Molecular Profiling/Prevention

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Agenda

• **Timing of Recurrence**
  - S1-6: Characterization of Late Metastases
  - S1-7: Molecular Tumor Characteristics Influence Adjuvant Endocrine Treatment Outcome
  - S1-8: Molecular Signaling Distinguishes Early ER Positive Breast Cancer Recurrences Despite Adjuvant Tamoxifen

• **Risk Assessment Tools:**
  - S4-3: Comparison of Risk Assessment Tools
  - S4-5: Comparison of PAM50 Risk of Recurrence Score with Oncotype DX and IHC4: A TransATAC St
  - S4-6: Quantitative Multigene RT-PCR Assay for DCIS

• **Prevention/ QOL with Endocrine Therapy**
  - P4-11-06 Uptake of SERMS/Other Prevention Strategies among High-Risk Women Seen in a Breast Center
  - S6-1: QOL in NCIC CTG MAP.3 Trial
  - S6-2: Patient Reported Indicators of Early Treatment Discontinuation with AIs
S1-6: Characterization of Late Metastases

• Current clinical/molecular tools don’t predict which ER+, HER2-negative patients are likely to recur after 5 years

• Samples collected from retrospective series of patients with frozen material available from 2 institutions (one for identifying the signature and one for validation)

• Tumors classified into 4 groups:
  – No relapse at 10 yrs (M0)
  – DM before 3 years (M0-3)
  – DM between 3 and 7 years (M3-7)
  – DM after 7 years (M7+)

Saghatrchan M, et al. SABCS 2011
S1-6: Characterization of Late Metastases

• Assessed Mammaprint, wound-healing signature and intrinsic subtypes: none distinguished between M0 and M7+
• Then considered M0 and M7+ low-risk Mammaprint tumors
• A 73-gene signature classified M7+ patients with 75% sensitivity and 66% of specificity
• M7+ associated with significant activation of inflammatory response and angiogenesis

Saghatcian M, et al. SABCS 2011
S1-7: Molecular Tumor Characteristics Influence Adjuvant Endocrine Treatment Outcome

- Combined marker of proliferation and estrogen-related genes to predict early vs late recurrences
- Evaluated 606 pts treated with 5 yrs of tamoxifen from 3 public datasets of Affymetrix HGU133A gene expression profiles
  - Proliferation score – average of 12 mitotic kinases
  - 4 gene Estrogen-related Score adopted from the ER group of Oncotype DX

Bianchini G, et al. SABCS 2011
In the upfront group (recurrences in first 2.5 years) almost all were in High MKS/Low ERS group
  - These tumors likely intrinsically resistant to Tamoxifen and possibly to AIs

High risk of recurrences after 5 years of Tamoxifen in the High MKS/High ERS group and in low MKS/low ERS group
  - ? Role for extended endocrine therapy in these groups

Bianchini G, et al. SABCS 2011
S1-8: Molecular Signaling Distinguishes Early ER-positive Recurrences

- 138 ER+ breast cancers; 11 had high quality biopsies and clinical data
- Looked at 91-gene classifier to try to distinguish between early (≤3 years) and late recurrences (>10 years)

Liu MC, et al. SABCS 2011
S1-8: Molecular Signaling Distinguishes Early ER-positive Recurrences

• Majority of the genes in the classifier relate to apoptosis and proliferation
• Found robust molecular differences between the tumors that recurred early rather than late
  – Early: increased expression of CALM1, CALM2, CALM3, SRC, CDK1, MAPK1
  – Late: increased expression of ESR1, ESR2, EGFR, BCL2, AR

Liu MC, et al. SABCS 2011
S4-3 Prospective Comparison of Risk Assessment Tools in Early Breast Cancer

• Assessed tools within the phase III Women’s Healthcare Study Group Plan B trial in which patients with N0 or N1 disease received chemotherapy based on RS (>11)
• Evaluated RS, Ki-67, central grade, uPA/PAI-1
• Results:
  – High compliance with RS results
  – Good concordance. High RS usually implies high risk by central G3, high Ki-67, high uPA/PAI-1
  – Substantial heterogeneity within low and intermediate RS groups

Gluz O, et al. SABCS 2011
S4-5: Comparison of PAM50 Risk of Recurrence Score with Oncotype DX and IHC4: A TransATAC Study

• PAM50: 50-gene test developed to identify the intrinsic breast cancer subtypes (luminal A/B, HER2-like, basal-like). Generates a Risk of Recurrence (ROR) Score
• TransATAC trial: 1782 specimens with centrally confirmed HR+
• Findings: PAM50 ROR score provided more prognostic information than Oncotype DX RS and resulted in fewer patients being assigned to an intermediate risk group.

Dowsett M, et al. SABCS 2011
S4-6: A Quantitative Multigene RT-PCR Assay for Predicting Recurrence Risk After Excision Alone for DCIS: ECOG 5194

- ECOG 5194:
  - Prospective multicenter study of 670 women with DCIS:
    - Low/intermediate grade. ≤ 2.5 cm
    - High grade, ≤ 1 cm
  - Treated with surgical excision with minimum of 3mm negative mg
  - No XRT
  - Tamoxifen an option beginning in 5/2000
  - Median age = 61; 76% postmenopausal; median tumor size = 7mm; 97% ER+; 29% used tamoxifen

Solin LJ, et al, SABCS 2011
S4-6: A Quantitative Multigene RT-PCR Assay for Predicting Recurrence Risk After Excision Alone for DCIS: ECOG 5194

• DCIS score - Evaluated 2 ways:
  – Continuous variable
  – 3 prespecified risks groups:
    • Low <39
    • Intermediate 39-54
    • High ≥ 55

• DCIS score validated as an independent predictor of an ipsilateral breast event (IBE):
  – HR = 2.34; p=0.02

Solin LJ, et al, SABCS 2011
S4-6: A Quantitative Multigene RT-PCR Assay for Predicting Recurrence Risk After Excision Alone for DCIS: ECOG 5194

<table>
<thead>
<tr>
<th>DCIS Score Risk Group</th>
<th>No (%)</th>
<th>Any IBE</th>
<th>Invasive IBE</th>
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</thead>
<tbody>
<tr>
<td>Low (&lt;39)</td>
<td>246 (75)</td>
<td>12.0%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Intermediate (39-54)</td>
<td>45 (14)</td>
<td>24.5%</td>
<td>8.9%</td>
</tr>
<tr>
<td>High (≥ 55)</td>
<td>36 (11)</td>
<td>27.3%</td>
<td>19.1%</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>.02</td>
<td>.01</td>
</tr>
</tbody>
</table>

Small Sub-groups (with wide confidence intervals)
- Pre-menopausal women (79)
- >1cm (67)
- Tamoxifen-treated (97)

Solin LJ, et al, SABCS 2011
P4-11-06 Uptake of SERMS/Other Prevention Strategies among High-Risk Women Seen in a Breast Center

• <5% of women offered tamoxifen for prevention accept it
• Objective: Assess demographic/clinical factors that influence SERM acceptance among high risk women
• Cross sectional survey of consecutive women seen at Columbia University Breast Center
• Eligibility for SERM use:
  – Gail score of ≥ 1.67%
  – LCIS
  – BRCA carrier
  – HR+ DCIS

P4-11-06 Uptake of SERMS/Other Prevention Strategies among High-Risk Women Seen in a Breast Center

• Results:
  – SERM use highest among DCIS patients (70%) compared to LCIS (30%) and high Gail risk (29%)
  – Referral to medical oncology also a strong predictor of SERM usage

MAP.3: Exemestane as Prevention

NCIC CTG MAP.3 Prevention Trial

Double-Blind

Postmenopausal women at increased risk for breast cancer

Randomize

Exemestane 25 mg/day x 5 years
n = 4560
February 2004 – March 2010

Placebo 1 pill/day x 5 years

Stratification
Aspirin use
Gail score (<2.0 vs. ≥ 2.0)

MAP.3: Exemestane as Prevention

Proportion of women with worsened dimensions of HRQOL (SF-36) at least once while on treatment

Menopause-specific and health-related QOL among Post-menopausal Women on MAP.3

- Menopause-specific and health-related qualities of life assessed using the MENQOL (4 scales: physical, vasomotor, psychosocial, sexual)
- Median follow-up = 35 months

Maunsell E, et al. SABCS 2011
S6-1: Menopause Specific and Health-Related QOL among Post-menopausal Women on MAP.3

- No clinically important worsening in symptoms over time based on mean change scores
- > bothersome vasomotor symptoms with exemestane
- Proportion of women on exemestane discontinuing early was greatest at 6 months

Maunsell E, et al. SABCS 2011
S6-2 Patient-Reported Predictors of Early Treatment Discontinuation with Exemestane or Anastrazole (MA27)

• MA27 randomized 686 postmenopausal women with ER+ breast cancer to anastrazole vs exemestane

• Functional Assessment of Cancer Therapy-Endocrine Symptoms (FACT-ES)
  – 46 items
    • 27 physical, functional, social emotional well being
    • 19 breast cancer-specific concerns and endocrine sx

Wagner LI, et al. SABCS 2011
S6-2 Patient-Reported Predictors of Early Treatment Discontinuation with Exemestane or Anastrazole (MA27)

- Treatment-related symptoms same between A and E
- Treatment-related symptoms negative affect QOL
- Patients bothered by treatment SEs at baseline and those who have emergence of joint pains in first 3 months predicts early discontinuation.

Wagner LI, et al. SABCS 2011
Conclusions

• Increased attention on “late relapsers”
• Practice changing? Oncotype for DCIS
  – Limitations:
    • No predictive data
    • Limited numbers of larger tumors, premenopausal women, women taking tamoxifen