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+)

Saghatchian 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

Saghatchian 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

S1-7: Molecular Tumor Characteristics Influence Adjuvant Endocrine Treatment Outcome

- 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. $\leq$ 2.5 cm
    - High grade, $\leq$ 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 $\geq$ 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

DCIS Score Risk Group	No (%)	Any IBE	Invasive IBE
Low (<39)	246 (75)	12.0%	5.1%
Intermediate (39-54)	45 (14)	24.5%	8.9%
High (≥ 55)	36 (11)	27.3%	19.1%
P-value		.02	.01

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 $\geq$ 1.67%
  - LCIS
  - BRCA carrier
  - HR+ DCIS

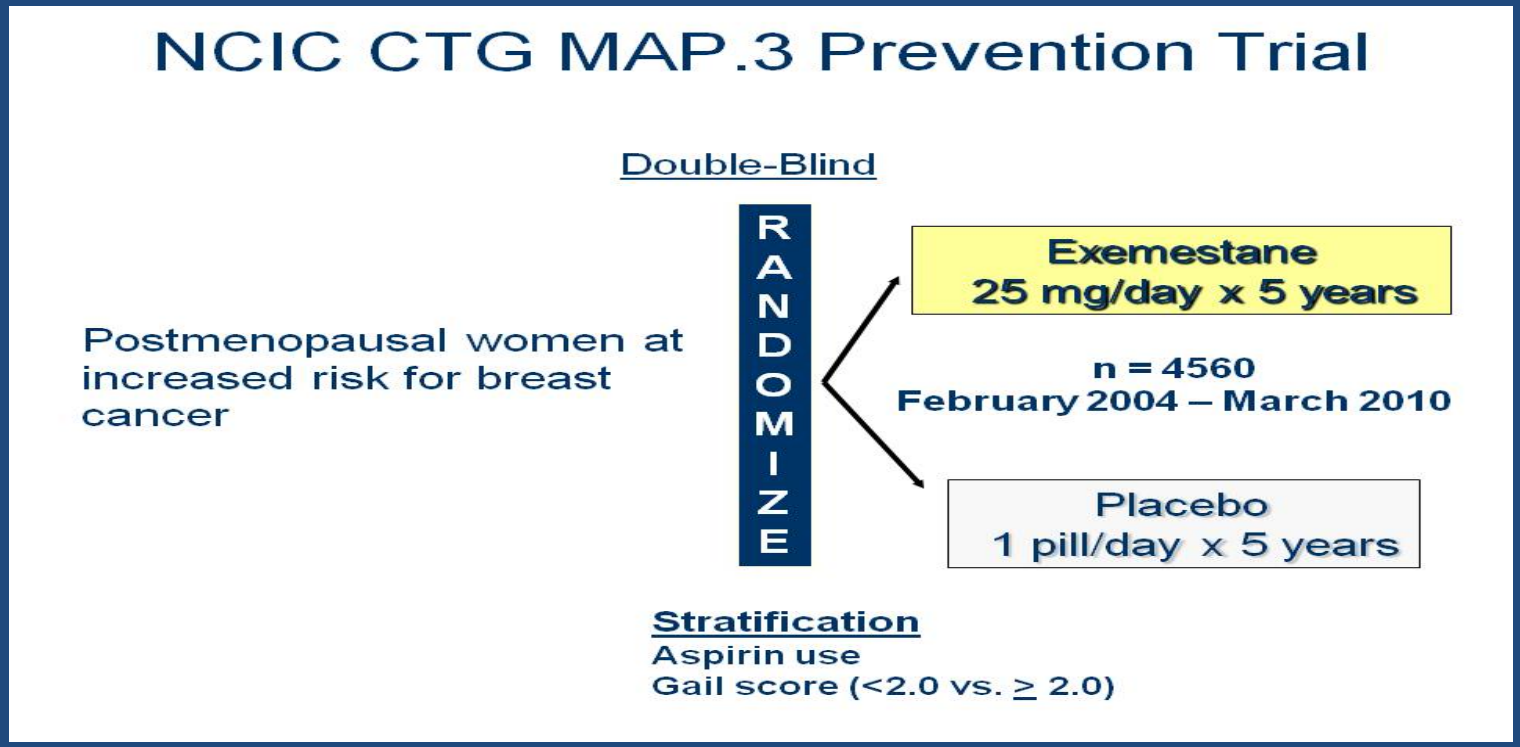
Reimers LL, et al, SABCS 2011.

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

Reimers LL, et al, SABCS 2011.

MAP.3: Exemestane as Prevention



Goss, et al. Abstract #1007, ASCO 2011

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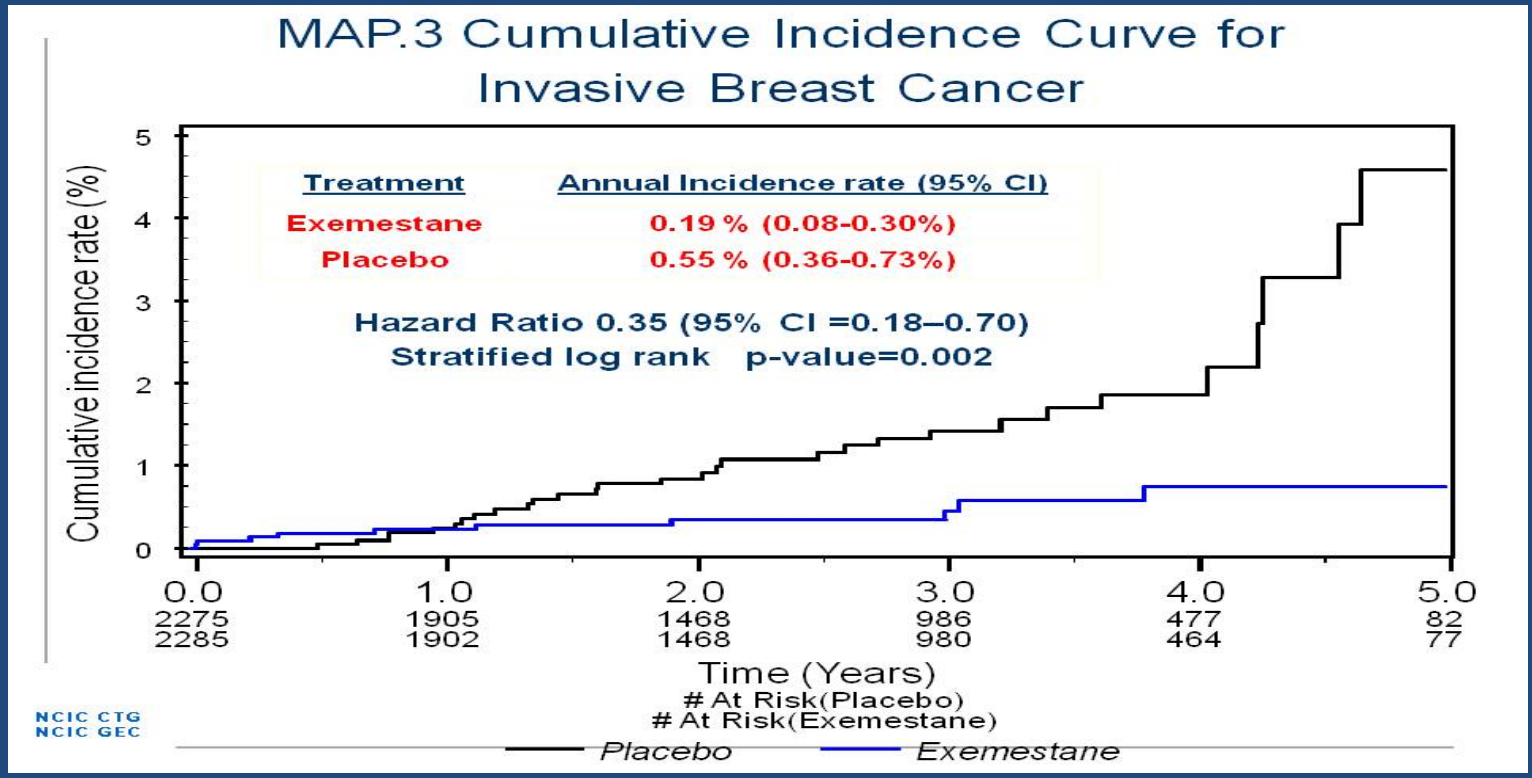

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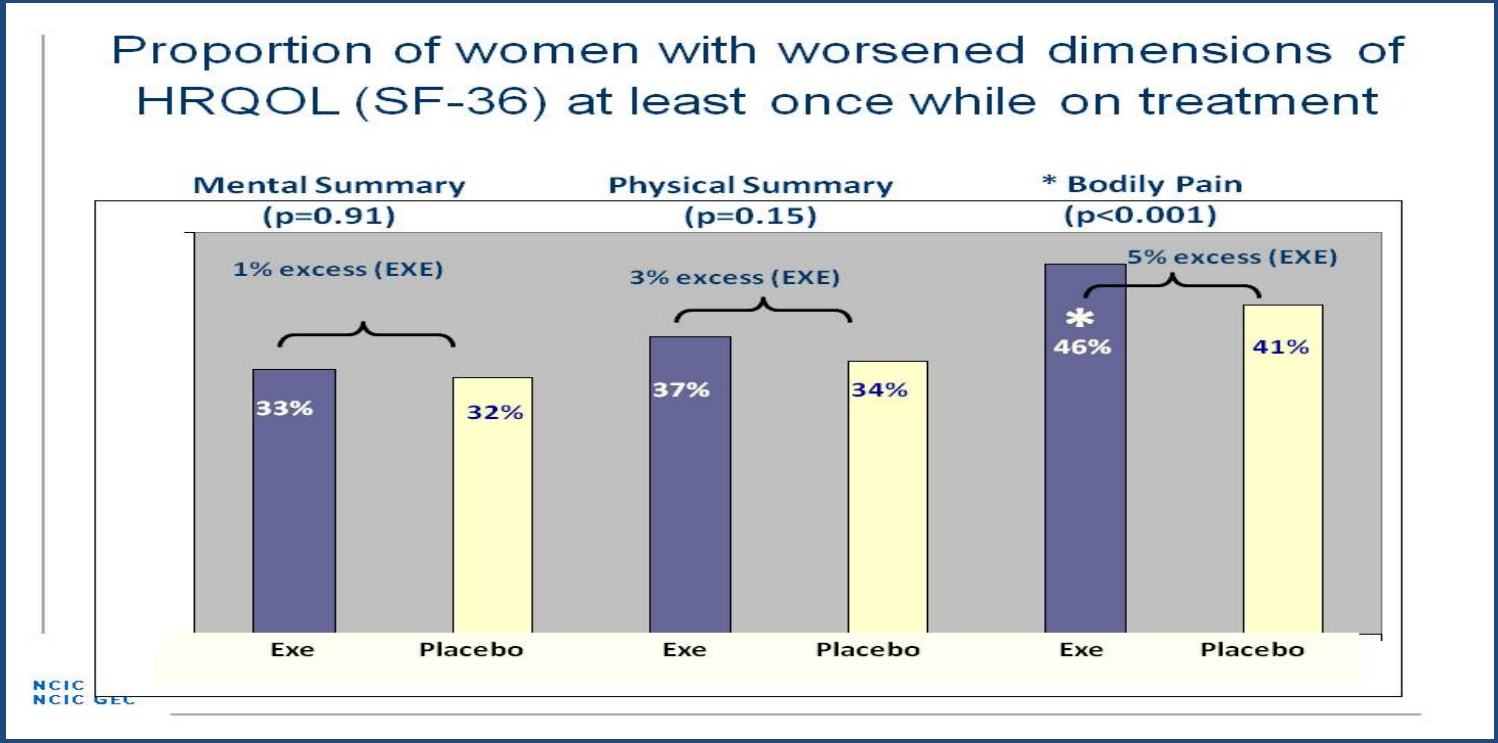

Goss, et al. Abstract #1007, ASCO 2011

S6-1: 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