Role of Trastuzumab in Small HER2+ Early Breast Cancer
Pros

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  – What is a small tumor?
  – Characteristics of low risk tumor
  – Role of HER2 as a prognostic factor

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Introduction

- What is a small tumor?
- Characteristics of low risk tumor
- Role of HER2 as a prognostic factor
**What is a ‘small’ tumor?**

**TNM classification of malignant tumor**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma <em>in situ</em>: intraductal carcinoma or lobular carcinoma <em>in situ</em> or Paget’s disease of the nipple with no associated tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤2 cm in greatest dimension</td>
</tr>
<tr>
<td>T1 mic</td>
<td>Microinvasion ≤0.1 cm into surrounding tissue</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor &gt;0.1 cm and ≤0.5 cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt;0.5 cm and ≤1 cm in greatest dimension</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor &gt;1 cm and ≤2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>The tumor &gt;2 cm and &lt;5 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>The tumor &gt;5 cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with direct extension to (a) chest wall or (b) skin</td>
</tr>
<tr>
<td>T4a</td>
<td>The tumor has spread into the chest wall</td>
</tr>
<tr>
<td>T4b</td>
<td>Oedema (including peau d’orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast</td>
</tr>
<tr>
<td>T4c</td>
<td>Both 4a and 4b</td>
</tr>
<tr>
<td>T4d</td>
<td>Inflammatory carcinoma</td>
</tr>
</tbody>
</table>

*T: primary tumour*

*Sobin L, *et al*. TNM classification of malignant tumours. 7th ed., 2010*
What other characteristics define a ‘low-risk’ patient?

- In addition to small tumour size, other factors are associated with a low risk of breast cancer recurrence\(^1,2\)
- Low-risk* patients are node negative
  - AND have all of the following features:\(^1\)
    - \(pT \leq 2\text{cm}\)
    - Histological and/or Nuclear Grade 1
    - Absence of extensive peritumoural vascular invasion\(^\S\)
    - Estrogen receptor and/or progesterone receptor expressed\(\|\)
    - HER2 neither overexpressed nor amplified
    - Aged \(\geq 35\) years

\(^\*\) Some panel members view \(pT1a\) and \(pT1b\) (i.e. \(pT < 1\) cm) tumours with node-negative disease as representing low risk even if higher grade and/or younger age

\(^\S\) Extensive peritumoural vascular invasion (i.e. neoplastic emboli seen in two or more blocks of the tumour) was recognized as a discriminatory feature of increased risk; its presence defined intermediate risk for node-negative disease, but did not influence risk category for node-positive disease

\(\|\) Some cases such as medullary carcinoma and apocrine carcinoma may be regarded as low risk despite the absence of HR expression

The effect of HER2 status on survival of patients with small breast tumors

Analysis of 965 patients with T1a/b node-negative tumors who did not receive adjuvant systemic therapy revealed lower recurrence-free survival rates in patients with HER2-positive breast cancer than those with HER2-negative disease.

No patient with HER2-positive breast cancer is ‘low-risk’

HER2 overexpression predicts recurrence in patients with small tumors (<2 cm)

- Small (<10 mm) HER2-negative cancers were associated with >90% 9-year distant disease-free survival, irrespective of histological grade.
- HER2 positivity predicts recurrence in both 1–10 mm and 11–20 mm tumors and is superior to ER as a prognostic factor in small tumors.

HER2-positive status is a greater risk factor than HR-positive or triple-negative status in patients with small tumors.

Patients with small tumors and HER2-positive disease have the lowest rates of recurrence-free survival when compared with HR-positive or TNBC.

- 1112 patients with a T1a,bN0 breast cancer diagnosed between 1990 and 2002 who did not receive chemotherapy or trastuzumab were assessed.

HR, hormone receptor
Survival of HER2-positive patients with small tumors is also dependent on age

- 1112 patients with a T1a,bN0 breast cancer diagnosed between 1990 and 2002 who did not receive chemotherapy or trastuzumab were assessed
- Younger patients with small tumors experience higher recurrence within 5 years when disease is left untreated

Prognosis for patients with small tumors and the role of HER2 status and other factors

No patient with HER2-positive breast cancer is ‘low-risk’

HER2-positivity is a negative prognostic factor for the probability of relapse in patients with small tumors who do not receive systemic adjuvant therapy\(^1\)

Age, hormone receptor status, the presence of lymphatic vessel invasion or poor nuclear grade can all affect prognosis in patients with small tumors\(^2-4\)

Several large, randomized trials established the benefits of adjuvant trastuzumab with chemotherapy.

However, the benefit for women with small, node-negative HER2-positive (HER2+) disease is unknown, as these patients were largely excluded from these trials.
Trastuzumab plus chemotherapy is likely to benefit patients with small, node-negative, HER2-positive BC.

Invasive 3-year DFS

<table>
<thead>
<tr>
<th>Tumors ≤2 cm</th>
<th>Patients (%) ± 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT only</td>
<td>n = 106</td>
</tr>
<tr>
<td>Trastuzumab + CT</td>
<td>n = 155</td>
</tr>
</tbody>
</table>

p < 0.0001

<table>
<thead>
<tr>
<th>Tumors ≤1 cm</th>
<th>Patients (%) ± 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT only</td>
<td>n = 45</td>
</tr>
<tr>
<td>Trastuzumab + CT</td>
<td>n = 54</td>
</tr>
</tbody>
</table>

p = 0.0198

Trastuzumab plus chemotherapy improves DFS rates in small tumors compared with chemotherapy alone.

Retrospective Study at Memorial Sloan-Kettering Cancer Center, New York, USA.

Outcomes of HER2-positive early breast cancer patients in the pre-trastuzumab and trastuzumab eras: a real-world multicenter observational analysis

The RETROHER study from Italy

Cohort A: adjuvant CTx (N=352) mostly until 2005
Cohort B: adjuvant CTx + trastuzumab (N=573) since 2006

Small tumors in pivotal trial
Trastuzumab treatment of patients with tumors ≤2 cm: HERA study

Patients with small tumours derive similar benefit from 1 year of trastuzumab treatment as the overall population

<table>
<thead>
<tr>
<th>Subgroup (number of patients)</th>
<th>Number of events trastuzumab vs. observation</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological tumour size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any (neoadjuvant chemo) (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>All patients (3401)</td>
<td>218 vs. 321</td>
<td>0.64 (0.54, 0.76)</td>
</tr>
</tbody>
</table>

HR, hazard ratio
## HERA: trastuzumab benefit extends to patients with relatively favourable prognosis

<table>
<thead>
<tr>
<th>Population/treatment</th>
<th>Patients, n</th>
<th>DFS events, n (%)</th>
<th>3-year DFS, %</th>
<th>Difference in 3-year DFS, %</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year trastuzumab</td>
<td>544</td>
<td>34 (6.3)</td>
<td>90.8</td>
<td>5.8</td>
<td>0.59</td>
</tr>
<tr>
<td>Observation</td>
<td>555</td>
<td>58 (10.5)</td>
<td>84.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node negative (1.1–2.0 cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year trastuzumab</td>
<td>252</td>
<td>12 (4.8)</td>
<td>91.3</td>
<td>4.6</td>
<td>0.53</td>
</tr>
<tr>
<td>Observation</td>
<td>258</td>
<td>23 (8.9)</td>
<td>86.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone receptor-negative and node-negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year trastuzumab</td>
<td>281</td>
<td>23 (8.2)</td>
<td>87.1</td>
<td>0.6</td>
<td>0.68</td>
</tr>
<tr>
<td>Observation</td>
<td>285</td>
<td>33 (11.6)</td>
<td>86.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone receptor-positive and node-negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year trastuzumab</td>
<td>263</td>
<td>11 (4.2)</td>
<td>94.8</td>
<td>11.3</td>
<td>0.46</td>
</tr>
<tr>
<td>Observation</td>
<td>270</td>
<td>25 (9.3)</td>
<td>83.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall study population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year trastuzumab</td>
<td>1703</td>
<td>218 (12.8)</td>
<td>80.6</td>
<td>6.3</td>
<td>0.64</td>
</tr>
<tr>
<td>Observation</td>
<td>1698</td>
<td>321 (18.9)</td>
<td>74.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DFS, disease-free survival  
BCIRG 006: Similar DFS benefit with trastuzumab in T1c vs. larger tumors


AC-TH vs. AC-T

Node−: HR better
Node+: HR better
Hormone receptor−: HR better
Hormone receptor+: HR better
Size <2 cm: AC-TH better
Size >2 cm: AC-T better

TCH vs. AC-T

Node−: HR better
Node+: HR better
Hormone receptor−: HR better
Hormone receptor+: HR better
Size <2 cm: TCH better
Size >2 cm: AC-T better

3-year DFS gain
Node-negative: 7%
All: 6%
BCIRG 006: Similar OS benefit with trastuzumab in T1c vs. larger tumors

Subgroup
- Node- vs. Node+
- Hormone receptor- vs. Hormone receptor+
- Size <2 cm vs. Size >2 cm

AC-TH vs. AC-T
- Node- vs. Node+
- Hormone receptor- vs. Hormone receptor+
- Size <2 cm vs. Size >2 cm

TCH vs. AC-T
- Node- vs. Node+
- Hormone receptor- vs. Hormone receptor+
- Size <2 cm vs. Size >2 cm

3-year OS gain
- Node-negative 2.5%
- All 3.5%

☆ OS, overall survival
N9831/B-31: Trastuzumab increases OS regardless of tumor size

<table>
<thead>
<tr>
<th>Tumour size (cm)</th>
<th>No. of events</th>
<th>HR with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>AC→P</td>
</tr>
<tr>
<td>0–2</td>
<td>1598</td>
<td>129</td>
</tr>
<tr>
<td>2.1–5.0</td>
<td>2096</td>
<td>239</td>
</tr>
<tr>
<td>5.1+</td>
<td>345</td>
<td>50</td>
</tr>
</tbody>
</table>

*H, trastuzumab; P, paclitaxel*  
Efficacy Of Adjuvant Trastuzumab Compared With No Trastuzumab for Patients With HER2-Positive Breast Cancer And Tumors ≤ 2cm: A Meta-analysis Of The Randomized Trastuzumab Trials


Long term follow up on behalf of the Trastuzumab Overview Group

O'Sullivan CCM, et al. ASCO 2014(abstract 508)
# Trials Included in This Analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>HER2+ Tumors</th>
<th>Timing of Trastuzumab</th>
<th>Duration of Trastuzumab</th>
<th>Chemotherapy regimen</th>
<th>Median follow up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA</td>
<td>5,102</td>
<td>Sequential</td>
<td>1 or 2 years</td>
<td>Any – 94% A; 26% A and T</td>
<td>8.0</td>
</tr>
</tbody>
</table>
| NCCTG N9831 | 3,505      | Concurrent or sequential | 1 year                  | AC → T  
             AC → w TH  
             AC → w T → H | 8.7                      |
| NSABP B-31 | 3,222        | Concurrent            | 1 year                  | AC → T  
             AC → TH      | 9.4                      |
| PACS 04 | 528          | Sequential            | 1 year                  | FEC → H  
             DE → H      | 5.0                      |
| FinHER  | 232          | Concurrent            | 9 weeks                 | D+/-H → FEC  
             V+/-H → FEC | 5.6                      |

A - doxorubicin; T - paclitaxel; w - weekly; H - trastuzumab; F - 5-fluorouracil; E - epirubicin; C - cyclophosphamide; D - docetaxel; V - vinorelbine
# Meta-analysis of randomized trastuzumab trials in patients with small tumors

## Study design
- Meta-analysis of five trials: HERA, NCCTG N9831, NSABP B31, PACS 04 and FinHER

## Study aim
- Assess efficacy of adjuvant trastuzumab vs. no adjuvant trastuzumab for patients with small tumors ≤2 cm

## Patient population
- 4220 patients had tumors ≤2 cm, a known number of axillary nodes and HR status
- Trastuzumab: n=2588; no trastuzumab: n=1632
- Analysis included patients with tumors ≤2cm (T1a, T1b and T1c) and 0–1, 2–3 and ≥4 positive lymph nodes
- Almost all patients had T1c disease with axillary node involvement

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*O’Sullivan CCM, et al. ASCO 2014(abstract 508)*
RESULTS: HR-Positive Disease: Tumor Size (≤ 2cm) & Nodal Status

N-2,263

Presented by: Ciara C. O'Sullivan  email: ciara.o'sullivan@nih.gov

Presented By Ciara O'Sullivan at 2014 ASCO Annual Meeting
Cumulative Incidence of Recurrence or Death: HR-Positive Disease with Tumors ≤ 2cm and N 0/1

Presented By Ciara O'Sullivan at 2014 ASCO Annual Meeting
HR-negative disease: Tumor Size ≤ 2cm & Nodal Status

N = 1,957
Cumulative Incidence of Recurrence or Death: HR-Negative Disease with Tumors ≤ 2cm

**Cumulative Recurrence**

- Observation
- Trastuzumab

8 year gain 9.4% (s.e. 2.8%)
Logrank p<0.0001
Hazard ratio 0.7

- 27.6% (±2.8)
- 33.4% (±3.0)
- 40.8% (±3.2)
- 48.5% (±3.5)
- 54.0% (±3.7)
- 59.5% (±3.9)
- 64.5% (±4.1)
- 69.5% (±4.3)
- 74.0% (±4.5)
- 78.5% (±4.7)

**Cumulative Deaths**

- Observation
- Trastuzumab

8 year gain 8.8% (s.e. 2.1%)
Logrank p=0.0001
Hazard ratio 0.6

- 8.3% (±1.8)
- 12.4% (±2.0)
- 17.5% (±2.2)
- 21.2% (±2.4)
- 25.5% (±2.6)
- 30.0% (±2.8)
- 34.6% (±3.0)
- 39.3% (±3.2)
- 44.0% (±3.4)
- 48.7% (±3.6)
Trastuzumab in the treatment of patients with small tumors* in pivotal trial

Results from trastuzumab adjuvant trials show that trastuzumab benefits patients regardless of tumor size$^{1-4}$

Meta-analyses show that patients with small tumors $\leq 2$ cm benefit substantially from adjuvant trastuzumab therapy in terms of both DFS and OS, regardless of HR status$^5$

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* T1c tumors
3. Slamon D, et al. SABCS 2008(abstract 52);
4. Romond EH, et al. SABCS 2012(abstract S5-5);
APT trial study design: Adjuvant paclitaxel and trastuzumab for node-negative HER2-positive breast cancer

- HER2+
- ER+ or ER–
- Node-negative tumour <3 cm

Planned N = 400

Paclitaxel (80 mg/m²) + trastuzumab (2 mg/kg) x 12 weeks (q1w)*

q3w doses of trastuzumab (6 mg/kg) x 13 weeks**

* Radiation and hormonal therapy was initiated after completion of paclitaxel
** Dosing could alternatively be 2 mg/kg IV weekly for 40 weeks

q3w, every 3 weeks
Key eligibility criteria\(^1,2\)
- HER2+ (IHC 3+ or FISH ≥2.0) invasive breast cancer
- Invasive tumour ≤3.0 cm
- One lymph node micrometastasis allowed if negative axillary dissection
- LVEF ≥50%
- No prior myocardial infarction or uncontrolled hypertension
- No grade ≥2 neuropathy
- No prior malignancy within past 5 years
- No prior history of invasive breast cancer

Statistical considerations\(^1,2\)
- **Primary endpoint:** DFS per STEEP\(^3\) criteria
- **Null hypothesis:** 3-year failure rate of 9.2% (unacceptable)
- **Alternate hypothesis:** 3-year failure rate of 5% (successful)
- Planned sample size of N = 400
- Interim futility analyses at 225 and 800 patient-years of follow-up
- Final analysis at 1600 patient-years, and reject null hypothesis with ≤39 events
- Group sequential Poisson test (one-sided type I error of 5%)
- 95% power accounting for futility analyses

- Results based on all data available as of 30 September 2013:
  - 1435 patient-years and median follow-up of 3.6 years

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## APT trial: Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>132</td>
<td>33</td>
</tr>
<tr>
<td>50–70 years</td>
<td>233</td>
<td>57</td>
</tr>
<tr>
<td>≥70 years</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td><strong>Size of primary tumour</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a &lt;0.5 cm</td>
<td>77</td>
<td>19</td>
</tr>
<tr>
<td>T1b 0.5–≤1.0</td>
<td>124</td>
<td>31</td>
</tr>
<tr>
<td>T1c 1.0–≤2.0</td>
<td>169</td>
<td>42</td>
</tr>
<tr>
<td>T2 2.0–≤3.0</td>
<td>36</td>
<td>9</td>
</tr>
<tr>
<td><strong>Histological grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I – Well differentiated</td>
<td>44</td>
<td>11</td>
</tr>
<tr>
<td>II – Moderately differentiated</td>
<td>131</td>
<td>32</td>
</tr>
<tr>
<td>III – Poorly differentiated</td>
<td>228</td>
<td>56</td>
</tr>
<tr>
<td><strong>HER2 status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>406</td>
<td>100</td>
</tr>
<tr>
<td><strong>HR status (ER and/or PR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>272</td>
<td>67</td>
</tr>
<tr>
<td>Negative</td>
<td>134</td>
<td>33</td>
</tr>
</tbody>
</table>

*PR, progesterone receptor*

# APT trial: Disease-free survival events

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
<th>Time to DFS event (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any recurrence or death</td>
<td>10 (2.5)</td>
<td>–</td>
</tr>
<tr>
<td>Local/regional recurrence*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral axilla (HER2-positive)</td>
<td>3 (0.7)</td>
<td>12, 20, 54</td>
</tr>
<tr>
<td>Ipsilateral breast (HER2-positive)</td>
<td>1 (0.2)</td>
<td>37</td>
</tr>
<tr>
<td>New contralateral primary breast cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2-positive</td>
<td>0 (0)</td>
<td>–</td>
</tr>
<tr>
<td>HER2-negative</td>
<td>3 (0.7)</td>
<td>12, 37, 59</td>
</tr>
<tr>
<td>Distant recurrence*</td>
<td>2 (0.5)</td>
<td>27, 46</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-breast cancer related</td>
<td>1 (0.2)</td>
<td>13</td>
</tr>
</tbody>
</table>

* Recurrence-free interval (RFI) event

# APT trial: Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate (%)</th>
<th>95% confidence interval (%)</th>
<th>Poisson p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year DFS (all patients)</td>
<td>98.7</td>
<td>97.6, 99.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3-year DFS (tumours &gt;1 cm)</td>
<td>–</td>
<td>96.0, 99.9</td>
<td>–</td>
</tr>
<tr>
<td>3-year DFS (tumours ≤1 cm)</td>
<td>–</td>
<td>98.4, 99.9</td>
<td>–</td>
</tr>
<tr>
<td>3-year DFS (HR-positive)</td>
<td>–</td>
<td>97.0, 99.9</td>
<td>–</td>
</tr>
<tr>
<td>3-year DFS (HR-negative)</td>
<td>–</td>
<td>97.7, 99.9</td>
<td>–</td>
</tr>
<tr>
<td>3-year RFI</td>
<td>99.2</td>
<td>98.3, 99.9</td>
<td>–</td>
</tr>
</tbody>
</table>

## APT trial: Adverse events

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>Maximum Grade [n (%)]</th>
<th>Total [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>81 (20)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>47 (12)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>39 (10)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26 (6)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>35 (9)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>28 (7)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>28 (7)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>23 (6)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>28 (7)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

**APT trial: Cardiac toxicity**

- Cardiac monitoring performed at:

![Cardiac Monitoring Chart]

<table>
<thead>
<tr>
<th>Event</th>
<th>n</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic congestive heart failure*</td>
<td>2</td>
<td>0.5 (0.1, 18.0)</td>
</tr>
<tr>
<td>Asymptomatic declines in LVEF**</td>
<td>13</td>
<td>3.2 (1.7, 5.4)</td>
</tr>
</tbody>
</table>

* Both patients had normalisation of LVEF after discontinuation of trastuzumab
** 11 of 13 patients were able to resume trastuzumab therapy after an interruption of trastuzumab

APT trial: Summary

- At a median follow-up of 3.6 years, the 3-year DFS rate was 98.7%
- Only 10 DFS events were seen in a total of 406 patients:
  - Two distant recurrences
  - Four invasive local/regional recurrences
  - Three contralateral HER2-positive tumours
  - One death due to ovarian cancer
- Few severe adverse events were noted
  - Only two patients experienced symptomatic CHF

The authors concluded that paclitaxel plus trastuzumab may be an acceptable treatment approach for low-risk HER2-positive BC

CHF, congestive heart failure

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 2.2015

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients
Adjuvant Tx in HR+ HER2+ disease

NCCN Guidelines Version 2.2015
Invasive Breast Cancer

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-POSITIVE DISEASE

- Tumor ≤ 0.5 cm
- Microinvasive

pN0

- Consider adjuvant endocrine therapy ± adjuvant chemotherapy with trastuzumab (category 2B)

pN1mi

- Adjuvant endocrine therapy or
- Adjuvant chemotherapy with trastuzumab followed by endocrine therapy

Tumor 0.6–1.0 cm

- Adjuvant endocrine therapy ± adjuvant chemotherapy with trastuzumab

Tumor > 1 cm

- Adjuvant endocrine therapy + adjuvant chemotherapy with trastuzumab (category 1)

Node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes)

- Adjuvant endocrine therapy + adjuvant chemotherapy with trastuzumab (category 1)

See Adjuvant Endocrine Therapy (BINV-J) and Neoadjuvant/Adjuvant Chemotherapy (BINV-K)
Adjuvant Tx in HR- HER2+ disease

NCCN Guidelines Version 2.2015
Invasive Breast Cancer

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-NEGATIVE - HER2-POSITIVE DISEASE

Histology:
- Ductal
- Lobular
- Mixed
- Metaplastic

Node positive (one or more metastases >2 mm to one or more ipsilateral axillary lymph nodes) → Adjuvant chemotherapy with trastuzumab (category 1)

Tumor ≤0.5 cm or Microinvasive → pN0 → Consider adjuvant chemotherapy with trastuzumab (category 2B)

Tumor 0.6–1.0 cm → pN1mi → Consider adjuvant chemotherapy with trastuzumab

Tumor >1 cm → Adjuvant chemotherapy with trastuzumab (category 1)

See Follow-Up (BINV-16)
**Current treatment guidelines recommend trastuzumab for some small tumors**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Trastuzumab treatment of small tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korean clinical guidelines</td>
<td>• Adjuvant chemotherapy plus trastuzumab for HER2-positive tumors that are node-positive or are node-negative and more than 1 cm</td>
</tr>
<tr>
<td>St. Gallen Consensus Statement¹</td>
<td>• Threshold for use of anti-HER2 therapy was defined as pT1b or larger tumour or node-positivity</td>
</tr>
<tr>
<td>ESMO clinical guidelines²</td>
<td>• The use of trastuzumab should be discussed with women with small, node-negative breast cancers</td>
</tr>
<tr>
<td></td>
<td>• Due to relatively high failure risk even in patients with N0 tumours &lt;1 cm, trastuzumab should also be considered in this patient group, in particular in ER-negative disease (IV B)</td>
</tr>
<tr>
<td>NCCN guidelines³</td>
<td>• Adjuvant chemotherapy plus trastuzumab for HER2-positive tumours that are node-positive or are node-negative and more than 1 cm</td>
</tr>
<tr>
<td></td>
<td>• For node-negative tumours that are 0.6–1.0 cm, the guidelines recommend considering adjuvant chemotherapy and trastuzumab</td>
</tr>
<tr>
<td></td>
<td>• For node-negative tumours that are 5 mm or less in size, no adjuvant therapy is recommended, other than consideration of hormonal therapy if the tumour is also ER-positive</td>
</tr>
</tbody>
</table>

**IV B = Retrospective cohort studies or case–control studies; Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended**

3. NCCN Clinical Practice Guidelines in Oncology v.2.2015.
Approval and Reimbursement of Adjuvant Trastuzumab in Asia

❖ Approval in Node (-) HER2 + eBC
  – China, Hong Kong, India, Japan
  – Korea, Singapore
  – Taiwan

❖ Reimbursement
  – China, Hong Kong, India, Japan
  – Korea, Singapore
  – Taiwan: Reimbursement only in node (+) eBC
Biomarker?

Increased expression of immune function genes may provide a means of predicting benefit from adjuvant trastuzumab.

- Immune gene enrichment was linked to increased RFS in arms B and C (+Trastuzumab) (HR, 0.35; 95% CI, 0.22 to 0.55; P < .001), whereas arm B and C patients who did not exhibit immune gene enrichment did not benefit from trastuzumab (HR, 0.89; 95% CI, 0.62 to 1.28; P = .53).

# Summary of Adjuvant Trastuzumab in Small HER2+ Breast Cancer

<table>
<thead>
<tr>
<th>ER Status</th>
<th>Tumor Size</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-</td>
<td>&lt;1mm</td>
<td>No</td>
</tr>
<tr>
<td>ER-</td>
<td>0.1 ~ 0.5 cm</td>
<td>Selectively</td>
</tr>
<tr>
<td>ER-</td>
<td>0.6 ~ 1.0 cm</td>
<td>Yes</td>
</tr>
<tr>
<td>ER-</td>
<td>1.1 ~ 2.0 cm</td>
<td>Yes</td>
</tr>
<tr>
<td>ER+</td>
<td>No</td>
<td>Generally Not</td>
</tr>
<tr>
<td>ER+</td>
<td>0.1 ~ 0.5 cm</td>
<td>Sometimes Consider</td>
</tr>
<tr>
<td>ER+</td>
<td>0.6 ~ 1.0 cm</td>
<td>Yes</td>
</tr>
<tr>
<td>ER+</td>
<td>1.1 ~ 2.0 cm</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Summary of Adjuvant Trastuzumab in Small HER2 + Breast Cancer
Current Situation in Korea

<table>
<thead>
<tr>
<th>ER-</th>
<th>&lt;1mm</th>
<th>0.1 ~ 0.5 cm</th>
<th>0.6 ~ 1.0 cm</th>
<th>1.1 ~ 2.0 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No (Frustration)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ER+</th>
<th>&lt;1mm</th>
<th>0.1 ~ 0.5 cm</th>
<th>0.6 ~ 1.0 cm</th>
<th>1.1 ~ 2.0 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Thank You!

2008 Oncology on Canvas: Expressions of a Cancer Journey
International Art Competition and Exhibition