S5-03 Final analysis of WSG-ADAPT HER2+/HR+ phase II trial: Efficacy, safety, and predictive markers for 12-weeks of neoadjuvant TDM1 with or without endocrine therapy versus trastuzumab+endocrine therapy in HER2-positive hormone-receptor-positive early breast cancer

Dr. Harbeck: Honoraria for lectures and consulting from Celgene, Genomic Health Inc., and Roche.

Final analysis of the WSG-ADAPT HER2+/HR+ phase II trial: Efficacy, safety, and predictive markers for 12-weeks of neoadjuvant T-DM1 with or without endocrine therapy vs. trastuzumab+endocrine therapy in HER2-positive hormone-receptor-positive early breast cancer

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**Adjuvant Dynamic marker-Adjusted Personalized Therapy trial (ADAPT)**

umbrella trial, n ~ 5,000

- Low risk + good response: endocrine therapy (ET)
- High risk + poor response: Chemotherapy ₹ ET
- HER2+
  - Pertuzumab, T-DM1: efficacy w/o chemotherapy
  - pCR
- TN
  - Added efficacy of platinum, nab-paclitaxel, PARP

WSG AM06 Principal Investigators: Nadia Harbeck (LKP), Munich; Ulrike Nitz, Mönchengladbach, Germany.

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**ADAPT HER2+/HR+:**

**Rationale**

- In HER2+ early breast cancer (eBC), the current standard (chemo- + anti-HER2 therapy) is independent of hormone receptor (HR) status
- HER2+/HR+ (triple positive) eBC is a distinct entity:
  - after neoadjuvant chemotherapy + anti-HER2 therapy:
    - pCR rates and their impact on outcome differ according to HR-status
- Endocrine + anti-HER2 therapy (w/o systemic chemotherapy) may thus be an effective neoadjuvant strategy
- So far, no efficacy data on
  - single agent T-DM1 in the neoadjuvant setting
  - combination of T-DM1 plus endocrine therapy

Cortazar et al, Lancet 2014; Rimawi et al, JCO 2013
ADAPT HER2+/HR+:
Trial design

**Endpoint**

*Standard chemotherapy recommended after surgery / 12 week biopsy (in case of clinical non-pCR), trastuzumab to be completed, for a total of one year.*

**Key Inclusion criteria**

- Confirmed ER and/or PR positive (≥1%) and HER2+ by central pathology
- cT1c - cT4a-c
- All cN
- No clinical evidence for distant metastasis (cM0)
- Adequate organ function
- LVEF ≥ 50%; LVEF within normal institutional limits by echocardiography; normal ECG
**ADAPT HER2+/HR+: Final Analysis**

- **Primary trial objective:**
  - Comparison of pCR rates of each T-DM1 arm (± ET) vs. trastuzumab + endocrine therapy (assumption 25% vs. 10%; power 80%, alpha 2.5% each, one-sided)
  - pCR: no invasive carcinoma in breast and nodes (ypT0/is ypNO)

- **Secondary objectives:**
  - Evaluation of dynamic testing
  - EFS, OS
  - Toxicity, safety

- **Pre-planned interim analysis (n=130)** presented at ASCO 2015

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**ADAPT HER2+/HR+: CONSORT Diagram**

- N = 463 screened
- N = 375 randomized
- N = 319 randomized A (T-DM1)
- N = 127 randomized B (T-DM1 + ET)
- N = 129 randomized C (Trastuzumab + ET)

- N = 119 started Tx
- N = 124 started Tx
- N = 122 started Tx

- Progress n=1 (0.8%)
- Adverse events n=1 (0.8%)

- N = 117 completed Tx by protocol (93.3%)
- N = 120 completed Tx by protocol (94.5%)
- N = 117 completed Tx by protocol (93.7%)

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## ADAPT HER2+/HR+: Baseline patient and tumor characteristics

<table>
<thead>
<tr>
<th></th>
<th>T-DM1</th>
<th>T-DM1 + ET</th>
<th>Trast. + ET</th>
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<tr>
<td><strong>n</strong></td>
<td>119</td>
<td>127</td>
<td>129</td>
</tr>
<tr>
<td><strong>Age</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>50.0</td>
<td>51.0</td>
<td>51.5</td>
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<tr>
<td>(range)</td>
<td>(21 - 76)</td>
<td>(27 - 76)</td>
<td>(23 - 77)</td>
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<tr>
<td><strong>cT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>60</td>
<td>62</td>
<td>60</td>
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<tr>
<td>(50.4%)</td>
<td>(48.8%)</td>
<td>(46.5%)</td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>59</td>
<td>65</td>
<td>69</td>
</tr>
<tr>
<td>(49.6%)</td>
<td>(51.2%)</td>
<td>(53.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>cN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>85</td>
<td>96</td>
<td>91</td>
</tr>
<tr>
<td>(71.4%)</td>
<td>(75.6%)</td>
<td>(70.5%)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>34</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>(28.5%)</td>
<td>(24.4%)</td>
<td>(29.5%)</td>
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</tr>
<tr>
<td><strong>PR</strong></td>
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<tr>
<td>negative</td>
<td>21</td>
<td>20</td>
<td>21</td>
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<tr>
<td>(17.6%)</td>
<td>(15.7%)</td>
<td>(16.3%)</td>
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</tr>
<tr>
<td>positive</td>
<td>98</td>
<td>106</td>
<td>108</td>
</tr>
<tr>
<td>(82.4%)</td>
<td>(83.5%)</td>
<td>(83.7%)</td>
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</tr>
<tr>
<td><strong>ER</strong></td>
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<tr>
<td>negative</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>(2.5%)</td>
<td>(0.8%)</td>
<td>(3.9%)</td>
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</tr>
<tr>
<td>positive</td>
<td>116</td>
<td>125</td>
<td>124</td>
</tr>
<tr>
<td>(97.5%)</td>
<td>(98.4%)</td>
<td>(96.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Central grading</strong></td>
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</tr>
<tr>
<td>3</td>
<td>97</td>
<td>103</td>
<td>98</td>
</tr>
<tr>
<td>(81.5%)</td>
<td>(81.1%)</td>
<td>(76.0%)</td>
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</tr>
<tr>
<td><strong>Ki67</strong></td>
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<td></td>
</tr>
<tr>
<td>median</td>
<td>40.0</td>
<td>40.0</td>
<td>35.0</td>
</tr>
<tr>
<td>(range)</td>
<td>(10 - 90)</td>
<td>(15 - 80)</td>
<td>(10 - 85)</td>
</tr>
</tbody>
</table>

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## ADAPT HER2+/HR+: all AEs pooled T-DM1 vs. T+ET with significance

<table>
<thead>
<tr>
<th>AE</th>
<th>T-DM1 arms (n)</th>
<th>%</th>
<th>Trastuzumab + ET (n)</th>
<th>%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>25</td>
<td>10.4</td>
<td>0</td>
<td>0.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>10.4</td>
<td>5</td>
<td>4.1</td>
<td>0.04</td>
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<tr>
<td>Dry mouth</td>
<td>15</td>
<td>6.2</td>
<td>1</td>
<td>0.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Nausea</td>
<td>50</td>
<td>20.7</td>
<td>6</td>
<td>4.9</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Fatigue</td>
<td>55</td>
<td>22.8</td>
<td>14</td>
<td>11.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>18</td>
<td>7.5</td>
<td>2</td>
<td>1.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>19</td>
<td>7.9</td>
<td>2</td>
<td>1.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Investigations (total)</td>
<td>56</td>
<td>23.2</td>
<td>11</td>
<td>9.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ALT</td>
<td>45</td>
<td>18.7</td>
<td>7</td>
<td>5.7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>AST</td>
<td>41</td>
<td>17.0</td>
<td>4</td>
<td>3.3</td>
<td>&lt; 0.01</td>
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<tr>
<td>Arthralgia</td>
<td>20</td>
<td>8.3</td>
<td>3</td>
<td>2.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>11</td>
<td>4.6</td>
<td>0</td>
<td>0.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Headache</td>
<td>39</td>
<td>16.2</td>
<td>3</td>
<td>2.5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Hot flush</td>
<td>9</td>
<td>3.7</td>
<td>14</td>
<td>11.5</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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ADAPT HER2+/HR+:
Safety

- Adverse event (AE) frequencies ≥ grade 3 with significant differences between arms (pooled T-DM1 vs. T+ET)
  - investigations (i.e. increase of liver enzymes: ALT, AST):
    - 10 (4.1%) vs. n=0 (p=0.02)

- Serious adverse events (SAE) related to therapy:
  - a total of 18 SAE reported
  - n=5 ≥ grade 3 SAE (2 with T-DM1, 3 with T+ET)
  - ALT increase, corneal cyst, hypertensive crisis (n=2), hypersensitivity
  - all patients recovered without sequelae
  - no grade 5 event

ADAPT HER2+/HR+: pCR (no invasive tumor in breast and nodes)

- p < 0.001

- 48/117 (41.0%)
- 51/123 (41.5%)
- 18/119 (15.1%)

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ADAPT HER2+/HR+: total pCR and near pCR

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ADAPT HER2+/HR+: pCR according to menopausal status*

*exploratory analysis
ADAPT HER2+/HR+:
Early response biomarkers

- Early response:
  - Definition: low cellularity (< 500 tumor cells) or Ki67 drop ≥ 30% in three-week biopsy
  - Significant association with pCR (OR 2.2; 95% CI 1.24-4.19)*

* OR = 1, exact CI; eq. alloc. method; n=75 (20.0%) missing; inference strictly exploratory

--

ADAPT HER2+/HR+:
Early response biomarkers

- Early response:
  - low cellularity (< 500 tumor cells) or Ki67 drop ≥ 30% in three-week biopsy

--
ADAPT HER2+/HR+:
Conclusions

- More than 40% pCR (breast and nodes) in T-DM1 treated patients after 12 weeks without systemic chemotherapy:
  - 41% T-DM1 and 41.5% T-DM1 + ET
  - 15.1% trastuzumab + ET
- Adding endocrine therapy to T-DM1 does not increase pCR; effect independent of menopausal status
- Very low overall toxicity; no new safety signals
- Early tumor response (low cellularity or Ki67 drop ≥ 30%) significantly associated with increased pCR (OR 2.2)

ADAPT HER2+/HR+:
Outlook

- Therapy de-escalation in HER2+/HR+ eBC is possible
- TDM-1 single agent warrants further evaluation in eBC
- Adding endocrine therapy to T-DM1 does not seem to affect T-DM1 efficacy
- Early tumor response predicts for pCR and can already be detected after 3 weeks
- Further biomarker analyses ongoing (e.g. early-response biomarkers, mutation analysis, and subtypes)
- Future trials need to separately investigate therapy concepts for HER2+/HR+ and HER2+/HR- disease
ADAPT HER2+/HR+: Thank you!

• Study Support: Roche; for MRI subproject: Bayer Diagnostics
• WSG central pathology (MHH): H. Kreipe, M. Christgen
• Pall: I. Reiser, P. Raeth, R. Walter-Kirst, and J. Schumacher (statistics)
• WSG ADAPT study sites, investigators, and study nurses
• WSG Data Safety Monitoring Board
• and to all our patients who agreed to participate in the ADAPT Trial and to donate their tumor tissue for translational research

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