EndoPredict (EPclin) score for estimating residual distant recurrence (DR) risk in ER+/HER2-breast cancer (br ca) patients treated with 5 years adjuvant endocrine therapy alone: Validation and comparison with the OncotypeDX recurrence score (RS)

Dr. Dowsett has disclosed that he consults for Genoptix, Radius, GTx, and Roche. Dr. Dowsett has also disclosed that he is a speaker for AstraZeneca. Dr. Dowsett has disclosed that his department receives contracts from AstraZeneca, Pfizer, and Puma. Dr. Dowsett has disclosed that he has received iCR Rewards for inventors Scheme.
Aims

1. To assess the prognostic value of the EP (EndoPredict) and EPclin scores in patients with ER+ve HER2-ve primary breast cancer in TransATAC

2. To compare the prognostic value of the scores with that of the OncotypeDx RS

Background

Identify molecular signatures to select patients who could be spared chemotherapy*

*Dowsett et al, Breast Cancer Res. 2007;9:R81.
International Web-based consultation on priorities for translational breast cancer research.

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Background

Identify molecular signatures to select patients who could be spared chemotherapy*

Estimate the residual risk of distant recurrence in ER+ patients after 5 years of treatment with endocrine therapy alone

• OncotypeDx 21-gene: Recurrence Score (RS) (Paik et al, NEJM 2004)

*Dowsett et al, Breast Cancer Res. 2007;9:R81.
International Web-based consultation on priorities for translational breast cancer research.
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San Antonio Breast Cancer Symposium – December 9-12, 2015
Background

Identify molecular signatures to select patients who could be spared chemotherapy*

Estimate the residual risk of distant recurrence in ER+ patients after 5 years of treatment with endocrine therapy alone

- OncotypeDx 21-gene: Recurrence Score (RS) (Paik et al, NEJM 2004)
  TransATAC: 1.231 postmeno, ER+, 5yr tam or anastr, no chemo

- RSPC: RS, age, type of hormonal therapy, tumour size, grade for N-

- PAM50/ROR: Prosigna (genes + T, N±)

- HOXB13/IL17BR + MGI: Breast Cancer Index (BCI)

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**Background**

Identify molecular signatures to select patients who could be spared chemotherapy*

Estimate the residual risk of distant recurrence in ER+ patients after 5 years of treatment with endocrine therapy alone

- **OncotypeDx 21-gene: Recurrence Score (RS)** (Paik et al, NEJM 2004)
  TransATAC: 1,231 postmeno, ER+, 5yr tam or anastr, no chemo (Dowsett et al, J Clin Oncol 2010, 28:1829-1834).
  - RSPC: RS, age, type of hormonal therapy, tumour size, grade for N-
  - PAM50/ROR: Prosinga (genes + T, N±)
  - HOXB13/IL17BR + MGI: Breast Cancer Index (BCI)

  *Dowsett et al, Breast Cancer Res. 2007;9:R81.
  International Web-based consultation on profiles for translational breast cancer research.

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**Components of the EPclin and definition of risk categories**

| Member 1 | ERCC4 | RB1BP1 |
| Member 2 | MADH1 | LEST |
| Member 3 | AZGP1 | DOK1 |
| Member 4 | MGP | STC2 |

ER+, HER2-ve, 5-year tamoxifen

**EP Score**

- **Nodal status + tumour size**

**EPclin Score**

- Risk class: low vs. high

- **EPclin 3.33 = 10% 10-year DR**

Filips et al, Clin Cancer Res 2011, 17:6012

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Statistical Analysis Plan

**Stepwise Primary Objectives:**
- Does EPclin have significant prognostic information in TransATAC?
- Do EP and/or EPclin add significant information to RS?
- Does EP add significant information to Clinical Treatment Score (CTS)?

CTS = nodal status + tumour size + grade + age + endocrine treatment

(Cuzick et al. J Clin Oncol. 2011; 29:4273-8)

Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients ER-positive, HER2-negative</th>
<th>Analysis (N=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>64.7 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>680 (73.3%)</td>
<td></td>
</tr>
<tr>
<td>1-3 positive nodes</td>
<td>188 (21.5%)</td>
<td></td>
</tr>
<tr>
<td>4 or more positive nodes</td>
<td>50 (5.4%)</td>
<td></td>
</tr>
<tr>
<td>Tumour size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1cm</td>
<td>130 (14.0%)</td>
<td></td>
</tr>
<tr>
<td>1-2cm</td>
<td>499 (55.7%)</td>
<td></td>
</tr>
<tr>
<td>2-5cm</td>
<td>290 (31.3%)</td>
<td></td>
</tr>
<tr>
<td>&gt;5cm</td>
<td>19 (2.1%)</td>
<td></td>
</tr>
<tr>
<td>Grade (40 missing values)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>244 (26.3%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>497 (53.9%)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>147 (15.8%)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>649 (69.9%)</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>353 (39.1%)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

N-neg 680 59
N-pos 248 69

RNA extracted by GHI
57 sample cross validation
S3-01 ENDOpredict (EPclin) Score for Estimating Residual Distant Recurrence (DR) Risk in ER+/HER2- Breast Cancer (BR CA) Patients Treated with 5 Years Adjuvant Endocrine Therapy Alone: Validation and Comparison with the OncoType DX Recurrence Score (RS)

Speaker: Mitch Dowsett

Slide 13 / 32

Relationship between EPclin score and fitted 10-year risk of distant recurrence in TransATAC

Curve from univariate proportional hazards model

N=546 (59%)
N=382 (41%)

Slide 14 / 32

Comparison of prognostic information provided by EP, EPclin and RS in TransATAC: node negative

Based on 10-year risk of distant recurrence

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Comparison of prognostic information provided by EP, EPclin and RS in TransATAC: node negative

Based on 10-year risk of distant recurrence

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Comparison of prognostic information provided by EP, EPclin and RS in TransATAC: node negative

Comparison of prognostic information provided by EP, EPclin and RS in TransATAC: node positive
Comparison of prognostic information provided by EP, EPclin and RS in TransATAC: node positive

Based on 10-year risk of distant recurrence

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Comparison of prognostic information provided by EP, EPclin and RS in TransATAC: node positive

CTS trained in TransATAC

Based on 10-year risk of distant recurrence

Distant recurrence rate according to pre-specified risk stratification in TransATAC:
EP vs EPclin: all patients

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Distant recurrence rate according to pre-specified risk stratification in TransATAC:
EP vs EPclin: node positive

Slide 24 / 32

Distant recurrence rate according to pre-specified risk stratification in TransATAC:
EP vs EPclin: node negative
Risk stratification using prespecified cut-offs for 10-year risk of distant recurrence

**EPclin:**
- low risk <10%
- high risk ≥10%

**RS:**
- low risk <10%
- intermediate risk 10-20%
- high risk >20%

non-low risk ≥10%

calibrated for node negative

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Distant recurrence rate according to pre-specified risk stratification in TransATAC:
- **EP vs RS** and **EPclin vs RS** in Node negative
S3-01 ENOPREDICT (EPCLIN) SCORE FOR ESTIMATING RESIDUAL DISTANT RECURRENCE (DR) RISK IN ER+/HER2- BREAST CANCER (BR CA) PATIENTS TREATED WITH 5 YEARS ADJUVANT ENDOCRINE THERAPY ALONE: VALIDATION AND COMPARISON WITH THE ONCOTYPE DX RECURRENCE SCORE (RS)

Speaker: Mitch Dowsett

Slide 27 / 32

Distant recurrence rate according to tertiles of EP vs RS in TransATAC: Node negative

Slide 28 / 32

Distant recurrence rate according to tertiles of EPclin vs RS in TransATAC: Node negative
S3-01 ENDOPREDICT (EPCLIN) SCORE FOR ESTIMATING RESIDUAL DISTANT RECURRENCE (DR) RISK IN ER+/HER2- BREAST CANCER (BR CA) PATIENTS TREATED WITH 5 YEARS ADJUVANT ENDOCRINE THERAPY ALONE: VALIDATION AND COMPARISON WITH THE ONCOTYPE DX RECURRENCE SCORE (RS)

Speaker: Mitch Dowsett

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San Antonio Breast Cancer Symposium - December 8-12, 2015

Distant recurrence rate according to tertiles of EP vs RS in TransATAC: Node positive

Slide 30 / 32

San Antonio Breast Cancer Symposium - December 8-12, 2015

Distant recurrence rate according to tertiles of EPclin vs RS in TransATAC: Node positive
Conclusions

- EPclin identified a low risk group of patients who may be spared chemotherapy
- EPclin provided more accurate prognostic information than the RS - partly but not entirely due to the EPclin including tumour size and nodal status
- Differences between EPclin and RS were greatest in node positive patients
- The bottom tertile of EPclin in node negative patients identified a group with extremely good prognosis
- The data highlight the importance of the inclusion of clinicopathologic factors (including type of endocrine treatment) for estimates of residual risk of distant recurrence

Acknowledgements

TransATAC investigators and pathologists
LATTE SC
ATAC patients

AstraZeneca  RM/ICR NIHR BRC