Adjuvant Therapy with Trastuzumab

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Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.
Histopathological Classification
Classification by Gene signature

- Luminal subtype A
- Luminal subtype B
- ERBB2+
- Basel-like
<table>
<thead>
<tr>
<th></th>
<th>ER+</th>
<th>ER-</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+</td>
<td>Luminal B</td>
<td>HER2 type</td>
</tr>
<tr>
<td>HER2-</td>
<td>Luminal A</td>
<td>Basal like</td>
</tr>
</tbody>
</table>
Adjuvant Treatment for a 2 x 2 Marker Model of Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>ER+</th>
<th>ER-</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+</td>
<td>trastuzumab</td>
<td>trastuzumab</td>
</tr>
<tr>
<td></td>
<td>chemo</td>
<td>chemo</td>
</tr>
<tr>
<td></td>
<td>endocrine</td>
<td></td>
</tr>
<tr>
<td>HER2-</td>
<td>endocrine</td>
<td>chemo</td>
</tr>
<tr>
<td></td>
<td>± chemo</td>
<td></td>
</tr>
</tbody>
</table>

Selection of patients is the major challenge
HER2 receptor dimer transmembrane signal transduction pathway

- Growth factor
- Binding site
- Tyrosine kinase activity
- Signal transduction to nucleus
- Nucleus
- Gene activation
- Cytoplasm
- Plasma membrane
- CELL DIVISION
Indicators of increased HER2 production

A = HER2 DNA
B = HER2 mRNA
C = HER2 receptor protein

1 = gene copy number
2 = mRNA transcription
3 = cell surface receptor protein expression
4 = release of receptor extracellular domain
HER2 overexpression

DNA synthesis is increased;
Cell cycle is rapid;
Metastasis is promoted

It proves to be a more malignant tumor.
Survival of node-negative breast cancer patients related to HER2 status

- Amplified: >10 copies/nucleus
- Not amplified: <3 copies/nucleus
- Borderline: excluded

Log rank p<0.001

Ross JS, Fletcher JA. Stem Cells 1998;16:413–28
Trastuzumab: Structure and Mechanism of Action

Antigen binding sites: derived from mouse

Humanized anti-HER2 monoclonal antibody
M.W. 148 kDa
Human IgG 95%, Murine IgG 5% (4D5)

ADCC (Antibody-dependent tumor cytotoxicity)

Direct inhibition of cell proliferation

NK cell
Tumor cell

Cytotoxicity
Growth inhibition signal

HER2 molecule
Fcγ receptor
Trastuzumab
Before treatment (5/22)

After 7 cycles of treatment (9/3)
Before treatment (7/10)

PaCO2 : 33.5mmHg
PaO2 : 56.9mmHg
(room air)

9/19 (After 8 cycles)

PaCO2 : 36.9mmHg
PaO2 : 68.8mmHg
(room air)
Dramatic Improvement on Treatment Results in HER2+ Recurrent Breast Cancer
Trastuzumab adjuvant study design

NSABP B-31

AC q3w x 4 → Pac q3w x 4

AC q3w x 4 → Pac q3w x 4 + H q1w x 52

Control Arm

HERA

Chemotherapy (neo-adjuvant or adjuvant) ± radiotherapy

H q3w 1 year (12 months)

H q3w 2 years (24 months)

Control Arm

BCIRG 006

AC q3w x 4 → Doc x 4

AC q3w x 4 → Doc x 4 + H q1w x 12 → H q3w x 13

Doc + Carbo x 6 + H q1w x 18 → H q3w x 11

Chemotherapy (neo-adjuvant or adjuvant) ± radiotherapy

AC q3w x 4 → Pac q1w x 12

AC q3w x 4 → Pac q1w x 12 → H q1w x 52

AC q3w x 4 → Pac + H q1w x 12 → H q1w x 40

R: Trastuzumab

Pac: Paclitaxel, Doc: Docetaxel, H: Trastuzumab, CT: Chemotherapy, Carbo: Carboplatin
Trastuzumab in Adjuvant Therapy
NCCTG N9831 Trial

HER2 positive (FISH+ or IHC 3+)
n=3,505

Group A
AC T

Group B
AC T H

Group C
AC T H

= AC (doxorubicin/cyclophosphamide 60/600 mg/m² q3w × 4)
= T (paclitaxel 80 mg/m²/wk × 12)
= H (trastuzumab 4 mg/kg loading dose + 2 mg/kg/wk × 51)
Trastuzumab in Adjuvant Therapy
NSABP B-31 Trial

Node positive HER2 positive (FISH+ or IHC 3+)

Randomize

Group 1

AC → T

Group 2

AC → T → H

N=2,006

= AC (doxorubicin/cyclophosphamide 60/600 mg/m² q3w × 4)

= T (paclitaxel 175 mg/m² q3w × 4 or 80 mg/m²/wk × 12)

= H (trastuzumab 4 mg/kg loading dose + 2 mg/kg/wk × 51)
Joint Analysis of HER2+ Adjuvant Trials
2 Arms of N9831 + B-31

Control Group (n=1,979): AC → T
- N9831 Group A: AC → T
- B-31 Group 1: AC → T

Trastuzumab Group (n=1,989): AC → T+H
- N9831 Group C: AC → T → H
- B-31 Group 2: AC → T → H

Legend:
- Red = AC (doxorubicin/cyclophosphamide 60/600 mg/m² q3w × 4)
- Turquoise = T (paclitaxel 80 mg/m²/wk × 12)
- Blue = T (paclitaxel 175 mg/m² q3w × 4 or 80 mg/m²/wk × 12)
- Orange = H (trastuzumab 4 mg/kg loading dose + 2 mg/kg/wk × 51)
Updated N9831/B-31 Joint Analysis

Disease-Free Survival*

Disease-free survival (%)

Follow-up (yrs)

AC ➔ T
(n=1,979; 397 events)

AC ➔ T+H
(n=1,989; 222 events)

N=619 events
HR*_{adj} = 0.48 (95% CI: 0.41-0.57)
*Nodes, receptor status, paclitaxel schedule, protocol

P < 0.00001

*Intent to treat events: recurrent disease, contralateral bc, 2nd primary, death
Updated N9831/B-31 Joint Analysis

Overall Survival*

258 (36%) of the 710 events needed for final analysis have occurred unadjusted HR=0.65 (95%CI: 0.51-0.84)
P=0.0007

*Intent to treat
BCIRG 006

**HER2+ (Central FISH)**

- **N+ or high risk N-**

**N=3,222**

Stratified by Nodes and Hormonal Receptor Status

**AC→T**
- 4 x AC
  - 60/600 mg/m²
- 4 x Docetaxel
  - 100 mg/m²

**AC→TH**
- 4 x AC
  - 60/600 mg/m²
- 4 x Docetaxel
  - 100 mg/m²
  - 1 Year Trastuzumab

**TCH**
- 6 x Docetaxel and Carboplatin
  - 75 mg/m²
  - AUC 6
  - 1 Year Trastuzumab

Slamon D., SABCS 2006
Disease Free Survival - 2\textsuperscript{nd} Interim Analysis

Absolute DFS benefits (from years 2 to 4):
- AC→TH vs AC→T: 6%
- TCH vs AC→T: 5%

HR (AC→TH vs AC→T) = 0.61 [0.48;0.76] P<0.0001
HR (TCH vs AC→T) = 0.67 [0.54;0.83] P=0.0003
Overall Survival – 2nd Interim Analysis

Survival (%)

<table>
<thead>
<tr>
<th>Year from randomization</th>
<th>Patients</th>
<th>Events</th>
<th>AC-&gt;T</th>
<th>AC-&gt;TH</th>
<th>TCH</th>
<th>HR (AC-&gt;TH vs AC-&gt;T) = 0.59 [0.42;0.85] P=0.004</th>
<th>HR (TCH vs AC-&gt;T) = 0.66 [0.47;0.93] P=0.017</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1073</td>
<td>80</td>
<td>1074</td>
<td>49</td>
<td>1075</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[99% 97% 95% 93% 92% 86%]
HERA trial design

Women with locally determined HER2-positive invasive early breast cancer

Surgery + (neo)adjuvant CT ± RT

Centrally confirmed IHC 3+ or FISH+ and LVEF ≥ 55%

Randomization

Observation

1 year trastuzumab
8 mg/kg → 6 mg/kg
3 weekly schedule

2 years trastuzumab
8 mg/kg → 6 mg/kg
3 weekly schedule

After ASCO 2005, option of switch to trastuzumab

CT, chemotherapy; RT, radiotherapy
ACCRUAL: 5090 WOMEN
478 sites in 39 Countries (2002-2005)

EU:
71.5% of women

EASTERN EUROPE:
≅11% of women

JAPAN:
≅12% of women

ASIA PACIFIC:

CENTRAL & SOUTH AMERICA:
5.5% of women

NORDIC COUNTRIES:

SOUTH AFRICA:

AUSTRALIA – NEW ZEALAND:

CANADA:

NORDIC COUNTRIES:

EASTERN EUROPE:

JAPAN:

≅ 12%

ASIA PACIFIC:

CENTRAL & SOUTH AMERICA:

5.5% of women
End Points and Analyses

End points
- primary: DFS
- secondary: OS, TTR, TTDR
  Safety (3 interim analyses of cardiac end points)

Interim efficacy analysis
- (n=475 events)
- ASCO 2005
- Piccart-Gebhart et al NEJM Oct 2005

DFS, disease-free survival;
OS, overall survival; TTR, time to recurrence; TTDR, time to distant recurrence
## Patient characteristics (1)

<table>
<thead>
<tr>
<th></th>
<th>Observation (n=1698)</th>
<th>1 year trastuzumab (n=1703)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>7.4</td>
<td>7.5</td>
</tr>
<tr>
<td>35-49</td>
<td>44.3</td>
<td>44.4</td>
</tr>
<tr>
<td>50-59</td>
<td>32.3</td>
<td>32.2</td>
</tr>
<tr>
<td>≥60</td>
<td>16.0</td>
<td>16.0</td>
</tr>
<tr>
<td><strong>Prior (neo)adjuvant CT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No anthracyclines</td>
<td>5.9</td>
<td>5.9</td>
</tr>
<tr>
<td>Anthracyclines, no taxanes</td>
<td>68.1</td>
<td>67.8</td>
</tr>
<tr>
<td>Anthracyclines + taxanes</td>
<td>26.0</td>
<td>26.3</td>
</tr>
</tbody>
</table>
### Patient characteristics (2)

<table>
<thead>
<tr>
<th></th>
<th>Observation (n=1698)</th>
<th>1 year trastuzumab (n=1703)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Menopausal status</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>45.3</td>
<td>44.9</td>
</tr>
<tr>
<td>Uncertain</td>
<td>13.8</td>
<td>15.1</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>40.8</td>
<td>40.0</td>
</tr>
<tr>
<td><strong>Hormone receptor status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>50.4</td>
<td>50.5</td>
</tr>
<tr>
<td>Positive</td>
<td>49.6</td>
<td>49.5</td>
</tr>
<tr>
<td><strong>Nodal status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant CT</td>
<td>10.5</td>
<td>11.4</td>
</tr>
<tr>
<td>Negative</td>
<td>32.7</td>
<td>31.9</td>
</tr>
<tr>
<td>1-3</td>
<td>28.9</td>
<td>28.5</td>
</tr>
<tr>
<td>&gt;4</td>
<td>27.9</td>
<td>28.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Status at randomisation
### Disease-free survival (ITT)

**Median FU 2 yrs**

<table>
<thead>
<tr>
<th>Months from randomisation</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients ( Habitual )</td>
<td>100</td>
<td>94</td>
<td>88</td>
<td>81</td>
<td>76</td>
<td>71</td>
<td>66</td>
</tr>
</tbody>
</table>

#### Events

- **3-year DFS**: 218 (80.6%)
- **HR**: 0.64
- **95% CI**: 0.54, 0.76
- **p value**: <0.0001

**Notes**:
- 6.3% decrease in DFS
- No. at risk:
  - Observation: 1698, 1535, 1330, 984, 639, 334, 127
  - 1 year trastuzumab: 1703, 1591, 1434, 1127, 742, 383, 140
Overall survival (ITT)
Median FU 2 yrs

- Patients (%)
  - 100
  - 80
  - 60
  - 40
  - 20
  - 0

- Observation
  - 1 year trastuzumab
  - ↓ 2.7%

- Months from randomisation
  - 0
  - 6
  - 12
  - 18
  - 24
  - 30
  - 36

- Events
  - 3-year OS
  - HR
  - 95% CI
  - p value
  - 59
    - 92.4
    - 0.66
    - 0.47, 0.91
    - 0.0115
  - 90
    - 89.7

- No. at risk
  - 1703
  - 1627
  - 1498
  - 1190
  - 794
  - 407
  - 146
  - 1698
  - 1608
  - 1453
  - 1097
  - 711
  - 366
  - 139
## Site of 1st DFS Event

(ITT Analysis)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Observation (n=1698)</th>
<th>1 year trastuzumab (n=1703)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. events</td>
<td>321 (18.9)</td>
<td>218 (12.8)</td>
</tr>
<tr>
<td>Distant event</td>
<td>233 (13.7)</td>
<td>152 (8.9)</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>22 (1.3)</td>
<td>26 (1.5)</td>
</tr>
<tr>
<td>Locoregional event</td>
<td>68 (4.0)</td>
<td>45 (2.6)</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>9 (0.5)</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td>2nd non-breast malignancy</td>
<td>8 (0.5)</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td>Death as 1st event</td>
<td>3 (0.2)</td>
<td>8 (0.5)</td>
</tr>
</tbody>
</table>
## Exploratory DFS subgroup analysis (ITT): 1 year trastuzumab vs observation (1)

<table>
<thead>
<tr>
<th>Subgroup (no. patients)</th>
<th>No. events T vs obs</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Region of the world</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe, Canada, SA, Australia, NZ (2438)</td>
<td>161 vs 235</td>
<td>0.66 (0.54, 0.81)</td>
</tr>
<tr>
<td>Asia Pacific, Japan (405)</td>
<td>21 vs 37</td>
<td>0.53 (0.31, 0.90)</td>
</tr>
<tr>
<td>Eastern Europe (369)</td>
<td>23 vs 36</td>
<td>0.54 (0.32, 0.91)</td>
</tr>
<tr>
<td>Central + South America (189)</td>
<td>13 vs 13</td>
<td>0.98 (0.45, 2.11)</td>
</tr>
<tr>
<td><strong>Age at randomisation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35 years (253)</td>
<td>19 vs 31</td>
<td>0.57 (0.32, 1.01)</td>
</tr>
<tr>
<td>35-49 years (1508)</td>
<td>89 vs 150</td>
<td>0.54 (0.42, 0.70)</td>
</tr>
<tr>
<td>50-59 years (1096)</td>
<td>71 vs 97</td>
<td>0.71 (0.52, 0.97)</td>
</tr>
<tr>
<td>≥60 years (544)</td>
<td>39 vs 43</td>
<td>0.91 (0.59, 1.41)</td>
</tr>
<tr>
<td><strong>Menopausal status at randomisation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal (491)</td>
<td>43 vs 49</td>
<td>0.80 (0.53, 1.21)</td>
</tr>
<tr>
<td>Uncertain (1373)</td>
<td>70 vs 135</td>
<td>0.48 (0.36, 0.64)</td>
</tr>
<tr>
<td>Postmenopausal (1535)</td>
<td>105 vs 137</td>
<td>0.75 (0.58, 0.97)</td>
</tr>
<tr>
<td><strong>Nodal status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neoadjuvant CT (372)</td>
<td>39 vs 50</td>
<td>0.66 (0.43, 1.00)</td>
</tr>
<tr>
<td>Negative (1099)</td>
<td>34 vs 58</td>
<td>0.59 (0.39, 0.91)</td>
</tr>
<tr>
<td>1-3 positive nodes (976)</td>
<td>50 vs 80</td>
<td>0.61 (0.43, 0.87)</td>
</tr>
<tr>
<td>≥4 positive nodes (953)</td>
<td>95 vs 132</td>
<td>0.64 (0.49, 0.83)</td>
</tr>
<tr>
<td><strong>All patients (3401)</strong></td>
<td>218 vs 321</td>
<td>0.64 (0.54, 0.76)</td>
</tr>
</tbody>
</table>

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**Overall Result**
Exploratory DFS subgroup analysis (ITT): 1 year trastuzumab vs observation (2)

<table>
<thead>
<tr>
<th>Subgroup (no. patients)</th>
<th>No. events T vs obs</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathological tumour size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any (neoadjuvant CT) (372)</td>
<td>39 vs 50</td>
<td>0.66 (0.43, 1.00)</td>
</tr>
<tr>
<td>0-2 cm (1351)</td>
<td>61 vs 95</td>
<td>0.65 (0.47, 0.90)</td>
</tr>
<tr>
<td>&gt;2-5 cm (1482)</td>
<td>97 vs 150</td>
<td>0.55 (0.43, 0.71)</td>
</tr>
<tr>
<td>&gt;5 cm (171)</td>
<td>20 vs 25</td>
<td>1.14 (0.63, 2.06)</td>
</tr>
<tr>
<td><strong>Hormone receptor status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER-negative + PgR-negative (1627)</td>
<td>126 vs 190</td>
<td>0.63 (0.50, 0.78)</td>
</tr>
<tr>
<td>ER-negative + PgR-positive (172)</td>
<td>12 vs 12</td>
<td>0.77 (0.34, 1.74)</td>
</tr>
<tr>
<td>ER-positive + PgR-negative (460)</td>
<td>26 vs 39</td>
<td>0.82 (0.50, 1.34)</td>
</tr>
<tr>
<td>ER-positive + PgR-positive (984)</td>
<td>46 vs 61</td>
<td>0.63 (0.43, 0.93)</td>
</tr>
<tr>
<td><strong>Histologic grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 - poorly differentiated (2047)</td>
<td>157 vs 201</td>
<td>0.73 (0.59, 0.90)</td>
</tr>
<tr>
<td>2 - moderately differentiated (1111)</td>
<td>47 vs 97</td>
<td>0.46 (0.33, 0.65)</td>
</tr>
<tr>
<td><strong>Surgery for primary tumour</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast-conserving procedure (1432)</td>
<td>77 vs 121</td>
<td>0.59 (0.44, 0.79)</td>
</tr>
<tr>
<td>Mastectomy (1968)</td>
<td>141 vs 200</td>
<td>0.68 (0.55, 0.84)</td>
</tr>
<tr>
<td><strong>Previous radiotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (2606)</td>
<td>183 vs 265</td>
<td>0.64 (0.53, 0.77)</td>
</tr>
<tr>
<td>No (795)</td>
<td>35 vs 56</td>
<td>0.64 (0.42, 0.98)</td>
</tr>
<tr>
<td><strong>Type of (neo)adjuvant CT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No anthracyclines (202)</td>
<td>12 vs 15</td>
<td>0.76 (0.35, 1.62)</td>
</tr>
<tr>
<td>Anthracyclines, no taxanes (2310)</td>
<td>132 vs 221</td>
<td>0.57 (0.46, 0.71)</td>
</tr>
<tr>
<td>Anthracyclines + taxanes (889)</td>
<td>74 vs 85</td>
<td>0.80 (0.59, 1.10)</td>
</tr>
<tr>
<td>All patients (3401)</td>
<td>218 vs 321</td>
<td>0.64 (0.54, 0.76)</td>
</tr>
</tbody>
</table>

Overall Result: 0.64 (0.54, 0.76)
## Adverse Events (AE)

<table>
<thead>
<tr>
<th></th>
<th>No. events (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observation (n=1466)</td>
<td>1 year trastuzumab (n=1688)</td>
<td></td>
</tr>
<tr>
<td>Patients with ≥1 grade 3/4 AE</td>
<td>88 (6.0)</td>
<td>190 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Patients with ≥1 serious AE</td>
<td>97 (6.6)</td>
<td>156 (9.2)</td>
<td></td>
</tr>
<tr>
<td>Fatal AE</td>
<td>3&lt;sup&gt;b&lt;/sup&gt; (0.2)</td>
<td>9&lt;sup&gt;c&lt;/sup&gt; (0.5)</td>
<td></td>
</tr>
<tr>
<td>Treatment withdrawals</td>
<td>172 (10.2&lt;sup&gt;d&lt;/sup&gt;)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>b</sup>Cardiac failure, suicide, unknown
<sup>c</sup>Cerebral haemorrhage, cerebrovascular accident, sudden death, appendicitis, intestinal obstruction, unknown following a road accident, carcinomatous lymphangitis, 2 unknown
The intestinal obstruction occurred after a second non-breast malignancy
<sup>d</sup>Safety in 6.8%, refusal in 2.5%, other in 0.8%
## Cardiac Safety

<table>
<thead>
<tr>
<th>Condition</th>
<th>Observation n=1708</th>
<th>1 yr trastuzumab n=1678</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Severe CHF (NYHA III and IV)</td>
<td>0 (0.0)</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>Symptomatic CHF (II, III and IV)</td>
<td>3 (0.2)</td>
<td>36 (2.1)</td>
</tr>
<tr>
<td>Confirmed significant LVEF drop</td>
<td>9 (0.5)</td>
<td>51 (3.0)</td>
</tr>
<tr>
<td>Trastuzumab discontinued due to cardiac problems</td>
<td></td>
<td>72 (4.3)</td>
</tr>
<tr>
<td>St. Gallen update</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk Assessment of Breast Cancer patients and Selection of optimal Adjuvant Therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>sensitive</th>
<th>sensitivity unknown</th>
<th>non-sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Risk</strong></td>
<td>Endocrine therapy no treatment</td>
<td>Endocrine therapy no treatment</td>
<td>Controversial</td>
</tr>
<tr>
<td>Node negative AND all of the following features:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological tumor diameter ≤2cm, AND Grade 1, AND Absence of extensive peritumoral vascular invasion, AND ER and/or PgR expressed, AND HER2/neu gene neither overexpressed nor amplified, AND Age ≥35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate Risk</strong></td>
<td>Endocrine Therapy alone or chemo→ Endocrine Therapy (chemo + Endocrine therapy)</td>
<td>Chemo→ Endocrine Therapy (Chemo + Endocrine therapy)</td>
<td>Chemo Trastuzumab</td>
</tr>
<tr>
<td>Node negative AND at least one of the following features:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological tumor diameter &gt;2cm, OR Grade 2–3, OR Presence of extensive peritumoral vascular invasion, OR ER and/or PgR absent, OR HER2/neu gene overexpressed or amplified, OR Age &lt;35 OR Node positive (1–3 involved nodes) AND ER and/or PgR expressed, AND HER2/neu gene neither overexpressed nor amplified</td>
<td></td>
<td>Trastuzumab</td>
<td></td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>Chemo→ Endocrine Therapy (Chemo + Endocrine therapy)</td>
<td>Chemo→ Endocrine Therapy (Chemo + Endocrine therapy)</td>
<td>Chemo Trastuzumab</td>
</tr>
<tr>
<td>Node positive (1–3 involved nodes) AND ER and/or PgR absent, OR HER2/neu gene overexpressed or amplified OR Node positive (4 or more involved nodes)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Trastuzumab Adjuvant Therapy makes changes in HER2+ breast cancer therapy

- The number of recurrence in HER2+ is expected to decrease dramatically in Japan.
- HER2+ breast cancer, which used to be a poor prognostic factor, will turn into a better prognostic factor with proper treatment.
- Trastuzumab treatment for a limited period (1 year) is cost-effectively advantageous.
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