Metastatic Breast Cancer
An Update

Generosa Grana, MD
Professor of Medicine, CMSRU
Director, MD Anderson Cancer Center at Cooper
Metastatic Breast Cancer

• Presentation
  – Sites of Disease
  – Prognosis

• Treatment Options
  – Hormonal Therapy
  – Chemotherapy
  – Biologic Therapy
  – Radiation

• Supportive Measures
  – Bisphosphonates etc
Disease Presentation

• Local / regional recurrence Vs. Metastatic Disease
• ~85% previously treated for breast cancer

• Presentation:
  – Symptoms & Exam
  – No demonstrated utility to serial scans or tumor markers in early stage disease
Determining Factors:

- Sites of recurrence
  - Skin, nodes > pleura, bone > lung, liver
  - Brain > meninges
- Time from diagnosis to recurrence
- Type of tumor (ER, Her 2neu)

- Significant improvements with available new drugs (chemo, hormonals, biologics)
Current selection of therapy

• Based on sites of disease – urgency!
• Previous therapy (prior anthracyclines, taxanes)
• Pre-existing toxicity (neuropathy, cardiomyopathy, other)
• ER / PR status
• Her 2 neu status
• Patient wishes (weekly vs. Q 3 week, oral vs. Iv, hair loss vs. Not, etc)
• Gene profiling / “personalized medicine” ???
Systemic Treatment Approach for Metastatic Breast Cancer

Metastatic Breast Cancer

- Positive hormone receptors
- Bone and soft tissue or limited visceral metastases
- Hormone responsive
- Disease-free interval ≥2 years

Hormonal Therapy
- Response
- No response

If disease progresses, second-line hormonal therapy

Chemotherapy
- No progression
- Progression of disease

Extensive metastases or visceral disease with organ dysfunction
- Negative hormone receptors
- No response to hormones

Second-line chemotherapy
Hormone Receptor Positive Disease
Open-label first-line ER+ postmenopausal patients with advanced breast cancer (target, N = 200; actual, N = 205)

Fulvestrant 500 mg IM on Days 0, 14, 28, and every 28 days thereafter

Anastrozole 1 mg/day PO

Progression

Follow-up

Progression

Follow-up

Endpoints at primary data cutoff

Primary endpoint

- Clinical benefit rate

Secondary endpoints

- ORR
- TTP
- Duration of response
- Duration of clinical benefit
- Safety

Exploratory endpoint

- Best response to subsequent therapy

FIRST: TTP at Follow-up Analysis

Proportion of Patients Alive and Progression Free

HR: 0.66 (95% CI: 0.47-0.92; P = .01)

Pts at Risk, n

<table>
<thead>
<tr>
<th>Treatment</th>
<th>102</th>
<th>74</th>
<th>65</th>
<th>52</th>
<th>45</th>
<th>34</th>
<th>20</th>
<th>6</th>
<th>0</th>
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</thead>
<tbody>
<tr>
<td>Fulvestrant 500 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrozole 1 mg</td>
<td></td>
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</tbody>
</table>

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

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)

Stratified by previous adjuvant tamoxifen

Treatment until disease progression

Women with progression encouraged to cross over to receive fulvestrant

• Primary endpoint: PFS
• Secondary endpoints: OS, safety

### 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</td>
<td>.007</td>
</tr>
<tr>
<td></td>
<td>(0.68-0.94)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ No previous adjuvant tamoxifen (n = 414)</td>
<td>17.0</td>
<td>12.6</td>
<td>0.74</td>
<td>.0055</td>
</tr>
<tr>
<td></td>
<td>(0.59-0.92)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Previous adjuvant tamoxifen (n = 280)</td>
<td>13.5</td>
<td>14.1</td>
<td>0.89</td>
<td>.37</td>
</tr>
<tr>
<td></td>
<td>(0.69-1.15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS (n = 694), mos</td>
<td>47.7</td>
<td>41.3</td>
<td>0.81</td>
<td>.049</td>
</tr>
<tr>
<td></td>
<td>(0.65-1.00)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>▪ No previous adjuvant tamoxifen (n = 414)</td>
<td>47.7</td>
<td>39.7</td>
<td>0.74</td>
<td>.0362</td>
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<tr>
<td></td>
<td>(0.56-0.98)</td>
<td></td>
<td></td>
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<tr>
<td>▪ Previous adjuvant tamoxifen (n = 280)</td>
<td>49.6</td>
<td>44.5</td>
<td>0.91</td>
<td>.59</td>
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<tr>
<td></td>
<td>(0.65-1.28)</td>
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</tbody>
</table>
Aromatase Inhibitor + CDK4/6 Inhibitor Improves PFS in ER+ MBC


- **PFS Probability**
- **Pts at Risk, n**
  - PD 991 + LET: 84, 75, 60, 53, 43, 35, 25, 18, 15, 14, 9, 5, 3, 1
  - LET: 81, 57, 38, 29, 22, 17, 11, 6, 5, 4, 3, 3, 1, 1

- **Median PFS, mos (95% CI)**
  - PD 991 + LET: 26.1 (12.7-26.1)
  - LET: 7.5 (5.6-12.6)

- **HR (95% CI)**
  - PD 991 + LET: 0.37 (0.21-0.63)
  - LET: < .001

- **Events, n (%)**
  - PD 991 + LET: 21 (25)
  - LET: 40 (49)

**Graphical Representation**
- Kaplan-Meier survival curve showing the progression-free survival probability over time for PD 991 + LET and LET groups.
- P-values indicating statistical significance.
BOLERO-2: Everolimus + Exemestane Improves PFS in HR+ MBC


Central Assessment

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

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

Patients at Risk, n

<table>
<thead>
<tr>
<th></th>
<th>Everolimus</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Wks</td>
<td>Patients</td>
<td>Patients</td>
</tr>
<tr>
<td>0-6</td>
<td>485</td>
<td>239</td>
</tr>
<tr>
<td>6-12</td>
<td>385</td>
<td>168</td>
</tr>
<tr>
<td>12-18</td>
<td>281</td>
<td>94</td>
</tr>
<tr>
<td>18-24</td>
<td>201</td>
<td>55</td>
</tr>
<tr>
<td>24-30</td>
<td>132</td>
<td>33</td>
</tr>
<tr>
<td>30-36</td>
<td>102</td>
<td>20</td>
</tr>
<tr>
<td>36-42</td>
<td>67</td>
<td>11</td>
</tr>
<tr>
<td>42-48</td>
<td>43</td>
<td>11</td>
</tr>
<tr>
<td>48-54</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>54-60</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>60-66</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>66-72</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>72-78</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>78-</td>
<td>0</td>
<td>0</td>
</tr>
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</table>
## 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</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%)

Her 2 neu positive Disease
CLEOPATRA: Study Design

Randomization stratified by geographic region and previous treatment status (neo/adjuvant chemotherapy received or not)

Study dosing q3w:
- Pertuzumab/placebo  840-mg loading dose, 420-mg maintenance
- Trastuzumab    8-mg/kg loading dose, 6-mg/kg maintenance
- Docetaxel       75 mg/m², escalating to 100 mg/m² if tolerated

Patients with HER2-positive MBC centrally confirmed (n = 808)

(n = 406) 1:1 (n = 402)

Placebo + Trastuzumab  Docetaxel* ≥6 cycles recommended
Pertuzumab + Trastuzumab

*<6 cycles allowed for unacceptable toxicity or PD; ≥6 cycles allowed at investigator discretion.

CLEOPATRA: PFS Assessed at an IRF

PFS (%)

Mos

Pts at Risk, n
Pertuzumab
Control

**EMILIA Study Design**


Key inclusion criteria:
- Previous treatment to include a taxane and trastuzumab in adjuvant, locally advanced or metastatic setting
- Documented progression of disease during or after treatment for advanced/metastatic disease, or within 6 mos of completing adjuvant therapy

Primary endpoints: PFS by IRF, OS, safety
Secondary endpoints: OS, QOL: FACT-B

Treatment continues until disease progression or unmanageable toxicity
No provision for cross-over

**HER2-positive (centrally confirmed) locally advanced or metastatic breast cancer (N = 991)**

- T-DM1 q3wk (n = 495)
- Lapatinib + Capecitabine q3wk (n = 496)
PFS by Independent (IRF) Review

MARIANNE: A Phase III Study of T-DM1 + Pertuzumab vs Trastuzumab + Taxane in Patients With MBC: Study Design

ClinicalTrials.gov. NCT01120184.

Patients with HER2+ progressive or recurrent locally-advanced breast cancer or previously untreated MBC (N = 1092)

Stratified by:
- World region
- Neo/adjuvant therapy (Y/N)
- Trastuzumab and/or lapatinib based therapy (Y/N)
- Visceral disease (Y/N)

- Primary endpoints: PFS as assessed by IRF, safety
- Secondary endpoints: OS, PFS by investigator, PRO analyses, biomarkers
Other Trials With Completed or Ongoing Accrual in MBC

• T-DM1 vs investigator’s choice (TH3RESA)
• Addition of pertuzumab to vinorelbine and trastuzumab (VELVET)
Other Novel Compounds Combined With Trastuzumab

- Neratinib
- Sunitinib
- Afatinib
- Vorinostat
- Everolimus
- Ridaforolimus
- Pazopanib
- HSP90 inhibitors
Triple Negative Disease

Much research focusing on:
Understanding the disease
Identifying targets
Testing new drugs / combinations
Future Choices

• Genetic profile of tumor
  – Caris, individual institutional research programs

• Genetic profile of host – metabolizing pathways???

• Better understanding of pathways and relationship between pathways
Molecular Portrait of Breast Cancers

Early Stage Breast Cancer
Oncotype DX™ Technology:
Final Gene Set

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

HER2
GRB7
HER2

ESTROGEN
ER
PGR
Bcl2
SCUBE2

INVASION
Stromelysin 3
Cathepsin L2

GSTM1

CD68

BAG1

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC
### Oncotype DX™ Clinical Validation:
#### B-14 Results – DRFS (cont)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>% of Patients</th>
<th>10-yr Rate Recurrence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (RS &lt;18)</td>
<td>51%</td>
<td>6.8%</td>
<td>4.0%, 9.6%</td>
</tr>
<tr>
<td>Intermediate (RS 18-30)</td>
<td>22%</td>
<td>14.3%</td>
<td>8.3%, 20.3%</td>
</tr>
<tr>
<td>High (RS ≥31)</td>
<td>27%</td>
<td>30.5%</td>
<td>23.6%, 37.4%</td>
</tr>
</tbody>
</table>
Gene Profiling – Treatment Selection – Metastatic Disease “Personalized Medicine”

Caris Molecular Intelligence Service Report Summary

**Agents Associated with Potential BENEFIT**

- **ON NCCN COMPENDIUM™**
  - tamoxifen, toremifene, fulvestrant, letrozole, anastrozole, exemestane, megestrol acetate, leuprolide, goserelin
  - fluorouracil, capecitabine
  - gemcitabine
  - everolimus

- **OFF NCCN COMPENDIUM™**
  - pemetrexed
  - irinotecan
  - temsirolimus
  - temozolomide, dacarbazine

**Agents Associated With Potential LACK OF BENEFIT**

- trastuzumab
- lapatinib, pertuzumab, ado-trastuzumab emtansine (TDM1)
- doxorubicin, liposomal-doxorubicin, epirubicin
- paclitaxel, docetaxel, nab-paclitaxel

**Potential Targets Associated with CLINICAL TRIALS**

- PTEN
- ER
- Her2/Neu
Breast Cancer Therapeutics: 2013

Angiogenesis:
- Sexaminib
- SU6668
- Bevacizumab
- HuMV833
- Cilengitide
- Vitaxin 2
- CAI
- Endostatin
- Angiostatin
- Thalidomide
- Neovastat
- 2-Methoxy Estradiol
- Sorafenib
- Sunitinib
- Vandetanib
- Motesanib diphosphate

Matrix Metalloproteinases:
- Batimastat BB-94
- Marimastat BB-2516
- BMS-275291
- BAY 12-9566
- COL3

Growth Factors
- Erlotinib
- SU6668
- Sexaminib
- Gefitinib
- Trastuzumab
- Lapatinib
- Tipifarnib
- BMS-214662
- Bortezomib
- CC49
- LMB-9
- Mab CO17-1A

Hormones
- Flavopiridol
- 17AAG
- Ad-p53
- Oblimersen

Survival Factors
- Bryostatin-1
- Everolimus
- Temsirolimus
- IL-12
- IL-4
- IL-15

WNT
- Cilengitide

Death Factors
- Oblimersen
- Everolimus
- Temsirolimus

Cytokines
- UCN-01
- Flavopiridol
- Cilengitide

Changes in Gene Expression
- Cell Proliferation
- Cell Death Apoptosis
- DNA damage sensor
- Senescence
- Mitochondria
- Apoptosis
- Bax
- Bcl-2
- Bad
- Bcl XL
- Bcl 2
- Bcl 3

Angiogenesis:
- Sexaminib
- SU6668
- Bevacizumab
- HuMV833
- Cilengitide
- Vitaxin 2
- CAI
- Endostatin
- Angiostatin
- Thalidomide
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Matrix Metalloproteinases:
- Batimastat BB-94
- Marimastat BB-2516
- BMS-275291
- BAY 12-9566
- COL3
Recent additions

• Chemotherapy:
  – Halaven
  – Others in testing

• Her2 neu based therapy:
  – Pertuzumab
  – Kadcyla
  – Neratinib – in testing

• Hormonal therapy:
  – Faslodex
  – Aromasin + Afinitor

• Novel Compounds
  – Parp inhibitors
  – Others
Hormonal Therapy Options for Metastatic Disease

Premenopausal
- Antiestrogens (SERMS)
  - Tamoxifen
  - Toremifene
- Ovarian Suppression
- Antiestrogens + os

Postmenopausal
- Antiestrogens (SERMS)
- Aromatase Inhibitors
- SERDS (Faslodex)
- Progestins
- Androgens
- Estrogen
Thank You.