Prediction of late distant recurrence after 5 years of endocrine treatment: A combined analysis of 2485 patients from the ABCSG-8 and transATAC studies using the PAM50 risk of recurrence (ROR) score

Dr. Sestak: Nothing to disclose.
Dr. Cuzick: Consulting Fees, Consultant to AstraZeneca; Other Financial, Grants from AstraZeneca.
Dr. Dowsett: Consulting Fees, Nanostring, Genoptix; Other Financial, Grants from AstraZeneca.
Dr. Filipits: Nothing to disclose.
Dr. Dubsky: Nothing to disclose.
Dr. Cowens: Salary, Employee of Nanostring; Ownership Interest, Stockholder of Nanostring.
Dr. Ferree: Salary, Employee of Nanostring; Patent Holder, Inventor on IP covering the NanoString technology; Ownership Interest, Stockholder of Nanostring.
Dr. Schaper: Consulting Fees, Consultant for Nanostring.
Dr. Fesl: Nothing to disclose.
Dr. Gnant: Consulting Fees, Amgen, Pfizer, Novartis, GlaxoSmithKline, Bayer, Sandoz, AstraZeneca, Genomic Health, Roche, Nanostring.
Introduction

- ER+ breast cancer high risk of recurrence for at least 10 years - even after 5 years of AI treatment
- Biomarkers are needed to predict risk of late recurrence
- Few studies have addressed prognostic value of molecular scores for late recurrence:
  - transATAC
    - ROR score
      Sestak et al., JNCI, 2013
  - ABCSG6/8
    - ROR score
      Gnant et al., IMPAKT, 2013
    - EndoPredict
      Dubsky et al., British Journal of Cancer, 2013

Background

- PAM50 (Prosigna™)
  - 50-gene test developed to identify the intrinsic breast cancer subtypes
    (luminal A/B, HER2-enriched, Basal-like)
    (Parker et al. JCO, 2009, 27, 1160;
     Nielsen et al. CCR, 2010, 16, 5222)

  ➔ ROR score using 46 gene signature including tumour size
     (excluded BIRC5, MYBL2, GRB7, CCNB1)

- Clinical Treatment Score (CTS)
  - Nodal status, grade, tumour size, age, treatment
  - Developed on transATAC data set
Objectives

• Primary:
  - Assess ability of ROR score to predict late distant recurrence in patients recurrence free after 5 years of endocrine treatment

• Secondary:
  - Stratification into three risk groups
    (Risk of 10-year DR: Low<10%, Intermediate 10-20%, high >20%)
  - Subgroup analyses
  - Luminal A vs Luminal B

Population evaluated

- ATAC
  - N=9366
  - Excluded:
    - Combination arm
    - Chemotherapy
    - No blocks received
    - Insufficient tumour material
  - transATAC
    - N=1125
    - Excluded:
      - Insufficient residual RNA
      - Failed PAM50 QC
  - PAM50
    - N=1007
    - Excluded:
      - Not recurrence free at 5 years (N=145)
    - N=862

- ABCSG-8
  - N=3714
  - Excluded:
    - No tissue specimen
    - No consent
  - Tissue database
    - N=1620
    - Excluded:
      - Insufficient residual RNA
      - Failed PAM50 QC
    - PAM50
      - N=1478
      - Excluded:
        - Not recurrence free at 5 years (N=203)
    - N=1275

Combined dataset
N=2137

*RNA extracted by QIAGEN
## Patients characteristics

<table>
<thead>
<tr>
<th></th>
<th>transATAC (N=862)</th>
<th>ABCSG-8 (N=1275)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, years (IQR)</td>
<td>10.0 (9.1-10.1)</td>
<td>10.3 (8.8-12.4)</td>
</tr>
<tr>
<td>Age &gt; 65 years</td>
<td>41.5%</td>
<td>39.3%</td>
</tr>
<tr>
<td>Node positive</td>
<td>24.9%</td>
<td>26.8%</td>
</tr>
<tr>
<td>Tumour size, mm (mean, SD)</td>
<td>19.0 (10.1)</td>
<td>16.7 (8.3)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>195 (22.6%)</td>
<td>242 (19.0%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>519 (60.2%)</td>
<td>1033 (81.0%)</td>
</tr>
<tr>
<td>Poor</td>
<td>148 (17.2%)</td>
<td>-</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>80 (9.3%)</td>
<td>68 (5.3%)</td>
</tr>
</tbody>
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## Distant recurrence – post 5 years

### HR (95% CI) for IQR

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTS</td>
<td>1.96 (1.73-2.21)</td>
<td>1.80 (1.57-2.06)</td>
</tr>
<tr>
<td>ROR score</td>
<td>2.69 (2.12-3.43)</td>
<td>2.07 (1.63-2.64)</td>
</tr>
</tbody>
</table>

*When added to other score

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**ROR score - multivariate analysis**

All patients (N=2137)  
HR=2.07 (1.63-2.64)

Node negative (N=1580)  
HR=2.11 (1.48-3.00)

Node positive (N=557)  
HR=2.15 (1.52-3.03)

HER2-negative (N=1974)  
HR=2.19 (1.69-2.84)

Node negative/HER2-negative (N=1455)  
HR=2.41 (1.65-3.50)

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**Luminal A vs Luminal B**

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Luminal A (N=1530 (71.6%))</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Luminal B (N=542 (25.4%))</td>
<td>2.89 (2.07 - 4.02)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
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Summary

• CTS strongest score for late distant recurrence
  — Driven by nodal status and tumour size

• ROR score added significant prognostic information for all subgroups
  — Luminal B subtypes 3 times higher risk of late distant recurrence than luminal A

• Results indicate that ROR score may stratify patients according to risk of late recurrence
  — May help identify those women with the potential to benefit from extended adjuvant endocrine therapy

Acknowledgements

ATAC/ABCSPG-8 participants

ATAC/ABCSPG-8 pathologists/trialists