PROGNOSTIC IMPACT OF RECURRENCE SCORE (RS) RESULTS, ENDOCRINE RESPONSE AND CLINICAL-PATHOLOGICAL FACTORS IN HIGH-RISK LUMINAL EARLY BREAST CANCER (EBC): RESULTS FROM THE WSG-ADAPT HR+/HER2- CHEMOTHERAPY (CT) TRIAL


On behalf of the ADAPT-Investigators,
West German Study Group, Moenchengladbach

06JUN2021
WSG-ADAPT HR+/HER2-

Background I

• OncotypeDX/Recurrence Score (RS) results was prognostic in high-risk HR+/HER2- EBC in several retro- and even prospective trials. However, evidence is scarce for patients treated by modern dose-dense chemotherapy.

• Combination of RS with tumor stage, grade, and type of endocrine therapy seems to add prognostic value to RS alone in node-negative luminal EBC\(^1\).

• Evidence on prognostic impact of RS in node-positive, particularly N2-3 EBC is limited, although WSG PlanB showed excellent outcome in RS 0-11 pN2-3 EBC after standard chemo- and endocrine therapy\(^2\).

\(^1\)Sparano et al, JCO 2021  
\(^2\)Nitz et al, BCRT 2017
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Background II

- Postmenopausal pN0-1 patients with RS ≤25\textsuperscript{1} and premenopausal pN0 patients with RS<16 (-20)\textsuperscript{2} may not benefit from adding chemo- to endocrine therapy.
- Early endocrine therapy (ET) response by Ki67 determination (Ki67\textsubscript{post}) after short-term preoperative ET is strongly prognostic in postmenopausal women receiving aromatase inhibitors\textsuperscript{3,4}.
- Irrespective of age or menopausal status, combination of RS ≤25 and ET-response (Ki67\textsubscript{post} ≤10\%) identifies patients with favorable outcome after ET alone in N0-1 EBC in the WSG ADAPT HR+/HER2- ET trial\textsuperscript{5}.
- In patients treated by chemo- and endocrine therapy, the independent prognostic impacts of Ki67\textsubscript{post} and RS have not yet been studied.

\textsuperscript{1}Kalinsky et al, SABCS 2020; \textsuperscript{2}Sparano et al, NEJM 2018
\textsuperscript{3}Smith et al, Lancet Oncology 2020; \textsuperscript{4}Ellis et al. JCO2017 \textsuperscript{5}Nitz et al, manuscript submitted 2021
**WSG-ADAPT HR+/HER2-**  
(NCT01779206)

**Trial design**

- Female patients >18 years
- ER and/or PR positive (>1%)/ HER2-negative unilateral EBC
- cT1-4c, cN0-3
- **Candidates for adjuvant chemotherapy by conventional prognostic criteria:** cT2 or G3 or Ki-67>15% or <35 years old or cN+
## Endpoints and Statistics

### Endpoints
- Primary endpoint: Invasive disease-free survival (iDFS*)
- Secondary endpoints: Distant DFS (dDFS); overall survival (OS)

### Objectives
- Primary objective: to compare iDFS between the two dose-dense chemotherapy arms (to be reported later)
- **Secondary objectives**: OS, dDFS; translational research, in particular impact of prognostic markers, e.g. clinicopathological factors (nodal status, tumor stage**, grade, ER, PR, Ki67 by central lab) RS and ET-response***

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* iDFS = time from registration to any invasive recurrence or secondary malignancy or death by any cause  
** Pathological nodal and tumor stage in all patients with surgery results prior to (neo)-adjuvant chemotherapy; clinical nodal and tumor stage in patients with surgery after neoadjuvant chemotherapy  
***ET response = Ki67_{post} ≤ 10% (after short induction endocrine therapy)
WSG-ADAPT HR+/HER2-

Consort diagramm

ET-Trial

2356 patients with documented ET alone

2290 pN0-1 patients with RS 0-11 or RS 12-25 and Ki67_tumor ≤10% (ITT population)

868 patients RS 0-11

1422 patients RS 12-25 and Ki67_tumor ≤10%

2279 FU available

N=5043 RS available

N=4310 postendocrine Ki-67 available

5625 registered

N=5314 started dynamic testing

N=311 clinical high risk

2335 allocated to CT followed by adjuvant ET

94 patients randomized to CT* prior to amendment

2241 patients randomized to CT after amendment

N=4 M1 disease

Arm A
4×Pac-4×EC q2w
N=1131

Arm B
8×Nab-pac-4×EC q2w
N=1106

RS 12-25, N0-1 and ET non-responders

RS >25 with/without pre-operative ET

N2-3 with/without RS and/or pre-operative ET

>1cm, G3 and Ki67 > 40% (without RS and pre-operative ET)

*2012-13 chemotherapy protocol (4×EC→Taxane 12 weeks vs. Taxane→4×EC)

1Harbeck et al, SABCS 2020

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# WSG-ADAPT HR+/HER2- CT Trial

## Baseline characteristics (n=2331)*

<table>
<thead>
<tr>
<th></th>
<th>No patients (%)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50 years</td>
<td>1128 (48.4)</td>
<td>51.0 (45.0-59.0)</td>
</tr>
<tr>
<td><strong>Neoadjuvant CT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>866 (37.2)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1245 (53.4)</td>
<td></td>
</tr>
<tr>
<td>2 or 3</td>
<td>694 (29.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Nodal status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1**</td>
<td>1045 (44.8)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1154 (49.5)</td>
<td></td>
</tr>
<tr>
<td>3 or 4</td>
<td>132 (5.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-11</td>
<td>67 (2.9)</td>
<td>25.0 (18.0-32.0)</td>
</tr>
<tr>
<td>12-25</td>
<td>916 (39.3)</td>
<td></td>
</tr>
<tr>
<td>&gt; 25</td>
<td>965 (41.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Recurrence Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>823 (35.3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1090 (46.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Grade</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>823 (35.3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1090 (46.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Ki67 baseline (%)</strong></td>
<td>25.0 (15.0-35.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Ki67 post</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10</td>
<td>365 (15.7)</td>
<td>15.0 (15.0-25.0)</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>1245 (53.4)</td>
<td></td>
</tr>
<tr>
<td><strong>ER (%)</strong>*</td>
<td>95.0 (85.0-100.0)</td>
<td></td>
</tr>
<tr>
<td><strong>PR (%)</strong>*</td>
<td>70.0 (15.0-90.0)</td>
<td></td>
</tr>
</tbody>
</table>

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* Median follow-up 58 months (range 0-84 months)

* RS, post-endocrine Ki67 and central grade/Ki67 missing in patients directly allocated to CT trial;
** n=16 patients had ypT0 after 3 weeks of ET (0.7%)
*** central assessment

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# WSG-ADAPT HR+/HER2- CT and ET cohorts

## Prognostic markers for iDFS

### Univariate analysis

<table>
<thead>
<tr>
<th>Marker</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>2917</td>
<td>171</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>1284</td>
<td>142</td>
<td>1.96</td>
<td>1.57, 2.44</td>
</tr>
<tr>
<td>N2-3</td>
<td>389</td>
<td>69</td>
<td>3.66</td>
<td>2.77, 4.84</td>
</tr>
<tr>
<td>T0-1</td>
<td>2474</td>
<td>125</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>1911</td>
<td>224</td>
<td>2.57</td>
<td>2.06, 3.20</td>
</tr>
<tr>
<td>T3-4</td>
<td>207</td>
<td>33</td>
<td>4.06</td>
<td>2.77, 5.97</td>
</tr>
<tr>
<td>Postendocrine Ki67≤10%</td>
<td>2361</td>
<td>158</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Postendocrine Ki67&gt;10%</td>
<td>1374</td>
<td>140</td>
<td>1.69</td>
<td>1.34, 2.12</td>
</tr>
<tr>
<td>RS 0-11</td>
<td>932</td>
<td>49</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>RS 12-25</td>
<td>2325</td>
<td>169</td>
<td>1.50</td>
<td>1.09, 2.07</td>
</tr>
<tr>
<td>RS&gt;25</td>
<td>956</td>
<td>122</td>
<td>3.18</td>
<td>2.28, 4.44</td>
</tr>
<tr>
<td>Baseline Ki67 (per 10%)</td>
<td>3928</td>
<td>322</td>
<td>1.20</td>
<td>1.13, 1.28</td>
</tr>
<tr>
<td>PR (per 10%)</td>
<td>4108</td>
<td>332</td>
<td>0.91</td>
<td>0.88, 0.93</td>
</tr>
</tbody>
</table>

*Hazard ratio (95% CI)*
WSG-ADAPT HR+/HER2- CT and ET Trial

N0-1/RS 12-25: Outcome by trial (treatment allocated according to ET-response)

CT trial: RS (as a continuous variable), N1 vs. N0 and T$\geq$2 vs. T$<$2 are significantly associated with poor iDFS and dDFS in multivariable analysis. Age, grade, ER, PR, Ki67 baseline were not significantly associated with prognosis.
WSG-ADAPT HR+/HER2- CT and ET Trial

N0-1/RS 12-25: dDFS by trial in age subgroups (treatment allocated according to ET-response)

**Age ≤50 years**

- 5-y dDFS: ET in ET-responders 97% [95% CI: 94-99]
- CT+ET in ET non-responders 92% [89-95]

- 42.5% had ET-response
- 23.3% had baseline Ki67 ≤ 10%
- 36.1% had N1

Log-rank p=.032, p=.03 in N1

**Age >50 years**

- 5-y dDFS: ET in ET-responders 95% [93-96]
- CT+ET in ET non-responders 94% [88-97]

- 81.6% had ET-response
- 25.6% had baseline Ki67 ≤ 10%
- 29.1% had N1

Log-rank p=.533

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N2-3 cohort, any RS, any ET-response
Distant disease-free survival (dDFS) according to RS

Multivariable analysis for dDFS*

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS continuous per unit</td>
<td>1.04</td>
<td>1.0, 1.08</td>
</tr>
<tr>
<td>N3 vs. N2</td>
<td>3.2</td>
<td>1.65, 6.21</td>
</tr>
</tbody>
</table>

* Adjusted for Ki67_{post}, ER, PR, age
Tumor stage, Ki67_{baseline}, grade were not associated with prognosis in univariable analysis
WSG-ADAPT HR+/HER2- CT Trial

RS>25 cohort, any N, any ET-response

dDFS by ET-response

Multivariable analysis for dDFS*

<table>
<thead>
<tr>
<th>Coding</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki67_{post} &lt;=10% vs. Ki67_{post} &gt; 10%</td>
<td>0.42</td>
<td>0.20, 0.87</td>
<td>0.02</td>
</tr>
<tr>
<td>Tumor size &gt; 2 cm vs. ≤ 2 cm</td>
<td>2.56</td>
<td>1.40, 4.66</td>
<td>0.002</td>
</tr>
<tr>
<td>N0 (reference)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>1.36</td>
<td>0.77, 2.39</td>
<td>0.292</td>
</tr>
<tr>
<td>N2-3</td>
<td>2.13</td>
<td>0.98, 4.63</td>
<td>0.058</td>
</tr>
<tr>
<td>PR (per 10% increase)</td>
<td>0.92</td>
<td>0.84, 1.00</td>
<td>0.057</td>
</tr>
</tbody>
</table>

*adjusted for RS (by unit) and Ki67_{post}/Ki67_{baseline}

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WSG-ADAPT HR+/HER2- CT Trial

(RS>25 cohort, any N, any ET-reponse): dDFS

Impact of tumor stage

5-y dDFS:
- 93%
- 79%
- 44%

Log-rank p<0.001 for all comparisons

Impact of number of involved lymph nodes (CT in adjuvant setting)

5-y dDFS:
- 0-1 positive LN 87%
- >1 positive LN 75%

Log-rank p=0.002 overall

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Conclusions

- Tumor size, nodal status, baseline and post-endocrine Ki67, PR expression and RS -- but not age and grade -- have significant prognostic impact
- Assessment of ET-response:
  - provides important prognostic information in luminal EBC, not only in N0-1/RS 12-25 patients to support chemotherapy decision making, also in chemotherapy-treated patients with RS >25
  - identifies about half of patients ≤ 50 years with N0-1/RS 12-25 EBC who have excellent 5-year outcome (97% 5y dDFS) with ET alone\(^1\); descriptive analysis showed even better outcome than that of patients without ET-response receiving CT followed by ET in the CT-trial.

\(^1\)Harbeck et al, SABCS 2020
Conclusions

- In patients with RS>25 and 0-1 positive lymph nodes, ET-response and/or T1 stage identify a subgroup with excellent outcome.
- Patients with RS 0-11 have an excellent prognosis, even those with 4-9 positive lymph nodes.
- Further de-escalation strategies need to include both tumor burden and multiple biological features for identification of patients at low risk of relapse despite certain high-risk tumor characteristics.
- In these patients, replacement of chemotherapy by an endocrine-based approach incorporating a CDK 4/6 inhibitor is currently being evaluated in the WSG ADAPTcycle trial.
WSG-ADAPT cycle

Trial Design

Prognosis Estimation

Efficacy Estimation

Biopsy

Candidates for (neoadjuvant chemotherapy)

Biopsy or surgery

• N2-3

• N0

• N1

RS (OncoType DX) Ki-67

3 weeks (+/- 1 week)

Ki-67

± 10%*

± 10%**

High risk

Intermediate risk

Low risk

• RS < 25

• RS > 25

• RS < 25

• RS > 25

Arm 1

Ribociclib

Aromatase Inhibitors (+GnRH Agonist, if premenopausal)*

Endocrine Therapy at Investigator’s Choice

Arm 2

CTx**

(16-24 weeks)

Endocrine Therapy at Investigator’s Choice

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• All operational team members