Locally Advanced Breast Cancer: Systemic and Local Therapy

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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-IIIA**
  - T3 - tumor > 5 cm
  - N2a - palpable adenopathy fixed/matted
  - N2b – internal mammary nodes (no axillary nodes)
Relation Between Clinical Presentation and Outcomes: LABC, IBC, and Non-LABC/IBC

A. Breast Cancer Specific Survival by Breast Cancer Group

B. Breast Cancer Specific Survival by IBC Definition

- Non-T4 Patients (m.s.t. >10 yrs.)
- LABC Patients (m.s.t. = 6.4 yrs.)
- IBC Patients (m.s.t. = 2.9 yrs.)

- 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
Metaanalysis of Randomized Trials Comparing Pre vs. Postoperative Systemic Chemotherapy
(9 trials, 3046 patients)
Mauri et al. JNCI 2005; 97: 188-194
Clinical Response

- **cCR**: 40% (AC) vs. 65% (AC → Docetaxel), P < 0.001
- **cPR**: 45% (AC) vs. 26% (AC → Docetaxel)
- **cNR**: 14% (AC) vs. 9% (AC → Docetaxel)

Pathologic Response

- **No Tumor**: 85% (AC) vs. 91% (AC → Docetaxel), P < 0.001
- **Non-Invasive**: 18.7% (AC) vs. 25.6% (AC → Docetaxel)

Breast pCR in B27: Effect of ER Status on Response

### Treatment

<table>
<thead>
<tr>
<th>Single agent taxane</th>
<th>TNBC</th>
<th>Non-TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>166</td>
<td>12%</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FAC/FAC/AC</th>
<th>TNBC</th>
<th>Non-TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>308</td>
<td>20%</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T-FAC/T-FEC</th>
<th>TNBC</th>
<th>Non-TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>588</td>
<td>28%</td>
<td>17%</td>
</tr>
</tbody>
</table>
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>N=131</td>
<td></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>
Pathological Complete Response and Accelerated Drug Approval in Early Breast Cancer

Tatiana M. Prowell, M.D., and Richard Pazdur, M.D.
1. Is pCR associated with long term outcomes (EFS, OS)?
   - Yes - individual patients with pCR have improved EFS and OS

2. Which pCR definition is best associated with long term outcome?
   - Use consistent definition – ypN0 plus ypT0/is or ypT0

3. Which subtype does pCR associated with long term outcomes?
   - Aggressive subtypes, including TNBC (EFS HR 0.24, p<0.001), HR+, grade 3 (HR 0.27, p<0.001), and HER2+ (HR 0.39, p<0.001)

4. What magnitude of pCR improvement in a randomized trial will predict 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

Cortazar et al. SABCS 2012, In Press
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
• **Approved Regimens:** Pertuzumab … every 3 weeks for 3 to 6 cycles as part of one of the following … regimens …:
  
  • *4 preoperative cycles .. with trastuzumab and docetaxel* followed by 3 postoperative cycles of … FEC.. in Study 2 (NeoSphere)
  
  • *3 preoperative cycles of FEC alone followed by 3 preoperative cycles of pertuzumab in combination with docetaxel and trastuzumab* …. in Study 3 (Tryphaena).
  
  • *6 preoperative cycles … with …TCH …* 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*…

• **Limitations of Use:**
  
  • The safety … as part of a doxorubicin-containing regimen has not been established…. 
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

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel</th>
<th>Docetaxel +</th>
<th>T+P</th>
<th>Docetaxel +</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T</td>
<td>T+P</td>
<td></td>
<td>+P</td>
</tr>
<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>

Highest pCR Rates in ER/PR-Negative Disease
TRYPHAENA: Study Schema

HER2-positive EBC centrally confirmed (n = 225)

Cycles 1–3

A
FEC
Pertuzumab + trastuzumab

B
FEC
Pertuzumab + trastuzumab

C
Docetaxel
Pertuzumab + trastuzumab

Cycles 4–6

Surgery

Docetaxel

Trastuzumab to complete 1 year

• All 3 arms were experimental

• Study dosing q3w:
  - FEC: 500 mg/m^2, 100 mg/m^2, 600 mg/m^2
  - Carboplatin: AUC 6
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Pertuzumab: 840 mg loading dose, 420 mg maintenance
  - Docetaxel: 75 mg/m^2 (escalating to 100 mg/m^2 if tolerated, in Arms A and B only)

Schneeweiss A et al. Presented at SABC. 2011 (abstr S5-6).
Tryphaena: Efficacy Results

Schneeweiss et al. Ann Oncol 2013; 24: 2278
## Role of Neoadjuvant Platinum in TNBC: Randomized Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No</th>
<th>Backbone Regimen</th>
<th>No Carbo</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeparSixto</td>
<td>315</td>
<td>Weekly paclitaxel + liposomal dox + bev</td>
<td>38%</td>
<td>59% P&lt; 0.05</td>
</tr>
<tr>
<td>C406063</td>
<td>433</td>
<td>Sequential weekly paclitaxel – AC +/- bev</td>
<td>41%</td>
<td>54% P=0.0029</td>
</tr>
<tr>
<td>Tamura et al</td>
<td>75</td>
<td>Sequential weekly pacl+/- Carb AUC5 - CEF</td>
<td>26%</td>
<td>62%</td>
</tr>
<tr>
<td>Alba et al</td>
<td>94</td>
<td>EC – Doc +/- Carbo AUC6</td>
<td>30%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Von Minckwitz et al. Lancet Oncol 2014; Sikov et al. JCO 2014; Alba et al. BRCT 2012; Tamura et al. ASCO 2014, Abstract 1107
pCR Rates by Subtype

ypT0 ypN0

TNBC

HER2-positive

<table>
<thead>
<tr>
<th>Subtype</th>
<th>PM</th>
<th>PMCb</th>
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</thead>
<tbody>
<tr>
<td>N=157</td>
<td>37.9%</td>
<td></td>
</tr>
<tr>
<td>N=158</td>
<td>58.7%</td>
<td></td>
</tr>
</tbody>
</table>

P<0.05

<table>
<thead>
<tr>
<th>Subtype</th>
<th>PM</th>
<th>PMCb</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=136</td>
<td>36.3%</td>
<td></td>
</tr>
<tr>
<td>N=137</td>
<td>33.1%</td>
<td></td>
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</table>

n.s.
CALGB 40603: Schema – Randomized Phase II

Paclitaxel 80 mg/m² wkly x 12

Paclitaxel 80 mg/m² wkly x 12
Bevacizumab 10 mg/kg q2wks x 9

Paclitaxel 80 mg/m² wkly x 12
Carboplatin AUC 6 q3wks x 4

Paclitaxel 80 mg/m² wkly x 12
Carboplatin AUC 6 q3wks x 4
Bevacizumab 10 mg/kg q2wks x 9

Surgery & XRT*

2 X 2 Randomization

Research biopsies - frozen and fixed

No Adjuvant Systemic Treatment Planned*

*MD discretion

&Research biopsies if residual tumor

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pCR Breast/Axilla (ypT0/is N0) + / - Carboplatin

41% (35-48%)  
54% (48-61%)

Odds ratio: 1.71
p = 0.0029

N=212
N=221
pCR Breast/Axilla (ypT0/is N0) +/- Bevacizumab

Odds ratio: 1.36  
$p = 0.0570$

44% (38-51%)  
52% (45-58%)

N=218  
N=215
### pCR Breast/Axilla (ypT0/is N0)

<table>
<thead>
<tr>
<th></th>
<th>No Carbo (n=212)</th>
<th>Carbo (n=221)</th>
<th>Bev effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Bev (n=218)</td>
<td>39%</td>
<td>49%</td>
<td>44%</td>
</tr>
<tr>
<td>Bev (n=215)</td>
<td>43%</td>
<td>60%</td>
<td>52%</td>
</tr>
<tr>
<td>Carbo effect</td>
<td>41%</td>
<td>54%</td>
<td>Carbo/Bev Interaction p=0.43</td>
</tr>
</tbody>
</table>

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Should Neoadjuvant Carboplatin now be Standard? Probably not, at least in my opinion

- Improvements in pCR could be the result of conversion of low volume residual disease to pCR
- Followup insufficient for IDFS and OS outcomes in GeparSixto and C40603
- No threshold identified in CTNeoBC analysis associated with improved EFS and OS
- Impact on breast conservation currently unknown
- Candidate predictive biomarkers to identify platinum-sensitive disease (ie, basal subtype, HRD assay)
**Primary Endpoint:**
- DFS in patients with basal-like TNBC

**Secondary Endpoints:**
- OS
- RFS

**Stratification factors:**
1) Disease stage at diagnosis (II or III)
2) Residual cancer burden after NAC (1~3 cm or >3 cm)
3) Platinum agent choice (cisplatin or carboplatin)
4) Anthracycline exposure (yes or no)

**Registration:**
Within 48 days

**Randomization:**
(1:1)

**Cisplatin 75 mg/m2**
OR
**Carboplatin AUC 6 Q3W x 4 doses**
(physician’s choice)

**Tissue collection PAM50 analysis**

**Residual cancer ≥1 cm**

**Within 84 days**

**Basal-like**

Radiotherapy (when applicable)
should be completed prior to protocol platinum therapy

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§ TNBC: ER/PR classified locally as negative, or Allred score ≤ 2, or < 5% weakly positive staining

*Taxane +/- Anthracycline based; platinum agents not allowed
## Role of Neoadjuvant & Adjuvant Bevacizumab

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Backbone</th>
<th>Main Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neoadjuvant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B40</td>
<td>1206</td>
<td>D+G/C→AC</td>
<td>pCR 28% vs. 23% (p=0.08)</td>
<td>HER2-neg only</td>
</tr>
<tr>
<td>GBG44</td>
<td>1948</td>
<td>EC→D</td>
<td>pCR 18% vs. 14% (p=0.04)</td>
<td></td>
</tr>
<tr>
<td>C40603</td>
<td>433</td>
<td>P+/C→AC</td>
<td>pCR 52% vs. 44% (p=0.057)</td>
<td>TNBC only</td>
</tr>
<tr>
<td>ARTemis</td>
<td>800</td>
<td>D→FEC</td>
<td>pCR 22% vs. 15% (p=0.059)</td>
<td>HER2-neg only</td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEATRICE</td>
<td>2591</td>
<td>MD choice</td>
<td>No difference in DFS</td>
<td>TNBC only</td>
</tr>
<tr>
<td>BETH</td>
<td>3509</td>
<td>TCH</td>
<td>No difference in DFS</td>
<td>HER2-pos only</td>
</tr>
<tr>
<td>E5103</td>
<td>4994</td>
<td>AC→wkly P</td>
<td>No difference in DFS</td>
<td>HER2-neg only</td>
</tr>
</tbody>
</table>

Presented by: Joseph Sparano, MD
Neoadjuvant Endocrine Therapy:
Aromatase Inhibitors are More Effective than Tamoxifen in Postmenopausal Women

Letrozole v Tam

Anastrozole v Tam

\( p = 0.004 \)

\( p = 0.05 \)

90/162

58/162

123/276

94/259

P-24 Eiermann et al  2001

IMPACT and PROACT Smith et al  2004
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 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)

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

Go off Study Drug

Neoadjuvant paclitaxel or Physician’s Choice

SURGERY

pCR

Adjuvant Therapy Physician’s Choice
Effect of Preoperative Clip Placement: 10-year local control rates

Oh et al. Cancer 2007; 110: 2420

- Residual disease > 1 cm
- pCR or residual disease < 1 cm

- 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
Sentinel Lymph Node Biopsy
Before or After Neoadjuvant Chemotherapy
Final Results from the Prospective, German Multiinstitutional SENTINA Trial


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SLNs detected and removed

- Arm A + B: SLNB prior to any therapy (99.1%)
  - 1013/1022

- Arm B: Re-SLNB after SLNB + NACT (60.8%)
  - 474/592

- Arm C: SLNB after NACT for cN1 → ycN0 (80.1%)
  - 219/360

P < 0.001
### False-Negative Rate

<table>
<thead>
<tr>
<th>ypN 0:</th>
<th>155 (70.8%)</th>
<th>ypN 0:</th>
<th>248 (52.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ypN 1:</td>
<td>64 (29.2%)</td>
<td>ypN 1:</td>
<td>226 (47.7%)</td>
</tr>
</tbody>
</table>

**Arm B**
- Re-SLNB after SLNB and NACT
- 33 / 64 (51.6%)

**Arm C**
- SLNB after NACT For cN1 → ycN0
- 32 / 226 (14.2%)

95% CI 38.7% - 64.2%

95% CI 9.9% - 19.4%
FNR in primary surgery compared to FNR in Arm C

FNR in primary surgery
- Literature review -

Kim et al. 2006 (n=3132)
Kuehn et al. 2004 (n=353)
Krag et al. 2007 (n=766)

FNR after NACT (cN1 – ycN0)
SENTINA  Arm C (n=226)
Optimising radiation treatment decisions for patients who receive neoadjuvant chemotherapy and mastectomy

Karen E Hoffman, Elizabeth A Mittendorf, Thomas A Buchholz

10 yr LRR
Clinical N2-3 Disease

5 yr LRR
< 35 and Clinical Stage II-III Disease

10 yr LRR
Clinical Stage III and pCR

5 yr LRR
Clinical T3N0
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
(Groups 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
(Groups 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

ARM 1: ALND + Nodal RT vs ARM 2: Axillary and Nodal RT

Negative Sentinel Lymph Node By Intra-op Evaluation

Positive SLN(s) on Final Pathology and ALND not performed

Register & Randomize

ARM 1: ALND + Nodal RT vs ARM 2: Axillary and Nodal RT

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
Conclusions – Systemic Therapy

- Preoperative systemic chemotherapy (PSCT)
  - Therapeutic goal is inducing pCR
  - Standard of care for inoperable (eg. 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 (eg. 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