Overview

• General Principles
  – Historical studies

• Prognostic implications of pCR by subtype
  – Highlighting the TNBC subtype

• Updates on Neoadjuvant Trials
  – ER+
  – TNBC
  – HER2+
Common Questions to Consider: Neoadjuvant Therapy

When is the neoadjuvant approach indicated?
Should you “tailor” therapy to response?
(Both chemotherapy and XRT)
Should you add non-cross-resistant drugs in nonresponse?
What Constitutes “Neo” Adjuvant Tx?

- Traditional indication - locally advanced disease
  - Achieve operability or BCT
- Newer indications:
  - Window for genetic testing
  - Biomarker exploration
  - Testing of new drugs and regimens
- Indications in the future:
  - *In vivo* chemosensitivity?
  - Adaptive treatment?
NSABP B-18

N=1450
clinical T1-3, N0-1

No difference in outcome chemotherapy preop vs postop:

DFS

DDFS

OS
If you know what you are going to give, it does not matter when you give it.

What if you don’t know? Probably best to give therapy adjuvantly.

Can you use this approach to individualize therapy? No, but we would like to.
Decisions, decisions...

**Adjuvant**

Surgery → Chemotherapy

One chance to make decisions and identify markers, e.g. ER, HER2, grade, clinical factors

**Upfront (traditional) factors**

**Neoadjuvant**

Chemotherapy → Surgery

Several chances to identify markers and make (or change) decisions …but when should you?

**Upfront**

Early response*

* unproven

**Overall response**

**Post-treatment markers***

Pathologic response*

* unproven
Response Predicts Outcome

Improving BCT is nice, but is not the only reason we give chemotherapy. Neoadjuvant therapy is appealing because response to chemotherapy predicts outcome.

NSABP B-27: Disease-free and overall survival by pCR

What do we do with this information?
What is the best way to measure response?
All Breast Cancers are not created equally: pCR Differs by Subtype

<table>
<thead>
<tr>
<th></th>
<th>T-FAC (N=82)*</th>
<th>AC-T (n=107)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A/B</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Normal-like</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>HER2+/ER-</td>
<td>45%</td>
<td>36%</td>
</tr>
<tr>
<td>Basal-like</td>
<td>45%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Rouzier, Clin CancRes’ 05; Carey, Clin Canc Res’07

- Response differs by subtype
- ER-negative has higher response to conventional cytotoxics
  - ? How can pCR be higher, but risk of recurrence also higher?
Residual Disease Allows Identification of Subsets with Higher Recurrence Risk

Regardless of subtype, pCR did well

Heterogeneity in outcome comes from those with residual disease

DFS in non-pCR:

Doubtless better outcome in luminal subtypes is from endocrine Rx
HER2+/ER- benefit now from HER2-targeted therapy
Ongoing efforts to target residual disease to improve outcomes...
Post-Preop Setting

DFCI–IU–UCSF–UNC Pilot: Feasibility of Novel Therapies After Preoperative Chemotherapy

MD discretion neoadjuvant regimen

Non pCR at operation

RT prn

Cohort A
Bevacizumab x 1yr

Cohort B
CM x 6m, bev x 1yr

Cohort C
Cape x 6m, bev x 1yr

Study halted due to poor accrual….

Can knowledge of residual risk after conventional agents be exploited?
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

Adapted from Hal Burstein
A Tale of Two Trials: Aberdeen (Non Cross-Resistant Drugs in Response)

- Taxanes worked
- Nonresponders didn’t respond much to additional cytotoxic therapy
A Tale of Two Trials: GEOR-TRIO (Non Cross-resistant Drugs in Nonresponse)

N=286
T2-3

N X N X N X N X

T A C T A C T A C T A C

pCR
7%
3%
23%

“nonresponse”

“response”

Only 2 cycles

- No benefit of changing therapy based on early nonresponse
  - Don’t pull the plug on good drugs early
  - Clinical/radiographic response assessment tools are inadequate

- Might it have worked if they randomized AFTER completion of TAC?

TAC=docetaxel, doxorubicin, cyclophosphamide
NX = vinorelbine, capecitabine

Von Minckwitz et al. SABCS 03
What about XRT? Should we omit XRT in pCR?

NSABP B-51

PI: Zagar

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

* All patients will receive additional systemic therapy as planned (i.e., hormonal therapy for patients with hormone receptor-positive breast cancer and trastuzumab or other anti-HER2 therapy for patients with breast cancer that is HER2-positive).
### There are Many Ongoing Neoadjuvant Trials…

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Title</th>
<th>N</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 40603</td>
<td>Randomized Phase II Trial of Carboplatin and/or Bevacizumab Added to Weekly Paclitaxel - Dose-Dense AC/EC in <strong>Triple Negative</strong></td>
<td>500</td>
<td>Sikov</td>
</tr>
<tr>
<td>CALGB 40601</td>
<td>Phase III Trial of Paclitaxel Combined with Trastuzumab, Lapatinib, or Both in <strong>Her2-Positive</strong> Primary Breast Cancer</td>
<td>400</td>
<td>Carey</td>
</tr>
<tr>
<td>ACOSOG Z1031</td>
<td>Phase III Trial Comparing 16 to 18 wk of Exemestane, Letrozole, or Anastrozole in Postmenopausal Stage II- III <strong>ER-Positive</strong></td>
<td>375</td>
<td>Ellis</td>
</tr>
<tr>
<td>ACOSOG Z1041</td>
<td>Phase III Trial Comparing FEC then Paclitaxel (P) + Trastuzumab (T) vs FEC+T then P+T in <strong>HER2-positive</strong></td>
<td>391</td>
<td>Buzdar</td>
</tr>
<tr>
<td>GeparQuattro</td>
<td>Phase III Study of EC and Docetaxel With Versus Without Capecitabine and/or Trastuzumab (closed)</td>
<td>1500</td>
<td>Von Minckwitz</td>
</tr>
<tr>
<td>GeparQuinto</td>
<td>Phase III Trial Integrating Bevacizumab, Everolimus (RAD001), and Lapatinib Into Current Neoadjuvant Chemotherapy Regimes</td>
<td>2550</td>
<td>Von Minckwitz</td>
</tr>
<tr>
<td>NSABP B-40</td>
<td>Phase III Trial Adding Capecitabine or Gemcitabine to Docetaxel Before AC With or Without Bevacizumab (<strong>HER2-negative</strong>)</td>
<td>1200</td>
<td>Bear</td>
</tr>
<tr>
<td>NSABP B-41</td>
<td>Phase III Trial in <strong>HER2-positive</strong> of AC - Weekly Paclitaxel Plus Trastuzumab, Lapatinib, or Trastuzumab Plus Lapatinib</td>
<td>522</td>
<td>Robidoux</td>
</tr>
</tbody>
</table>
# ER+ Neoadjuvant Tx

## Neoadjuvant: Chemo vs Endocrine
(postmenopausal, ER or PR+, IIB-IIIA, Rx duration 3 mths)

<table>
<thead>
<tr>
<th></th>
<th>Endocrine (Ana or Exe)</th>
<th>Chemotherapy (pac200/dox60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td># pts (%)</td>
<td>121 (100)</td>
<td>118 (100)</td>
<td>-</td>
</tr>
<tr>
<td>CR Palpation</td>
<td>10%</td>
<td>10%</td>
<td>&gt;.50</td>
</tr>
<tr>
<td>CR/PR palpation</td>
<td>65%</td>
<td>64%</td>
<td>NS</td>
</tr>
<tr>
<td>Breast</td>
<td>33%</td>
<td>24%</td>
<td>.06</td>
</tr>
<tr>
<td>Conservation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCR</td>
<td>6%</td>
<td>3%</td>
<td>&gt;.50</td>
</tr>
<tr>
<td>Median TTR</td>
<td>57 days</td>
<td>51 days</td>
<td>&gt;.98</td>
</tr>
<tr>
<td>Prog on Rx</td>
<td>9%</td>
<td>9%</td>
<td>&gt;.50</td>
</tr>
</tbody>
</table>

Semiglazov 2007 Cancer 110:244
ER+ Neoadjuvant Tx: ACOSOG Z1031

Neoadjuvant AI therapy

- ACOSOG Z1031
- RCT: Ex vs An vs Let
- Postmenopausal
- >2 cm (T2-4, N0-3, M0)
- ER+ and Allred 6-8
- 16-18 weeks duration
- Endpoint: clinical response by caliper

<table>
<thead>
<tr>
<th></th>
<th>Exem</th>
<th>Let</th>
<th>Anast</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>124</td>
<td>127</td>
<td>123</td>
</tr>
<tr>
<td>CR</td>
<td>22%</td>
<td>21%</td>
<td>18%</td>
</tr>
<tr>
<td>PR</td>
<td>41</td>
<td>54</td>
<td>51</td>
</tr>
<tr>
<td>Stable</td>
<td>23</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>PROG</td>
<td>7</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Total R</td>
<td>63</td>
<td>75</td>
<td>69</td>
</tr>
</tbody>
</table>

Surgery, PEPI similar all 3 arms PEPI ‘0’ Lum A vs B = 27 vs 11%

Ellis JCO 2011 29:2342
TNBC Neoadjuvant Therapy Options.....

- Anthracycline/taxane backbone
  - ? Add platinum
  - ? Add bevacizumab
  - ? Add PARP inhibitor
Carboplatin/Gemcitabine +/- Iniparib (Telli, PI)

**PrECOG 0105 Schema**

- Newly Diagnosed
  - Stage I-IIIA (T ≥ 1cm by MRI)
  - Triple-negative (ER/PR ≤ 5%)
  - or BRCA1/2 mutation

- Carboplatin AUC 2 D 1, 8
- Gemcitabine 1000 mg/m² D 1, 8
- Iniparib 5.6 mg/kg D 1, 4, 8, 11

Every 21 days x 6 cycles n = 80

- Definitive Surgery
- Assess Pathologic Response

**Results**

**Intent-to-treat population**

<table>
<thead>
<tr>
<th>Pathologic Response (n=80)</th>
<th>All patients</th>
<th>BRCA 1/2 wild-type</th>
<th>BRCA 1/2 mutant</th>
<th>TN &amp; BRCA 1/2 mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 80</td>
<td>n = 61</td>
<td>n = 19</td>
<td>n = 16</td>
</tr>
<tr>
<td>pCR [RCB 0]; n (%)</td>
<td>29 (36%)</td>
<td>20 (33%)</td>
<td>9* (47%)</td>
<td>9* (56%)</td>
</tr>
<tr>
<td>90% CI</td>
<td>27–46</td>
<td>23–44</td>
<td>27–68</td>
<td>33–77</td>
</tr>
<tr>
<td>RCB 0/1; n (%)</td>
<td>45 (56%)</td>
<td>31 (51%)</td>
<td>14 (74%)</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>90% CI</td>
<td>46–66</td>
<td>40–62</td>
<td>52–89</td>
<td>52–91</td>
</tr>
</tbody>
</table>

* One BRCA1 carrier had bilateral TNBC & achieved pCR in both breasts

Presented By Melinda L. Telli, MD at 2013 ASCO Annual Meeting
GeparSIXTO: Triple Negative Neoadjuvant Trial (Von Minckwitz, PI)

Subtype Specific Targeted Therapy

N=595 centrally confirmed TNBC or Her2-positive breast cancer

PM

PMCb

R

Pacitaxel 80 mg/m² q1w
Non-pegylated liposomal doxorubicin 20 mg/m² q1w
Carboplatin AUC 1.5 q1w
Bevacizumab 15 mg/kg q3w

Her2-pos: Trastuzumab 6(8) mg/kg q3w (for 1 year)
Lapatinib 750 mg/d 18 wks

*Reduced from AUC 2 at amendment 1 after enrolment of 330 patients

Presented at the 2013 ASCO Annual Meeting. Presented data is the property of GBG and AGO-B.
GeparSIXTO: Triple Negative Neoadjuvant Trial (Von Minckwitz, PI)

pCR Rates by Subtype

\[
\text{ypT0 ypN0}
\]

<table>
<thead>
<tr>
<th>Subtype</th>
<th>PM</th>
<th>PMCb</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNBC</td>
<td>37.9%</td>
<td>58.7%</td>
</tr>
<tr>
<td>HER2-positive</td>
<td>36.3%</td>
<td>33.1%</td>
</tr>
</tbody>
</table>

\(P<0.05\) vs n.s.
CALGB 40603
Neoadjuvant TX of TNBC

Sikov et al. SABCS 2013, Abstract CALGB 40603 (S4-01)
Given this design, pCR rates are “estimated” and not reported…

Veliparib/Carbo “graduated” in TNBC

RUGO et al. SABCS 2013, Abstract ISPY2 (S4-02)
“Cup half full:” We are making progress in neoadjuvant tx of TNBC……

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ypT0/is ypN0</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC</td>
<td>39%</td>
</tr>
<tr>
<td>EC-Doc</td>
<td>33%</td>
</tr>
<tr>
<td>EC-Doc+B</td>
<td>43%</td>
</tr>
<tr>
<td>PM+B</td>
<td>44%</td>
</tr>
<tr>
<td>PMCb+B</td>
<td>64%</td>
</tr>
</tbody>
</table>

Presented at the 2013 ASCO Annual Meeting. Presented data is the property of GBG and AGO-B.
HER2+ Neoadjuvant Therapy Options.....

• Anthracycline/taxane/trastuzumab backbone
  – ? Add lapatinib
  – ? Add pertuzumab
Neo ALTTO (BIG 01-06/EGF 106903) Study Design

Eligibility (N = 450)

<table>
<thead>
<tr>
<th>Invasive operable HER 2+ breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>T &gt; 2 cm</td>
</tr>
<tr>
<td>LVEF ≥ 50%</td>
</tr>
</tbody>
</table>

Stratification

| T ≤5 cm vs >5cm; ER/PR positive or negative; N 0-1 vs N ≥ 2; Conservative surgery vs not |

L = lapatinib, T = trastuzumab, P = paclitaxel

† Neoadjuvant therapy consisted of 6 wks of anti-HER2 therapy alone (biologic window) followed by 12 wks of the same anti-HER2 therapy with weekly paclitaxel; total neoadjuvant therapy duration of 18 wks

* Same anti-HER2 therapy as in the neoadjuvant phase for an additional 34 wks

## Neo ALLTO Efficacy: pCR and tpCR

<table>
<thead>
<tr>
<th>Response</th>
<th>L (N = 154)</th>
<th>T (N = 149)</th>
<th>L + T (N = 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pCR (no invasive cancer in the breast)</strong></td>
<td>24.7%</td>
<td>29.5%</td>
<td>51.3%</td>
</tr>
<tr>
<td><em>p-value: 0.34 (L vs T); 0.0001 (L +T vs T)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>tpCR (no invasive cancer in the breast or LNs)</strong></td>
<td>20.0%</td>
<td>27.6%</td>
<td>46.9%</td>
</tr>
<tr>
<td><em>p - value: 0.13 (L vs T); 0.001 (L+T vs T)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Excludes 15 patients with non-evaluable nodal status

Intergroup/CALGB 40601: HER2+ Neoadjuvant Trial (Lisa Carey, PI)

N=400
HER2+
Stage II-III

Breast imaging
Blood
MUGA
Tumor Biopsy

Paclitaxel x 16 wks
Trastuzumab

Paclitaxel x 16 wks
Lapatinib

Paclitaxel x 16 wks
Trastuzumab + lapatinib

Surgery
Dose-dense AC
(recommended)

Trastuzumab x 1y
(recommended)

Endocrine Rx and RT prn

Biomarker cross-validation with Neo-ALTTO (J. Baselga, PI)
Presented By Lisa A. Carey, MD at 2013 ASCO Annual Meeting

Intergroup/CALGB 40601: Results
HER2+ Neoadjuvant Trial

C40601: pCR in Breast

- THL: 56% (n=116)
- TH: 46% (n=118)
- TL: 37% (n=62)

p = 0.12 THL vs TH (p = 0.12 TH vs TL)
**FDA approval of Pertuzumab in the NEOadjuvant setting of HER2+ Breast Cancer September 2013**
**FDA approval of Pertuzumab in the NEOadjuvant setting of HER2+ Breast Cancer September 2013**

“Cup half full:” We are making progress in neoadjuvant tx of HER2+ BC……

pCR rates in HER2-positive BC

ypT0/is ypN0

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ypT0/is ypN0</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECH-DocH</td>
<td>44.6%</td>
</tr>
<tr>
<td>DocHP</td>
<td>39.3%</td>
</tr>
<tr>
<td>PacHL</td>
<td>46.8%</td>
</tr>
<tr>
<td>FECHP-DocHP</td>
<td>50.7%</td>
</tr>
<tr>
<td>TCHP</td>
<td>51.9%</td>
</tr>
<tr>
<td>PMHL</td>
<td>56.3%</td>
</tr>
<tr>
<td>PMCBHL</td>
<td>53.7%</td>
</tr>
</tbody>
</table>


Presented at the 2013 ASCO Annual Meeting. Presented data is the property of GBG and AGO-B.
Conclusions: Neoadjuvant versus Adjuvant Therapy

- There are a few clear clinical indications for neoadjuvant chemotherapy.
  - Inoperability
  - Desire for BCT
- The same regimen given before or after surgery does not matter, neoadjuvant has benefits in some circumstances.
- “Tailored” therapy during treatment is unproven and has real risks.
- There are clear research indications for neoadjuvant chemotherapy:
  - Quicker evaluation of novel combinations or drugs
  - Biomarker exploration
  - Identification of very high risk subpopulation
Thank you

“Whoa—way too much information!”