ADAPT HER2+/HR+ (triple-positiv)

Nadia Harbeck, München
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

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 chemo-therapy) 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

T-DM1 3.6 mg/kg
Endocrine therapy
Trastuzumab Endocrine therapy

1 2 3 4 5 6 7 8 9 10 11 12

pCR vs. Surgery*
EOT

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

Hofmann et al, Trials 2013
ADAPT HER2+/HR+:
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 ypN0)

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

- Pre-planned interim analysis (n=130) presented at ASCO 2015
ADAPT TP: Rekrutierung

Oktober 2012 – April 2015 (48 aktive Zentren)

48 Pat. → ÜBAG Mönchengladbach
32 Pat. → Rotkreuzklinikum München
27 Pat. → Kliniken Essen Mitte
21 Pat. → St. Elisabeth Krankenhaus Köln
17 Pat. → Ev. Waldkrankenhaus Spandau Berlin
15 Pat. → Universitätsfrauenklinik Köln
ADAPT HER2+/HR+: CONSORT Diagram

N = 463 screened

N = 375 randomized

N = 119 randomized
A (T-DM1)

N = 118 started Tx

Progress n=1 (0.8%)
Incl. crit. violated n=1

N = 117 completed Tx by protocol (98.3%)

N = 127 randomized
B (T-DM1 + ET)

N = 124 started Tx

Adverse events n=1 (0.8%)
Progress n=1 (0.8%)
Consent withd. n=2 (1.6%)
Incl. crit. violated n=2 (1.6%)
Other n=1 (0.8%)

N = 120 completed Tx by protocol (94.5%)

N = 129 randomized
C (Trastuzumab + ET)

N = 122 started Tx

Progress n = 2 (1.6%)
Pat. decision n = 2 (1.6%)
Consent withd. n=7 (5.4%)
Other n=1 (0.8%)

N = 117 completed Tx by protocol (90.7%)

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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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>119</td>
<td>127</td>
<td>129</td>
</tr>
<tr>
<td><strong>age</strong> median (range)</td>
<td>50.0</td>
<td>(21 – 78)</td>
<td>51.0</td>
</tr>
<tr>
<td><strong>cT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>60</td>
<td>(50.4%)</td>
<td>62</td>
</tr>
<tr>
<td>≥2</td>
<td>59</td>
<td>(49.6%)</td>
<td>65</td>
</tr>
<tr>
<td><strong>cN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>85</td>
<td>(71.4%)</td>
<td>96</td>
</tr>
<tr>
<td>≥1</td>
<td>34</td>
<td>(28.5%)</td>
<td>31</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>21</td>
<td>(17.6%)</td>
<td>20</td>
</tr>
<tr>
<td>positive</td>
<td>98</td>
<td>(82.4%)</td>
<td>106</td>
</tr>
<tr>
<td><strong>ER</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>3</td>
<td>(2.5%)</td>
<td>1</td>
</tr>
<tr>
<td>positive</td>
<td>116</td>
<td>(97.5%)</td>
<td>125</td>
</tr>
<tr>
<td><strong>central grading</strong></td>
<td>3</td>
<td>(81.5%)</td>
<td>97</td>
</tr>
<tr>
<td><strong>Ki67</strong> median (range)</td>
<td>40.0</td>
<td>(10 – 90)</td>
<td>40.0</td>
</tr>
</tbody>
</table>
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)
ADAPT HER2+/HR+: total pCR and near pCR
ADAPT HER2+/HR+: pCR according to menopausal status*

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

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*exploratory analysis

14.11.2016
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 TP – wie ordnen sich die Ergebnisse international ein?

- **I-SPY2 (AACR 2016):**
  - T-DM1+P > Paclitaxel + Trastuzumab
- **KRISTINE (ASCO 2016)**
- **adjuvante Studien zu T-DM1:**
  - Katherine (post-neoadjuvant)
  - KAITLIN
- **ADAPT TP II**
- …
Pathologic complete response rates after neoadjuvant trastuzumab emtansine (T-DM1) + pertuzumab vs docetaxel + carboplatin + trastuzumab + pertuzumab (TCH+P) treatment in patients with HER2-positive early breast cancer (KRISTINE/TRIO-021)

Sara A. Hurvitz,¹ Miguel Martin,² W. Fraser Symmans,³ Kyung Hae Jung,⁴ Chiun-Sheng Huang,⁵ Alastair M. Thompson,⁶ Nadia Harbeck,⁷ Vicente Valero,³ Danil Stroyakovskiy,⁷ Hans Wildiers,⁸ Karen Afenjar,⁹ Rodrigo Fresco,¹⁰ Hans-Joachim Helms,¹¹ Jin Xu,¹² Yvonne G. Lin,¹² Joseph Sparano,¹³ Dennis Slamon¹

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Presented by: Dr Sara Hurvitz
KRISTINE: Background

Dual HER2-blockade in the neoadjuvant setting

- Combined use of pertuzumab and trastuzumab with docetaxel significantly improved pathologic complete response (pCR) in the neoadjuvant setting vs trastuzumab and docetaxel.

T-DM1 and pertuzumab

- In patients with HER2-positive MBC, T-DM1:
  - Improved survival in patients who had previously received trastuzumab and a taxane.
  - Was noninferior to trastuzumab plus taxane as a first-line treatment in patients who had not received prior chemotherapy.
- Clinically meaningful pCR rates (>40%) were observed after 12 weeks of neoadjuvant T-DM1 in patients with HER2-positive/hormone receptor positive EBC (WGS-ADAPT).

KRISTINE presents the first phase 3 data for a neoadjuvant regimen that omits standard chemotherapy for HER2-positive BC

pCR by Central ER/PR Receptor Status

**ER and PR negative**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>pCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCH+P</td>
<td>73%</td>
</tr>
<tr>
<td>T-DM1+P</td>
<td>54%</td>
</tr>
</tbody>
</table>

**Difference (95% CI):**

-19.0 (−33.3, −4.6)

**ER and/or PR positive**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>pCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCH+P</td>
<td>44%</td>
</tr>
<tr>
<td>T-DM1+P</td>
<td>35%</td>
</tr>
</tbody>
</table>

**Difference (95% CI):**

−8.6 (−20.5, 3.2)

*ypT0/is, ypN0; patients with missing or unevaluable pCR status were considered nonresponders. Twenty patients had “unknown” ER/PR status by central analysis.*
Maintenance of HRQoL and Physical Function

Maintenance of HRQoL

HR (95% CI): 0.60 (0.46–0.78)

Maintenance of physical function

HR (95% CI): 0.47 (0.36–0.62)

Data are based on the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and QLQ-modified breast cancer module (BR23). Maintenance of health-related quality of life (HRQoL) and physical function were assessed as the time to deterioration defined as the time from baseline to first 10-point (or greater) decrease.

Only data from the neoadjuvant treatment phase including pre-surgery visit are used. Patients of the ITT population with a baseline assessment and at least 1 post-treatment assessment are included in this analysis.

PRESENTED AT: ASCO ANNUAL MEETING ‘16

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ADAPT TP - was ist jetzt zu tun?

- Follow-up
- Klinische Publikation der finalen Analyse ist in Vorbereitung
- Translationale Projekte (Mutationsstatus, Subtypen, etc.) laufen
  – Erste Ergebnisse in San Antonio 2016
- Weitere Unterstützung der Therapiestrategie zur De-Eskalation und Personalisierung beim HER2+ HR+ Mammakarzinom: Teilnahme an ADAPT TP II
ADAPT TP II – wie geht es weiter?

- PI: Dr. O. Gluz, Mönchengladbach
- Studienstart: Q1 2017
ADAPT TP II – wie geht es weiter?

- PI: Dr. O. Gluz, Mönchengladbach
- Studienstart: Q1 2017
- IT-gestützte Lebensqualitätsanalysen (CANKADO)
Danke

• Allen Patientinnen
• Allen ADAPT HER2+ HR+ Zentren

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• Zentralpathologie: H. Kreipe, M. Christgen, H. Christgen
• WSG und palleos Team: O. Gluz, R. Kates (Statistik), I. Reiser, P. Raeth, R. Walter-Kirst, J. Schumacher (Statistik) sowie allen Projektmanagern
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