LUMINAL
BREAST CANCER

(Neo) Adjuvant chemotherapy

Elżbieta Senkus

Dept. of Oncology and Radiotherapy
Medical University of Gdańsk
Conflict of interest

- **honoraria**: AstraZeneca, Pierre Fabre, Pfizer, Roche
- **travel support**: AstraZeneca, Egis, Novartis, Pfizer, Roche
What are we talking about?

507 primary breast cancers

http://massgenomics.org/
who needs ChT???
no benefit – alive anyway

no benefit – dead anyway

Overall Survival (%)

Years after Mastectomy

0 1 2 3 4 5 6 7 8 9 10
• at risk of relapse
• sensitive to treatment
risk of relapse ↔ treatment sensitivity ↔ prognostic factors ↔ predictive factors
Who benefits from ChT?

EBCTCG, Lancet 2012
Are all breast cancers equally sensitive to ChT?

GeparDuo neoadj. ddAT vs AC-T
Who is at risk?

Cardoso, NEJM 2016
Who benefits from ChT?

Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials

Lancet 2012; 379: 432-44
Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

(F) ER status ($\chi^2 = 0.4; 2p = 0.7; NS$)

- ER-po or $403/1095 (36.8\%)$  $464/1043 (44.5\%)$  $-40.5$  $180.4$  $0.80$ (SE $0.07$)
- ER+  $831/3100 (26.8\%)$  $1063/1377 (33.5\%)$  $-84.6$  $338.5$  $0.77$ (SE $0.05$)
- ER unknown  $182/559 (32.6\%)$  $174/513 (33.9\%)$  $-14.9$  $72.3$  $0.81$ (SE $0.11$)

Subsets of ER+

- ER+, chemotherapy+endocrine vs endocrine  $659/2622 (25.1\%)$  $853/2675 (31.9\%)$  $-56.2$  $247.0$  $0.80$ (SE $0.06$)
- ER 10-99 fmol/mg  $416/1371 (30.3\%)$  $544/1442 (37.7\%)$  $-35.3$  $162.5$  $0.80$ (SE $0.07$)
- ER $\geq$100 fmol/mg  $274/1146 (23.9\%)$  $337/1160 (29.1\%)$  $-20.6$  $95.6$  $0.81$ (SE $0.09$)
- ER+, age $\leq$55 years  $250/845 (29.6\%)$  $316/943 (33.5\%)$  $-19.4$  $102.4$  $0.83$ (SE $0.09$)
- ER+, age 55-69 years  $542/2071 (26.2\%)$  $677/2055 (32.9\%)$  $-53.9$  $215.3$  $0.78$ (SE $0.06$)
- ER+, poorly differentiated  $100/461 (21.7\%)$  $120/477 (25.2\%)$  $-12.2$  $45.8$  $0.77$ (SE $0.12$)
- ER+, moderately/well differentiated  $228/955 (23.1\%)$  $286/1026 (27.9\%)$  $-27.8$  $112.8$  $0.78$ (SE $0.08$)

Total  $1416/4754 (29.8\%)$  $1701/4733 (35.9\%)$  $-139.9$  $581.3$  $0.786$ (SE $0.037$

Figure 6: Subgroup analyses of breast cancer mortality (mortality with recurrence, by log-rank subtraction) for any anthracycline-based regimen versus no chemotherapy.
Who benefits from ChT?

ER expression???

- IBCSG Trials VII and 12–93
- IBCSG Trial IX

Pagani, BCRT 2009, Regan, Breast 2005
Who benefits from ChT?

Ki67???

IBCSG Trial IX

PACS01

Viale, JNCI 2008, Penault-Llorca, JCO 2009
Who benefits from ChT?

- All patients
- RS <18
- RS 18-31
- RS >31

**Graphs:**
- Proportion of distant recurrence-free survival over years for different risk groups (RS) and treatment options (Tam + chemo vs Tam). The graphs illustrate the benefit of chemotherapy in different risk strata.

**Bar Chart:**
- Absolute increase in proportion of distant recurrence-free survival (DRF) at 10 years (mean ± SE) for low, intermediate, and high risk groups.

**Table:**
- Number of patients (n) for each risk category.

**Source:** Paik, JCO 2006

**Note:** The oncotyping logo is present on the page.
Clinical vs genomic risk

Cardoso, NEJM 2016
Data are conflicting…

GEICAM 9906

PAM50 low

PAM50 intermediate/high

Martin, BCRT 2013
Data are conflicting...

NCIC CTG MA.21

Stratified HR=1.54 (95% CI=0.88-2.68; p=0.130)

Stratified HR=0.69 (95% CI=0.44-1.10; p=0.118)

PAM50 luminal

PAM50 non-luminal
and confusing...

<table>
<thead>
<tr>
<th>MULTI-PARAMETER ASSAYS EVALUATED IN OPTIMA PRELIM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>oncotype DX</strong></td>
</tr>
<tr>
<td>16 (+5) gene RT-PCR performed by GH1</td>
</tr>
<tr>
<td>Risk score</td>
</tr>
<tr>
<td><strong>prosigna</strong></td>
</tr>
<tr>
<td>50 gene - nCounter performed at OICR</td>
</tr>
<tr>
<td>Risk score</td>
</tr>
<tr>
<td><strong>agenda</strong></td>
</tr>
<tr>
<td>70 (+/80) gene array performed by Agendia</td>
</tr>
<tr>
<td>Risk category</td>
</tr>
<tr>
<td><strong>mammaPrint</strong></td>
</tr>
<tr>
<td>4-gene IHC performed on TMA at OICR</td>
</tr>
<tr>
<td>Risk score</td>
</tr>
<tr>
<td><strong>AQUA technology</strong></td>
</tr>
<tr>
<td>4-gene fluorescent IHC performed on TMA by Genoptix</td>
</tr>
<tr>
<td>Risk score</td>
</tr>
<tr>
<td><strong>MammaTyper</strong></td>
</tr>
<tr>
<td>4-gene RT-PCR performed by Stratifyer</td>
</tr>
<tr>
<td>Subtyping</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

ESMO 2015
AGREEMENT BETWEEN TESTS

<table>
<thead>
<tr>
<th>Number of other tests agreed with test</th>
<th>Oncotype DX</th>
<th>ROR_PT</th>
<th>MammaPrint</th>
<th>IHC4</th>
<th>IHC4-AQUA</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>119 (39%)</td>
<td>119 (39%)</td>
<td>119 (39%)</td>
<td>119 (39%)</td>
<td>119 (39%)</td>
</tr>
<tr>
<td>3</td>
<td>85 (28%)</td>
<td>78 (26%)</td>
<td>74 (25%)</td>
<td>67 (22%)</td>
<td>76 (25%)</td>
</tr>
<tr>
<td>2</td>
<td>54 (18%)</td>
<td>51 (17%)</td>
<td>46 (15%)</td>
<td>36 (12%)</td>
<td>32 (11%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kappa statistic (95% confidence interval)</th>
<th>MammaPrint (Low)</th>
<th>ROR_PT (Low/Int)</th>
<th>IHC4 (Low/Int)</th>
<th>IHC4-AQUA (Low/Low-Mid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS ≤25 (OPTIMA low risk)</td>
<td>0.40 (0.30-0.50)</td>
<td>0.45 (0.34-0.55)</td>
<td>0.52 (0.40-0.64)</td>
<td>0.41 (0.31-0.52)</td>
</tr>
<tr>
<td>MammaPrint</td>
<td>0.53 (0.43-0.63)</td>
<td>0.33 (0.21-0.44)</td>
<td>0.42 (0.30-0.53)</td>
<td></td>
</tr>
<tr>
<td>ROR_PT (Low/Int)</td>
<td></td>
<td>0.39 (0.27-0.50)</td>
<td>0.43 (0.31-0.54)</td>
<td></td>
</tr>
<tr>
<td>IHC4</td>
<td></td>
<td></td>
<td>0.60 (0.50-0.70)</td>
<td></td>
</tr>
</tbody>
</table>

kappa >0.8 – good concordance
kappa 0.4-0.6 – intermediate concordance
And is the effect of chemo always related to “chemo”?

NSABP B-30

[Graphs showing disease-free survival (DFS) and overall survival (OS) with and without amenorrhea.]

Can this be achieved with endocrine therapy only?
What’s the absolute benefit?

PREDICT Tool: Breast Cancer Survival; Results

Five year survival
93 out of 100 women are alive at 5 years with no adjuvant therapy after surgery
An extra 1 out of 100 women treated are alive because of hormone therapy
An extra 2 out of 100 women treated are alive because of hormone therapy & chemotherapy

Ten year survival
83 out of 100 women are alive at 10 years with no adjuvant therapy after surgery
An extra 3 out of 100 women treated are alive because of hormone therapy
An extra 5 out of 100 women treated are alive because of hormone therapy & chemotherapy

To view the numbers in bars hover pointer over each bar-segment (Or tap segment if using a mobile device)

Overall Survival at 5 and 10 years (percent)
patients want to be treated...
Which ChT?

anthracyclines

EBCTCG, Lancet 2012
Anthracyclines?

3452 patients: CMF vs anthracyclins

Di Leo, Lancet Oncol 2011
Anthracyclines?

ABC Trials Schema

Node+ or High Risk Node-Negative
Stratification Variables
Number of + Nodes (0, 1-3, 4-9, 10+); Hormone Receptor (ER or PgR+, Both Negative)

ARM 1 (TaxAC Options)
A  TAC q 3 wk → B  AC q 3 wk → C  AC q 2 wk → D  AC q 2 wk

ARM 2 (TC)

ABC Trials: Invasive Disease Free Survival

Alive and Inv. Disease-Free (%)

Years from Randomization

Blum, ASCO 2016
Anthracyclines?

Forest Plot of IDFS By Hormone and Nodal Status

<table>
<thead>
<tr>
<th>Nodes(+) ER/PgR Neg</th>
<th>HR</th>
<th>95% CI</th>
<th>Int.P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.31</td>
<td>0.86-1.99</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>1.58</td>
<td>0.90-2.79</td>
<td>0.71</td>
</tr>
<tr>
<td>4+</td>
<td>1.34</td>
<td>0.62-2.91</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodes(+) ER or PgR (+)</th>
<th>HR</th>
<th>95% CI</th>
<th>Int.P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.69</td>
<td>0.39-1.19</td>
<td>0.026</td>
</tr>
<tr>
<td>1-3</td>
<td>1.14</td>
<td>0.77-1.69</td>
<td></td>
</tr>
<tr>
<td>4+</td>
<td>1.46</td>
<td>0.95-2.26</td>
<td></td>
</tr>
</tbody>
</table>

Overall | 1.23 | 1.01-1.50

Blum, ASCO 2016
Which ChT?

*taxanes*

EBCTCG, Lancet 2012
Which ChT?
Alternative scheduling???

**Dose-dense ChT**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose dense</th>
<th>Conventional</th>
<th>Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baldini 2003</td>
<td>73</td>
<td>77</td>
<td>0.87 (0.49, 1.55)</td>
</tr>
<tr>
<td>Citron 2005</td>
<td>998</td>
<td>994</td>
<td>0.85 (0.68, 1.06)</td>
</tr>
<tr>
<td>Venturini 2005</td>
<td>610</td>
<td>604</td>
<td>0.87 (0.67, 1.13)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1681</strong></td>
<td><strong>1675</strong></td>
<td><strong>0.86 (0.73, 1.01)</strong></td>
</tr>
</tbody>
</table>

Overall survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Dose dense</th>
<th>Conventional</th>
<th>Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Hormone Receptor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citron 2005</td>
<td>636</td>
<td>639</td>
<td>0.92 (0.67, 1.26)</td>
</tr>
<tr>
<td>Venturini 2005</td>
<td>311</td>
<td>317</td>
<td>0.98 (0.68, 1.46)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>947</strong></td>
<td><strong>956</strong></td>
<td><strong>0.94 (0.74, 1.21)</strong></td>
</tr>
<tr>
<td>Negative Hormone Receptor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citron 2005</td>
<td>325</td>
<td>337</td>
<td>0.77 (0.57, 1.04)</td>
</tr>
<tr>
<td>Venturini 2005</td>
<td>255</td>
<td>249</td>
<td>0.80 (0.54, 1.18)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>580</strong></td>
<td><strong>582</strong></td>
<td><strong>0.79 (0.62, 0.99)</strong></td>
</tr>
</tbody>
</table>

Overall survival

Duarte, Breast 2012
When cytotoxic chemotherapy is indicated for luminal disease:

- the specific choice of regimen depends on the position within the spectrum of degree of endocrine responsiveness and risk of relapse.
- On average, for ‘luminal B-like’ tumors, the Oxford overview supports the inclusion of both an anthracycline and a taxane.
- while in ‘luminal A-like’ tumors, there is little evidence of an advantage compared with older regimens such as AC and CMF.
- If given, chemotherapy for ‘luminal B-like’ disease should not extend beyond four courses of the same treatment, especially, for patients with a lower burden of disease.
- The addition of taxanes should be considered for patients with more extensive disease burden.
- A slim majority considered that there was a high-risk group for which dose-dense therapy with G-CSF support should be preferred.
Why preop systemic therapy??

PRIMARY SYSTEMIC THERAPY
= treatment of choice

LOCALLY ADVANCED
OR INFLAMMATORY BC

PRIMARY SYSTEMIC THERAPY
= option

LARGE OPERABLE BC
PROS

- earlier treatment of micrometastatic disease
- \textit{in vivo} treatment sensitivity assessment
- increased operability of inoperable tumors
- decreased extent of surgery
- translational studies

CONS

- delay in local treatment (risk of tumor progression)
- loss of prognostic information from full pathological assessment of untreated tumor
Efficacy = adjuvant ChT

Wolmark, JNCI Monogr 2001, Mauri, JNCI 2005
other measures of efficacy...

<table>
<thead>
<tr>
<th>Study</th>
<th>Neoadjuvant</th>
<th>Adjuvant</th>
<th>Relative risk (fixed)</th>
<th>Weight (%)</th>
<th>Relative risk (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Marsden</td>
<td>16 of 149</td>
<td>31 of 144</td>
<td></td>
<td>2.39</td>
<td>0.50 (0.29, 0.87)</td>
</tr>
<tr>
<td>Institut Curie</td>
<td>22 of 95</td>
<td>31 of 86</td>
<td></td>
<td>2.47</td>
<td>0.64 (0.40, 1.02)</td>
</tr>
<tr>
<td>NSABP23</td>
<td>299 of 743</td>
<td>302 of 752</td>
<td></td>
<td>22.77</td>
<td>0.80 (0.70, 0.92)</td>
</tr>
<tr>
<td>EORTC10</td>
<td>203 of 323</td>
<td>262 of 341</td>
<td></td>
<td>19.33</td>
<td>0.82 (0.74, 0.91)</td>
</tr>
<tr>
<td>ABCSG12</td>
<td>71 of 214</td>
<td>85 of 209</td>
<td></td>
<td>6.52</td>
<td>0.82 (0.63, 1.05)</td>
</tr>
<tr>
<td>USA25</td>
<td>15 of 26</td>
<td>16 of 27</td>
<td></td>
<td>1.10</td>
<td>0.67 (0.62, 1.53)</td>
</tr>
<tr>
<td>Institut Curie</td>
<td>73 of 200</td>
<td>66 of 190</td>
<td></td>
<td>5.13</td>
<td>1.65 (0.90, 1.97)</td>
</tr>
<tr>
<td>London21</td>
<td>11 of 100</td>
<td>9 of 110</td>
<td></td>
<td>0.65</td>
<td>1.34 (0.58, 3.11)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>650 of 1850</td>
<td>802 of 1859</td>
<td></td>
<td>60.46</td>
<td>0.82 (0.76, 0.89)</td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 9.43$, 7 d.f., $P = 0.22$, $I^2 = 25.8%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 5.10$, $P &lt; 0.001$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Neoadjuvant</th>
<th>Adjuvant</th>
<th>Relative risk (fixed)</th>
<th>Weight (%)</th>
<th>Relative risk (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECTO14</td>
<td>154 of 438</td>
<td>570 of 975</td>
<td></td>
<td>20.20</td>
<td>0.63 (0.46, 0.61)</td>
</tr>
<tr>
<td>Bordeaux13</td>
<td>74 of 134</td>
<td>196 of 196</td>
<td></td>
<td>10.24</td>
<td>0.55 (0.47, 0.64)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>228 of 572</td>
<td>715 of 1011</td>
<td></td>
<td>39.54</td>
<td>0.54 (0.48, 0.60)</td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 0.16$, 1 d.f., $P = 0.69$, $I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 11.32$, $P &lt; 0.001$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total         | 878 of 2422 | 1517 of 2870|                     | 100.00     | 0.71 (0.67, 0.75)     |
| Test for heterogeneity: $\chi^2 = 53.86$, 9 d.f., $P < 0.001$, $I^2 = 83.2\%$ |
| Test for overall effect: $Z = 10.02$, $P < 0.001$ |

Mieog, Br J Surgery 2007
no impact on postop complications

? ↓ cardiac toxicity and infections
but...

impact of less aggressive local treatment???
more recurrences after BCT in downstaged tumors
Who benefits from preop treatment?

HR 0.36 (95% CI 0.31–0.42)
pCR vs tumor phenotype

Liedtke, JCO 2008
Which patients benefit most?

Huober, BCRT 2010
Which patients benefit most?

invasive ductal carcinoma

invasive lobular carcinoma
and who doesn’t benefit???

9020 patients from GBG studies (1051 – lobular cancer)

Loibl, BCRT 2014
and who doesn’t benefit???

9020 patients from GBG studies (1051 – lobular cancer)
Meaning of pCR

surrogate for cure?

selection of best prognosis patients?
Does ↑pCR translate into improved long-term outcomes???

NSABP B-27

---

**Overall Survival**

<table>
<thead>
<tr>
<th>Trt</th>
<th>N</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Op AC</td>
<td>784</td>
<td>192</td>
</tr>
<tr>
<td>Pre-Op ACT</td>
<td>793</td>
<td>182</td>
</tr>
<tr>
<td>Pre-Op AC + Post Op T</td>
<td>777</td>
<td>189</td>
</tr>
</tbody>
</table>

**DFS**

<table>
<thead>
<tr>
<th>Trt</th>
<th>N</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Op AC</td>
<td>784</td>
<td>304</td>
</tr>
<tr>
<td>Pre-Op ACT</td>
<td>783</td>
<td>292</td>
</tr>
<tr>
<td>Pre-Op AC + Post Op T</td>
<td>777</td>
<td>286</td>
</tr>
</tbody>
</table>

Rastogi, JCO 2008
Does $\uparrow pCR$ translate into improved long-term outcomes??

FDA metaanalysis
### pCR in luminal BC

#### Clinical tumour stage
- T1 (n=785)
- T2 (n=7328)
- T3 (n=2493)
- T4a-c (n=781)
- T4d (n=482)

#### Clinical nodal status
- Negative (n=6320)
- Positive (n=5487)

#### Histological type
- Ductal (n=8567)
- Lobular (n=1221)
- Mixed (n=475)

#### Tumour grade
- 1 (n=426)
- 2 (n=4392)
- 3 (n=3217)

#### Clinical tumour subtype
- Hormone receptor positive, HER2 negative, grade 1/2 (n=1986)
- Hormone receptor positive, HER2 negative, grade 3 (n=630)
- HER2 positive, hormone receptor positive, trastuzumab (n=385)
- HER2 positive, hormone receptor positive, no trastuzumab (n=701)
- HER2 positive, hormone receptor negative, trastuzumab (n=354)
- HER2 positive, hormone receptor negative, no trastuzumab (n=471)
- Triple negative (n=1157)

![Pathological complete response (%)](image)

Cortazar, Lancet 2014
Is pCR really important in luminal BC?
Is pCR really important in luminal BC?

6,377 patients treated with neoadjuvant anthracycline-taxane based chemotherapy

von Minckwitz, JCO 2012
so maybe endocrine therapy???