ONCOLOGIA: esperienze cliniche a confronto.
Il carcinoma mammario metastatico

Sequenza ottimale del trattamento

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Chemotherapy vs Endocrine Therapy

• Methods
  – Randomized trials of chemotherapy alone vs endocrine therapy alone

• Results
  – 8 trials identified (N = 817)
  – No significant difference for OS—HR: 0.94 (95% CI: 0.79-1.12; \( P = .5 \))
  – Significant difference favoring chemotherapy for ORR—OR: 1.25 (95% CI: 1.01-1.54; \( P = .04 \))
    • However the 2 largest trials demonstrated trends in opposite directions
  – Toxicity: little information available on adverse events and QOL
    • Increased toxicity with chemotherapy (nausea, vomiting and alopecia)
    • 3 of 7 trials noted QOL aspects, with differing results

• Authors’ conclusions
  – “In women with metastatic breast cancer and where hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy is recommended except in the presence of rapidly progressive disease”

EFECT: Study Design

**Previous nonsteroidal AI failure**

- **Fulvestrant** loading dose + Placebo for Exemestane (n = 351)
  - 500 mg Day 1, 250 mg Days 14 & 28, and monthly thereafter
  - Progression
  - Survival
  - Analysis after 580 events (progression or death)

- **Exemestane** 25 mg/day orally + Placebo for Fulvestrant (n = 340)
  - Progression
  - Survival

Time to Progression (ITT)

Fulvestrant
Exemestane

Median, mos
3.7
3.7

HR: 0.963 (95% CI: 0.819-1.133; P = .6531)

Objective Response and Clinical Benefit Rate

- In population evaluable for response

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Fulvestrant (n = 270)</th>
<th>Exemestane (n = 270)</th>
<th>OR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR rate (CR + PR)</td>
<td>20 (7.4)</td>
<td>18 (6.7)</td>
<td>1.12 (0.578-2.186)</td>
<td>.736</td>
</tr>
<tr>
<td>CB rate (OR + SD ≥ 24 wks)</td>
<td>87 (32.2)</td>
<td>85 (31.5)</td>
<td>1.03 (0.72-1.487)</td>
<td>.853</td>
</tr>
</tbody>
</table>

*Analyses are not adjusted for baseline covariates.

FIRST: Study Design

• Randomized, open-label phase II trial
  – Primary endpoint: CBR, defined as CR, PR, or SD for at least 24 wks

Postmenopausal women with previously untreated hormone receptor-positive advanced breast cancer (N = 205)

Fulvestrant 500 mg by intramuscular injection Days 0, 14, 28, and every 28 days thereafter (n = 102)

Anastrozole 1 mg/day orally (n = 103)

Until disease progression or other event requiring discontinuation

FIRST: Fulvestrant Significantly Increased TTP in Secondary Analysis

Fulvestrant
Anastrozole

<table>
<thead>
<tr>
<th>Patients at Risk, n</th>
<th>Fulvestrant (n = 102)</th>
<th>Anastrozole (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulvestrant</td>
<td>102</td>
<td>103</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>74</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>39</td>
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<tr>
<td></td>
<td>45</td>
<td>30</td>
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<tr>
<td></td>
<td>34</td>
<td>21</td>
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<tr>
<td></td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fulvestrant (n = 102)</th>
<th>Anastrozole (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients progressing, n (%)</td>
<td>63 (61.8)</td>
<td>79 (76.7)</td>
</tr>
<tr>
<td>Median TTP, mos</td>
<td>23.4</td>
<td>13.1</td>
</tr>
<tr>
<td>Clinical benefit rate, %</td>
<td>72.5</td>
<td>67.0</td>
</tr>
</tbody>
</table>

Postmenopausal women with hormone receptor–positive MBC (N = 707)

Stratified by previous adjuvant tamoxifen

Treatment until disease progression

Anastrozole 1 mg/day PO + Fulvestrant 500 mg on Day 1, 250 mg on Days 14 and 28, 250 mg every 28 days thereafter (n = 355)

Anastrozole 1 mg/day PO (n = 352)

Women with progression encouraged to cross over to receive fulvestrant

SWOG S0226: PFS and OS Overall and by Previous Adjuvant Tamoxifen

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Anastrozole + Fulvestrant</th>
<th>Anastrozole</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (n = 694), mos</td>
<td>15.0</td>
<td>13.5</td>
<td>0.80 (0.68-0.94)</td>
<td>.007</td>
</tr>
<tr>
<td>No previous adjuvant tamoxifen (n = 414)</td>
<td>17.0</td>
<td>12.6</td>
<td>0.74 (0.59-0.92)</td>
<td>.0055</td>
</tr>
<tr>
<td>Previous adjuvant tamoxifen (n = 280)</td>
<td>13.5</td>
<td>14.1</td>
<td>0.89 (0.69-1.15)</td>
<td>.37</td>
</tr>
</tbody>
</table>

| Median OS (n = 694), mos              | 47.7                      | 41.3        | 0.81 (0.65-1.00)     | .049    |
| No previous adjuvant tamoxifen (n = 414) | 47.7                      | 39.7        | 0.74 (0.56-0.98)     | .0362   |
| Previous adjuvant tamoxifen (n = 280) | 49.6                      | 44.5        | 0.91 (0.65-1.28)     | .59     |
The PI3K/AKT/mTOR Pathway

- mTOR signaling plays a key role in
  - Cell growth
  - Cell proliferation
  - Regulation of
    - Apoptosis
    - Angiogenesis
    - Lymphocytes
    - Homeostasis
    - Metabolism

BOLERO-2: Study Design

- Primary endpoint: PFS (investigator assessment)
- Secondary endpoints: OS, ORR, clinical benefit rate, safety

Randomized 2:1; stratified by sensitivity to previous hormonal therapy, presence of visceral metastases

Treatment until disease progression or unacceptable toxicity

Postmenopausal women with ER-positive advanced breast cancer who progressed on previous nonsteroidal AI therapy*

- Exemestane 25 mg/day + Everolimus 10 mg/day (n = 485)
- Exemestane 25 mg/day + Placebo (n = 239)

* > 50% of patients in each arm with ≥ 3 previous therapies

BOLERO-2: Everolimus + Exemestane Improves PFS in HR+ MBC

Everolimus + exemestane (median PFS: 10.6 mos)
Placebo + exemestane (median PFS: 4.1 mos)

HR: 0.36 (95% CI: 0.27-0.47; log-rank P < .001)

Patients at Risk, n
Everolimus Placebo
485 239
385 168
281 94
201 55
132 33
102 20
67 11
43 11
28 6
18 3
9 3
3 1
2 0
0 0

## BOLERO-2: Final PFS Analysis (18-Mo Follow-up)

<table>
<thead>
<tr>
<th>PFS, Mos</th>
<th>EVE + EXE</th>
<th>PBO + EXE</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local review</td>
<td>7.8</td>
<td>3.2</td>
<td>0.45 (0.38-0.54)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Central review</td>
<td>11.0</td>
<td>4.1</td>
<td>0.38 (0.31-0.48)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>With visceral mets</td>
<td>6.83</td>
<td>2.76</td>
<td>0.47 (0.37-0.60)</td>
<td>--</td>
</tr>
<tr>
<td>Without visceral mets</td>
<td>9.86</td>
<td>4.21</td>
<td>0.41 (0.31-0.55)</td>
<td>--</td>
</tr>
<tr>
<td>Bone-only mets</td>
<td>12.88</td>
<td>5.29</td>
<td>0.33 (0.21-0.53)</td>
<td>--</td>
</tr>
<tr>
<td>Progression after neo/adj therapy</td>
<td>11.50</td>
<td>4.07</td>
<td>0.39 (0.25-0.62)</td>
<td>--</td>
</tr>
</tbody>
</table>

- OS data still not mature (HR: 0.77; 95% CI: 0.57-1.04)
- Most common grade 3/4 AEs were stomatitis (8%), hyperglycemia (5%), fatigue (4%)

# BOLERO-2 (12-Mo Follow-up): Safety

<table>
<thead>
<tr>
<th>Adverse Events, %</th>
<th>Exemestane + Everolimus (n = 482)</th>
<th>Exemestane + Placebo (n = 238)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>59</td>
<td>8</td>
</tr>
<tr>
<td>Rash</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Noninfectious pneumonitis</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14</td>
<td>6</td>
</tr>
</tbody>
</table>

Aromatase Inhibitor + CDK4/6 Inhibitor Improves PFS in ER+ MBC

Qual’è la sequenza ottimale di trattamento?

- Prima linea: AI o fulvestrant; fulvestrant + AI proponibile in pazienti therapy-naïve
  - quale intervallo dalla terapia adiuvante?
  - associazione o sequenza programmata?

- Proseguire la terapia endocrina fino alla comparsa di resistenza
Qual’è la sequenza ottimale di trattamento?

• Seconda linea: everolimus + exemestane a progressione da AI non steroideo (se non mts viscerali sintomatiche)

• Dopo everolimus: monoterapia ormonale o blocco del pathway di PI3K

• L’associazione dell’inibitore delle CDK4/6 palbociclib con letrozole in prima linea appare molto promettente; sono in corso studi di fase III
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