Update on the Practical Management of HER2-Positive Breast Cancer

Antonio C. Wolff, MD, FACP
Breast Cancer Program
San Diego, Aug 5 2011

“Easy” Questions from Joyce …

• HER2 testing and equivocal results …
• TCH vs ACTH options …
• Subcentimeter HER2+ breast cancer …

A few extra background slides at the end of the slide set

Disclosure Slide

• Genentech provides funding to Johns Hopkins to support an early phase clinical trial that has Dr. Wolff as site PI

→ Dr. Wolff is not a pathologist and (hopefully) does not pretend to come across as one …

HER2 Testing circa MMXI …

• Goals and outcomes from the ASCO/CAP efforts
  – Standardization versus confusion?
  – Are things better?
• Lessons from the cooperative group trials
  – Round-Robin exercise by NCCTG/BCIRG/NSABP
  – Ring study data in ALTTO

Current Assumptions on Benefit from HER2-Targeted Therapy in HER2 Normal Disease

• Metastatic setting
  – Trastuzumab – most likely no benefit
  • Low/medium-level evidence from CALGB 9840 and various phase II trials
  – Lapatinib – definitely no benefit
  • High-level evidence from phase III paclitaxel ± lapatinib

• Adjuvant setting
  – Trastuzumab – benefit??
  • Low-level evidence from 1st generation trials
  • Ongoing trial NSABP B47
  – Lapatinib – no data

HER2 Testing (Dis)Concordance in Adjuvant Trastuzumab Trials

<table>
<thead>
<tr>
<th>Concordance Central vs Local Lab (circa 2006)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N9831</td>
</tr>
<tr>
<td>IHC 3+ (HercepTest)</td>
</tr>
<tr>
<td>FISH + (PathVysion)</td>
</tr>
</tbody>
</table>

Magnitude of false-neg HER2 testing unclear but real …
1. What is the optimal testing algorithm for the assessment of HER2 status?
2. What strategies can help ensure optimal performance, interpretation, and reporting of established assays?

- Guideline appendices:
  - Appendix C: Evidence of HER2 Status and Trastuzumab Benefit
  - Appendix D: Evidence of HER2 Testing Variation
  - Appendix E: Statistical Requirements for Assay Validation
  - Appendix F: Tissue Handling Requirements and Control Materials
  - Appendix G: Interpretation Criteria & Test Reporting
  - Appendix H: Regulatory Requirements for Laboratories
  - Appendix I: International External QA Initiatives

2011 Clinical Notice for ASCO/CAP Guideline Recommendations for ER/PgR and HER2 Testing

I. Reconciles the two guidelines:
   - Changed cold ischemia time from "short" to ≤ 1h
   - Record time between tissue removal and start of fixation
   - Confirmed fixation time in NBF (formalin) as 6 to 48h
   - < 6h for needle cores not ok; unclear if HER2 ok > 48h
   - Handling of specimens obtained remotely
   - Specimen bisection; record times and fixative used
   - Selection of an optimal sample for testing
   - A preference for core needle biopsies, but pathologists to use discretion in selecting sample for testing

II. Reminder of the intent behind creating the HER2 "equivocal" categories:
   - Trigger HER2 reflex testing using another validated assay if the first test "equivocal"
   - i.e., IHC if an equivocal FISH; FISH if an equivocal IHC
   - "...provide clinicians and their patients with additional information for clinical decision making."
   - Figs 1 & 2 clearly state that patients with uniform IHC staining between 10-30% or FISH ratio ≥ 2.0 were eligible for the trastuzumab adjuvant trials
2011 Clinical Notice for ASCO/CAP Guideline Recommendations for ER/PgR and HER2 Testing

– Jan 2007: “Available data from the adjuvant trials at present are insufficient to reliably exclude these patients from therapy with trastuzumab …”

– Apr 2011: “The Panel did not recommend withholding anti-HER2 treatment in those patients with an equivocal HER2 test (or tests) whose results fell within ranges that would have allowed them to be treated in the first generation of adjuvant HER2-targeted trials.”

Impact of ASCO/CAP Guidelines on HER2 Interpretation in Breast Cancer

- All Mayo Clinic Rochester cases of invasive breast cancer HER2 3+ (Herceptest > 10% cells) between 2001-2007 (n = ?)
- 144 had available slides and blocks
  - IHC re-reviewed by 3 pathologists (three cases reclassified as 2+)
  - PathVysion FISH done on remaining 141 cases
  - IHC re-scored and FISH scored using ASCO/CAP parameters

<table>
<thead>
<tr>
<th>HER2 Status</th>
<th>IHC (n = 141)</th>
<th>FISH &gt; 2 (n = 14)</th>
<th>FISH 1.8-2.2 (n = 37)</th>
<th>FISH &lt; 1.8 (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2+ (111-30%)</td>
<td>12 (8.5%)</td>
<td>6</td>
<td>2 (1.8 and 2.1)</td>
<td>4</td>
</tr>
<tr>
<td>3+ (31-50%)</td>
<td>6 (4.3%)</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>3+ (51-70%)</td>
<td>4 (2.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3+ (&gt; 70%)</td>
<td>119 (84.4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Case #6 had IHC 35% and FISH 1.8 & 1.8; Case #10 had IHC 30% and FISH 2.1 & 1.8
**FISH performed in a subset (8 of 119 cases) with IHC 3+ in > 70% of cells

Reclassification of HER2 IHC and FISH in N9831 using 2007 ASCO/CAP Guideline

<table>
<thead>
<tr>
<th>HER2 Status</th>
<th>IHC (n = 204)</th>
<th>FISH &lt; 1.8 (n = 218)</th>
<th>FISH 1.8-2.0 (n = 14)</th>
<th>FISH &gt; 2.0-2.2 (n = 37)</th>
<th>FISH &gt; 2.2 (n = 253)</th>
<th>FISH not done (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or +</td>
<td>66 (48%)</td>
<td>2 (2%)</td>
<td>9 (7%)</td>
<td>49 (36%)</td>
<td>10 (7%)</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>69 (31%)</td>
<td>5 (2%)</td>
<td>16 (7%)</td>
<td>125 (57%)</td>
<td>6 (3%)</td>
<td></td>
</tr>
<tr>
<td>3+ (10-30%)</td>
<td>15 (14%)</td>
<td>1 (1%)</td>
<td>6 (6%)</td>
<td>78 (73%)</td>
<td>7 (7%)</td>
<td></td>
</tr>
<tr>
<td>3+ (&gt; 30%)</td>
<td>68 (3%)</td>
<td>6 (0.2%)</td>
<td>6 (0.2%)</td>
<td>2287 (94%)</td>
<td>72 (3%)</td>
<td></td>
</tr>
</tbody>
</table>

Her2 and Chromosome 17 Effect on Patient Outcome in N9831

- HRs for trastuzumab benefit (n = 1888)
  - IHC 3+ 0.46
  - FISH ratio ≥ 2.0 0.49
  - Both 0.45 (p < 0.001)
- HER2 amplified/p17 vs HER2 amplified/n17
  - Similar HR within trastuzumab arm (copy number matters!)
  - HR favors those with p17 within chemo arm
- Like in HERA/2 right ER+ vs ER- patients gained similar reduction in HR, but had lower rate of relapse in early follow-up
  - Endocrine Rx (and accurate determination of ER/PgR status) matters!

Lab Compliance with ASCO/CAP HER2 Testing Guideline

- Survey submitted in late 2008 with the HER2 IHC immunoproficiency testing program
- Questions on:
  - Pathology practice characteristics
  - Assay validation using FISH or another IHC assay
  - Pathologist HER2 scoring competency
- 757 of 907 (83.5%) surveys returned

CAP Laboratory Accreditation Program

<table>
<thead>
<tr>
<th>Year</th>
<th>HER2 IHC</th>
<th>HER2 FISH</th>
<th>ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>125</td>
<td>174</td>
<td>97</td>
</tr>
<tr>
<td>2005</td>
<td>156</td>
<td>191</td>
<td>139</td>
</tr>
<tr>
<td>2006</td>
<td>188</td>
<td>210</td>
<td>168</td>
</tr>
<tr>
<td>2007</td>
<td>659</td>
<td>263</td>
<td>233</td>
</tr>
<tr>
<td>2008</td>
<td>976</td>
<td>295</td>
<td>283</td>
</tr>
<tr>
<td>2009</td>
<td>1000</td>
<td>320</td>
<td>370</td>
</tr>
<tr>
<td>2010</td>
<td>1050</td>
<td>315</td>
<td>550</td>
</tr>
<tr>
<td>2011</td>
<td>1120</td>
<td>318</td>
<td>1200</td>
</tr>
</tbody>
</table>

Impact of ASCO/CAP Guidelines on HER2 Interpretation in Breast Cancer

Shah et al, Hum Pathol 41:103, 2010

Perez et al, JCO 28:4307, 2010

Nakhleh et al, Arch Path Lab Med 134:728, 2010

College of American Pathologists 2011
Implementation of ASCO/CAP HER2 Guideline at a Tertiary Center (MDACC)

- 2006: 1033 core needle biopsies (67% invasive)
  - Average duration of fixation 4h (half submitted after 3 pm)
  - HER2 FISH/IHC concordance at 98%
  - 10.8% of FISH results were inconclusive, but results became informative when additional tissue submitted

- 2007: 1186 core needle biopsies (68% invasive)
  - Duration of formalin fixation increased to \( \geq 6h \)
  - HER2 FISH/IHC concordance increased to 98.5%
  - FISH results inconclusive reduced from 10.8% to 3.4%
  - Costs savings $34,000
  - 40% reduction in need to repeat ER/PgR (38 to 23 cases)

Middleton et al, Arch Path Lab Med 133:775, 2009

Round-Robin Review of HER2 Testing in the Context of Adjuvant Breast Ca Therapy

- Primary goals
  - Concordance of HER2 results by 3 central labs (NCCTG, BCIRG, and NSABP)
  - Round-robin impact on adjudication
  - HER2 heterogeneity (different blocks, same patient)
- Secondary goal
  - Impact of trastuzumab in patients with HER2 normal disease by panel adjudicated Round-Robin review

Perez et al, SABCS Abstr PD10-02, 2011

Methods

- Blinded Round-Robin exchange of specimens from trials with local & central confirmatory HER2 testing (n = 389)
  - N9831, BCIRG 005, and BCIRG 006
- Central IHC/FISH results:
  - HER2 normal: 96 local normal (005) and 62 local + (9831)
  - HER2 positive: 37 +/-, 33 +/-, and 36 -/+;
  - 123 patients with > 1 block (n = 125)
  - No blocks from B31
- Methods
  - HercepTest (IHC 3+ in > 10% invasive cells)
  - PathVysion (FISH ratio \( \geq 2 \))
- HER2 status independently determined at each site; discordant cases adjudicated in face-to-face meeting

Perez et al, SABCS Abstr PD10-02, 2011

Overall Concordance

<table>
<thead>
<tr>
<th>Total Cases N=389</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC</td>
</tr>
<tr>
<td>Not Read 6</td>
</tr>
<tr>
<td>1 Read 2</td>
</tr>
<tr>
<td>2 Reads 7</td>
</tr>
<tr>
<td>23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FISH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Read 6</td>
</tr>
<tr>
<td>1 Read 2</td>
</tr>
<tr>
<td>1 Read 10</td>
</tr>
<tr>
<td>2 Reads 7</td>
</tr>
<tr>
<td>23</td>
</tr>
<tr>
<td>23</td>
</tr>
</tbody>
</table>

96% IHC concordant
27% FISH concordant

4% IHC discordants: 2/3s IHC 2+
3% FISH discordants: median ratio 1.8

Perez et al, SABCS Abstr PD10-02, 2011

Round-Robin Conclusions

- Adjudication improved concordance:
  - IHC from 92% to 96%, FISH from 92% to 97%
- Heterogeneity within same patient, different block
  - IHC 10%, FISH 5%
- Despite technical standardization, 8% initial discordance among expert pathologists
  - Heterogeneity and/or interpretation
    - Does it justify routine re-testing? No, this heterogeneity was only observed in tumor originally called HER2+!

Perez et al, SABCS Abstr PD10-02, 2011
**Concordance in HER2 Status between ALTTO Central Labs (Ring Study)**

<table>
<thead>
<tr>
<th>HER2 IHC</th>
<th>Mayo</th>
<th>IEO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (0-1+)</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>Equivocal (2+)</td>
<td>-</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HER2 FISH</th>
<th>Mayo</th>
<th>IEO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Amplified (&lt;1.8)</td>
<td>-</td>
<td>22</td>
</tr>
<tr>
<td>Equivocal (1.8-2.2)</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALTTO Eligibility (both tests)</th>
<th>Mayo</th>
<th>IEO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Eligible</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>Eligible</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

**Concordance in ER Status between ALTTO Central Labs (Ring Study)**

<table>
<thead>
<tr>
<th>ER</th>
<th>Mayo (single antibody)</th>
<th>IEO (dual antibody)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-negative</td>
<td>19</td>
<td>ER-negative</td>
</tr>
<tr>
<td>ER-positive</td>
<td>10</td>
<td>ER-positive</td>
</tr>
</tbody>
</table>

**Assays to Measure HER2 ... Circa MMXI**

- Immunohistochemistry assays
  - C241 and 4D5 MoAbs (not commercial)
  - HercepTest A085 polyclonal Ab
  - Pathway CB11 MoAb
- Fluorescence in situ hybridization assays
  - PathVysion HER2:CEP17 ratio
  - pharmDx kits HER2:CEP17 ratio
  - INFORM kit HER2 gene copy number
-ISH assays w/ fluorescence
  - SPECT Light chromogenic ISH
  - EnzMet GenePro silver enhanced ISH
  - Inform Dual ISH two-color chromogenic ISH
- Functional assays
  - HERmark HER2 total protein and homodimers
- Gene expression profiling assays
  - Oncotype Dx real-time RT-PCR
  - TargetPrint DNA microarray

**ALTTO Ring Study Conclusion**

"Same test on same tissue = same result"
“Easy” Questions from Joyce …

- HER2 testing and equivocal results …
- TCH vs ACTH options …
- Subcentimeter HER2+ breast cancer …

Trials of One Year of Trastuzumab

<table>
<thead>
<tr>
<th>Trial</th>
<th>Strategy</th>
<th>DFS HR</th>
<th>X-over to trastuz.</th>
<th>DFS HR</th>
<th>OS HR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-31/N8831</td>
<td>AC-Tx ± concurrent T</td>
<td>0.48 (2005)</td>
<td>20.9%</td>
<td>0.52 (2011)</td>
<td>0.61 (2011)</td>
<td>Perez 2005, Perez 2011</td>
</tr>
<tr>
<td>HERA</td>
<td>Chemo ± sequential T</td>
<td>0.64 (2007)</td>
<td>52%</td>
<td>0.76 (2011)</td>
<td>0.85 NS (2011)</td>
<td>Smith 2007, Gianni 2011</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>AC-Tx ± concurrent T</td>
<td>0.64 (2009)</td>
<td>1.6%</td>
<td></td>
<td>0.63 (2009)</td>
<td>Slamon 2009 (third abstract)</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>AC-Tx vs TCh-T</td>
<td>0.75 (2009)</td>
<td>1.6%</td>
<td></td>
<td>0.77 (2009)</td>
<td>Slamon 2009 (third abstract)</td>
</tr>
<tr>
<td>N9831</td>
<td>AC-Tx ± sequential T</td>
<td>0.87 (2005)</td>
<td>-</td>
<td>0.75 NS (2009)</td>
<td></td>
<td>Perez 2005 &amp; 2009 (abstract)</td>
</tr>
<tr>
<td>PACS04</td>
<td>FEC or E0 ± sequential T</td>
<td>0.96 (2009)</td>
<td>-</td>
<td>-</td>
<td>NS</td>
<td>Spielmann 2009</td>
</tr>
</tbody>
</table>

Lessons from First Generation Trials

- Trastuzumab works, whether concomitantly, sequentially, or late after cross-over
- Cardiac toxicity is less with a non-anthracycline, but not prohibitive with concomitant
  - Symptomatic CHF in B31/N8831 was 0.5% (AC) vs 2% (AC-TH) and 86% (31 of 36) had complete or partial resolution (Russell, JCO 2010)
- However, there is indirect evidence that a concomitant approach and that includes an anthracycline may be superior
- Trials like ALTTO and TEACH will refine our approach to HER2-positive disease

Approach to Adjuvant Therapy Decisions

1980-2005
Largely based on anatomy
- Nodal status
- Tumor size
(Endocrine Rx added if ER+)

Since 2005 …
Greater focus on biologic subtype
- ER+, HER2-
- HER2+
- Triple negative

Does anatomy (tumor burden) matter in the biologic era?

Adapted from Eric Winer
Ten Year Outcome of Node-Negative, LVI Negative Early Breast Cancer: Site of First Relapse by Tumor Size

<table>
<thead>
<tr>
<th>Tumor size (cm)</th>
<th>Local relapse</th>
<th>Regional relapse</th>
<th>Distant relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1: 0.1-1.0 cm</td>
<td>40 (9.3%)</td>
<td>9 (2.1%)</td>
<td>41 (9.5%)</td>
</tr>
<tr>
<td>Cohort 2: 1.1-2.0 cm</td>
<td>45 (8.9%)</td>
<td>17 (3.4%)</td>
<td>81 (16%)</td>
</tr>
<tr>
<td>Cohort 3: 2.1-5.0 cm</td>
<td>27 (11%)</td>
<td>15 (6.0%)</td>
<td>63 (25%)</td>
</tr>
</tbody>
</table>

*Distant metastasis as first site of relapse becomes increasingly more frequent as primary tumor size increases*

Chia et al, J Clin Oncol 22:1630, 2004

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T1a-b HER2+

**IEO (n = 150)**

Eligibility Requirements for Adjuvant Trastuzumab Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Eligibility Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-31</td>
<td>• Node-positive disease</td>
</tr>
<tr>
<td>N-9831</td>
<td>• Node-positive disease OR • High-risk node-negative disease: tumor ≥2 cm and ER- or PR-</td>
</tr>
<tr>
<td>HERA</td>
<td>• Node-positive disease OR • Node-negative disease with tumor ≥1 cm</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>• Node-positive disease OR • Node-negative disease AND one of the following risk factors:</td>
</tr>
<tr>
<td>FinHER</td>
<td>• Node-positive disease OR • Node-negative disease with tumor ≥2 cm and PR-negative</td>
</tr>
</tbody>
</table>

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Key Issues in HER2 Therapy …

- **Testing Standardization**
  - Tissue handling, assays, and interpretation
  - Guidelines are living documents
- **Choice of regimen**
  - Sequential or concomitant, A or not, long or short?
- **How low is too low?**
  - Size matters
  - Reasonable for T1b, but stretching if T1a

“*It Takes a Village …*”

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**The Limbo Game …**

*BINV-7, HER2+/ER-*

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**Eligibility Requirements for Adjuvant Trastuzumab Trials**

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<td>• Node-positive disease OR • Node-negative disease with tumor ≥1 cm</td>
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<tr>
<td>BCIRG 006</td>
<td>• Node-positive disease OR • Node-negative disease AND one of the following risk factors:</td>
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<tr>
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“*It Takes a Village …*”

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**The Limbo Game …**

*BINV-7, HER2+/ER-*
Thank you …

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@awolff

"I simply misremembered it wrong."
Rep. Mark Kirk (R-IL), Friday, Jun 4 2010
### Outcome After Mastectomy for T1N0 Cancer

<table>
<thead>
<tr>
<th>Tumor size (cm)</th>
<th># of patients</th>
<th>Recurrence 1st decade</th>
<th>Recurrence after 1st decade</th>
<th>Total Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 cm</td>
<td>171</td>
<td>15</td>
<td>5</td>
<td>20 (12%)</td>
</tr>
<tr>
<td>1.1-2.0 cm</td>
<td>303</td>
<td>66</td>
<td>13</td>
<td>79 (26%)</td>
</tr>
</tbody>
</table>

- Size was most important predictor of outcome
- Other histologic factors had little influence on prognosis if ≤ 1 cm
- Ipsilateral breast recurrence not a confounding factor
- Diagnosed pre-1970 (prior to mammography)

Rosen et al., JCO 7:1239, 1989

### Node-Negative Early Breast Cancer: Overall Survival by Tumor Grade

- Cohort 1: 0.1-1.0 cm

Chia et al., J Clin Oncol 22:1630, 2004

### Adjuvant Trastuzumab Data

#### Efficacy

- Chia et al., J Clin Oncol 22:1630, 2004

#### Cardiac Toxicity

- Herceptin® Product Information, FDA Oct 2010

### ALTTO Central Pathology Ring Study

- **Objective:** To assess whether the central lab results can be duplicated in the other central lab
- **Method:** IEO and Mayo exchanged 30 cases that discordant in each central lab (local pos/central neg) for re-testing
  - HER2 local pos/central neg: 20 IEO, 5 Mayo
  - ER local pos/central neg: 5 IEO, 20 Mayo
  - ER local neg/central pos: 5 IEO, 5 Mayo
  - Re-test IHC according to own method

McCullough et al., SABCS Abstr P3-10-36, 2011
Time-Dependent Effects of Adjuvant Rx
SEER 1992 – 2007

Jatoi I et al, J Clin Oncol 2011;29:1