Elżbieta Staroslawska, Juan de la Haba-Rodriguez, Seock-Ah Im, Jose Luiz Pedrini, Brigitte Poirier, Paolo Morandi, Vladimir Semiglazov, Vichien Srimuninnimit, Giulia Bianchi, Tania Szado, Jayantha Ratnayake, Graham Ross, Pinuccia Valagussa

Highest pCR Rates in ER/PR-Negative Disease

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel + T</th>
<th>Docetaxel + T+P</th>
<th>T+P</th>
<th>Docetaxel + +P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>29%</td>
<td>46%</td>
<td>17%</td>
<td>24%</td>
</tr>
<tr>
<td>ER and/or PR-Pos</td>
<td>20%</td>
<td>26%</td>
<td>6%</td>
<td>17%</td>
</tr>
<tr>
<td>ER/PR-Negative</td>
<td>37%</td>
<td>63%</td>
<td>27%</td>
<td>30%</td>
</tr>
</tbody>
</table>

**TRYPHAENA**® Phase II Neoadjuvant Trastuzumab and Pertuzumab in HER2-Positive EBC: Study Design

- **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)

EBC=early-stage breast cancer; FEC=5-fluorouracil, epirubicin, cyclophosphamide


*Genentech/Roche Sponsored Study*
TRYPHAENA* Phase II Neoadjuvant Trastuzumab and Pertuzumab in HER2-Positive EBC: Pathologic Complete Response by Hormone Receptor Status

C=carboplatin; EBC=early-stage breast cancer; ER=estrogen receptor; FEC=5-fluorouracil, epirubicin, cyclophosphamide; H=trastuzumab; P=pertuzumab; PR=progesterone receptor; T=docetaxel


*Genentech/Roche Sponsored Study
Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA)

A. Schneeweiss¹*, S. Chia², T. Hickish³, V. Harvey⁴, A. Eniu⁵, R. Hegg⁶, C. Tausch⁷, J. H. Seo⁸, Y.-F. Tsai⁹, J. Ratnayake¹⁰, V. McNally¹⁰, G. Ross¹⁰ & J. Cortés¹¹

Schneeweiss et al. Ann Oncol 2013; 24: 2278
Accelerated FDA Approval
(Product Information Brochure)

**Indication**

- Use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.

- This indication is based on demonstration of an improvement in pathological complete response rate.

- No data are available demonstrating improvement in event-free survival or overall survival

**Limitations of Use:**

- The safety … as part of a doxorubicin-containing regimen has not been established

- The safety … administered for greater than 6 cycles for early breast cancer has not been established
Pertuzumab should be administered every 3 weeks for 3 to 6 cycles as part of one of the following treatment regimens for early breast cancer:

- 4 preoperative cycles in combination with trastuzumab and docetaxel followed by 3 postoperative cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) as given in Study 2 (NeoSphere).

- 3 preoperative cycles of FEC alone followed by 3 preoperative cycles of pertuzumab in combination with docetaxel and trastuzumab as given in Study 3 (Tryphaena).

- 6 preoperative cycles … in combination with docetaxel, carboplatin, and trastuzumab (TCH) (escalation of docetaxel above 75 mg/m2 is not recommended) as given in Study 3 (Tryphaena).

- Following surgery, .. Continue … trastuzumab to complete 1 year of treatment. ….insufficient evidence to recommend continued use of pertuzumab for greater than 6 cycles….:
I-SPY2 TRIAL

Population of patients

Outcome:
Complete response at surgery
Outcome: Complete response at surgery

Arm 2 graduates to small focused Phase III trial

Population of patients

RANDOMIZE

ARM

Adaptively

Experimental arm 1
Experimental arm 2
Experimental arm 3
Experimental arm 4
Experimental arm 5
Standard therapy
I-SPY2 TRIAL

Goal: Greater than 85% success rate in Phase III, with focus on patients who benefit added to the mix
Variable Outcomes in Residual Disease
### AJCC TNM stage after neoadjuvant chemotherapy and breast cancer outcome

**Carey et al. JNCI 2005 Aug 3;97(15):1137-42**

<table>
<thead>
<tr>
<th>Stage</th>
<th>TN</th>
<th>No. of patients (%)</th>
<th>5-year DDFS (95% CI)</th>
<th>5-year OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>22 (17%)</td>
<td>95% (72%-99%)</td>
<td>95% (72%-99%)</td>
</tr>
<tr>
<td>I</td>
<td>T1N0</td>
<td>20 (15%)</td>
<td>84% (58%-95%)</td>
<td>90% (65%-97%)</td>
</tr>
<tr>
<td>II</td>
<td>IIA-T0-1N1;T2N0 IIB-T2N1;T3N0</td>
<td>38 (29%)</td>
<td>72% (52%-85%)</td>
<td>71% (49%-85%)</td>
</tr>
<tr>
<td>III</td>
<td>III A-T0-3N2;T3N1 IIIB-Any T4 IIIC-Any N3</td>
<td>52 (39%)</td>
<td>47% (32%-61%)</td>
<td>61% (45%-74%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P&lt;sub&gt;trend&lt;/sub&gt;&lt;.001</td>
<td>P&lt;sub&gt;trend&lt;/sub&gt; &lt;.001</td>
</tr>
</tbody>
</table>
Measurement of Residual Breast Cancer Burden to Predict Survival After Neoadjuvant Chemotherapy


http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

### Pathologic Review of Specimen:

<table>
<thead>
<tr>
<th></th>
<th>HR (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Tumor Bed Area (mm x mm)</td>
<td>1.24, p=0.02</td>
</tr>
<tr>
<td>Overall invasive cancer cellularity (as % of area)</td>
<td>7.37, p=0.001</td>
</tr>
<tr>
<td>Number of positive lymph nodes</td>
<td>1.11, p=0.002</td>
</tr>
<tr>
<td>Largest diameter of lymph node metastasis (mm)</td>
<td>1.17, p=0.06</td>
</tr>
</tbody>
</table>

**All Patients**

**ER-Neg**

**ER-Pos**
RCB 1-3 Provides Complementary Information to Post-Treatment AJCC Stage (T/FEC treated patients)

- Stage I
- Stage II
- Stage III
Mitotic counts in breast cancer after neoadjuvant systemic chemotherapy and development of metastatic disease

Janice Diaz · Lesley Stead · Nella Shapiro · Rosanne Newell · Olivier Loudig · Yungtai Lo · Joseph Sparano · Susan Fineberg

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients (N=80)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.97</td>
<td>0.93, 1.01</td>
<td>0.129</td>
</tr>
<tr>
<td>HER2/neu positive</td>
<td>0.96</td>
<td>0.11, 8.44</td>
<td>0.970</td>
</tr>
<tr>
<td>Estrogen receptor positive</td>
<td>0.82</td>
<td>0.28, 2.40</td>
<td>0.713</td>
</tr>
<tr>
<td>RCB-III</td>
<td>1.92</td>
<td>0.42, 8.82</td>
<td>0.406</td>
</tr>
<tr>
<td>Mitotic count &gt; 13/10 hpf</td>
<td>11.21</td>
<td>2.19, 57.37</td>
<td>0.004</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC Score III (N=43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.97</td>
<td>0.93, 1.02</td>
<td>0.262</td>
</tr>
<tr>
<td>HER2/neu positive</td>
<td>0.89</td>
<td>0.10, 8.02</td>
<td>0.916</td>
</tr>
<tr>
<td>Estrogen receptor positive</td>
<td>0.81</td>
<td>0.27, 2.44</td>
<td>0.706</td>
</tr>
<tr>
<td>Mitotic count ≥ 13/10 hpf</td>
<td>8.64</td>
<td>1.62, 46.02</td>
<td>0.012</td>
</tr>
</tbody>
</table>
Prognostic Effect of Mitotic Counts in RCB3 (N=43)

Product-Limit Survival Estimates

Logrank p=0.0011

Survival Probability

mitotic_count_greater_than_14  No  Yes
Neoadjuvant Endocrine Therapy
Neoadjuvant Endocrine Therapy: Aromatase Inhibitors are More Effective than Tamoxifen in Postmenopausal Women

Letrozole v Tam
- Letrozole: 56% (90/162)
- Tamoxifen: 36% (58/162)
- $p=0.004$

Anastrozole v Tam
- Anastrozole: 45% (123/276)
- Tamoxifen: 36% (94/259)
- $p=0.05$

P-24 Eiermann et al. 2001
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) vs ATAC (Adjuvant)

<table>
<thead>
<tr>
<th>Time to event (mo)</th>
<th>Proportion event-free (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>85</td>
</tr>
<tr>
<td>18</td>
<td>80</td>
</tr>
<tr>
<td>24</td>
<td>75</td>
</tr>
<tr>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>36</td>
<td>65</td>
</tr>
<tr>
<td>42</td>
<td>60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug A vs Drug T vs Drug C</th>
<th>HR</th>
<th>95.2% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA vs TAM</td>
<td>0.83</td>
<td>0.71-0.96</td>
<td>0.0129</td>
</tr>
<tr>
<td>Comb vs TAM</td>
<td>1.02</td>
<td>0.88-1.18</td>
<td>0.7718</td>
</tr>
</tbody>
</table>

Smith et al JCO 2005
# Outcome Prediction for Estrogen Receptor-Positive Breast Cancer Based on Postneoadjuvant Endocrine Therapy Tumor Characteristics

Matthew J. Ellis, Yu Tao, Jingqin Luo, Roger A’Hern, Dean B. Evans, Ajay S. Bhatnagar; Hilary A. Chaudri Ross, Alexander von Kameke, William R. Miller, Ian Smith, Wolfgang Eiermann, Mitch Dowsett

## Table 4. The preoperative endocrine prognostic index*

<table>
<thead>
<tr>
<th>Pathology, biomarker status</th>
<th>RFS</th>
<th>BCSS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>Points</td>
</tr>
<tr>
<td>Pathological tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/2</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>T3/4</td>
<td>2.8</td>
<td>3</td>
</tr>
<tr>
<td>Node status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Positive</td>
<td>3.2</td>
<td>3</td>
</tr>
<tr>
<td>Ki67 level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%–2.7% (0–1†)</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>&gt;2.7%–7.3% (1–2†)</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>&gt;7.3%–19.7% (2–3†)</td>
<td>1.7</td>
<td>1</td>
</tr>
<tr>
<td>&gt;19.7%–53.1% (3–4†)</td>
<td>2.2</td>
<td>2</td>
</tr>
<tr>
<td>&gt;53.1% (&gt;4†)</td>
<td>2.9</td>
<td>3</td>
</tr>
<tr>
<td>ER status, Allred score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>2.8</td>
<td>3</td>
</tr>
<tr>
<td>3–8</td>
<td>—</td>
<td>0</td>
</tr>
</tbody>
</table>

*HR: Hazard Ratio; BCSS: Breast Cancer Specific Survival.
Alternate approaches for clinical stage II or III Estrogen Receptor positive breast cancer NeoAdjuvant TrEatment (ALTERNATE) in postmenopausal women: A Phase III Study

Post-menopausal Clinical Stage II or III ER+ (Allred 6-8) HER2-

- Anastrozole (A) x 6 mos (if 4-wk Ki67 ≤10%)
- Fulvestrant (F) x 6 mos (if 4-wk Ki67 ≤10%)
- A + F x 6 mos (if 4-wk Ki67 ≤10%)

Surgery

- A x 4.5 years (if Modified PEPI 0)
- F x 1.5 yrs → A x 3 yrs (if Modified PEPI 0)
- (A + F) x 1.5 yrs → A x 3 yrs (if Modified PEPI 0)

Follow

4- or 12-wk Ki67>10%

- Go off Study Drug
- Neoadjuvant paclitaxel or Physician’s Choice
- SURGERY
- pCR

Primary Endpoints:
1st Phase: Modified PEPI 0 rate
2nd Phase: RFS in Modified PEPI 0

Sample size: n=2820
1st phase: n=400 each arm
2nd phase: n=540 each arm

Modified PEPI > 0

- Go off Study Drug
- Adjuvant Therapy
- Physician’s Choice
Local Therapy
Placement of Radiopaque Clips for Tumor Localization in Patients Undergoing Neoadjuvant Chemotherapy and Breast Conservation Therapy

- Retrospective review of 373 patients who received neoadjuvant doxorubicin-containing chemotherapy between 1990-2005
- Locoregional recurrence patterns evaluated in patients with (N=138) and without (N=211) clip placement
- Clip placement group more likely to be node-negative (52% vs. 31%) and less likely to have stage III disease (20% vs. 38%)

Oh et al. Cancer 2007; 110: 2420
Clinically T1–3, N1 Breast Cancer Documented Positive Axillary Nodes by FNA or by Core Needle Biopsy

Minimum of 12 weeks of Standard Neoadjuvant Chemotherapy Plus Anti-HER2 Therapy for Patients with HER2-Positive Tumors

Definitive Surgery with Histologic Documentation of Negative Axillary Nodes (Either by Axillary Dissection or by Sentinel Node Biopsy ± Axillary Dissection)

STRATIFICATION
- Type of surgery (mastectomy, lumpectomy)
- Hormone receptor status (ER-positive and/or PgR-positive; ER- and PgR-negative)
- HER2 status (negative, positive)
- Adjuvant chemotherapy (yes, no)
- pCR in breast (yes, no)

RANDOMIZATION

Arm 1
(Group 1A and 1B)*, **
No Regional Nodal XRT
- Group 1A Lumpectomy: No regional nodal XRT with WBI
- Group 1B Mastectomy: No regional nodal XRT and no chestwall XRT

Arm 2
(Group 2A and 2B)*, **
Regional Nodal XRT
- Group 2A Lumpectomy: Regional nodal XRT with WBI
- Group 2B Mastectomy: Regional nodal XRT and chestwall XRT
Clinically T1-3 N1 M0 Breast cancer
Axillary ultrasound with FNA or core biopsy documenting positive lymph node

Neoadjuvant Chemotherapy, clinically negative axilla on PE after neoadjuvant chemotherapy

Pre-registration

Surgery with Sentinel Lymph Node Surgery

Sentinel Lymph Node not Identified
- No Registration & Randomization

Positive Sentinel Lymph Node Identified
- Intra-operative Registration & Randomization

Negative Sentinel Lymph Node By Intra-op Evaluation
- Positive SLN(s) on Final Pathology and ALND not performed
- Negative LNs on Final Pathology
  - No Registration & Randomization or Follow-up
  - Offer participation in NSABP B-51/RTOG 1304 Trial

**Z11102: Role of Axillary Dissection**

**ARM 1:** ALND + Nodal RT vs **ARM 2:** Axillary and Nodal RT
Conclusions – Systemic Therapy

- **Preoperative systemic chemotherapy (PSCT)**
  - Therapeutic goal is inducing pCR
  - Standard of care for inoperable (e.g., IBC) or operable LABC
  - Option for operable disease when cytoreduction indicated
  - Addition of anti-HER2 therapy in HER2/neu positive disease enhances efficacy
  - Addition of other targeted therapies unproven

- **Preoperative endocrine therapy**
  - Less potential for cytoreduction that PSCT
  - Reasonable standard for elderly patients with large tumors or PSCT resistant disease (e.g., Lobular carcinoma)
  - Potential to identify individuals with tumors resistant to endocrine therapy who may be candidates for chemotherapy
Conclusions – Local Therapy

- **Surgery**
  - Mastectomy absolutely indicated in some settings (eg, IBC)
  - Potential candidates for BCT should have tumor clip placement before PSCT
  - SN biopsy after NAC in non-IBC associated with high FNR – may be acceptable if RT is planned

- **Radiotherapy**
  - Recommendation for chest wall and regional nodal RT should be based upon clinical stage prior to PSCT
  - Patients with pCR may be at high risk for local-regional recurrence
EXTRAS
Trends in Inflammatory Breast Carcinoma Incidence and Survival: The Surveillance, Epidemiology, and End Results Program at the National Cancer Institute

Kenneth W. Hance, William F. Anderson, Susan S. Devesa, Heather A. Young, Paul H. Levine

B. Age-Specific Incidence by Breast Cancer Group

C. Age-Specific Incidence by IBC Definition

Rates per 100,000 woman-years

Non-T4 Patients
LABC Patients
IBC Patients

Rates per 100,000 woman-years

Total IBC
ClinOnly IBC
ClinPath IBC
PathOnly IBC

Age-at-Diagnosis
Age-at-Diagnosis
Age at Diagnosis: LABC, IBC, and Non-LABC/IBC