Neoadjuvant Therapy for Breast Cancer 2014: Current Status, Significant Recent Data, and the Impact of FDA Guidelines on its Future

William M. Sikov, MD, FACP
Associate Professor of Medicine
Alpert Medical School of Brown University
Providence, Rhode Island

NCoBC
24th Interdisciplinary Breast Center Conference
Las Vegas, Nevada
March 15-19, 2014

Neoadjuvant Therapy 2014

• Traditional indications for neoadjuvant therapy
  – Permit resection in patients with unresectable cancers
  – Allow/facilitate BCS in patients with large tumors relative to breast size

Neoadjuvant Therapy 2014

• Recent data on neoadjuvant therapy
  – Meta-analysis
  – FDA guidelines and actions
  – HER2-positive breast cancer
  – Triple negative breast cancer
  – Hormone receptor-positive/HER2-negative
  – RCB update
  – Correlative studies
• Update on role of neoadjuvant therapy in 2014
Meta-analysis of Neoadjuvant Chemo Trials
• 12 randomized controlled trials for which pCR defined and DFS/OS data available (N=12993)

Association of pCR on EFS and OS

Meta-analysis of Neoadjuvant Chemo Trials
• Definition of pCR (+/- DCIS, breast vs. breast/axilla) does not affect its prognostic value.
• Frequency of pCR and impact on Event-Free Survival varies by type:

<table>
<thead>
<tr>
<th></th>
<th>ER+/HER2- Grade 1-2</th>
<th>ER+/HER2+ Grade 3</th>
<th>ER2-/HER2-</th>
<th>HER2+/ER+</th>
<th>HER2+/ER-</th>
<th>TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR rate</td>
<td>7%</td>
<td>16%</td>
<td>50%</td>
<td>30%</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>HR for pCR/not</td>
<td>0.63</td>
<td>0.27*</td>
<td>0.25*</td>
<td>0.58*</td>
<td>0.24*</td>
<td></td>
</tr>
</tbody>
</table>

*statistically significant

• Remember: Not all non-pCRs recur/die, and not all pCRs survive free of disease

FDA guidelines re: Neoadjuvant Rx - 2012
• Difficulty of testing new agents or regimens – even those that show promise in advanced breast cancer - in the adjuvant setting
• FDA can grant accelerated approval on the basis of a surrogate endpoint that is ‘reasonably likely to predict clinical benefit’
• Correlation between pCR and DFS/OS, especially in aggressive subtypes (HER2+, TNBC)
• After accelerated approval, subsequent demonstration of improvement in DFS or OS is required; the indication may be withdrawn if confirmatory trials do not show benefit
Neoadjuvant therapy in HER2+ patients

- Even without trastuzumab, patients with HER2+ BC have relatively high pCR rates (31% ER-, 18% ER+)
- The addition of trastuzumab significantly increased pCR rates (43% vs. 20% in 2 randomized trials) and improves RFS by 36% and OS by 34%
- Failure to achieve pCR (and to eventually recur and die) has been attributed to resistance to trastuzumab
- In vitro, and in patients with metastatic HER2+ BC, addition of second HER2-targeted agent may reverse this resistance

Neoadjuvant therapy in HER2+ patients

Lapatinib – Blocks activation of HER2 Tyrosine Kinase

- A number of studies (NeoALTTO, CHER-LOB, NSABP B-41, CALGB 40601) have demonstrated higher pCR rates with the addition of lapatinib to chemotherapy + trastuzumab
- Recent update of NeoALTTO confirms prognostic significance of achieving pCR
- However, addition of lapatinib substantially increases incidence of diarrhea, rash and LFT abnormalities, and ~1/3 of patients discontinue drug prior to completion of neoadjuvant treatment
While not statistically significant (in large part due to sample size), results support the concept that increasing the pCR rate in HER2+ patients will reduce recurrences (and, likely, deaths).

Neoadjuvant therapy in HER2+ patients

Pertuzumab - Blocks formation of HER2:HER3 dimers

- TRYPHAENA - Randomized phase II study of chemo regimens with trastuzumab + pertuzumab (N=225) (TRYPHAENA) (n=225) pCR
  - FE(100)C x 3 + T/P then Docetaxel 75 x 3 + T/P 51%
  - FE(100)C x 3 then Docetaxel 75 x 3 + T/P 45%
  - Docetaxel 75 + Carboplatin AUC 6 + T/P 52%
- Higher pCR rates seen in ER- vs. ER+
- No increase in cardiac toxicity than typically seen with chemo + trastuzumab
- More grade 3 anemia, thrombocytopenia with TCHP

Neoadjuvant therapy in HER2+ patients

Pertuzumab – NeoSphere study – pCR breast rates

- Significantly higher pCR rate with addition of pertuzumab
- pCRs seen with dual HER2-targeted therapy only (16.8%)
  - 6% ER+, 29% ER-
Neoadjuvant therapy in HER2+ patients

Pertuzumab - Blocks formation of HER2:HER3 dimers

- On 9/30/2013, based on results from the NeoSphere and TRYPHAENA studies, FDA granted accelerated approval to use of pertuzumab (P) in neoadjuvant setting
  - Docetaxel and trastuzumab (DT) + P x 4 + post-op FEC x 3
  - FEC (w/o T or P) x 3 followed by DT + P X 3
  - Docetaxel, carboplatin, trastuzumab + P x 4
  - 7 Use with other regimens (AC followed weekly paclitaxel + T + P)
- Decision to approve was likely influenced by existence of a large adjuvant trial of chemo + trastuzumab +/- pertuzumab (APHINITY) powered to detect DFS/OS that recently completed accrual

Neoadjuvant therapy in TNBC

Carboplatin

- Most sporadic TNBCs resembles BRCA-associated breast cancers in terms of
  - Histologic appearance and biologic behavior
  - ‘Basal-like’ gene expression pattern
- BRCA mutations interfere with DNA damage repair
- Carboplatin induces double-strand DNA breaks
  - Single agent platinum analogs have demonstrated high response/pCR rates in BRCA-mutated cancers
  - High pCR rates in pilot studies of addition of carboplatin to standard neoadjuvant chemo in TNBC

Neoadjuvant therapy in TNBC

CALGB 40603: Schema – Randomized Phase II

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

Surgery

XRT

No Adjuvant Systemic Treatment Planned

*Research biopsies if residual tumor

*MD discretion
Neoadjuvant therapy in TNBC

**CALGB 40603: pCR Breast/Axilla (ypT0/is N0)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=212</th>
<th>N=221</th>
<th>N=218</th>
<th>N=215</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Carboplatin</td>
<td>41% (38-44%)</td>
<td>54% (48-61%)</td>
<td>44% (38-51%)</td>
<td>52% (45-58%)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Bevacizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.71</td>
<td></td>
<td>1.36</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0029</td>
<td></td>
<td>0.0570</td>
<td></td>
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</tbody>
</table>

- **Neoadjuvant therapy in TNBC**

**Carboplatin (Cb)**

- CALGB 40603 confirms results of GeparSixto (n=315)
  - Addition of weekly Cb (to chemo regimen of weekly P, doxorubicin + bevacizumab) raised pCR from 44% to 64%
- ISPY-2 – Pilot study of addition of carboplatin and PARP inhibitor veliparib to standard chemo (n=60)
  - Raised pCR from 26% to 52%
  - Contribution of Cb vs. Cb + veliparib
- In all studies, addition of Cb increased hematologic toxicities, missed doses and dose reductions
- No long-term results (DFS/OS) available

**Bevacizumab (Bev)**

- CALGB 40603 confirms results from GeparQuinto
  - Addition of Bev to standard chemotherapy raised pCR from 33% to 43% (n=663)
  - In NSABP B-40 addition of Bev increased pCR in HER2-, but NS in TNBC (47% to 52%) (n=320)
- In these studies, addition of Bev associated with increased FN, HTN, mucositis, HFS, cardiac and post-op complications
- Long-term benefits of Bev questioned by BEATRICE (Bev added in adjuvant chemo in stage I-III TNBC)
Neoadjuvant therapy in ER+/HER2-

- Despite high clinical RR, neoadjuvant chemotherapy associated with low pCR rates (<10%)
- Except in grade III cancers, no clear benefit with pCR
- Neoadjuvant endocrine therapy previously reserved for elderly, frail women - more recently studied in younger post-menopausal women
- Optimal duration not known; in absence of clinical progression, should be continued for a minimum of 3-4 months; 6 months or longer may be better
- PEPI (Preoperative Endocrine Prognostic Index) score may predict DFS/OS, benefits from adjuvant chemo

Neoadjuvant therapy in ER+/HER2-

- ACOSOG Z1031 compared anastrozole, letrozole and exemestane x 16-18 weeks in 377 patients with Stage II-III disease
  - Rates of clinical response (63-75%) and breast-conserving surgery were similar with the 3 agents
  - Patients with biologically less aggressive cancers (luminal A vs. luminal B; lower baseline Ki-67 vs. higher) were more likely to achieve PEPI 0
  - Which patients benefit most from this approach

Update on RCB as Prognostic Tool

![Residual Cancer Burden Calculator](image)
Update on RCB as Prognostic Tool

Correlative Studies in Neoadjuvant Setting: Predictive and Prognostic

PIK3CA Mutations in HER2+ Breast Cancer

• Rationale
  – PIK3CA mutations are common in Breast Ca and have been associated with resistance to HER2-targeted therapies
  – May lead to constitutive activation of PI3K pathway, not inhibited by blocking activation of RTK
  – In the GeparQuinto and GeparSixto trial, 20.8% of HER2+ patients (equal % in ER+ and ER-) had PIK3CA mutations in Exon 9 or 20 (90% of mutations)

PIK3CA mutations in HER2+ BR Ca
PIK3CA mutations in HER2+ BR Ca

- Impact of PIK3CA mutations on pCR rates in NeoALTTO

![PIK3CA mutations in HER2+ BR Ca](image)

Correlative Studies in Neoadjuvant Setting: Predictive and Prognostic

- Tumor-infiltrating lymphocytes (TILs)
  - Tumor microenvironment is immunosuppressive
  - Lymphocytic infiltrate correlates with RFS/OS
  - With effective antitumor therapy, presence of TILs correlates with improved outcomes
    - FinHer trial: In patients who received Herceptin with chemo, increase in TILs correlated with DDFS

![Correlative Studies in Neoadjuvant Setting](image)

TILs and Response to Neoadjuvant therapy

- In GeparQuatro - EC-docetaxel + trastuzumab (with concurrent or sequential capecitabine)
  - Multivariate analysis of factors influencing pCR rate

<table>
<thead>
<tr>
<th>Variable</th>
<th>P Value</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stromal TILs (per 10% increment)</td>
<td>0.038</td>
<td>1.16 (1.01-1.22)</td>
</tr>
<tr>
<td>Age (&lt;50 vs &gt;50yrs)</td>
<td>0.24</td>
<td>1.53 (0.76-3.11)</td>
</tr>
<tr>
<td>Nodal status (pos vs neg)</td>
<td>0.00</td>
<td>1.06 (0.53-2.16)</td>
</tr>
<tr>
<td>Histologic Grade (1.2 vs 3)</td>
<td>0.44</td>
<td>0.76 (0.38-1.53)</td>
</tr>
<tr>
<td>Tumor stage (T4 vs T1-3)</td>
<td>0.43</td>
<td>1.47 (0.57-3.76)</td>
</tr>
<tr>
<td>ER status (neg vs pos)</td>
<td>0.03</td>
<td>2.14 (1.07-4.28)</td>
</tr>
</tbody>
</table>
**TILS and Immune down-regulators**

- In GeparSixto, extent of lymphocytic infiltration correlates with benefit seen from addition of carboplatin
- In TNBC, for every 10% increase in TILs, there is
  - 14% reduction in risk of recurrence or death ($p=0.02$)
  - 18% reduction in risk of distant recurrence ($p=0.04$)
  - 19% reduction in risk of death ($p=0.01$)
- In early stage HER2+ cancers, patients with higher levels of intratumoral CTLA-4 and PD-1 get the largest benefit from addition of trastuzumab

**TILS and Immune down-regulators**

- How to release immune response when TILs present and induce it when they are not?

**Neoadjuvant Therapy 2014**

- Traditional indications for neoadjuvant therapy
  - Permit resection in patients with unresectable cancers
  - Allow/facilitate BCS in patients with large tumors relative to breast size
Neoadjuvant Therapy 2014

• Traditional indications for neoadjuvant therapy
  – Permit resection in patients with unresectable cancers
  – Allow/facilitate BCS in patients with large tumors relative to breast size

• Additional reasons for neoadjuvant therapy
  – Delay surgery to complete genetic testing, or to coordinate scheduling with reconstruction
  – Avoid full ALND in cN1 or cN0/SLN+ patients
  – Assess response to determine subsequent systemic therapy
  – Support approval of or new indication for agent
  – Correlate clinical/pathologic response (or resistance) with biomarkers

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The following slides are to be projected during the discussion period after all 3 speakers in the neoadjuvant session have finished
NRG 9353: Schema

Clinical T1-3N1M0 BC
Axillary Node (+) (FNA or Core Needle Biopsy)
Necadjuvant Chemo (+ Anti-HER-2 Therapy for HER-2 neu + Pts)
Path Negative Axillary Nodes at Surgery
(Axillary Dissection or SNB + Axillary Dissection)
Randomization

No Regional Nodal XRT with Breast XRT if BCS and No Chest Wall XRT if Mastectomy
Regional Nodal XRT with Breast XRT if BCS and Chest Wall XRT if Mastectomy

• N= 1636 - Primary endpoint – Is nodal XRT necessary if cN0 converted to SLN?

ALLIANCE A11101

Clinical T1-3N1M0 BC
Axillary Node (+) (FNA or Core Needle Biopsy)
Necadjuvant Chemo (+ Anti-HER-2 Therapy for HER-2 neu + Pts)

SNB: Positive
Randomization

Breast/Chest Wall + Regional Nodal XRT
Axillary Dissection + Breast/Chest Wall + Regional Nodal XRT

• N=2918 - Primary endpoint – Is nodal XRT not inferior to ALND and nodal XRT in persistent SLN+?

NSABP B-52

Stage II-III HER2+, ER or PR+ (>1%); n=212

Docetaxel, carboplatin, trastuzumab & pertuzumab x 6
Randomize

Docetaxel, carboplatin, trastuzumab & pertuzumab x 6 + AI (+/- LHRH analog)

• Primary endpoint: pCR breast/axilla
Alliance A011106 – ‘Alternate’

- Clinical stage II-III, ER+/HER2-, postmenopausal
- N= 400; randomized to
  - Anastrozole vs. Fulvestrant vs. Both
  - Rebiopsy at 4 wks; if Ki67 > 10%, switch to chemo if Ki67<10%, continue endocrine therapy x 24 wks
  - After surgery, if PEPI = 0, adjuvant endocrine therapy x 4.5 yrs (if fulvestrant, F x 1.5 yrs, then A)
  - If PEPI >0, adjuvant chemo of MD choice
  - Primary endpoint – compare % endocrine resistant tumors (Ki67>10% at 4 weeks or PEPI >0 at surgery) between the 3 treatment arms.

BKM120 is a pan-PI3K inhibitor

ATEMP Trial Schema

Trastuzumab-DH1  q3weeks X17
N=275

Paclitaxel + Trastuzumab x12→
Trastuzumab q3weeks x13
N=125

Stage I
HER2+
ER+ or ER-
P5 0-1
Adequate organ fx
N=500

*HER2-positive defined as HER2 3+ or FISH+.
will be confirmed by central HER2 testing prior to study enrollment.
Adjuvant endocrine therapy can be administered concurrently with study treatment.

Pt Sara Falaney, MD, MPH
Veliparib ‘Brightness’ Study

- Clinical stage II-III (excluding T4d), TNBC
- All patients receive weekly P x 12 → ddAC x 4
- N=624 Randomized (1:1:2) to
  - Placebo carboplatin infusion/placebo PO veliparib
  - Carboplatin AUC 6 x 4 /placebo PO veliparib
  - Carboplatin/Veliparib 50 mg PO BID x 12 weeks
- Primary endpoint is pCR breast/axilla
- Designed to determine addition of veliparib improves pCr vs. control +/- carboplatin