Controversy in Early Breast Cancer
Clinical Practice: Chemotherapy Benefit in Luminal (ER+) Disease – Mixed Messages

Message Yes! Benefit to all women whose recurrence risk justifies adjuvant chemotherapy

Message No! Not all women have added benefit to endocrine therapy despite higher risk of recurrence

K. Albain, SABCS 2011 Webcast 12/6
Confounding Factors in the Treatment of ER+ (Luminal) Early Breast Cancer

- Heterogeneity: ER level, Ki67, intrinsic subtype (luminal A/B, HER2 enriched or not), multigene assay categories
- De novo resistance (prior to adjuvant ET)
- Secondary resistance (develops during adjuvant ET)
- Cross-talk with other pathways
- Variable chemotherapy sensitivity/resistance
- Heterogeneity most likely explains controversy across trials of efficacy of adjuvant anthracyclines and taxanes (or not) and differential effect of same regimen by age

This Presentation

- Summary of recent (and conflicting) philosophies of the Oxford Overview and St. Gallen in ER+
- Role of multigene assays in addressing this controversy:
  - to select which patients with ER+ disease will benefit from chemotherapy added to endocrine therapy
  - many assays are prognostic, but will focus only on prediction
- Implications for clinical practice

The EBCTCG Overview and St. Gallen
### EBCTCG 2011 Chemotherapy Meta-analysis

**Summary: Breast Cancer Mortality**

<table>
<thead>
<tr>
<th>Trial Grouping</th>
<th>ER+ and ER poor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR  SE       2p</td>
</tr>
<tr>
<td>CMF vs no chemo</td>
<td>0.76 (0.05)   0.0001</td>
</tr>
<tr>
<td>CAF vs no chemo</td>
<td>0.64 (0.09)   &lt;0.0001</td>
</tr>
<tr>
<td>4AC/EC vs no chemo</td>
<td>0.78 (0.09)   0.01</td>
</tr>
<tr>
<td>4AC vs CMF</td>
<td>0.98 (0.05)   0.07</td>
</tr>
<tr>
<td>CAF/CEF vs 4AC</td>
<td>0.78 (0.06)   0.0004</td>
</tr>
<tr>
<td>Anthra then T vs shorter anthra</td>
<td>0.86 (0.04)   0.0005</td>
</tr>
<tr>
<td>Anthra + taxane vs expanded anthracycline alone</td>
<td>0.94 (0.06)  0.33</td>
</tr>
</tbody>
</table>

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### ER+ Anthra/CMF plus ET vs ET Control

**Age < 55**

- **1853 women**
- 10-y gain 7.5% (vs 2.9) Logrank 2p = 0.00004

**Age 55-69**

- **2894 women**
- 10-y gain 8.2% (vs 2.9) Logrank 2p = 0.00001
Anthracyclines vs No Chemotherapy by Subsets of ER+

<table>
<thead>
<tr>
<th>Category</th>
<th>Anthracycline</th>
<th>No Anthracycline</th>
<th>Ratio of overall death rates</th>
<th>Anthracycline</th>
<th>No Anthracycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+, chemo-end. vs end only</td>
<td>0.64</td>
<td>0.70</td>
<td>0.95</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>Extensive disease</td>
<td>0.42</td>
<td>0.40</td>
<td>1.05</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>ER+ 65-80</td>
<td>0.42</td>
<td>0.40</td>
<td>1.05</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>ER+, p53 mutated</td>
<td>0.42</td>
<td>0.40</td>
<td>1.05</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>ER+, grade 1</td>
<td>0.42</td>
<td>0.40</td>
<td>1.05</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>ER, p100+</td>
<td>0.42</td>
<td>0.40</td>
<td>1.05</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>ER+, node positive</td>
<td>0.42</td>
<td>0.40</td>
<td>1.05</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>ER, 10-50 fm/mg</td>
<td>0.42</td>
<td>0.40</td>
<td>1.05</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>ER, 50-99 fm/mg</td>
<td>0.42</td>
<td>0.40</td>
<td>1.05</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>ER, 100+ fm/mg</td>
<td>0.42</td>
<td>0.40</td>
<td>1.05</td>
<td>0.40</td>
<td>0.40</td>
</tr>
</tbody>
</table>

What We Learn from the New EBCTCG 2011 Chemotherapy Overview in ER+ Disease

- Major benefit overall to anthracyclines and taxanes, reducing breast cancer mortality by about 1/3 (the same as in ER-poor disease)
- No apparent heterogeneity by age, grade, T size, nodes, presence of tamoxifen - when factors generally considered one at a time
- Even in strongly ER+ disease, chemotherapy impacted outcome, though not to the same extent as in less strongly ER+ disease in the largest trial S8814 which had heterogeneity

SWOG 8814 CAF-Tam vs Tamoxifen Recurrences Only

ER 10-99 fm/mg ER 100+

Interaction p = 0.04

Interaction p = 0.04
“What worries me (not just in breast cancer, but in many other diseases) is false-negative subgroup analyses of results that, overall, are highly significant; patients can die from under-use as well as from over-use of toxic treatments”


BUT… for ER+, There are Caveats…
The Overview Cannot Do Everything!

- Biologic heterogeneity is real, not fully explored
- Optimal endocrine therapy not uniformly given
- Interaction of tamoxifen timing with other factors
- Selection for more chemosensitive disease within recent trials - earlier trials enriched with indolent (luminal A) ER+ disease (controls of ET alone or no treatment)
- Importance of menopause status, not age; impact of amenorrhea
- ER level alone, or any other factor considered one at a time, may not be sufficient to define who can avoid, as well as who should definitely have CT
- HER2 status not available for most trials until recently

K Albain, SABCS 2011 Webcast 12/6

Theoretical Spectrum of Sensitivity to Adjuvant Systemic Therapy by Intrinsic Subtypes

Hayes DF. J Clin Oncol 2012 (editorial)
## St. Gallen 2011: “Shorthand” Determination of Breast Cancer Subtypes

<table>
<thead>
<tr>
<th>Intrinsic Subtype</th>
<th>Surrogate Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>ER and/or PgR(+) or HER2(-) Ki-67 low (&lt;14%)*</td>
</tr>
<tr>
<td>Luminal B1</td>
<td>ER and/or PgR(+) or HER2(-) Ki-67 high</td>
</tr>
<tr>
<td>Luminal B2</td>
<td>ER and/or PgR(+) or HER2(+) Any Ki-67</td>
</tr>
<tr>
<td>HER2 over-expression</td>
<td>ER and PgR absent, HER2(+)</td>
</tr>
<tr>
<td>Basal-like</td>
<td>Triple negative ductal (not medullary, adenoid cystic)</td>
</tr>
</tbody>
</table>

* Using PAM50 cutoff from Cheang et al. JNCI 2009

<table>
<thead>
<tr>
<th>'Subtype'</th>
<th>Type of therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Luminal A'</td>
<td>Endocrine therapy alone</td>
<td>Few require cytotoxins (e.g. high nodal status).</td>
</tr>
<tr>
<td>'Luminal B (HER2 negative)'</td>
<td>Cytotoxics + endocrine therapy</td>
<td>Inclusion and type of cytotoxics may depend on level of endocrine expression, perceived risk and patient preference.</td>
</tr>
<tr>
<td>'Luminal B (HER2 positive)'</td>
<td>Cytotoxics + anti-HER2</td>
<td>No data are available to support the omission of cytotoxics in this group.</td>
</tr>
<tr>
<td>'HER2 positive (non luminal)'</td>
<td>Cytotoxics + anti-HER2</td>
<td>Patients at very low risk may be observed without treatment.</td>
</tr>
<tr>
<td>'Triple negative (ductal)'</td>
<td>Cytotoxics</td>
<td>Medullary and apocrine carcinomas may not require any adjuvant cytotoxics if node negative.</td>
</tr>
</tbody>
</table>

### The Role of Multigene Assays in Addressing the Controversy

- **Annals Oncol 2011**
Lot of Help for Prognosis, but Limited Data for Prediction of Chemotherapy Benefit ER+

<table>
<thead>
<tr>
<th>Factor or Assay</th>
<th>Validated for Prognosis</th>
<th>Validated for <em>prediction</em> in trials with ET alone control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER level</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Estrogen-regulated gene signature</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Proliferation (Ki67)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HER2</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Grade/GG</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>PAM50/Intrinsic subtypes</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>IHC4 score</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>IHC panel***</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>21 gene</td>
<td>Yes</td>
<td>Yes No*, N+*</td>
</tr>
<tr>
<td>70 gene</td>
<td>Yes</td>
<td>N/A**</td>
</tr>
</tbody>
</table>

*   validated in a prospectively planned retrospective study
**  but, supportive data exists for predictive utility in population-based nonrandomized or neoadjuvant studies
*** including Ki67 index, HER-2, ER, PR

K Altman, SABCS 2011 Webcast 126

DDFS Low, High Risk: ET versus ET/CT (N0-3+)

Bender, et al. PASCO 2009

(... from a non-randomized data base)
Evaluate Clinical-Pathological Risk and 70-Gene Signature Risk

Clinical-pathological and 70-gene both HIGH risk

55%

Clinical-pathological and 70-gene both LOW risk

10%

Discordant cases Clin-Path HIGH 70-gene LOW

35%

Clin-Path LOW 70-gene HIGH

N=3300

EORTC-BIG MINDACT TRIAL

6,600 Women with N0-3+ Completed Accrual 7/2011

70-gene HIGH

Use Clin-Path risk to decide Chemo or not

Use 70-gene risk to decide Chemo or not

Chemotherapy

Potential CT sparing in 20-28% pts

Endocrine therapy

21 Gene Recurrence Score Assay: Strongly Predictive in NSABP B-20 (ER+ N0)

Tam + Chemo

0 1 2 3 4 5

Recurrence Score

0.0 0.1 0.2

Distant Recurrence at 10 Years

Benefit from CMF

21 Gene RS Assay

Pre-REGISTER

n = 7047

REGISTER

Specimen Banking

Secondary Study Group 1

RS < 11

~29% of Population

Primary Study Group

RS 11-25

~44% of Population

Secondary Study Group 2

RS > 25

~27% of Population

ARM A

Hormonal Therapy Alone

ARM B

Hormonal Therapy

ARM C

Chemotherapy Plus Hormonal Therapy

ARM D

Chemotherapy Plus Hormonal Therapy

results expected in 2014

ARM B

n = 4390

ARM A

~29% of Population

ARM C

~44% of Population

ARM D

~27% of Population

Pre-REGISTER

Pre-REGISTER

Pre-REGISTER
**S8814 CAFT vs T ER+ N+ Postmenopausal**

No benefit to CAFT over time if low RS
Strong benefit if high RS

**Disease-Free Survival by Treatment**

**Low risk (RS < 12)**

- Tamoxifen (n=55, 15 events)
- CAF-T (n=91, 26 events)

Stratified log-rank p = 0.97 at 10 years

**High risk (RS ≥ 31)**

- Tamoxifen (n=46, 22 events)
- CAF-T (n=57, 20 events)

Stratified log-rank test p = 0.56 at 10 years

**Intermediate risk (RS 18-30)**

- Tamoxifen (n=47, 26 events)
- CAF-T (n=71, 28 events)

Stratified log-rank test p = 0.033 at 10 years

- **Interaction p = 0.021**

Albain, et al. Lancet Oncology 2010

**Breast Cancer Specific Survival by RS**

- **Interaction p = 0.021**

Albain, et al. Lancet Oncology 2010

**DFS survival hazard ratios (adjusted by number of positive nodes) for chemotherapy benefit by linear RS over time:**

**Modelled HR Estimates**

<table>
<thead>
<tr>
<th></th>
<th>All Years</th>
<th>First 5 years</th>
<th>After 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td><strong>Nodes (4+)</strong></td>
<td>2.44 (1.75-3.42)</td>
<td>2.49 (1.58-3.92)</td>
<td>2.37 (1.44-3.91)</td>
</tr>
<tr>
<td>Chemotherapy at RS=0</td>
<td>1.12 (0.61-2.06)</td>
<td>1.58 (0.66-3.76)</td>
<td>0.78 (0.34-1.83)</td>
</tr>
<tr>
<td>RS/50 (50 point difference)</td>
<td>2.71 (1.37-5.36)</td>
<td>5.77 (2.42-13.79)</td>
<td>0.92 (0.30-2.83)</td>
</tr>
<tr>
<td>Chemo*RS/50</td>
<td>0.43 (0.18-1.01)</td>
<td>0.30 (0.10-0.89)</td>
<td>0.66 (0.16-2.82)</td>
</tr>
<tr>
<td>Interaction p-value</td>
<td>0.053 (-)</td>
<td>0.029 (-)</td>
<td>0.58 (-)</td>
</tr>
</tbody>
</table>

Nevertheless... the cumulative benefit of CAFT persists up to 10 years

Albain, et al. Lancet Oncology 2010
S1007 RxPONDER Schema

Node-positive (1-3 nodes) HR-positive and HER2-negative breast cancer

Patients consent to study, representation RS testing, discussion of potential trial, tumor tissue submission and linkage to cancer registry data

RS already Available

Physician and patients discuss randomization knowing the RS

Patients consent to study, representation RS testing, discussion of potential trial, tumor tissue submission and linkage to cancer registry data

RS already Available

Physician and patients discuss randomization knowing the RS

S1007 RxPONDER Accrual 8/24/12

• Registration 1 (goal 9400)
  1290
• Registration 2 (goal 4000)
  288 Chemotherapy + endocrine therapy
  292 Endocrine therapy alone

Variable Pathologic Complete Remission Rates with Chemotherapy before Surgery by Intrinsic Subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percent pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>0</td>
</tr>
<tr>
<td>Luminal B</td>
<td>19%</td>
</tr>
<tr>
<td>HER2</td>
<td>39%</td>
</tr>
<tr>
<td>Basal-like</td>
<td>73%</td>
</tr>
<tr>
<td>Claudin low</td>
<td>39%</td>
</tr>
</tbody>
</table>

C. Perou, 9th International Congress on the Future of Breast Cancer, 2010
No pCRs if Good 70-Gene Signature

Pathologic CRs not Observed in Lower 21 Gene Recurrence Scores in Neoadjuvant Study (incl. N+, taxanes)

NSABP Planned Phase III “Neoadjuvant TAILORx” for Level 1 Evidence
Neoadjuvant Meta-analysis: Canonical Pathways Associated with pCR Differ by Subtype

Future Directions and the Patient in Our Office Today

SWOG Phase III adjuvant endocrine therapy + everolimus/placebo in high-risk, node-positive, hormone receptor-positive, HER2-neu normal breast cancer

Current RxPONDER trial S1007

New adjuvant trial
It’s time to give prospective (clinical trial) attention to “biologically indolent but higher clinical risk” luminal breast cancer

- However you want to define it... High ER level/low prolif, low RS, good risk 70 gene, luminal A, etc
- These patients should probably not be entered within trials testing cytotoxic therapy, or else agents with novel mechanisms of action need to be added to standard therapy
- New trial designs needed for them, especially with higher risk
- Pay attention to the lesson of S8814: overall positive benefit to anthracyclines added to tamoxifen, but a sizable subgroup in the trial did not appear to benefit
SWOG S8814 Next Phase

- Whole transcriptome expression analyses on stored RNA using next generation sequencing techniques
- Identify novel genes not identified in the research leading up to the 21 gene RS assay
- Prognosis in patients treated with tamoxifen alone and CAF followed by tamoxifen
- Prediction of CAF benefit
- Identify candidate genes and pathways that can be tested further in other trials such as S1007 (RxPONDER)

Highlights of early TCGA findings using 500 tumors

1. Basal-like tumors form a distinct subtype by gene expression, DNA methylation, protein patterns, and by microRNA expression profiling (75% of triple-negative breast cancers are of the Basal-like subtype)

2. The 10 most frequently mutated genes in ER+/HER2- tumors occur within a diversity of pathways and includes PIK3CA(48%), TP53(20%), MAP3K1(18%), GATA3(14%), CDH1(9%), MLL3(8%), MAP2K4(6%), PTEN(5%), RUNX1(4%) and AKT1(3%).

3. DNA methylation analysis identifies Basal-like tumors as showing a hypo-methylation phenotype and a subset of luminal B cases as having frequent promoter CpG island hyper-methylation phenotype.

4. Integrated pathway analyses identifies distinct mechanisms of PIK3CA pathway activation by subtype

5. Complex and numerous DNA copy number changes are associated with the Basal-like, HER2-enriched, and LumB subtypes, and are independent predictors of poor outcomes

6. HER2+ tumors are molecularly heterogeneous and tumors that are clinical HER2+ AND HER2-enriched subtype appear to show activation of HER2 and HER1 signaling

Chemotherapy for Early Stage ER+ BC* - Mixed Messages, Both True!

<table>
<thead>
<tr>
<th>Message</th>
<th>Summary</th>
</tr>
</thead>
</table>
| Yes     | EBCTCG 2011  
 | Anthra, taxane major and durable benefits overall and for major subsets |
| No      | Biologic heterogeneity defined by multigene assays cannot be ignored  
 | Consistent evidence across studies  
 | New tactics needed to identify and treat the chemo-insensitive cohort |

*Excluding very small N0, or small HER2+ tumors
My View

• Need to put into practice now our new knowledge about tumor biology in ER+ disease, while not ignoring the real benefit of chemotherapy in many women with ER+ disease.
• Limitations in defining the chemo-resistant group by one-factor-at-a-time analyses – however you choose to do it with combination of factors, the result seems to be the same… there is a group that does not benefit regardless of risk.
• Results have been consistent and support the hypotheses being studied in the 3 large prospective trials
• In the meantime, we need to be vigilant to neither overtreat or undertreat with chemotherapy and multigene assays can provide additional guidance and should be offered to all women who would consider chemotherapy.

SUMMARY

• Modern adjuvant/neoadjuvant chemotherapy benefits patients with luminal breast cancer in general (2011 Oxford Overview)
• However, across all risk levels, biologic subtypes of ER+ disease differ widely in degree of chemotherapy sensitivity
• Avoidance of chemotherapy is justified in HER2 non-enriched subgroups that are highly endocrine responsive with low proliferation (variably defined by low 21 gene RS, luminal A, low risk 70 gene)
• High risk scenarios with this biologic profile require alternate strategies to increase cure rates

Thank You for Inviting Me!