Role of Trastuzumab in Small HER2+ Early Breast Cancer

CONS

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Founding Convenor
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The Shilla Jeju Hotel, Jeju Island
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Disclosures

• Janice Tsang

• Consultant or Advisory Role: AstraZeneca, Eisai, GlaxoSmithKline, Novartis & Pfizer
“Role of Trastuzumab in Small HER2+ Early Breast Cancer ”
Role of Trastuzumab in Early Breast Cancer

CONS
“Role” – From Wikipedia...

• “A role (also rôle or social role) is a set of connected behaviours, rights, obligations, beliefs, and norms as conceptualised by people in a social situation.
Is there a role?...And from what perspective?

“Role of Trastuzumab in Small HER2+ Early Breast Cancer”

-From oncologists’ point of view
-From patients’ point of view
-From family or carers’ point of view
-From healthcare administrators or Mx
Support from Professor Seock-Ah Im...

“Role of Trastuzumab in Small HER2+ Early Breast Cancer - PROS”

1) “Evidence-based Medicine”
2) “Data”
3) “Guideline”...

From principal investigator and oncologist’s point of view...
From Oncologists’ Perspective...
(including EBM and “Data”...)

“Role of Trastuzumab in Small HER2+ Early Breast Cancer”

Even among the oncologists, there are different perspectives with mixed concerns...
Defining “Small HER2+” EBC...
Unanswered Questions before we could generalize to ALL Small HER2 + EBC...

1. The extent of benefits derived from adjuvant trastuzumab observed needs to be considered in light of the small number of RFS events and deaths in these studies.

2. With the exception of the Breast Cancer International Research Group BCIRG-006 trial, patients with node-negative tumours < 1 cm in size were excluded from the landmark adjuvant trials.
Unanswered Questions before we could generalize to ALL Small HER2 + EBC...

3. A meta-analysis of the adjuvant trastuzumab trials found that the use of trastuzumab resulted in an approximately 50% reduction in the risk of early recurrence and mortality, irrespective of nodal status.

4. If the same benefit applies to small, <1 cm, HER2-positive tumors it would result in an absolute risk reduction of 4% to 5%

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
Favorable Prognosis Seen for Patients with HER2-Positive BC and Hormone Receptor (HR)-Positive Tumors ≤ 2cm & 0/1 N+ Treated with Chemotherapy/ Hormones/ Trastuzumab


5 year DFS 91%
5 year OS 97%

"Is there an advantage of trastuzumab compared with no trastuzumab for patients with small tumors?"
Efficacy Analysis

• **Aim:**
  – Compare efficacy of trastuzumab vs. no trastuzumab in pts with small HER2-positive breast cancer (BC) in the adjuvant randomized trastuzumab trials

• **Methods:**
  – Analysis performed separately for hormone receptor (HR)-positive and HR-negative cohorts
  – Individual patient meta-analysis: tumors ≤ 2 cm (T1a, T1b and T1c) & 0-1, 2-3 and ≥ 4 positive nodes.

Presented by: Ciara C. O’Sullivan  email: ciara.o’sullivan@nih.gov
## HER2-Positive Tumors ≤ 2cm

<table>
<thead>
<tr>
<th>Trial</th>
<th>HER2+ Tumors</th>
<th>HER2+ Tumors ≤2cm</th>
<th>Received Trastuzumab</th>
<th>DID NOT receive Trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA</td>
<td>5,102</td>
<td>2,002</td>
<td>1,320</td>
<td>682</td>
</tr>
<tr>
<td>NCCTG N9831</td>
<td>3,505</td>
<td>756</td>
<td>405</td>
<td>351</td>
</tr>
<tr>
<td>NSABP B-31</td>
<td>3,222</td>
<td>1,146</td>
<td>711</td>
<td>435</td>
</tr>
<tr>
<td>PACS 04</td>
<td>528</td>
<td>235</td>
<td>106</td>
<td>129</td>
</tr>
<tr>
<td>FinHER</td>
<td>232</td>
<td>81</td>
<td>46</td>
<td>35</td>
</tr>
<tr>
<td><strong>TOTAL PTS</strong></td>
<td><strong>12,589</strong></td>
<td><strong>4,220</strong></td>
<td><strong>2,588</strong></td>
<td><strong>1,632</strong></td>
</tr>
</tbody>
</table>

Presented by: Ciara C. O'Sullivan  
email: ciara.o'sullivan@nih.gov
DFS for HR-Negative Disease Treated With or Without Trastuzumab: Tumors ≤ 2cm

<table>
<thead>
<tr>
<th>Study</th>
<th>Logrank p Value</th>
<th>Obs</th>
<th>Tras</th>
<th>Time in Years</th>
<th>Percentage Disease Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA</td>
<td>0.071</td>
<td>621</td>
<td>328</td>
<td>0  2  4  6  8 10</td>
<td>0.8  0.6  0.4  0.2  0.0</td>
</tr>
<tr>
<td>N9831</td>
<td>0.048</td>
<td>342</td>
<td>174</td>
<td>0  2  4  6  8 10</td>
<td>0.8  0.6  0.4  0.2  0.0</td>
</tr>
<tr>
<td>NSABP_B31</td>
<td>1.7e-06</td>
<td>181</td>
<td>183</td>
<td>0  2  4  6  8 10</td>
<td>0.8  0.6  0.4  0.2  0.0</td>
</tr>
<tr>
<td>FinHer</td>
<td>0.7</td>
<td>25</td>
<td>25</td>
<td>0  2  4  6  8 10</td>
<td>0.8  0.6  0.4  0.2  0.0</td>
</tr>
<tr>
<td>PACS04</td>
<td>0.6</td>
<td>45</td>
<td>45</td>
<td>0  2  4  6  8 10</td>
<td>0.8  0.6  0.4  0.2  0.0</td>
</tr>
</tbody>
</table>

Study-to-study heterogeneity is statistically significant

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

• Patients with tumors ≤ 2 cm benefitted substantially in terms of both DFS and OS from trastuzumab therapy

  - But, almost all had T1c disease and positive axillary lymph nodes, i.e. a very selected group of patients

• Proportional benefit was similar for HR-positive and HR-negative cohorts, but the patterns and incidence of relapse appeared to differ over follow up time

• Trastuzumab therapy contributed to the very favorable results we previously reported for patients with HR-positive tumors ≤2cm with 0-1 pos nodes

A retrospective analysis of data on all women with node-negative, HER2-positive breast cancers < 2 cm diagnosed between 1 January 2001 and 31 December 2011 and treated at 4 cancer centers in Sydney, Australia was undertaken. The primary outcomes were recurrence-free survival (RFS) and overall survival (OS). Results: In total, 128 patients with node-negative, HER2-positive breast cancers < 2 cm were identified.

Small HER2-Positive Breast Cancer: Should Size Affect Adjuvant Treatment? Annette Tognela, Jane Beith, Belinda Kiely, Patricia Bastick, Jodi Lynch, Joseph Descollar, Kelly Mok

Abstract
Limited data exist regarding the effect of adjuvant trastuzumab in women with small, node-negative, HER2-positive breast cancers. We examined outcomes for women with ≤ 2-cm, node negative, HER2-positive breast cancer treated in 4 cancer centers in Australia and found that adjuvant trastuzumab administered with chemotherapy reduced recurrence and improved survival.

Introduction: The adjuvant trastuzumab trials largely excluded women with small, node-negative, HER2-positive breast cancers. Accordingly, limited data exist regarding the effect of trastuzumab in the management of these patients. Our aim was to assess the outcomes of, and treatments administered to, women with small (< 2 cm), node-

Small HER2+ Early Breast Cancer is a heterogeneous population...

**TABLE 1. Retrospective Series Including Outcomes for Patients With Small HER2-Positive Tumors**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>HER2+</th>
<th>Stage</th>
<th>% Who Received HER2-Directed Therapy</th>
<th>Outcomes in HER2+ Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rom 2013^1^</td>
<td>960</td>
<td>106</td>
<td>T1a-cN0</td>
<td>42.5%</td>
<td>1-y: DFS: 97.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DDFS: 98.5%</td>
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<td></td>
<td></td>
<td>OS: 100%</td>
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<td>10-y: DFS: 73%</td>
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<td></td>
<td>LRFS: 92%</td>
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<td></td>
<td>MFS: 80%</td>
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<td></td>
<td>OS: 84%</td>
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<td>10-y: RFS: 65.9%</td>
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<td></td>
<td></td>
<td>DRFS: 71.2%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>BCSS: 75.5%</td>
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<tr>
<td>Rouanet 2014^2^</td>
<td>714</td>
<td>44</td>
<td>T1a-bN0</td>
<td>None</td>
<td>5-y: RFS: 77.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DRFS: 86.4%</td>
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<td></td>
<td></td>
<td>5-y: DFS: 92% (HR+)</td>
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<td></td>
<td>DFS: 91% (HR-)</td>
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<td></td>
<td>RFI: 94.9% (HR+)</td>
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<td>RFI: 95.1% (ER-)</td>
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<td>5-y: OS: 95% (HR+, no TR)</td>
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<td>OS: 93% (T1a HR-, no TR)</td>
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<td>OS: 100% (T1b HR-, no TR)</td>
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**Abbreviations:** +, positive; -, negative; BCSS, breast cancer-specific survival; DDFS, distant disease-free survival; DFS, disease-free survival; DRFS, distant recurrence-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LRFS, local recurrence-free survival; MFS, metastasis-free survival; OS, overall survival; RFI, recurrence-free interval; RFS, recurrence-free survival; TR, trastuzumab.
Small HER2+ Early Breast Cancer is a heterogeneous population...

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These retrospective analyses suggest that patients with stage I HER2-positive cancers may have worse outcomes compared with those with other breast cancer subtypes. However, more recent studies have suggested that small HER2-positive cancers have favorable outcomes overall, even in the absence of trastuzumab-based chemotherapy.
HER2+ EBC that express Hormone Receptor (HR) are clearly different from those that are HR negative at the molecular level, resulting in different responses to chemotherapy and HER-2 directed agents

“HR positive, HER2+ breast cancers appear to be heterogeneous with a significant percentage having the luminal A phenotype...Further clinical trials could focus on the potential omission of chemotherapy in favour of coinhibiting ER and HER2 in this subset of HER2+ breast cancers”

Unanswered Questions before we could generalize to ALL Small HER2 + EBC...

5. Another limitation is that it is not possible to determine the benefit of trastuzumab therapy above and beyond that provided by adjuvant chemotherapy, as most of the small tumour patients receive both trastuzumab with adjuvant chemotherapy.

6. The use of adjuvant trastuzumab alone in the small HER2+ EBC especially those T1a and T1b tumours needs further exploration and study.
No single standard treatment exists for patients with small, node-negative, HER2 positive EBC...

“The regimen we used in this study was associated with patient outcomes that were better than expected on the basis of historical data. However, the study does not provide data to support the use of trastuzumab-based chemotherapy in all patients with small HER2-positive tumors, and there will be many patients with T1a disease and some with T1b disease who will decide with their physicians to avoid the toxic effects of a trastuzumab-based regimen.”

7. From the “APT” group, the same group is currently planning another clinical trial (ATEMPT), comparing TDM1 with trastuzumab plus paclitaxel in T1 HER2-positive patients, which may provide alternative future regimens for these patients.

Unanswered Questions before we could generalize to ALL Small HER2 + EBC...

Unanswered Questions before we could generalize to ALL Small HER2 + EBC...

8. Future studies with prospective biomarker analysis might better define the subgroup of these small HER2+ patients at increased risk of a poorer outcome who are most likely to benefit from adjuvant trastuzumab, and hopefully stratifying those who could be spared from adjuvant chemotherapy but deriving absolute benefits from adjuvant trastuzumab as distinct from those gaining from the combination.

-Tumour infiltrating lymphocytes (TILs) may be used to define patients with T1a,bN0 that would derive the highest benefit of trastuzumab and chemotherapy in the adjuvant setting
- controversy of the “most effective” or “the safest” regimen...balancing the potential toxic effects of the adjuvant chemotherapy and trastuzumab in women with relatively favourable outcome

Is there a role?...And from what perspective?

“Role of Trastuzumab in Small HER2+ Early Breast Cancer”

- From oncologists’ point of view
- From patients’ point of view
- From family or carers’ point of view
- From healthcare administrators or Mx
From Patients, Family & Carers’ Perspective...

“Role of Trastuzumab in Small HER2+ Early Breast Cancer”
Patient-Centred MDT Approach...

Tumour features:
T, N, Grade, LVI, L.N., margins, Special receptor status (s.a. breast)

Patient Characteristics:
Age, Co-morbidities, PS, Prior Therapy

Patient Preference:
Work/Family/Self

Clinical Trials Guidelines Recent Reports

Toxicity Profile

Molecular Profile
Global Breast Cancer Conference – majority of participants serve the ASIAN populations...
Affordability is an issue...

<table>
<thead>
<tr>
<th>Trastuzumab</th>
<th>HK$ 19,000 @</th>
<th>US$ 2400@</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year Trastuzumab</td>
<td>HK$ 261,250</td>
<td>US$ 33,000</td>
</tr>
<tr>
<td>TDM-1</td>
<td>HK$ 60,000@</td>
<td>US$ 7000@</td>
</tr>
<tr>
<td>1-year TDM-1</td>
<td>HK$ 1,080,000</td>
<td>US$ 136,421</td>
</tr>
</tbody>
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Affordability is an issue...

| Trastuzumab | HK$ 19,000 @ | US$ 2400@
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Matching Science with **AFFORDABILITY**

...
From Government & Health Administrators’ Perspective...

“Role of Trastuzumab in Small HER2+ Early Breast Cancer”
## Affordability is an issue...

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</tbody>
</table>

Context and Place of Treatment....e.g. Hong Kong? AP region?
Most of the anti-cancer drugs are not funded by the government...
Available funded programmes need to go through Means Test....
**Even Adj Trastuzumab is a challenge....**
Real World Evidence vs EBM...

“In a system which has no additional funding for regulation...the cost is taken directly from patient care...”

Real World Evidence vs EBM...

“In a system which has no additional funding for regulation…the cost is taken directly from patient care.”

PRINCIPLES OF HER2 TESTING1,2

HER2 testing by validated IHC assay2,3

- IHC 0,1+ → HER2 (-)
- IHC 2+ → Equivocal result
- IHC 3+ → HER2 (+)

Average HER2 copy number <4.0 signals/cell → ISH (-)
Average HER2 copy number ≥4.0 and <6.0 signals/cell → Equivocal result
Average HER2 copy number ≥6.0 signals/cell → ISH (+)

HER2/CEP17 ratio ≥2.0

Average HER2 copy number <4.0 signals/cell → ISH (+)4
Average HER2 copy number ≥4.0 signals/cell → ISH (+)

HER2 testing by validated dual-probe ISH assay2,3

HER2/CEP17 ratio <2.0

Average HER2 copy number <4.0 signals/cell → ISH (-)
Average HER2 copy number ≥4.0 and <6.0 signals/cell → Equivocal result
Average HER2 copy number ≥6.0 signals/cell → ISH (+)

Must reflex test with ISH (if same specimen), or order new test with IHC or ISH (if new specimen available).

Must reflex test with ISH or with IHC (if same specimen), or order new test with ISH or IHC (if new specimen available).

Must reflex test with dual-probe ISH or with IHC (if same specimen), or order new test with ISH or IHC (if new specimen available).

Must reflex test with IHC (if same specimen), test with alternative ISH chromosome 17 probe, or order a new test with ISH or IHC (if new specimen available).

1 NCCN endorses the ASCO/CAP HER2 testing guideline. For additional information, see http://bit.ly/ASCO-CAP-HER2GuidelineResources.
2 Laboratory must participate in a quality assurance accreditation program for HER2 testing. Otherwise, tissue specimen should be sent to an accredited laboratory for testing. Healthcare systems and providers must cooperate to ensure the highest quality testing.
3 Evidence from trastuzumab adjuvant trials show that HER2 testing by ISH or IHC have similar utility to predict clinical benefit from HER2-targeted therapy.
4 See ASCO/CAP HER2 Guideline Data Supplement 2E (available at http://www.asco.org/sites/www.asco.org/files/final_her2_testing_ds_10-3-13.pdf) for more information on these rare scenarios.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-POSITIVE DISEASE

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

- Tumor ≤0.5 cm
- pN0

or

- Tumor 0.6–1.0 cm
- pN0
- pN1mi

or

- Tumor >1 cm
- pN0
- pN1mi
- Microinvasive

adjacent node metastasis

Histology:
- Ductal
- Lobular
- Mixed
- Metaplastic

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

adjacent node metastasis

See Adjuvant Endocrine Therapy (BIVN-J) and Neoadjuvant/Adjuvant Chemotherapy (BIVN-K)

See Follow-Up (BIVN-16)

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-NEGATIVE - HER2-POSITIVE DISEASE

Consider adjuvant chemotherapy with trastuzumab (category 2B)

Consider adjuvant chemotherapy with trastuzumab

Consider adjuvant chemotherapy

Consider adjuvant chemotherapy

Adjuvant chemotherapy with trastuzumab (category 1)

Adjuvant chemotherapy with trastuzumab

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

See Neoadjuvant/Adjuvant Chemotherapy (BINV-K)

See Principles of HER2 Testing (BINV-A)

Mixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

There are limited data to make chemotherapy recommendations for those >70 y old. Treatment should be individualized with consideration of comorbid conditions.

The prognosis of patients with T1a and T1b tumors that are node negative is uncertain even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.

A pertuzumab-containing regimen can be administered to patients with greater than or equal to T2 or greater than or equal to N1, HER2-positive, early-stage breast cancer.
The prognosis of patients with T1a and T1b tumours that are node negative is UNCERTAIN even when HER2 is amplified or over-expressed. This is a population of breast cancer patients that was NOT STUDIED in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy. “

See Principles of HER2 Testing (B1V-A).

Mixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. Early evidence suggests similar benefits from ovarian suppression (i.e., LHRH agonist) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable.

There are limited data to make chemotherapy recommendations for those >70 y old. Treatment should be individualized with consideration of comorbid conditions.

The prognosis of patients with T1a and T1b tumors that are node negative is uncertain even when HER2 is amplified or over-expressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.

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This house believes that...

“Role of Trastuzumab in Small HER2+ Early Breast Cancer” is still UNCERTAIN and QUESTIONABLE, at least NOT APPLICABLE TO ALL small HER2+ early breast cancer patients.
감사합니다
Thank You!

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Role of Trastuzumab in Small HER2+ Early Breast Cancer

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