La terapia adiuvante 2011
Post-St.Gallen

Michela Donadio
Marinella Mistrangelo
Oncologia Medica Senologica
Breast Unit Osp San Giovanni Battista
Torino
Strategies for subtypes: dealing with the Diversity of Breast Cancer

Recommendations
Consensus & Controversy
Clinical trials are...

... useful for defining whether one treatment is better than another

... useful for defining the average improved treatment outcome

... not useful for defining how to treat an individual patient

The evidence that is useful for treating an individual patient is a matter of interpretation and debate
Consider 10 areas of controversy

- Surgery: Sentinel node
- Radiation: DCIS, Accelerated, Partial, Post Mx
- Pathology: ER, PgR, HER2, Ki-67, Grade
- Multi-gene signatures
- Endocrine therapies: Ov. Supp., tam, AIs
- Chemotherapies: esp. Anthr., taxanes, platin
- Targeted therapies
- Neo-adjuvant systemic therapy
- Bisphosphonates
- Male Breast Cancer
Surgery: Axilla cN0

• Is the use of IHC to look for low volume disease in the SN routinely indicated?
  
  YES 22,2%   NO 71,1%   A 6,7%

• In completion of axillary dissection routinely indicated for patients with ITCs undergoing mastectomy?
  
  YES 6,4%   NO 91,5%   A 2,1%

• In completion of axillary dissection routinely indicated for patients with ITCs undergoing BCT?
  
  YES 0%   NO 93,3%   A 6,7%
Patients with a clinically negative axilla should proceed to completion axillary dissection if sentinel node biopsy shows:

- Isolated tumour cells in marginal sinus and body of node?
  - YES 0%  NO 97.7%  A 2.3%

- Micrometastasis less than 0.2 mm in a single sentinel node?
  - YES 4.3%  NO 91.3%  A 4.3%

- Metastasis of 0.2 mm - 2 mm in a single sentinel node?
  - YES 18.6%  NO 76.7%  A 4.7%
RT: DCIS

- Should RT be considered standard for entirely excised DCIS?
  YES 67.6%  NO 24.3%  A 8.1%

- Can RT be avoided in elderly (>70)?
  YES 58.3%  NO 33.3%  A 8.3%

- Can RT be avoided in low grade/low risk DCIS?
  YES 61.7%  NO 31.9%  A 6.4%
RT: Accelerated

• Should accelerated Whole Breast RT (WBRT) be considered an acceptable option?
  YES 91.5%  NO 4.3%  A 4.3%

• Should standard breast RT be preferred if extensive vascular invasion present?
  YES 34.8%  NO 32.6%  A 32.6%
RT: Partial Breast Irradiation

In association with breast conserving surgery, Partial Breast Irradiation (intraoperative) is acceptable:

- as the definitive irradiation, without any external beam therapy?
  
  YES 61.8%   NO 11.8%   A 26.5%

- Instead of external beam boost to tumor bed?
  
  YES 60.9%   NO 17.4%   A 21.4%
Radiation Therapy: Partial breast (PBRT)

- Should PBRT be applied in selected patients?
  - Elderly (> age 70)?
    - Yes: 86.7%, No: 6.7%, Abstain: 6.7%
  - Lymphoma survivors after mantle field RT?
    - Yes: 37.2%, No: 25.6%, Abstain: 37.2%
Radiation Therapy: After MX

• Should post Mx RT be standard for pts with N+ ≥ 4?
  YES 87,8%  NO 4,9%  A 7,3%

• Should post Mx RT be recommended to all pts with N+ 1 to 3 or pT > 1?
  YES 18,2%  NO 70,5%  A 11,4%
  - only if young?
  YES 51,2%  NO 41,9%  A 7%
  - if with extensive vascular invasion?
  YES 56,5%  NO 26,1%  A 17,4%
Pathology: Defining Subtypes

Should definition of subtypes of breast cancer use only readily available and reproducible pathological variables?

ER, PgR
HER2
Grade
Ki 67

YES 91.3%   NO 8.7%   A 0%
Pathology: Defining Subtypes

Basal like

- Use also CK 5/6 + and/or EGFR +?
  - YES 7,3%  NO 80,5%  A 12,2%

Luminal B

- Use also ER+ PgR- and/or high Ki 67 (> 14%) and/or G3 with or without HER2-positive?
  - YES 51,1%  NO 35,6%  A 13,3%
Pathology: Defining Subtypes

Luminal A

- Use only ER + and PgR+, Her2-negative and Ki67 ≤ 14%?
  
  **YES 84.8%**  **NO 10.9%**  **A 4.3%**

HER2 positive

- Use only FDA defin. (> 10 % or x 2) ?
  
  **YES 68.1%**  **NO 23.4%**  **A 8.5%**
Pathology: Subtypes

• Choice of therapy depends on tumour subtype as defined by multi-gene array analysis?
  
  YES  19,5%  NO  75,6%  A  4,9%

• For practical purposes tumour subtype can be ascertained by non-genetic testis for ER, PgR, HER2 and Ki 67?
  
  YES  82,9%  NO  12,2%  A  4,9%

• Choice of cytotoxic therapy should be influenced by tumour subtype?
  
  YES  74,4%  NO  18,6%  A  7%
Multi-gene Signatures

- Should Oncotype DX be used to predict ChT response in an endocrine-responsive cohort?
  - Yes   - No   - A
  - MAY

- Should Mammaprint be used to predict ChT responsiveness?
  - Yes   - No   - A
  - MAY

Si : 83.7%
No: 14%
Multi-gene Signatures

• Should or May Oncotype DX be used to predict ChT response in an endocrine-responsive cohort?
  YES 84,4%  NO 11,1%  A 4,4%

• Should Mammaprint be used to predict ChT responsiveness?
  YES 29,8%  NO 63,8%  A 6,4%
Multi-gene tests
SVILUPPO DI PROFILI GENICI

STRUMENTO PROGNOSTICO
Identificazione di pazienti a peggior prognosi

Oncotype DX
Test genetico che analizza l’espressione di 21 geni su tessuto tumorale in paraffina mediante tecnica RT-PCR per definire un recurrence score ossia una stima accurata del rischio di ricaduta a distanza per ogni singolo tumore

MammaPrint
Test genetico che analizza l’espressione di 70 geni su tessuto tumorale fresco mediante tecnica DNA microarray con definizione di un gruppo di tumori a buona e a cattiva prognosi

Paik S. et al. NEJM 2004
Habel LA. et al. BCR 2006
Van De Vijver M.J. et al. NEJM 2002
ONCOTYPE DX: test genetico che analizza l’espressione di 21 geni per definire un “recurrence score” (RS) per ogni singolo tumore

RS = + 0.47 × HER-2 group score
   - 0.34 × ER group score
   + 1.04 × proliferation group
   + 0.10 × invasion group score
   + 0.05 × CD68
   - 0.08 × GSTM1
   - 0.07 × BAG1

<table>
<thead>
<tr>
<th>Category</th>
<th>RS (0 – 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>RS &lt; 18</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>RS ≥ 18 and &lt; 31</td>
</tr>
<tr>
<td>High risk</td>
<td>RS ≥ 31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-actin</td>
<td></td>
</tr>
<tr>
<td>GAPDH</td>
<td></td>
</tr>
<tr>
<td>RPLP0</td>
<td></td>
</tr>
<tr>
<td>GUS</td>
<td></td>
</tr>
<tr>
<td>TFRC</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proliferation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67</td>
<td></td>
</tr>
<tr>
<td>STK15</td>
<td></td>
</tr>
<tr>
<td>Survivin</td>
<td></td>
</tr>
<tr>
<td>Cyclin B1</td>
<td></td>
</tr>
<tr>
<td>MYBL2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estrogen</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>Bcl2</td>
<td></td>
</tr>
<tr>
<td>SCUBE2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Invasion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stromelysin 3</td>
<td></td>
</tr>
<tr>
<td>Cathepsin L2</td>
<td></td>
</tr>
</tbody>
</table>

| CD68                 |                      |
| GSTM1                |                      |
| BAG1                 |                      |
What is the clinical utility of multi-gene tests in ER+/HER2 – breast cancer?

1. Assessment of base-line risk after adjuvant endocrine therapy;

2. Prediction of expected benefit from adjuvant chemotherapy added to endocrine therapy
1. Gene expression assays including the intrinsic subtypes, Oncotype Dx and Mammaprint are providing new and valuable information that is not provided by the standard clinical and pathological variables.

2. Gene expression assays are reproducible and quantitative, but cost and access is a barrier to common usage.

3. The best treatment plan is guided by a combination of standard clinical assays (ER, HER2, node status and tumor size) and genomic markers, and the two together are more powerful than either alone.

C. Perou, San Gallo 2011
Summary

• Current generation of multigene prognostic assays provide essentially identify ER+/Her2- tumors with high expression of proliferation genes

• All of the assays predict chemotherapy response

• While none of them reached TMUGS level 1 evidence, 21-gene RS has reached level 1b according to modification proposed by Simon, Paik, and Hayes (JNCI 2010).
Endocrine Therapy: Establishing Standards for Premenopausal

- Tam alone?
  - YES 93,6%  NO 6,4%  A 0%

- Ovarian function suppression (OFS) plus Tam?
  - YES 82,9%  NO 12,2%  A 4,9%

- OFS plus Tam is preferable than Tam alone?
  - YES 27,5%  NO 57,5%  A 15%

- OFS alone (in extraordinary circumstances)?
  - YES 71,4%  NO 26,2%  A 2,4%

- AI + OFS is a valid option in case of contraindicated Tam?
  - YES 75,6%  NO 13,3%  A 11,1%
Endocrine Therapy: Establishing Standards for Postmenopausal

- Should all receive an AI?
  YES 50%  NO 50%  A 0%
- Should N-positive receive an AI?
  YES 79.1%  NO 20.9%  A 0%
- Should any receive Tam alone?
  YES 89.1%  NO 10.9%  A 0%
- If an AI, need it be started up front?
  YES 41.3%  NO 52.2%  A 6.5%
- Consider switch to Tam in pts intolerant to AIs
  YES 97.8%  NO 0%  A 2.2%
TEAM Trial: Design

Postmenopausal HR-positive BC women
Adequate primary therapy of early breast cancer

RANDOMIZATION

Tamoxifen
Exemestane

2.5y 3y

Exemestane

Total of 5 years’ treatment*

N = 9779 accrued

Co-primary endpoints
DFS at 2.75 years
DFS at 5 years

* Therapy provided on open label basis
The TEAM Trial Main Endpoints (ITT DFS)

TEAM will answer 2 key clinical questions:

1. Are there any differences before the switch between upfront exemestane and tamoxifen?

2. Is adjuvant exemestane (5y) superior to sequential tamoxifen (2.5-3y) followed by exemestane (2.5-3y)?
SABCS 2008:
DFS Comparison at 2.75 Years (ITT)

Years since randomization

Numbers at risk:
Tamoxifen
4868  33/4765  79/4636  69/4516  86/4364  121/4099
Exemestane
4898  36/4809  73/4708  53/4615  62/4473  128/4179

Cumulative Probability

HR=0.89 (95% CI 0.77-1.03)
Adjusted Log rank $P=0.12$
disease-free; the Kaplan-Meier-estimated 5-year DFS percentages were 85% and 86%, respectively (HR 0.97, 95% CI 0.88–1.08; p=0.60; figure 2). In the per-protocol analysis, DFS at 5 years was 86% in the sequential group and 87% in the exemestane group, respectively (0.93, 0.82–1.05; p=0.22). The HR for exemestane with respect to tamoxifen followed by exemestane was 0.90 (0.78–1.04; p=0.14) before the switch and 1.06 (0.91–1.24; p=0.42) after the switch.

**Figure 2:** Disease-free survival at 5 years in the intention-to-treat population
Dashed lines (at 2.5 years and 3 years) represent the period in which patients on tamoxifen should be switched to exemestane, according to the protocol.
Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial

<table>
<thead>
<tr>
<th>Treatments followed by exemestane</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>Exemestane</td>
</tr>
<tr>
<td>G1 (well)</td>
<td>73/83 (89%)</td>
</tr>
<tr>
<td>G2 (moderate)</td>
<td>313/325 (46%)</td>
</tr>
<tr>
<td>G3-G4 (poor)</td>
<td>261/112 (22%)</td>
</tr>
<tr>
<td>Could not be assessed or known</td>
<td>54/410 (12%)</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
</tr>
<tr>
<td>T1a stage</td>
<td>276/2844 (10%)</td>
</tr>
<tr>
<td>T1b stage</td>
<td>432/2704 (73%)</td>
</tr>
<tr>
<td>N stage</td>
<td>204/2559 (40%)</td>
</tr>
<tr>
<td>Positive</td>
<td>447/2276 (20%)</td>
</tr>
<tr>
<td>Progesterone-receptor status</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>463/3615 (13%)</td>
</tr>
<tr>
<td>Negative</td>
<td>153/812 (27%)</td>
</tr>
<tr>
<td>Not assessed</td>
<td>61/236 (26%)</td>
</tr>
<tr>
<td>Most extensive surgery</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>427/2182 (20%)</td>
</tr>
<tr>
<td>Wide localisation</td>
<td>285/2486 (12%)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>440/3327 (13%)</td>
</tr>
<tr>
<td>No</td>
<td>263/1501 (16%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>256/140 (15%)</td>
</tr>
<tr>
<td>No</td>
<td>455/3185 (12%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>18/140 (11%)</td>
</tr>
<tr>
<td>60-69</td>
<td>161/1007 (12%)</td>
</tr>
<tr>
<td>70-99</td>
<td>239/1996 (12%)</td>
</tr>
<tr>
<td>≥90</td>
<td>27/9105 (32%)</td>
</tr>
<tr>
<td>Overall estimate</td>
<td>714/4858 (15%)</td>
</tr>
</tbody>
</table>

Figure 3: Subgroup analyses of disease-free survival

Data are n/N (%) of events at randomisation. Dashed line represents a hazard ratio of 1.00, and the solid line is the overall hazard ratio of 0.97.

Treatment effect was consistent between all subgroups (figure 3). No significant interaction was noted between treatment and prognostic factors (figure 3). No heterogeneity of treatment effect was noted for the different countries (data not shown; p=0.37).
OS at 5 years was 91% of patients in the sequential group and 91% in the exemestane group (figure 4A); no significant difference was noted in the OS between the exemestane and sequential treatment groups (HR 1.00, 95% CI 0.89–1.14; p>0.99; figure 4A). Causes of death...
Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Tamoxifen followed by exemestane (n=4868)</th>
<th>Exemestane monotherapy (n=4898)</th>
<th>Total (n=9766)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total disease-free-survival events</strong></td>
<td>714 (15%)</td>
<td>712 (15%)</td>
<td>1426 (15%)</td>
</tr>
<tr>
<td>Local recurrence only*</td>
<td>68 (1%)</td>
<td>59 (1%)</td>
<td>127 (1%)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>420 (9%)</td>
<td>400 (8%)</td>
<td>820 (8%)</td>
</tr>
<tr>
<td>New primary breast cancer†</td>
<td>33 (&lt;1%)</td>
<td>40 (&lt;1%)</td>
<td>73 (&lt;1%)</td>
</tr>
<tr>
<td>Intercurrent deaths</td>
<td>193 (4%)</td>
<td>213 (4%)</td>
<td>406 (4%)</td>
</tr>
<tr>
<td>All deaths‡</td>
<td>475 (10%)</td>
<td>485 (10%)</td>
<td>960 (10%)</td>
</tr>
<tr>
<td>Breast cancer§</td>
<td>291 (6%)</td>
<td>277 (6%)</td>
<td>568 (6%)</td>
</tr>
<tr>
<td>Second malignant disease</td>
<td>49 (1%)</td>
<td>55 (1%)</td>
<td>104 (1%)</td>
</tr>
<tr>
<td><strong>Endometrial cancer</strong></td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td><strong>Cardiac related</strong></td>
<td>28 (&lt;1%)</td>
<td>43 (&lt;1%)</td>
<td>71 (&lt;1%)</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>4 (&lt;1%)</td>
<td>8 (&lt;1%)</td>
<td>12 (&lt;1%)</td>
</tr>
<tr>
<td>Pulmonary related</td>
<td>16 (&lt;1%)</td>
<td>12 (&lt;1%)</td>
<td>28 (&lt;1%)</td>
</tr>
<tr>
<td>Cerebral related</td>
<td>14 (&lt;1%)</td>
<td>19 (&lt;1%)</td>
<td>33 (&lt;1%)</td>
</tr>
<tr>
<td>Vascular related</td>
<td>3 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
<td>7 (&lt;1%)</td>
</tr>
<tr>
<td>Other</td>
<td>50 (1%)</td>
<td>36 (&lt;1%)</td>
<td>86 (&lt;1%)</td>
</tr>
<tr>
<td>Unknown reason</td>
<td>20 (&lt;1%)</td>
<td>31 (&lt;1%)</td>
<td>51 (&lt;1%)</td>
</tr>
</tbody>
</table>

Data are number (%), unless otherwise indicated. * includes ipsilateral breast cancer. † Without distant metastasis. ‡ Includes all intercurrent deaths (ie, death without a relapse in breast cancer). § Cause of death was defined as breast cancer or the presence of a distant metastasis before death.

Cardiac related deaths were numerically higher with exemestane than with sequential treatment, however this difference was not significant (p = 0.11)
Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial

Sequential treatment

Sintomi ginecologici 20%
Sanguinamenti postmen 5%
Alterazioni endometrio 4%
Trombosi venose 2%
Alterazioni muscoloschel. 44%

The safety profile in the TEAM trial were consistent with the known profiles of exemestane and tamoxifene and the differences were largely attributed to their different modes of action.

Because of the differences in the profiles of the adverse events between exemestane monotherapy and sequential treatment consideration of the safety of these treatment strategies might play an important part in treatment decisions.
At a median follow-up of 5.1 years, TEAM found no evidence of a difference between exemestane monotherapy and the tamoxifen-exemestane sequence group. However, there are two limitations to the TEAM data. First, the data are immature, with about 20% of patients still on trial treatment. Second, treatment compliance seems suboptimum, especially in the sequence group (47% of patients in the sequence group and 19% of those in the monotherapy group discontinued before 5 years for a reason other than a disease-free-survival event).

The TEAM trial shows that tamoxifen still has a part to play in the treatment of early breast cancer. Perhaps the appropriate role of tamoxifen is as part of a switching strategy to maximise the treatment benefits while minimising the risks of both treatments or, in increasingly rare cases, as monotherapy. Further follow-up in the mono-therapy versus sequence trials is needed to determine the robustness of these data and whether any long-term differences emerge between the two strategies. More important,
Aggiornamento
studio ATAC
Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial

Jack Cuzick, Ivana Sestak, Michael Baum, Aman Buzdar, Anthony Howell, Mitch Dowsett, John F Forbes, on behalf of the ATAC/LATTE investigators

Riduzione assoluta delle ricadute del 2.7% a 5 anni e del 4.3% a 10 anni (pazienti a recettori positivi)

Riduzione assoluta delle ricadute a distanza del 2.6% a 10 anni

Curve HR: tasso di ricaduta rimane più basso nel gruppo ANA rispetto a TAM durante lo studio sebbene pare ci sia meno differenza dopo l’ottavo anno
Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial

Jack Cuzick, Ivana Sestak, Michael Baum, Aman Buzdar, Anthony Howell, Mitch Dowsett, John F Forbes, on behalf of the ATAC/LATTE investigators

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole (n=3092)</th>
<th>Tamoxifen (n=3094)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>425 (13.7%)</td>
<td>431 (13.9%)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>6 (0.2%)</td>
<td>24 (0.8%)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>17 (0.5%)</td>
<td>28 (0.9%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>8 (0.3%)</td>
<td>19 (0.6%)</td>
</tr>
<tr>
<td>Lung</td>
<td>51 (1.6%)</td>
<td>34 (1.1%)</td>
</tr>
<tr>
<td>All gastrointestinal*</td>
<td>104 (3.4%)</td>
<td>72 (2.3%)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>66 (2.1%)</td>
<td>44 (1.4%)</td>
</tr>
<tr>
<td>Gastric</td>
<td>12 (0.4%)</td>
<td>8 (0.3%)</td>
</tr>
<tr>
<td>Bladder</td>
<td>7 (0.2%)</td>
<td>9 (0.3%)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>12 (0.4%)</td>
<td>5 (0.2%)</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>10 (0.3%)</td>
<td>13 (0.4%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11 (0.4%)</td>
<td>12 (0.4%)</td>
</tr>
<tr>
<td>Skin (non-melanoma)</td>
<td>102 (3.3%)</td>
<td>107 (3.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>117 (3.8%)</td>
<td>123 (4.0%)</td>
</tr>
</tbody>
</table>

*Colorectal, gastric, gallbladder, anus, duodenum, liver, oesophagus, pancreas.

Table 2: Non-breast cancers in the safety population

![Graph showing fracture rates](image)

Figure 4: Fracture rates in the full study population
Numbers at risk differ in some cases from those provided in the 100-month analysis because of additional follow-up data.
“... This 10-year analysis of the ATAC trial confirms the previously reported efficacy and tolerability benefits of anastrozole as initial adjuvant therapy for post menopausal women with early hormone-receptor-positive breast cancer...”

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number randomised</th>
<th>Median follow-up (months)</th>
<th>Disease-free survival hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC1</td>
<td>3116</td>
<td>120</td>
<td>-</td>
</tr>
<tr>
<td>Anastrozole for 5 years</td>
<td>3125</td>
<td>-</td>
<td>0.86 (0.78-0.95)*</td>
</tr>
<tr>
<td>Anastrozole and tamoxifen for 5 years</td>
<td>3125</td>
<td>33</td>
<td>NA</td>
</tr>
<tr>
<td>BIG 1-984</td>
<td>Tamoxifen for 5 years</td>
<td>2459</td>
<td>76</td>
</tr>
<tr>
<td>Letrozole for 5 years</td>
<td>2463</td>
<td>-</td>
<td>0.88 (0.78-0.99)</td>
</tr>
<tr>
<td>Letrozole for 5 years</td>
<td>156</td>
<td>71</td>
<td>-</td>
</tr>
<tr>
<td>Tamoxifen for 2 years followed by letrozole for 5 years</td>
<td>1548</td>
<td>-</td>
<td>1.65 (0.84-3.32)</td>
</tr>
<tr>
<td>Letrozole for 2 years followed by tamoxifen for 2 years</td>
<td>1540</td>
<td>-</td>
<td>0.96 (0.76-1.21)</td>
</tr>
<tr>
<td>TEAM*</td>
<td>Tamoxifen for 2-3 years followed by exemestane for 2-3 years</td>
<td>4858</td>
<td>32</td>
</tr>
<tr>
<td>Exemestane for 5 years</td>
<td>4998</td>
<td>-</td>
<td>0.89 (0.77-1.03)</td>
</tr>
<tr>
<td>IES8</td>
<td>Tamoxifen for 5 years</td>
<td>2372</td>
<td>56</td>
</tr>
<tr>
<td>Tamoxifen for 2-3 years followed by exemestane for 2-3 years</td>
<td>2352</td>
<td>-</td>
<td>0.76 (0.66-0.88)</td>
</tr>
<tr>
<td>ABCSG8/ARNO*</td>
<td>Tamoxifen for 5 years</td>
<td>1606</td>
<td>28</td>
</tr>
<tr>
<td>Tamoxifen for 2 years followed by anastrozole for 5 years</td>
<td>1618</td>
<td>-</td>
<td>0.60 (0.44-0.81)†</td>
</tr>
<tr>
<td>ITA*</td>
<td>Tamoxifen for 5 years</td>
<td>225</td>
<td>64</td>
</tr>
<tr>
<td>Tamoxifen for 2 years followed by anastrozole for 3 years</td>
<td>223</td>
<td>-</td>
<td>0.57 (0.38-0.85)†</td>
</tr>
<tr>
<td>MA.17*</td>
<td>Tamoxifen for 5 years</td>
<td>2534</td>
<td>30</td>
</tr>
<tr>
<td>Tamoxifen for 5 years followed by letrozole for 5 years</td>
<td>2592</td>
<td>-</td>
<td>0.58 (0.45-0.76)</td>
</tr>
<tr>
<td>NSABP B33®</td>
<td>Tamoxifen for 5 years</td>
<td>779</td>
<td>30</td>
</tr>
<tr>
<td>Tamoxifen for 5 years followed by exemestane for 5 years</td>
<td>785</td>
<td>-</td>
<td>0.68 (p=0.07)‡</td>
</tr>
<tr>
<td>ABCSG6®</td>
<td>Tamoxifen for 5 years</td>
<td>469</td>
<td>62</td>
</tr>
<tr>
<td>Tamoxifen for 5 years followed by anastrozole for 3 years</td>
<td>387</td>
<td>-</td>
<td>0.64 (0.45-0.99)†</td>
</tr>
</tbody>
</table>

NA = not applicable. *Hormone-receptor-positive patients only. †Breast cancer recurrence only, not disease-free survival. 95% CI was not provided in the paper.
Reflection and Reaction

Michael Gnant

However, the limited magnitude of the average benefit reported in the 10-year analysis of ATAC strongly suggests that only a few patients derive actual benefit from anastrozole—the majority might not.

Thus—and I am somewhat disappointed by this conclusion—physicians and patients remain relatively unguided in their choice of treatment for patients with endocrine-responsive breast cancer.

In addition to an excess in side-effects that might impair patients’ quality of life (eg, arthralgia) in patients treated with anastrozole compared with tamoxifen, the similar overall survival rates might stop physicians from recommending aromatase inhibitors to everybody. In particular, there was some evidence of an increase in colorectal and lung cancer after aromatase inhibitor treatment, which is concerning and was probably not caused by chance alone.

The optimistic note from the 10-year update of the ATAC trial is that the benefit of 5 years’ treatment with anastrozole persists and even seems to increase over time.

Although the benefit of anastrozole persists beyond the active treatment period, the clinically most important side-effect of aromatase inhibition—an increase in fractures because of reduced serum oestrogen concentrations—subsides soon after intake of the active drug is stopped. In addition to the clear-cut advantages of aromatase inhibitors in terms of avoiding endometrial changes including cancers and thromboembolism, this is reassuring.
Efficacy: TAM→LET vs LET

Nessuna differenza significativa tra la sequenza TAM→LET e 5 anni di monoterapia con LET

Nelle pazienti che hanno iniziato il trattamento con TAM è stato osservato un maggior numero (non significativo) di recidive

NEJM 2009;361:766-76
Efficacy: LET→TAM vs LET

Nessuna differenza significativa tra la sequenza LET→TAM e la monoterapia con letrozolo per 5 anni

NEJM 2009;361:766-76
Endocrine Therapy: Establishing Standards for Postmenopausal

• Is 5 years aon AI sufficient for low-moderate risk?
  YES 80,5%  NO 12,2%  A 7,3%

• Should (Could) more than 5 years AI be offered to pts with node positive disease?
  YES 34,1%  NO 54,5%  A 11,4%

• Should more than 5 years AI be offered to pts < 55 irrespective of N status?
  YES 4,5%  NO 86,4%  A 9,1%
Endocrine Therapies

• Is CYP2D6 determination important for the choice of endocrine therapy in:
  - postmenopausal women (AI vs Tam)?
    YES 2,1%  NO 95,7%  A 2,2%
  - premenopausal women?
    YES 2,2%  NO 95,7%  A 2,2%

• Should pts receiving Tam have CYP2D6 testing?
  YES 2,1%  NO 97,9%  A 0%
Endocrine Therapies

Should the choice of AI or Tam be dependent upon biological features (e.g. N+, Ki 67)?

YES 47.7%  NO 52.3%  A 0%
Endocrine Therapies:
Biologic and host variables

- Should overexpressed or amplified HER2 be an indication for always adding chemotherapy?
  - YES 84.4%   NO 11.1%   A 4.4%

- Should overexpressed or amplified HER2 be an indication for AIs in postmenopausal pts?
  - YES 39%   NO 51.2%   A 9.8%

- Should obesity be considered a general contraindication for AIs in postmenopausal pts?
  - YES 10.9%   NO 76.1%   A 13%
Chemotherapy
Basic Questions

Factors arguing for inclusion of chemotherapy are:

- Histological grade 3 tumor?
  YES 95,5%  NO 2,3%  A 2,3%

- Ki67 > 14%?
  YES 68,8%  NO 14,6%  A 16,7%

- Low hormone receptor status (< 50%)?
  YES 68,1%  NO 31,9%  A 0%

- Positive HER2 status?
  YES 95,7%  NO 4,3%  A 0%

- Triple negative status?
  YES 97,7%  NO 2,3%  A 0%
Chemotherapy
Basic Questions

Factors arguing for inclusion of chemotherapy are:

- Any positive node?
  YES 40.4%    NO 59.6%    A 0%

- > 3 positive nodes?
  YES 88.4%    NO 9.3%    A 2.3%

- Lymphovascular invasion?
  YES 40.4%    NO 48.9%    A 10.6%
Chemotherapy
Basic Questions

Factors arguing for inclusion of chemotherapy are:

where available, approved genetic testing such as Oncotype Dx or Mammaprint should (may) be used to select a chemotherapy in addition to endocrine treatment?

YES 83,7%  NO 14%  A 2,3%
Chemotherapy
Luminal A

• Is Luminal A phenotype less responsive to chemotherapy?
  YES 86,4%  NO 4,5%  A 9,1%

• Is chemotherapy less useful if added to endocrine therapy for pts, with Luminal A phenotype?
  YES 85,4%  NO 0%  A 14,6%

• Is there a chemotherapy regimen known to be suitable for Luminal A?
  YES 14%  NO 83,7%  A 2,3%
Chemotherapy
Luminal B

• Should the ChT regimen for Luminal B contain anthracyclines?
  YES 70.5%  NO 13.6%  A 15.9%

• Should the ChT regimen for Luminal B contain taxanes?
  YES 63%  NO 26.1%  A 10.9%
Chemotherapy
HER2-positive

• Is there a ChT regimen known to be preferred for HER2 positive phenotype?
  YES 37%  NO 58,7%  A 4,3%

• May the ChT regimen for HER2-positive disease contain anthracyclines?
  YES 97,8%  NO 2,2%  A 0%

• Should the ChT regimen for HER2-positive disease contain anthracyclines?
  YES 74,4%  NO 23,3%  A 2,3%

• Should the ChT regimen for HER2-positive disease contain taxanes?
  YES 82,6%  NO 10,9%  A 6,5%
Chemotherapy
Basal like

• Should the ChT regimen for basal like phenotype contains anthracyclines and taxanes?
  YES  **82,2%**  NO  **13,3%**  A  **4,4%**

• Should the ChT regimen for basal like phenotype contains alkylating agents?
  - CMF  YES  **92,7%**  NO  **2,4%**  A  **4,9%**
  - Platinum agents  YES  **17,8%**  NO  **64,4%**  A  **17,8%**

• Should dose-dense ChT be considered?
  YES  **52,3%**  NO  **40,9%**  A  **6,8%**

• Should antiangiogenic treatment be added to ChT for basal like phenotype?
  YES  **2,4%**  NO  **88,1%**  A  **9,5%**
Targeted Therapy

- Is trastuzumab for 1 year, with be given concurrent ChT (usually a taxane) or following ChT, a standard adjuvant treatment for HER2-positive phenotype?
  - YES 100%  NO 0%  A 0%

  ... also for tumors between 5 mm and < 1 cm?
  - YES 78,7%  NO 14,9%  A 6,4%

  ... also for tumors pT1a pN0?
  - YES 23,9%  NO 60,9%  A 15,2%

  ... shorter than 1 year?
  - YES 25,6%  NO 62,8%  A 11,6%

  ... longer than 1 year?
  - YES 4,7%  NO 83,7%  A 11,6%
Studies investigating clinical outcome of pT1pN0 tumors by HER-2 and hormone receptors (HRs) status. Methods

- 7 retrospective studies reported between 2003 and 2010

- Evaluation of disease- and distant disease-free survival by HER-2 and HER-2/HRs

- HER-2 centrally evaluated in all studies

Reviewed by Oakman C et al, Educational book – ESMO meeting, Milan – October 2010
Studies investigating clinical outcome of pT1pN0 tumors by HER-2 and hormone receptors status.

- 600 pts. with HER-2 + tumors
% HER-2 + disease ranging between 7 and 10%

• **Absolute risks of distant relapse**
  - HER-2 +: 5 yrs. ± 10-15%, 10 yrs. 22-28%

• Increased risk of disease relapse if HER-2 + (hazard ratios ranging between 2.4 and 8.99)
  Overall 7,164 pts. with pT1pN0 tumors (median follow-up 4.5 - 12.4 yrs.)

• Two studies suggest a worse outcome for triple negative than for ER+/HER-2 negative tumors

Reviewed by Oakman C et al, Educational book – ESMO meeting, Milan – October 2010
Caveats
- heterogeneity in adjuvant therapies
- HRs status not always centrally revised
- in 3 out of 7 studies pT1c tumors were eligible
- only 2 out of 7 studies evaluate outcome by combination of HER2 and hormone receptor status

“Take-home” messages
there is a substantial degree of concordance in considering HER-2+ patients with pT1pN0 tumors at increased risk of relapse compared to the HER-2 negative population (2 to 9 fold increase)

Reviewed by Oakman C et al, Educational book – ESMO meeting, Milan – October 2010
Treatment Of Node-negative Infracentimetric HER2+ Invasive Breast Carcinomas

- Retrospective multicenter series
- 96 Invasive breast carcinomas T1a-bN0
- Prospective determination of HER2
- Microinvasion and multifocal/multicentricity excluded
- Median size: 8 mm (2-10mm)
- 25 (20%) tumors ≤5 mm

- Therapy: chemo and trastuzumab given to “poor prognosis” features (high MI, high grade and HR-).
- 40/96 patients had therapy
- 90% (37/40) patients had chemo + trastuzumab
- 7% (3/40) patients had trastuzumab alone

Rodrigues et al. ASCO 2009
Treatment Of Node-negative Infracentimetric HER2+ Invasive Breast Carcinomas

Recurrences occurred on the “Good Prognosis group”: 9% vs. 0%

Recurrences may have been avoided by active therapy in the “Good Prognosis” group

Rodrigues et al. ASCO 2009
Benefits of trastuzumab-based therapy for women with small, node-negative, HER2-positive breast cancer

• To estimate the possible benefits of trastuzumab-based therapy
• Single institution, retrospective study
• ≤2cm, node-negative, HER2+ breast cancer
• Pre- vs. post- adjuvant trastuzumab
• 2 cohorts:
  – “No Trastuzumab”: n= 106
  – “Trastuzumab”: n= 155
  – chemotherapy and ≥ 9 weeks of trastuzumab

# Benefits of trastuzumab-based therapy for women with small, node-negative, HER2-positive breast cancer

<table>
<thead>
<tr>
<th></th>
<th>NO TRASTUZUMAB</th>
<th>TRASTUZUMAB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=108</td>
<td>N=149</td>
</tr>
<tr>
<td><strong>Locoregional/contralateral RFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-year</td>
<td>92%</td>
<td>99%</td>
</tr>
<tr>
<td>Number of events at 4 years</td>
<td>8 (7.5%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td><strong>Distant RFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-year</td>
<td>95%</td>
<td>100%</td>
</tr>
<tr>
<td>Number of events at 4 years</td>
<td>6 (5.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-year</td>
<td>97%</td>
<td>99%</td>
</tr>
<tr>
<td>Number of events at 4 years</td>
<td>3 (2.8%)</td>
<td>1 (0.7%)</td>
</tr>
</tbody>
</table>

Women with small, node-negative, HER2+ primary breast cancers have an excellent outcome following adjuvant chemotherapy with trastuzumab.

Absolute benefits vs. treatment-related side-effects

Absolute risk of relapse

Proportional benefit

Absolute benefit

↑ Risk of Relapse and ↑ Proportional Benefit ➞ ↑ Absolute benefit

Absolute benefit

Side-effects (long-term)
Cardiac events in patients treated with adjuvant trastuzumab in the context of phase III trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No. pts</th>
<th>Cardiac event rate</th>
<th>Recovery rate</th>
<th>Cardiac death</th>
</tr>
</thead>
<tbody>
<tr>
<td>* B-31 + N9831</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- AC → P</td>
<td>1,775</td>
<td>0.5</td>
<td>43</td>
<td>0.11</td>
</tr>
<tr>
<td>- AC → P + H → H</td>
<td>1,799</td>
<td>2.0</td>
<td>86</td>
<td>0.17</td>
</tr>
<tr>
<td>* HERA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Anthra-based</td>
<td>1,698</td>
<td>0.7</td>
<td>-</td>
<td>0.1</td>
</tr>
<tr>
<td>- Anthra-based → H</td>
<td>1,703</td>
<td>4.3</td>
<td>81</td>
<td>0</td>
</tr>
<tr>
<td>* FinHER</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- D → Anthra-based</td>
<td>116</td>
<td>1.7</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>- D + H → Anthra-based</td>
<td>116</td>
<td>0.9</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>* BCIRG 006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- AC → D</td>
<td>1,073</td>
<td>0.7</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>- AC → D + H → H</td>
<td>1,074</td>
<td>2.0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>- TCH → H</td>
<td>1,075</td>
<td>0.4</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

Summary

• Incidence of long-term side effects by adjuvant anthracyclines or trastuzumab does not seem to outweigh benefits deriving from these treatments.

• Considering the fact that absolute benefits from adjuvant therapies will be smaller in pT1pN0 than in more advanced stage tumors, adjuvant treatments with the smallest risk of long-term side-effects should be prioritized.
Targeted Therapy

• Should trastuzumab be given concurrently with ChT?
  YES 85,7%  NO 9,5%  A 4,8%

• Could trastuzumab be given subsequently with ChT?
  YES 83,7%  NO 9,7%  A 7%

• Trastuzumab alone (+/- endocrine therapy) is appropriate?
  YES 67,4%  NO 23,3%  A 9,3%
IHC 3+ or FISH+ Node-positive and high-risk node-negative EBC

n=5102

- Trastuzumab q3w after standard adjuvant therapy
- 1 vs. 2 years of treatment
- Crossover permitted after 1st interim efficacy analysis (885/1698= 52%)

EBC, early breast cancer; CT, chemotherapy; RT, radiotherapy; q3w, every 3 weeks
Endpoints and analyses

- **Endpoints**
  - primary: DFS
  - secondary: OS, TTR, TTDR
    - Safety (3 interim analyses of cardiac end points)
- 1 year trastuzumab versus observation: efficacy analyses
  - 1st interim analysis (n=475 events)
  - 2-year follow-up (n=539 events)
    - ASCO 2006; Smith et al Lancet 2007
  - **4-year follow-up (n=827 events)**
    - St Gallen PTEBC 2009; Gianni et al Lancet Oncology 2011

DFS, disease-free survival; OS, overall survival; TTR, time to recurrence; TTDR, time to distant recurrence
HERA: DFS and overall survival over time

Attenuazione dell’efficacia del trastuzumab nel tempo dovuta al cross-over in più della metà delle pazienti braccio di osservazione

Gianni et al 2011
### Randomized Trials of Trastuzumab for Early Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemo</th>
<th>Concurrent vs Sequential T</th>
<th>HR/DFS</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-31</td>
<td>AC/T</td>
<td>CON</td>
<td>0.48</td>
<td>++</td>
</tr>
<tr>
<td>NCCTG N9831</td>
<td>AC/T</td>
<td>CON</td>
<td>0.48</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SEQ</td>
<td>0.70</td>
<td>+</td>
</tr>
<tr>
<td>HERA</td>
<td>Various</td>
<td>SEQ</td>
<td>0.76</td>
<td>+</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>AC/T</td>
<td>CON</td>
<td>0.64</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>TCH</td>
<td>CON</td>
<td>0.75</td>
<td>+</td>
</tr>
<tr>
<td>NOAH</td>
<td>AT/CMF</td>
<td>CON</td>
<td>0.59</td>
<td>++</td>
</tr>
<tr>
<td>FinHER</td>
<td>FEC/D</td>
<td>CON</td>
<td>0.32</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>FEC/V</td>
<td>CON</td>
<td>0.92</td>
<td>-</td>
</tr>
<tr>
<td>FNCC-LCC PACS 004</td>
<td>(F) EC</td>
<td>+/- D</td>
<td>SEQ</td>
<td>1.27</td>
</tr>
</tbody>
</table>

**Legend:**

++ significant HR < 0.7; + significant, HR ≥ 0.7; (-) for not significant difference
Concurrent chemotherapy & trastuzumab utilizing adjuvant anthracyclines and taxanes: offers the lowest risk of tumor recurrence

- All ++ studies characterized by concurrent chemotherapy and trastuzumab, with utilization of both anthracycline and taxanes based chemotherapy during adjuvant treatment

- All + or (-) studies either omitted an anthracycline or a taxane, or offered sequential treatment

- The true clinical significance of these differences is not well defined and may be modest

- There are trade-offs to consider including slightly greater risk of CHF with anthracycline-based regimens

Burstein H, San Gallen 2011
Adjuvant Systemic treatment for individual patients HER2 positive tumors (I)

- HER2 positive tumors (IHC 3+ and/or FISH ≥2) benefit from adjuvant anti HER2 therapy

No other clinical or pathological feature is predictive of benefit though stage, ER status, and other factors are prognostic

Oncologists should be aware of the technical quality of HER2 testing done for their patients

Burstein H, San Gallen 2011
Adjuvant Systemic treatment for individual patients HER2 positive tumors (II)

- Direct and indirect evidence suggests that the optimal adjuvant trastuzumab-based therapy includes anthracycline and taxane based chemotherapy, with some concurrent administration of trastuzumab & chemotherapy.

  Trade-offs may include different toxicity profile, and in particular, a slightly greater risk of CHF with anthracycline-based treatments.

  There are no data for adjuvant trastuzumab in the absence of ChT.

  Most trials use 1 year of trastuzumab; limited data for shorter durations.

Burstein H, San Gallo, 2011
Neoadjuvant Systemic Therapy

- Should neoadjuvant therapy be given only in order to alter the surgical outcome (less than mastectomy)?
  - YES 37,2%  NO 60,5%  A 2,3%

- Should the neoadjuvant treatment modality used be the most likely to alter surgical outcome (chemo/endocrine trastuzumab)?
  - YES 73,2%  NO 12,2%  A 14,6%
Neo Adjuvant Systemic Therapy

• In neoadjuvant ChT reasonable
  - for pts with low proliferating breast cancer (e.g. Ki67 < 14%)
    YES 24,4%  NO 64,4%  A 11,4%

  - in highly endocrine-responsive disease (e.g. lobular cancer)?
    YES 19,1%  NO 76,6%  A 4,3%

• If indicated, should neoadjuvant ChT regimen contain
  - taxanes?
    YES 83%  NO 8,5%  A 8,5%
  - anthracycline?
    YES 88,9%  NO 6,7%  A 4,4%
  - alkylating agents (e.g. platinum)
    YES 85,7%  NO 11,9%  A 2,4%
Neo Adjuvant Systemic Therapy

• Should neoadjuvant regimens for HER2-positive disease always contain anti-HER2 drug?
  
  YES 82.2%  NO 8.5%  A 4.3%

• In dual HER-2-targeting a reasonable option for the preoperative setting for HER2-disease?

  YES 21.7%  NO 67.4%  A 10.9%
Neoadjuvant Systemic Therapy

In neoadjuvant endocrine therapy alone a reasonable option for postmenopausal pts, with highly endocrine-responsive disease?

YES 97.8%  NO 2.2%  A 0%

- if yes, for which duration (choose one)?
- 3-4 months  YES 15.2%
- 4-8 months  YES 39.1%
- Maximal response  YES 45.7%
Biphosphonates

• Should Zoledronic acid, given during adjuvant endocrine therapy, be recommended to?
  - premenopausal pts, irrespective of OFS?
    YES 10,4 %   NO 81,3 %   A 6,3 %
  - postmenopausal pts?
    YES 21,3 %   NO 72,2 %   A 6,4 %

• Should denosumab substitute Zol ac.?
  YES 2,4 %   NO 82,9 %   A 14,6 %
Biphosphonates

Does Zoledronic acid given once every 6 months during adjuvant endocrine therapy, improve DFS?

YES 22,9%  NO 64,6%  A 12,5%
Biphosphonates

Does Zoledronic acid given once every 6 months during adjuvant endocrine therapy, improve DFS in postmenopausal pts?

YES 33,3%  NO 43,6%  A 23,1%
Male Breast Cancer (ER+)

- Should adjuvant Tamoxifen be given to all
  YES 85,1%   NO 6,4%   A 8,5%

- May AIs be considered (if contraindications to Tam; e.g. thrombosis)?
  YES 53,5%   NO 32,6%   A 14%

- Could an AI be given in node positive disease as extended endocrine treatment?
  YES 28,3%   NO 41,3%   A 30,4%
Grazie per l’attenzione