Pathologic complete response is not a valid surrogate for long-term outcome for early-stage breast cancer. Debates and Didactics in Hematology and Oncology, August 8th, Sea Island, GA

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Professor and Vice-Chair for Educational Affairs, Department of Hematology and Medical Oncology, Emory University, Chief of Hematology and Medical Oncology, Georgia Cancer Center for Excellence, Grady Memorial Hospital
Association of PCR following pre-op chemotherapy and outcome by breast cancer subtype

But meta-analyses designed to show small differences using large numbers of patients
Prognostic impact of pathologic complete response (pCR) on disease-free survival according to breast cancer intrinsic subtype.

von Minckwitz G et al. JCO 2012;30:1796-1804
## PCR rate following pre-op chemotherapy and outcome according to subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percent PCR</th>
<th>Importance of PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>&lt; 10%</td>
<td>Not important</td>
</tr>
<tr>
<td>Luminal B (HER2-negative)</td>
<td>20%</td>
<td>Probably</td>
</tr>
<tr>
<td>HER2-positive, ER-positive</td>
<td>10 to 30%</td>
<td>Maybe</td>
</tr>
<tr>
<td>HER2-positive, ER-negative</td>
<td>50 to 60%</td>
<td>Probably but not conclusive</td>
</tr>
<tr>
<td>Triple negative</td>
<td>30%</td>
<td>Probably</td>
</tr>
</tbody>
</table>

Let’s hope PCR is not important for outcome!
Pre-op management of ER-positive cancers

• If chemotherapy is not important for a large number of ER-positive cancers post-op (luminal A, recurrence score less than 30 ≈ 110,000 patients diagnosed annually) why give it pre-op?

• What is the best pre-operative approach for down-staging ER-positive cancers (since achieving a PCR is less important?)
Pre-operative therapy of ER-positive cancers stratified by recurrence score

Stage I-III HR-positive breast cancer

- RS ≤ 10: Exemestane*
- RS 11-24: TC x 6 cycles
- RS ≥ 25: TC x 6 cycles

Goserelin added to exemestane if premenopausal
TC = docetaxel plus cyclophosphamide
* Given to maximal response

Zelnak et al Proc ASCO 2013
Phase 2 trial of pre-operative therapy tailored by 21-gene recurrence score

<table>
<thead>
<tr>
<th>RS ≤ 10</th>
<th>11 ≥ RS &lt; 25</th>
<th>RS ≥ 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=9</td>
<td>n=9</td>
<td>n=10</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Exemestane</td>
<td>TC x 6</td>
</tr>
</tbody>
</table>

Radiologic Response

<table>
<thead>
<tr>
<th></th>
<th>RS ≤ 10</th>
<th>11 ≥ RS &lt; 25</th>
<th>RS ≥ 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>6 (66.7%)</td>
<td>6 (66.7%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>3 (33.3%)</td>
<td>3 (33.3%)</td>
<td>1 (10%)</td>
</tr>
</tbody>
</table>

Pathologic Complete Response

<table>
<thead>
<tr>
<th></th>
<th>RS ≤ 10</th>
<th>11 ≥ RS &lt; 25</th>
<th>RS ≥ 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4/18 (22.2%)</td>
</tr>
</tbody>
</table>

Breast-Conserving Surgery

<table>
<thead>
<tr>
<th></th>
<th>RS ≤ 10</th>
<th>11 ≥ RS &lt; 25</th>
<th>RS ≥ 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/7 (28.6%)</td>
<td>3/6 (50%)</td>
<td>4/10 (40%)</td>
<td>11/18 (61.1%)</td>
</tr>
</tbody>
</table>

Chemotherapy associated with higher response rate in intermediate RS cancers

Zelnak et al Proc ASCO 2013
Phase III NeoALTTO Study Design

**Baseline**
- Lapatinib + trastuzumab

**6 weeks**
- Lapatinib
- Trastuzumab

**12 weeks**
- Lapatinib + paclitaxel
- Trastuzumab + paclitaxel

**9 weeks**
- Lapatinib

**FEC X 3**
- Trastuzumab

**34 weeks**
- Lapatinib + trastuzumab

**Tumor biopsy blood sample PET/CT scan**
- Week 2
- Week 8

**Tumor biopsy blood sample PET/CT scan**
- Radiotherapy (if indicated)

**Blood sample**

NeoALTTO Primary Outcome Measure: pCR*

*Pathologic complete response (pCR) rate defined as the absence of invasive cancer in the breast at the time of surgery.

<table>
<thead>
<tr>
<th></th>
<th>Lapatinib n = 154</th>
<th>Trastuzumab n = 149</th>
<th>Lapatinib + Trastuzumab n = 152</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR HR+ Subset</td>
<td>16%</td>
<td>23%</td>
<td>42%</td>
<td>0.03</td>
</tr>
<tr>
<td>pCR HR- Subset</td>
<td>34%</td>
<td>37%</td>
<td>61%</td>
<td>0.005</td>
</tr>
</tbody>
</table>
NeoALTTO: Does pCR Translate Into Improved EFS and OS?

- Found correlation between pCR and EFS and OS
- 3-year EFS was 86% for those who achieved pCR, 72% for those who did not ($P = 0.0003$)
- OS was 94% for those who achieved pCR, 87% for those who did not ($P = 0.005$)
- Most notable in HR-negative disease
- Not powered to detect difference in survival between study arms

Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO)

Surgery

At least 4 cycles of (neo) adjuvant chemotherapy

Design 1
no concurrent taxane

Design 2
concurrent taxane (12 weeks)

RANDOMIZATION

Trastuzumab (n=2097)

Lapatinib

Break

Lapatinib (n=2091)

Trastuzumab

12 weeks

6 weeks

34 weeks

Lapatinib + Trastuzumab (n= 2093)

Hormone receptor-positive: ≈57%
Node-negative: 40%

Available at: http://www.cancer.gov/search/clinical_trials.gov
DISEASE-FREE SURVIVAL (DFS) ANALYSIS

Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting
DFS BY HORMONE RECEPTOR STATUS

**HR positive**

- **Arm** | **No. pts** | **No. events** | **4yr DFS rate** | **Hazard ratio c.f. Tras*** | **p-value**
- Lap+Tras | 1203 | 133 | 90% | 0.87 (0.69,1.10) | 0.233
- Tras->Lap | 1205 | 141 | 89% | 0.92 (0.73,1.16) | 0.477
- Tras | 1200 | 150 | 88% |

*95% CI

**HR negative**

- **Arm** | **No. pts** | **No. events** | **4yr DFS rate** | **Hazard ratio c.f. Tras*** | **p-value**
- Lap+Tras | 890 | 121 | 86% | 0.82 (0.65,1.04) | 0.107
- Tras->Lap | 886 | 143 | 84% | 1.00 (0.79,1.26) | 0.990
- Tras | 897 | 151 | 83% |

*95% CI

**Interaction tests**

\[ p = 0.70 \ L + T \]

\[ p = 0.60 \ T \rightarrow L \]

Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting
Why is ALTTO negative to date?

• Accrued 40% of patients with node-negative disease resulting in event rate too low to determine difference between arms
  – Neo-ALTTO accrued higher risk cancers
  – Pivotal adjuvant trastuzumab trials accrued less than 10% patients with node-negative disease

• Almost 60% of patients had ER-positive cancers
  – Follow up may be too short to see a difference between arms
Pathologic complete response (PCR) is consistently lower in ER+ HER2+ breast cancers compared to ER- HER2+ breast cancers.

Reviewed in Nahta and O'Regan BRCT 2012
pCR Correlates With Better EFS in Subsets of BC, Including HER2+ BC: a FDA led Meta-Analysis
(N = 11,955 / 1,989 HER2+)

PCR is prognostic in ER- cancer but not ER+ cancers that co-express HER2

ER-negative, HER2-positive   ER-positive, HER2-positive

von Mitchwitz et al SABCS 2011
Intrinsic subtyping of HER2-positive breast cancers

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2</td>
<td>48%</td>
</tr>
<tr>
<td>LUM A</td>
<td>34%</td>
</tr>
<tr>
<td>LUM B</td>
<td>17%</td>
</tr>
<tr>
<td>Basal</td>
<td>1%</td>
</tr>
<tr>
<td>Claudin-low</td>
<td>5%</td>
</tr>
<tr>
<td>Normal</td>
<td>3%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
</tr>
</tbody>
</table>

**HR-positive:**
- HER2: 48%
- LUM A: 34%
- LUM B: 17%
- Basal: 1%
- Claudin-low: 5%
- Normal: 3%
- Total: 100%

**HR-negative:**
- HER2: 51%
- LUM A: 24%
- LUM B: 12%
- Basal: 5%
- Claudin-low: 3%
- Normal: 5%
- Total: 100%

N = 156 (HR-positive)
N = 109 (HR-negative)

Carey et al Proc ASCO 2014
Likelihood of PCR is inversely related to level of ER expression for HER2+ breast cancers

- HER2+/HR-
- HER2+/ER+
- HER2+/ER+++
Importance of pathologic complete response

Overall Survival

Liedtke et al. JCO 2008; 26(8): 1275-81
Recurrence is directly related to amount of cancer in the breast

- RCB I (n = 2)
- RCB 0 (n = 16)
- RCB II (n = 17)
- RCB III (n = 9)

Log-rank P = 5.5 x 10^{-7}
Triple negative subtypes

Basal-like 1: cell cycle, DNA repair and proliferation genes

Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)

IM: immune cell processes (medullary breast cancer)

M: Cell motility and differentiation, EMT processes

MSL: similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

LAR: Androgen receptor and downstream genes, luminal features

Lehmann et al JCI 2011
Results
Pathologic response in TNBC subtypes

<table>
<thead>
<tr>
<th></th>
<th>Responders (RCB 0-1%)</th>
<th>Non-responders (RCB 2-3%)</th>
<th>BRCA1/2 mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL1</td>
<td>n = 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL2</td>
<td>n = 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IM</td>
<td>n = 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAR</td>
<td>n = 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>n = 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSL</td>
<td>n = 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNS</td>
<td>n = 6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[n = 51\]

Presented By Deborah Toppmeyer, MD at 2013 ASCO Annual Meeting
PCR is not predictive for the majority of breast cancers

- PCR is very low for luminal A cancers and is not predictive of outcome
- PCR is low for luminal B cancers and may be predictive of outcome (chemotherapy not the answer for most of these cancers)
- PCR is predictive for ER-negative cancers but a subset of patients have a favorable outcome without achieving PCR
- PCR probably not important for most HER2-positive, ER-positive cancers