Paziente Oligometastatico
Successive Terapie Sistemiche?
(Breast Cancer. Why?)

P Pronzato
Roma, 18.11.2012
<table>
<thead>
<tr>
<th></th>
<th>Early disease</th>
<th>Locally advanced disease</th>
<th>Oligometastatic disease</th>
<th>Metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease extend</td>
<td>small primary tumor, no lymph node metastases</td>
<td>large primary tumor, lymph node metastases</td>
<td>solitary or few metastatic lesions</td>
<td>multiple organ metastases</td>
</tr>
<tr>
<td>Chance of cure</td>
<td>high (90%)</td>
<td>medium (50%)</td>
<td>zero?</td>
<td>zero</td>
</tr>
<tr>
<td>Treatment intent</td>
<td>curative</td>
<td>curative</td>
<td>curative?</td>
<td>curative?</td>
</tr>
<tr>
<td>Type of treatment</td>
<td>locoregional + adjuvant systemic</td>
<td>locoregional + adjuvant systemic</td>
<td>systemic + local?</td>
<td>systemic</td>
</tr>
</tbody>
</table>
Treatment End Points
MBC : Treatment End Points

- Prolongation of Survival
- Improvement of Quality of Life
- And Cure?
Overall Survival according to response to front line CT in MBC

Median FU: 16 years

PA Greenberg, JCO 1996
Effect of Tumor Response on Survival

- **Tumor response is a highly significant predictor of survival** (p < 0.0001)
- Compared with no response:
  - CR, HR 0.48 (95% CI, 0.40 to 0.57)
  - PR, HR 0.69 (95% CI, 0.62 to 0.77)
- Median survival time:
  - CR, 28.8 months (95% CI, 25.4 to 45.3)
  - PR, 21.3 months (95% CI, 19.2 to 22.4)
  - No response, 14.6 months (95% CI, 13.9 to 15.4)

P Bruzzi, JCO 2005
Is MBC Survival improving?

Figure 1. Overall survival from time of recurrence.

S Giordano, Cancer 2004
• Is so unexpected to find a 5% 10-yr OS (from relapse) among

  – HR+/HER2- (independently from extension and achievement of CR)

  – HER2+ responding (even <CR) to anti- HER2+
Guide Lines
Waiting for....

• Chemotherapy prolongs survival for isolated local or regional recurrence of breast cancer. The CALOR trial (Chemotherapy as Adjuvant for Locally Recurrent Breast Cancer); IBCSG 27-02; NSABP B-37; BIG 1-02
  – S Aebi
  – Scheduled at San Antonio, December 6
Metastatic Breast Cancer

• *Is still valid the paradigm that MBC is incurable?*

• *Is oligometastatic disease (aggressively treated) incurable?*
17) A small but very important subset of patients with MBC, for example those with oligo-metastatic disease, can achieve complete remission and a long survival. A multimodal approach should be considered for these selected patients. A prospective clinical trial addressing this specific situation is needed.

18) The true value of the removal of the primary tumour in patients with stage IV breast cancer is currently unknown. However, it can be considered in selected patients. Of note, some studies suggest that surgery is only valuable if performed with the same attention to detail (e.g. attaining clear margins and addressing disease in the axilla) as in patients with early stage disease. Prospective clinical trials to confirm the value of this approach, the best candidates and timing are currently ongoing.
Results
Primary breast carcinoma

Treatment:
- Surgery
- +/- systemic therapy (+/- anthracycline)
- +/- radiotherapy

Isolated recurrence

Local treatment (with curative intent):
- Surgery
- and/or radiotherapy

Stage IV NED breast carcinoma

Chemotherapy

Three doxorubicin-based trials
No prior anthracycline

Docetaxel-based trial
1998 - 2004
Prior anthracycline
No prior taxane

+/- hormonal therapy
if ER+ or unknown
(in 2 of the 3 doxorubicin-based trials, and in the docetaxel-based trial)

259 pts

26 pts

EO Hanrahan, Cancer 2005
FIGURE 4. This chart illustrates the duration and probability of disease-free survival for the three doxorubicin-based studies combined. Dotted lines indicate 95% confidence intervals.

FIGURE 6. This chart illustrates the duration and probability of breast carcinoma-specific survival for the three doxorubicin-based studies combined. Dotted lines indicate 95% confidence intervals.
FIGURE 2. This chart illustrates the duration and probability of disease-free survival for the docetaxel-based study. Dotted lines indicate 95% confidence intervals.

FIGURE 3. This chart illustrates the duration and probability of overall survival for the docetaxel-based study. Dotted lines indicate 95% confidence intervals.
Fig. 1 Estimated overall survival, progression-free interval, and relapse-free interval by multidisciplinary treatment.

Fig. 2 Estimated overall survival by response to multidisciplinary treatment.

Decision Making Process
Decision Drivers

- Extent of Disease
- HER2
- ER and PgR
- Life Expectancy (age and comorbidities)
- Pretreatments
Decision Drivers

• Extent of Disease
• HER2
• ER and PgR
• Life Expectancy (age and comorbidities)
• Pretreatments
Process

- Staging
- Local Therapy
- Systemic Therapy
  - “Adjuvant Style”
  - “MBC Style”
Believing in Local Therapies

Table 2. Resection of pulmonary metastases from breast cancer*

<table>
<thead>
<tr>
<th>First author (reference)</th>
<th>No. of patients</th>
<th>Median OS (mo)</th>
<th>5-y OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedel, 2002 (70)</td>
<td>467</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Planchard, 2004 (69)</td>
<td>125</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>Friedel, 1994 (71)</td>
<td>91</td>
<td>ND</td>
<td>27</td>
</tr>
<tr>
<td>Murabito, 2000 (72)</td>
<td>62 (28 complete resection)</td>
<td>Complete resection: 79; incomplete resection: 15.5</td>
<td></td>
</tr>
<tr>
<td>McDonald, 1994 (73)</td>
<td>60</td>
<td>42</td>
<td>37.8</td>
</tr>
<tr>
<td>Livartowski, 1998 (74)</td>
<td>40</td>
<td>70</td>
<td>54</td>
</tr>
<tr>
<td>Tanaka, 2005 (75)</td>
<td>39</td>
<td>32</td>
<td>30.8</td>
</tr>
<tr>
<td>Lanza, 1992 (76)</td>
<td>37</td>
<td>47</td>
<td>49.5</td>
</tr>
<tr>
<td>Staren, 1992 (77)</td>
<td>33</td>
<td>58</td>
<td>36</td>
</tr>
<tr>
<td>Girard, 1994 (78)</td>
<td>32</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>McCormack, 1978 (79)</td>
<td>28</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Rena, 2007 (80)</td>
<td>27</td>
<td>ND</td>
<td>38</td>
</tr>
<tr>
<td>Ludwig, 2003 (81)</td>
<td>21</td>
<td>96.9</td>
<td>53</td>
</tr>
<tr>
<td>Mountain, 1978 (82)</td>
<td>21</td>
<td>27</td>
<td>14</td>
</tr>
</tbody>
</table>

* ND = no data; OS = overall survival.
Believing in Local Therapies

Table 3. Resection of liver metastases from breast cancer*

<table>
<thead>
<tr>
<th>First author (reference)</th>
<th>No. of patients</th>
<th>Median OS (mo)</th>
<th>5-y OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adam, 2006 (83)</td>
<td>85</td>
<td>46†</td>
<td>41†</td>
</tr>
<tr>
<td>Pocard, 2001 (84)</td>
<td>65</td>
<td>ND</td>
<td>46 (4-y)</td>
</tr>
<tr>
<td>Elias, 2003 (85)</td>
<td>54</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Pocard, 2000 (86)</td>
<td>52</td>
<td>42</td>
<td>65 (3-y)</td>
</tr>
<tr>
<td>Raab, 1998 (87)</td>
<td>34</td>
<td>27</td>
<td>18.4</td>
</tr>
<tr>
<td>Sakamoto, 2005 (88)</td>
<td>34</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Vlastos, 2004 (89)</td>
<td>31</td>
<td>63</td>
<td>61</td>
</tr>
<tr>
<td>Yoshimoto, 2000 (90)</td>
<td>25</td>
<td>42†</td>
<td>33†</td>
</tr>
<tr>
<td>Elias, 1995 (91)</td>
<td>21</td>
<td>38.2†</td>
<td>24†</td>
</tr>
<tr>
<td>Ercolani, 2005 (92)</td>
<td>21</td>
<td>40.3</td>
<td>25</td>
</tr>
<tr>
<td>Singletary, 2003 (13)</td>
<td>21</td>
<td>40 (DFS)</td>
<td>55 (3-y DFS)</td>
</tr>
<tr>
<td>Pocard, 1997 (93)</td>
<td>21</td>
<td>ND</td>
<td>60</td>
</tr>
</tbody>
</table>

* DFS = disease-free survival; ND = no data; OS = overall survival.
† Since diagnosis of liver metastases.
Believing in Local Therapies

Does Radiotherapy Have Curative Potential in Metastatic Patients? The Concept of Local Therapy in Oligometastatic Breast Cancer

Kathrin Dellas
Relative and Absolute Risk Reduction

<table>
<thead>
<tr>
<th></th>
<th>Deaths without Adjuvant</th>
<th>Red RR 20%</th>
<th>Deaths in spite of Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>40</td>
<td>-8</td>
<td>32</td>
</tr>
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</table>

NNT: \(\frac{100}{8} = 12.5\)
Relative and Absolute Risk Reduction

Selecting pts on the base of individual risk

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<thead>
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<th>Red RR 20%</th>
<th>Deaths in spite of Adjuvant</th>
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<tbody>
<tr>
<td><strong>100</strong></td>
<td><strong>80</strong></td>
<td><strong>-16</strong></td>
<td><strong>64</strong></td>
</tr>
</tbody>
</table>

NNT: $\frac{100}{16} = 6.25$
Which Systemic Therapy?
List of Agents

- **Hormonotherapy**
  - Tamoxifen
  - Anastrozole or Letrozole
  - Exemestane
  - Fulvestrant HD

- **Anti-HER2**
  - Trastuzumab
  - Lapatinib
  - TDM1
  - Pertuzumab

- **Chemotherapy**
  - Anthracycline (incl liposomal)
  - Taxane (incl nab-paclitaxel)
  - Capecitabine
  - Vinorelbine
  - Eribulin

- **Bevacizumab**
Since the risk is high.....

• HER2+
  – Trastuzumab + CT → Trastuzumab + HT

• TNBC
  – “Adjuvant Style” POLICT (anthra → Tax)
  – Other CT (MonoCT, Cape-Vin, Carbo-Gem)
  – Pac + Beva

• HR+ / HER2-
  – HT +/- CT
And the Bio Shifts?

- **HER2+ → HER2-**  Hold Trastuzumab
- **HER2- → HER2+**  Add Trastuzumab

- **HR+ → HR-**  Hold HT
- **HR- → HR+**  Add HT
How long?

• The answer is easy at (least apparently) for
  – HT
  – “Adjuvant Style CT”

• The answer is difficult (or no answer) for
  – Trastuzumab
  – Other CT
  – Bevacizumab
Temptative algorythm 1

HER2+

Previous adjuvant T >1 year or no Adjuvant T

Taxane + Trastuzumab \(\rightarrow\) (HT*) + Trastuzumab

< 1 year adjuvant T

Vinorelbine+ Trastuzumab \(\rightarrow\) (HT*) + Trastuzumab

* Change from NSAI to Exemestane and vice versa; change from Tam to AI in postm
Temptative algorythm 2

- **Previous adjuvant CT >1 year or no CT**
  - Taxane based CT

- **< 1 year adjuvant CT**
  - Change CT, considering: Cape (+/- Vino), CMF, Carbo-Gem,
Temptative algorythm 3

**HER2-/ HR+**

- Previous adjuvant CT >1 year or no CT
  - Taxane Based CT and HT*
- < 1 year adjuvant CT
  - Capecitabine (+/- Vino) and HT*

* Consider concomitant HT and Change from NSAI to Exemestane and vice versa; change from Tam to AI in postm
A Role for “Neo”?  
YES
Fig 2. Overall survival as a function of response to chemotherapy (pathologic complete response [pCR] v residual disease [RD]) and triple-negative status (triple-negative breast cancer [TNBC] v non-TNBC).
Conclusions
The reasonable approach

- Consider “True” Oligometastatic Disease as a story apart
- After Local Treatment, Consider an “Adjuvant Style” Systemic Treatment based on HER2/HR and pretreatments
- If Systemic Treatment is started, Consider at a point the Local Treatment and a subsequent Systemic also on the basis of a Response