S4-3. Prospective comparison of risk assessment tools in early breast cancer (recurrence score, uPA/PAI-1, central grade, and luminal subtypes): Final correlation analysis from the phase III WSG-Plan B trial

- Dr. Gluz has no relevant financial relationships to disclose.
- Dr. Kreipe has no relevant financial relationships to disclose.
- Dr. Degenhardt has no relevant financial relationships to disclose.
- Dr. Kates has no relevant financial relationships to disclose.
- Dr. Christgen has no relevant financial relationships to disclose.
- Dr. Liedtke has disclosed that she is on the speakers bureau with Sanofi Aventis.
- Dr. Shak disclosed that he is an employee of Genomic Health.
- Dr. Clemens has no relevant financial relationships to disclose.
S4-3. Prospective comparison of risk assessment tools in early breast cancer (recurrence score, uPA/PAI-1, central grade, and luminal subtypes): Final correlation analysis from the phase III WSG-Plan B trial

- Dr. Markmann has no relevant financial relationships to disclose.
- Dr. Uleer has no relevant financial relationships to disclose.
- Dr. Augustin has no relevant financial relationships to disclose.
- Dr. Thomssen has not relevant financial relationships to disclose.
- Dr. Nitz has disclosed that he receives grant/research support from Sanofi Aventis and Amgen.
- Dr. Harbeck has disclosed that she is on the speakers bureau with Sanofi Aventis and Amgen. She has also disclosed that she is a consultant for Sanofi Aventis and Amgen.
Prospective comparison of risk assessment tools in early breast cancer (Recurrence Score, uPA/PAI-1, central grade, and luminal subtypes): Final correlation analysis from the phase III WSG planB trial

Gluz O¹,², Kreipe HH³, Degenhardt T¹, Christgen M³, Kates R ¹, Liedtke C ¹,⁴, Shak S⁵, Clemens M ⁶, Markmann S⁷, Uleer C⁸, Augustin D⁹, Thomssen C¹⁰, Nitz U ¹,², and Harbeck N ¹,¹¹ on behalf of the planB investigators

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Background

- Adjuvant chemotherapy indication is mainly based on assessment of recurrence risk
- Overtreatment is frequent in low and intermediate risk groups in HR+ disease → may be reduced by optimizing prognostic tools

Candidate tools are

- Recurrence Score® (RS)
- Ki-67 (“luminal A vs. B”)
- Central grade
- uPA/PAI-1

Used for clinical decision making in planB

Evaluated in planB
**planB trial: Design**

**HER2-negative primary breast cancer**

- pT1-4
- free margins
- pN+
- pN0 high risk

- pT>2cm
- G2-3
- uPA/PAI-1↑
- HR-
- age ≤35 years

**HR-**

- 0-3 LN and RS>11 or ≥4 LN

**HR+**

- 0-3 LN and RS≤11

**RANDOMIZATION**

- T75C600 x 6*
- E90C600x4 → Doc100 x4*

**Recurrence Score**

- Endocrine therapy*

* endocrine therapy and RT according to national guidelines

08.12.2011
planB trial: Recruitment

3196 registered and 2448 randomized patients from 91 study sites
Event-free survival (EFS) for anthracycline-free regimen versus standard chemotherapy in HER2-negative primary breast cancer.
  - Results expected by 2016

**Primary endpoint**

**Secondary Endpoint**
  - Toxicity 6 x TC vs 4 x EC → 4 x Doc (poster session P5-18-03, Friday 12/9/11)
  - Overall survival
  - Cost effectiveness

**Extensive translational program**

**FFPE Biobank:**
  - 3193 registered patients evaluable for central pathology
  - 2551 evaluable RS
  - 314 available for uPA/PAI-1 testing in HR+
## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Recurrence Score population n=2549*</th>
<th>Central tumor bank population n=3033</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td>Median</td>
<td>56 years</td>
<td>56 years</td>
</tr>
<tr>
<td><strong>Nodal status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN0</td>
<td>62%</td>
<td>62%</td>
</tr>
<tr>
<td>pN1</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>pN2/3</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Tumor size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 20 mm</td>
<td>55%</td>
<td>55%</td>
</tr>
<tr>
<td>&gt; 20 mm</td>
<td>45%</td>
<td>45%</td>
</tr>
<tr>
<td><strong>Central grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>G2</td>
<td>63%</td>
<td>57%</td>
</tr>
<tr>
<td>G3</td>
<td>32%</td>
<td>39%</td>
</tr>
</tbody>
</table>

*Baseline data not available for two patients
Methods

Blinded analysis by two experienced breast pathologists (HK and MC, University of Hanover)

- ER/PgR by IHC (cutoff 1 %)
- HER2 by IHC and if 2+ confirmed by FISH
- Central grade by Elston-Ellis criteria
- Central Ki-67 labeling index by IHC
  - “luminal A vs. B” differentiated by cutoffs of 14% and 20%
- uPA/PAI-1 (local, by ELISA Femtelle® test)
  - Cutoff: high risk if uPA>3 ng/mg and/or PAI-1>14 ng/mg
Risk distribution by RS

planB cutoffs
- High risk (>25): 18%
- Intermediate risk (12-25): 60%
- Low risk (0-11): 22%

RS Commercial Cut-Offs
- High risk (>30): 48%
- Intermediate risk (18-30): 13%
- Low risk (0-17): 39%

Legend:
- High risk (>25)
- Intermediate risk (12-25)
- Low risk (0-11)
Shared decision making according to Recurrence Score in planB trial

- 18% of patients potentially spared chemotherapy → 88% acceptance

**planB cutoffs**

- 18% of patients potentially spared chemotherapy
- 22% of patients potentially spared chemotherapy
- 60% of patients potentially spared chemotherapy

**Dropout rates**

- high risk: n=45, **8.2%**
- intermediate risk: n=249, **16.1%**
  - N0 patients with RS 12-18 34%
- low risk: n=19, **4.1%**
Risk distribution
“luminal A vs. B” subtypes (n=1062) and uPA/PAI-1 (n=314)

Ki-67 cutoff 14%
- Luminal A (<14%): 55%
- Luminal B (≥14%): 45%

Ki-67 cutoff 20%
- Luminal A (<20%): 36%
- Luminal B (≥20%): 64%

63% N0, 37% N+
Recurrence score by Ki-67

- **Ki-67 <14**
  - low risk (0-11)
  - intermediate risk (12-25)
  - high risk (>25)
- **Ki-67 ≥14**
  - low risk (0-11)
  - intermediate risk (12-25)
  - high risk (>25)
Recurrence score by central grade

Concordance is limited

- If the RS is high it is quite likely that central grade is high
- However, the converse is not true

- high risk (>25)
- intermediate risk (12-25)
- low risk (0-11)
Recurrence score by uPA/PAI-1

Concordance is limited

- If the RS is high, it is quite likely that uPA/PAI-1 is high
- However, the converse is not true
Correlation of RS with biological factors

Spearman Correlation with RS

- Correlation of RS with biological factors
- Spearman Correlation with RS
- Ki-67
- Central grade
- Local grade
- PR
- ER
- PAI-1
- uPA
- n.s.
- p<0.001
planB trial risk assessment: Conclusions I

- Adjuvant chemotherapy could be spared in 18% of HR+ patients on the basis of their excellent prognosis as identified by RS <12.
- Routine risk assessment by Recurrence Score feasible: High compliance of patients / physicians with Oncotype DX® results.
- Risk concordance: high RS usually implies high risk by
  - Central G3
  - “luminal B” subtype (HR+, Ki-67 high)
  - high uPA/PAI-1
- Risk assessment within low and intermediate RS risk groups exhibits substantial heterogeneity according to central grade, luminal subtype, and uPA/PAI-1.
planB trial risk assessment: Conclusions II

- Outcome data (EFS) needed for definite statement regarding clinical significance of this heterogeneous risk group assessment.
- Upcoming WSG-ADAPT trial will further investigate under- / overtreatment in the adjuvant setting.
WSG-ADAPT trial: HR+ sub-protocol

Prognosis
(RS, Ki-67)

Endocrine therapy
3 weeks

Efficacy
(RS, Ki-67)

High risk

Low risk

Intermediate risk

Good proliferation response

Low proliferation response

Chemotherapy

Core Biopsy

Core Biopsy/Surgery

Pls: N. Harbeck; U. Nitz
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- All planB study centers, investigators, and study nurses

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Hofmann M.
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Könnecke P.
Krabisch P.
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Kümmel S.
Kurbacher C.
Kusche J.
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Liedtke C.
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