Combining Endocrine Therapy and Targeted Agents in Advanced Breast Cancer

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Historical Timeline of Therapies for HR+ Advanced Breast Cancer

1896
- Oophorectomy

1977
- SERMs
  - Tamoxifen
  - Toremifene

1990s
- AIs
  - Anastrozole
  - Letrozole
  - Exemestane

2002
- ERDs
  - Fulvestrant

2008-2009
- ERDs
  - High-dose Fulvestrant

2010
- Targeting mechanisms of endocrine resistance: PI3K/Akt/mTOR pathway

2012
- Targeting mechanisms of endocrine resistance: Her2 pathway

Abbreviations: AIs, aromatase inhibitor; ERDs, estrogen receptor downregulator; HR+; hormone receptor positive; SERMs, selective estrogen receptor modulators.

* Marginal improvement over lower dose fulvestrant.

Metastatic/ER+ breast cancer

**Her2 neg./ER+**
- Sequential hormonal therapy
- Life-threatening highly symptomatic

**Her2 pos./ER+**
- Hormones + trastuzumab or lapatinib

**Chemotherapy:** anthracyclines, taxanes, capecitabine, vinorelbine, etc...

**Targeted therapy:** bevacizumab (consider in selected cases)

**Chemotherapy** + Trastuzumab, lapatinib
### Current endocrine agents

#### Premenopausal
- Selective Estrogen Receptor Modulator (SERM) (tamoxifen, toremifen)

#### Posmenopausal
- Aromatase inhibitors (letrozol, anastrozol, exemestane)
- Selective Estrogen Receptor Modulator (SERM) (tamoxifen, toremifen)
- Selective Estrogen Receptor Downregulator (fulvestrant)
- Others: progestins, androgens, high dose estrogens

### Current targeted agents

#### Her2 positive
- Trastuzumab
- Pertuzumab
- T-DM1
- Lapatinib
- LHRH agonists (luprolide, goserelin, triptorelin)
- Surgical oophorectomy
- RT oophorectomy
- Aromatase inhibitor + castration
- Fulvestrant + castration
- Others: progestins, androgens, estrogens

#### Her2 negative
- Bevacizumab

#### Her2 neg./ER+
- Everolimus
Cross-talk between signal transduction pathways and ER signaling in endocrine-resistant breast cancer
Breast cancer genome sequencing results

(A) The genome wheels show point mutations, copy number changes, and chromosomal translocations in aromatase inhibitor (AI)–sensitive and AI-resistant breast cancer cases.
Her2+++ / ER+ ("triple positive")
Does HER2 positivity confer intrinsic resistance to hormonal treatment?

Serum Her2 sub-study (n=566)

Letrozole vs Tamoxifen

**Postmenopausal Advanced BC 1st line**

Mouridsen et al, JCO 2003

**HER2-positive tumours are less responsive to hormonal treatment in the absence of anti-HER2 therapy**

TAnDEM Study: anastrozol +/- trastuzumab

Patient Population
- ER+ / PgR+ (HR+)
- Postmenopausal
- HER2 positive, MBC
- No prior chemo for MBC
- Prior Tam allowed

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole (N=104)</th>
<th>Anastrozole + Trastuzumab (N=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>2.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.63; 95% CI, 0.47 to 0.84</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>P = .0016</td>
<td></td>
</tr>
</tbody>
</table>

Anastrozole 1mg

Anastrozole 1mg + Trastuzumab

J Clin Oncol 27:5529-5537
EGF30008: PFS in the Her2 positive population

Patient Population
- ER+/PgR+ (HR+)
- Postmenopausal
- HER2+, HER2- or unknown
- Stage IIIb / IIIc, IV
- No prior treatment for MBC

Letrozole (N=108)
Letrozole + Lapatinib (N=111)

Progressed or died: 89 (82%) vs 88 (79%)
Median PFS, mo: 3.0 vs 8.2
Hazard ratio (95% CI): 0.71 (0.53, 0.96) p-value: 0.019

Letrozole
2.5mg + Lapatinib
1500 mg

Letrozole
2.5mg + Placebo

J Clin Oncol. 2009 Nov 20; 27(33):5538-46
Outcomes of hormonal therapy in Her2 positive MBC

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole + Placebo</td>
<td>3.0 m.</td>
<td>7%</td>
</tr>
<tr>
<td>Letrozole + lapatinib¹</td>
<td>8.2 m.</td>
<td>10%</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>2.4 m.*</td>
<td>7%</td>
</tr>
<tr>
<td>Anastrozole + trastuzumab²</td>
<td>4.8 m.*</td>
<td>20%</td>
</tr>
</tbody>
</table>

* ITT analysis.

In centrally confirmed ER/PR= median PFS, 5.6 v 3.8 months; P = .006

Her2− / ER+ breast cancer: signalling through the PI3K/Akt/mTOR pathway as a key mechanism of endocrine resistance
Combined Targeting of Both ER and Growth Factor Receptor Pathways May Be a Promising Treatment Approach for HR+ Advanced Breast Cancer

Phase II neoadjuvant RCT

<table>
<thead>
<tr>
<th>Letrozole + Placebo</th>
<th>Letrozole + Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR* (palp.)</td>
<td>Ki67 resp.</td>
</tr>
<tr>
<td>59%</td>
<td>30%</td>
</tr>
<tr>
<td>p=0.061</td>
<td>P &lt; .01</td>
</tr>
</tbody>
</table>

n=270
Postmen., ER and/or PR+
Untreated LABC (>2cm)
No multicentric ,bilateral or inflammatory BC

TAMRAD: a GINECO randomized phase II trial

<table>
<thead>
<tr>
<th>Tamoxifen + Placebo</th>
<th>Tamoxifen + Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBR*</td>
<td>TTP</td>
</tr>
<tr>
<td>42%</td>
<td>4.5m</td>
</tr>
<tr>
<td>p=.045</td>
<td>HR=0.54; p=.002</td>
</tr>
</tbody>
</table>

n=111
Postmen., ER and/or PR+
Previous chemo allowed
Previous AI (adj. or MBC)
Previous adj. Tam allowed

<table>
<thead>
<tr>
<th>Letrozole + Everolimus</th>
<th>Tamoxifen + Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>68%</td>
<td>57%</td>
</tr>
<tr>
<td>61%</td>
<td>8.6m</td>
</tr>
<tr>
<td>HR=0.45</td>
<td>P = .007</td>
</tr>
</tbody>
</table>

Primary endpoint

Baselga et al, J Clin Oncol. 2009 Jun 1;27(16):2630-7
Bachelot, SABCS 2010
Bourgier C et al. ECCO/ESMO 2011

Median follow-up: 22.5 m.
BOLERO-2: Exemestane ± Everolimus in Non-Steroidal Aromatase Inhibitor-Refractory Advanced Breast Cancer

Phase 3 study; N = 724
Postmenopausal women with ER⁺ HER2⁻ advanced breast cancer refractory to letrozole or anastrozole
Recurrence during or within 12 mo after end of adjuvant treatment or progression during or within 1 mo after end of treatment for advanced disease

Primary endpoint:
- PFS

Secondary endpoints:
- OS, ORR, CBR, safety, QoL, bone markers

-everolimus 10 mg/d + Exemestane 25 mg/d (n = 485)
- Placebo + Exemestane 25 mg/d (n = 239)

- Stratification
  - 1. Sensitivity to prior hormonal therapy
  - 2. Presence of visceral disease
- No crossover

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life.

BOLERO-2: Primary Endpoint, PFS (Local Assessment)

HR = 0.45 (95% CI = 0.38, 0.54)
Log-rank P value: < .0001

Everolimus + Exemestane: 7.8 mo
(E/N = 310/485)

Placebo + Exemestane: 3.2 mo
(E/N = 200/239)

Number of patients still at risk

Abbreviations: CI, confidence interval; E/N, patients with events/total patients; HR, hazard ratio; PFS, progression-free survival.

BOLERO-2: Overall Response Rate and Clinical Benefit Rate (Local Assessment)

Abbreviations: CBR, clinical benefit rate; ORR, overall response rate.

## BOLERO-2: Most Common Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Exemestane (n = 482), %</th>
<th>Placebo + Exemestane (n = 238), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</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>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Noninfectious pneumonitis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adverse events of special interest.

Hortobagyi G, et al. SABCS 2011; abstract S3-7 (oral).
Other potential targets
ER+ MBC: targeting EGFR

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Population</th>
<th>No. of patients</th>
<th>Median PFS, mo</th>
<th>HT alone</th>
<th>HT + anti-ErbB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osborne et al(^1) Rand. Phase II</td>
<td>Tamoxifen +/- gefitinib</td>
<td>ITT</td>
<td>206(^\dagger)</td>
<td>8.8</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>Cristofanilli et al(^2) Rand. Phase II</td>
<td>Anastrozole +/- gefitinib</td>
<td>ITT</td>
<td>93(^$)</td>
<td>8.4</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>Mauriac et al(^3) Rand. Phase II</td>
<td>Anastrozole +/- gefitinib</td>
<td>ITT</td>
<td>71(^&amp;)</td>
<td>44.1% (1 year PFS)</td>
<td>45.7% (1 year PFS)</td>
<td></td>
</tr>
<tr>
<td>Johnston et al(^4) Rand. Phase III</td>
<td>Letrozole +/- lapatinib</td>
<td>Her2– ≥6m. from adj Tam</td>
<td>752</td>
<td>15</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Her2– &lt;6m. from adj Tam</td>
<td>200</td>
<td>3.1</td>
<td>8.3</td>
<td></td>
</tr>
</tbody>
</table>

\(^*\)Increased slightly in exploratory analysis of centrally confirmed ER status, 3.8 vs 5.6 mo.

\(^\dagger\)Stratum 1 of trial defined as never receiving tamoxifen or completed adjuvant tamoxifen > 1 year prior.

\(^\$\) Of 174 planned \(^&\) Of 108 planned

ER+ MBC: targeting angiogenesis

Spanish Group for Breast Cancer Research (GEICAM): LEA trial

Letrozole* or Fulvestrant

<table>
<thead>
<tr>
<th>PFS(m)</th>
<th>PFS events</th>
<th>Survival (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.8</td>
<td>131</td>
<td>42</td>
</tr>
<tr>
<td>18.4</td>
<td>117</td>
<td>41</td>
</tr>
</tbody>
</table>

n=378
MBC or IIIB inoperable
ER+ / Her2−
1st line HT
Endpoint: PFS

PFS(m) = .14
HR=0.83 (0.65 - 1.06)

Letrozole* or Fulvestrant
Bevacizumab

* 90% of the pts received Letrozole

Martin et al, SABCS 2012 Abstract S1-7
**ER+ MBC: targeting IGF1**

- Obese women with breast cancer have worse prognosis than women with normal body mass index.
- Endocrine therapy resistance is in part mediated by insulin resistance in obese women with breast cancer.
  - Phase I trial of exemestane in combination with metformin and rosiglitazone in nondiabetic obese postmenopausal women with hormone receptor-positive metastatic breast cancer.
Conclusions: Endocrine therapy + Targeted Therapy

- **ER+ / Her2 +++**: *Trastuzumab* and *Lapatinib* validated in combo with AI, in the 1st line
  - Low disease burden
  - No established or imminent `visceral crisis`
  - Not severely symptomatic
  - Close monitoring for treatment failure
- **ER+ / Her2 −**: *Everolimus* represents major progress, after failure of Non Steroidal AI
  - No established or imminent `visceral crisis`
  - Not severely symptomatic