ADAPT: Her 2+/ HR -

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Final analysis of the WSG-ADAPT HER2+/HR- phase II trial:
Efficacy, safety, and predictive markers for 12-weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel in HER2+/HR- early breast cancer (EBC)

pCR CORRELATES WITH BETTER EFS
IN SUBSETS OF BC INCLUDING HER2+ BC
A FDA led Meta-analysis (N=11,955 patients / 1,989 HER2+)

HER2+
HR=0.39, P* < 0.001

HER2+ HR+
HR=0.58, P* = 0.001

HER2+ HR-
HR=0.25, P* < 0.001

Cortazar; Lancet 2013 (in press)
ADAPT HER2+/HR-:
Rationale

- HER2+/HR+ (*triple positive*) and HER2+/HR- eBC are distinct entities:
  - after neoadjuvant chemotherapy + anti-HER2 therapy:
    - pCR rates and their impact on outcome differ according to HR-status
- pCR is an valid surrogat for outcome in HER2+/HR- eBC
- Early response as predictor of pCR after 12 weeks of treatment may be an important clinical information for further therapeutic strategy
- Subpopulations sufficiently treated by dual blockade only are not yet defined

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

<table>
<thead>
<tr>
<th>1</th>
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<th>9</th>
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<th>11</th>
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<tbody>
<tr>
<td>Trastuzumab</td>
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<td>Pertuzumab</td>
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<td>Paclitaxel</td>
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- **Endpoint**: pCR vs. pCR

- **Surgery**:
  - pCR

- **EOT**

- **Prognosis**
  - Biopsy

- **Efficacy**
  - Three week therapy

- **Standard chemotherapy/ completion of 1yr Trastuzumab obligatory in all cases except pCR at surgery (optionally 1 yr trastuzumab only)**

11/14/2016

Infomaterial ADAPT - WSG GmbH
ADAPT HER2+/HR-:
Key Inclusion Criteria

- ER / PR negative (<1%) and HER2+ by central pathology
- cT1c - cT4a-c
- all cN
- M0
- Adequate organ function
  - LVEF > 50%; LVEF within normal institutional limits by echocardiography; normal ECG
ADAPT HER2+/HR+: Endpoints

- **Primary trial objective:**
  - Trial tests non-inferiority of pCR in responders (T+P) vs. (T+P+Pac) with pCR: no invasive carcinoma in breast and nodes (ypT0/is ypN0)
  - Assumed pCR rate in P+T+Pac arm was 60%
  - Study was planned for n=220 patients (randomization P+T vs. P+T+Pac 2.5:1)

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

At the pre-planned interim analysis (IA), the DSMB recommended a 2nd IA for validation of trial assumptions and re-evaluation of responder definition (e.g. Ki67 drop ≥ 30% or <500 invasive tumor cells after 3 weeks of therapy).
Treatment compliance - second biopsies

N= 160 screened

N=134 randomized (ITT)

N=92 randomized P+T
N=90 started Tx
N=62 assessable 2nd biopsy

N=42 randomized P+T+Pac
N= 41 started Tx
N= 23 assessable 2nd biopsy

Adverse events n= 0
Progressive disease n= 5(5.5%)
Consent withdrawn n =2 (2.2%)

N=84 completed Tx by protocol 91.3%

N=38 completed Tx by protocol 92.9%

Adverse events n= 2 (4.8%)
Progressive disease n= 0
Pat. decision n= 1(2.4%)
Other n=2 (4.8%)
### ADAPT HER2+/HR-:
#### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>P + T (n=92)</th>
<th>P + T + Pac (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (range)</td>
<td>54 (28-74)</td>
<td>51.5 (30-78)</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>8 (8.7%)</td>
<td>2 (4.8%)</td>
</tr>
<tr>
<td>cT1</td>
<td>38 (41.3%)</td>
<td>17 (40.5%)</td>
</tr>
<tr>
<td>cT2</td>
<td>47 (51.1%)</td>
<td>22 (52.4%)</td>
</tr>
<tr>
<td>cT3-4</td>
<td>7 (7.6%)</td>
<td>3 (7.1%)</td>
</tr>
<tr>
<td>cN0</td>
<td>50 (54.3%)</td>
<td>26 (61.9%)</td>
</tr>
<tr>
<td>G1/2</td>
<td>7 (7.6%)</td>
<td>5 (11.9%)</td>
</tr>
<tr>
<td>G3</td>
<td>77 (83.7%)</td>
<td>34 (81.0%)</td>
</tr>
<tr>
<td>Ki67 (median)</td>
<td>50% (15-90)</td>
<td>50% (10-90)</td>
</tr>
</tbody>
</table>

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ADAPT HER2+/HR-:
primary endpoint: pCR according to responder status
ADAPT HER2+/HR-: secondary endpoint (ypT0, ypN0)

![Graph showing PCR rates for different conditions.]

- A (T+P): 34.4% (ypT0), 24.4% (ypT0, ypN0)
- B (T+P+PAC weekly): 90.5% (ypT0), 78.6% (ypT0, ypN0)
ADAPT HER2+/HR-:
Safety

- **Pooled AE`s**
  - All AE (all grades) P+T 153 versus P+T+Pac 269
  - Pooled adverse event (AE) frequencies ≥ grade 3:
    P+T 9 vs P+T+Pac 14 (Δ mainly due to neurotoxicity)

- **Serious adverse events (SAE) related to therapy:**
  - a total of 6 SAE`s reported
  - n= ≥ grade 5 SAE (with T+P 4, with T+P + Pac1)
  - Most frequently observed SAEs: 3 hypersensitivity/infusion related reaction, 1 cardiac failure, 1 hypertension, lower respiratory tract infection
  - all patients recovered without sequelae
  - no grade 5 event
ADAPT HER2+/HR-: all AEs pooled
T + P vs. T+P + Pac with significance

<table>
<thead>
<tr>
<th>AE</th>
<th>T+P (62)</th>
<th>68.9 %</th>
<th>T+P + Pac (40)</th>
<th>97.6 %</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>1.1</td>
<td>1</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>1</td>
<td>1.1</td>
<td>3</td>
<td>7.3</td>
<td>0.09</td>
</tr>
<tr>
<td>Ear/labyrinth disorders</td>
<td>1</td>
<td>1.1</td>
<td>3</td>
<td>7.3</td>
<td>0.09</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>1</td>
<td>1.1</td>
<td>4</td>
<td>9.8</td>
<td>0.03</td>
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<tr>
<td>GI disorders diarhoea</td>
<td>33</td>
<td>26</td>
<td>36.7</td>
<td>28.9</td>
<td></td>
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<tr>
<td>GI disorders diarhoea</td>
<td>25</td>
<td>19</td>
<td>61.0</td>
<td>46.3</td>
<td>0.01</td>
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<tr>
<td>vomiting</td>
<td>2</td>
<td>2.2</td>
<td>1</td>
<td>2.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>16.7</td>
<td>15</td>
<td>36.6</td>
<td>0.01</td>
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<tr>
<td>Infections/infestations</td>
<td>10</td>
<td>11.1</td>
<td>13</td>
<td>31.7</td>
<td>0.01</td>
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<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>4</td>
<td>9.8</td>
<td></td>
<td>0.01</td>
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<tr>
<td>Nervous system disorders</td>
<td>14</td>
<td>15.6</td>
<td>23</td>
<td>56.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Skin disorders</td>
<td>16</td>
<td>17.8</td>
<td>26</td>
<td>63.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>8</td>
<td>8.9</td>
<td>16</td>
<td>39.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
ADAPT HER2+/HR-:
Conclusions

- WSG ADAPT HER2+/HR- is a unique phase II trial in focusing only on HER2+ HR- early breast cancer (eBC)
- 90.5% pCR rate with T+P+Pac is substantial
- Adding chemotherapy to dual blockade more than doubles pCR rate in HER2+ HR- eBC
- 34.4% pCR rate with P + T is clinically meaningful (e.g. frail patients, small tumors)
- Early response at 3-weeks seems to be positively correlated with pCR. Yet, missing data does not allow any definite conclusions
Her 2+

Aktuelle Studien
Data from the literature
KRISTINE (Phase III): (N=444)

KRISTINE Study Design

- Centrally confirmed HER2-positive, operable, locally advanced or inflammatory breast cancer
- Tumor >2cm

N=432

Primary endpoint: pCR by local assessment (ypT0/is, ypN0)
- Stratification factors: local HR status, geographic location, and clinical stage at presentation

Wisconsin Institute for Medical Research

Hurvitz SA, et al. ASCO 2016 (abs 500)
Data from the literature: KRISTINE (Phase III): pCR rates

Primary Endpoint: pCR (ypT0/is, ypN0)

- Difference: -11.3
- 95% CI: -20.5, -2.0
- Stratified 2-sided $P$-value: 0.0155

<table>
<thead>
<tr>
<th>Treatment</th>
<th>pCR (%)</th>
<th>Cases</th>
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<tbody>
<tr>
<td>TCH+P</td>
<td>56%</td>
<td>123/221</td>
</tr>
<tr>
<td>T-DM1+P</td>
<td>44%</td>
<td>99/223</td>
</tr>
</tbody>
</table>

Hurvitz SA, et al. ASCO 2016 (abs 500)
Data from the literature: KRISTINE (Phase III): pCR rates

**pCR by Central ER/PR Receptor Status**

- **ER and PR negative**
  - Difference (95% CI): -19.0 (-33.3, -4.6)
  - pCR (%): 73% (60/82) vs 54% (45/83)

- **ER and/or PR positive**
  - Difference (95% CI): -8.6 (-20.5, 3.2)
  - pCR (%): 44% (56/128) vs 35% (46/131)

**ADAPT HER2+/HR-**
- T+P: 34.4%
- T+P+pac: 90.5%

**ADAPT HER2+/HR+**
- T-DM1: 40.0%
- T-DM1+Et: 41.5%

_Hurvitz SA, et al. ASCO 2016 (abs 500)_
**Data from the literature: KRISTINE (Phase III): toxicity**

GRADE ≥3 ADVERSE EVENTS WITH INCIDENCE OF ≥3% IN EITHER TREATMENT ARM: NEOADJUVANT PHASE

<table>
<thead>
<tr>
<th>Adverse event preferred term, %</th>
<th>TCH+P (n=219)</th>
<th>T-DM1+P (n=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>25.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>15.1</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>9.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>9.1</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>5.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.2</td>
<td>1.3</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>4.1</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Safety population.*

Hurvitz SA, et al. ASCO 2016 (abs 500)
KRISTINE

pCR by Central ER/PR Receptor Status

ER and PR negative
Difference (95% CI): −19.0 (−33.3, −4.6)

ER and/or PR positive
Difference (95% CI): −6.6 (−20.5, 3.2)

pCR (%) ±

73% 54%
60/82 45/83

44% 35%
56/128 46/131

*pT0/is, ypN0, patients with missing or un evaluable pCR status were considered nonresponders. Twenty patients had unknown ER/PR status for central analysis.

15% 0%

Febrile Neutropenia

Hurvitz et al. ASCO 2016
Nitz et al. ASCO 2016
Conclusions

- Neoadjuvant TCH+P achieved a superior pCR rate compared with T-DM1+P (56% vs 44%)

- Neoadjuvant TCH+P was associated with a higher BCS rate (53% vs 42%)

- Neoadjuvant T-DM1+P had a more favorable safety profile
  - Lower incidence of grade ≥3 adverse events (13% vs 64%), serious adverse events (5% vs 29%), and adverse events leading to treatment discontinuation (3% vs 9%)

- Neoadjuvant T-DM1+P was associated with longer maintenance of patient-reported HRQoL and physical function

KRISTINE: Key Endpoints

pCR (1°)

- TCH+P: 123/221 (56%, P=0.015)
- T-DM1+P: 99/223 (44%)

Toxicity TDM1+P (2°):
- QOL + physical function better
- SAE 5% (vs 29%)

Hurvitz et al. ASCO 2016
Carey et al. ASCO 2016
Vielen Dank....