Metastatic breast cancer update

Linda Vahdat
Today’s agenda

• Discuss metastatic breast cancer
  – definition

• Translation of clinical trial results into standard care
  – What does it mean?

• New strategies and therapies
  – Exciting therapies in trials
What is metastatic breast cancer?

• Breast cancer that has spread outside the lymph nodes in the neck
• Frequent question: If it spreads to the lungs does that mean I have lung cancer?
  – No, it is breast cancer.

  – Metastatic breast cancer is also called advanced breast cancer or stage 4 breast cancer
Approach to stage 4 breast cancer

• Balancing needs to shrink tumor versus side effects of therapy.

• Studies have shown that giving more therapy to “eradicate” any visible tumor did not result in women with breast cancer living longer than those who got less intense therapy and had residual tumor.
It is still important to expand the number of options.....
Stage 4 Breast Cancer

• Relapse rate over time

Year of recurrence associated with a trend towards improved overall survival

- 1950s: cyclophosphamide, methotrexate
- 1960s: 5-fluorouracil, vinblastine, vincristine, fluoxymesterone
- 1970s: doxorubicin, mitomycin-C, tamoxifen
- 1980s: mitoxantrone, etoposide, aminogluthethimide, megestrol acetate, goserelin, leuprolide
- 1990s: paclitaxel, docetaxel, vinorelbine, gemcitabine, trastuzumab, capecitabine, epirubicin, pamidronate, toremifene, anastrozole, letrozole, exemestane

Giordano SH et al, Cancer 2004
Result: the more options the better

How do we maximize this?
2013: Trends in breast cancer therapy

Metastatic Breast Cancer
Moving towards targeted therapy

Molecular subtypes playing a bigger role
Genome-wide view of breast cancer

Molecular portrait correlates with outcome

Sorlie T, PNAS 2001
2012: Approach to pts with metastatic breast cancer

Hormone receptor +
- Luminal A
- Luminal B
- Luminal-HER 2
- HER 2 enriched

HER 2 neu +
- Triple negatives
- Normal-like
- BRCA 1 tumors

Basaloid breast cancer

Hormones, chemo, biologics

HER 2 neu directed therapy + Chemo, other biologics

Chemo
Treatment options Stage 4 breast cancer

Standard treatments
1. Chemotherapy
2. Hormonal therapy
3. Radiation therapy
4. Biologic therapy

Clinical Trials
1. Phase I trials
2. Phase II trials
3. Phase III trials
Picking a treatment
So many choices….

Clinical symptoms
Side effects
QOL issues
Practical issues
Prior therapies

Efficacy =>< Toxicity Equation
Most recent NCCN list

<table>
<thead>
<tr>
<th>Preferred Single Agents</th>
<th>Preferred Chemotherapy Combinations</th>
</tr>
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<tbody>
<tr>
<td>Anthracyclines</td>
<td>CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>FEC (fluorouracil/epirubicin/cyclophosphamide)</td>
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<tr>
<td>Epirubicin</td>
<td>AC (doxorubicin/cyclophosphamide)</td>
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<tr>
<td>Pegylated liposomal doxorubicin</td>
<td>EC (epirubicin/cyclophosphamide)</td>
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<tr>
<td>Taxanes</td>
<td>AT (doxorubicin/docetaxel; doxorubicin/paclitaxel)</td>
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<tr>
<td>Paclitaxel</td>
<td>CMF (cyclophosphamide/methotrexate/fluorouracil)</td>
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<tr>
<td>Docetaxel</td>
<td>Docetaxel/capecitabine</td>
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<tr>
<td>Albumin-bound paclitaxel</td>
<td>GT (gemcitabine/paclitaxel)</td>
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<tr>
<td>Capecitabine</td>
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<tr>
<td>Gemcitabine</td>
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<tr>
<td>Other microtubule inhibitors</td>
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<td>Vinorelbine</td>
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<td>Eribulin</td>
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<td>Other Single Agents</td>
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<tr>
<td>Cyclophosphamide</td>
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<tr>
<td>Mitoxantrone</td>
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<td>Cisplatin</td>
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<td>Etoposide (po) (category 2B)</td>
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<td>Vinblastine</td>
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<tr>
<td>Fluorouracil Cl</td>
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<tr>
<td>Ixabepilone</td>
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<tr>
<td>Preferred Agents With Bevacizumab</td>
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<tr>
<td>Paclitaxel</td>
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Discussion

 prefers CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil) for HER2-positive disease.

Other Combinations
- Ixabepilone + capecitabine (category 2B)

Preferred First-line Agents For HER2-positive Disease
- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

Other First-line Agents For HER2-positive Disease
- Trastuzumab with:
  - Paclitaxel ± carboplatin
  - Docetaxel
  - Vinorelbine
  - Capecitabine

Agents For Trastuzumab-exposed HER2-positive Disease
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents
Let’s talk about HER 2 neu directed therapy

Many new drugs recently approved
HER 2 neu based therapy

Trastuzumab
Lapatinib
Pertuzumab
TDM1
HER2 Overexpression Leads to Increased Cell Proliferation

Sliwkowski et al, Semin Oncol 1999
Figure 1 Heterodimer formation of members of the HER family and downstream signaling

HER 2 neu + Breast cancer

- Herceptin
- Lapatinib
- Pertuzumab: approved 6/2012
- TDM1: approved 2/2013
- Neratinib: soon
- Afatinib: soon
- HSP90 inhibitors: soon too.
Pertuzumab

- Monoclonal Ab with a distinct binding site to trastuzumab
- Prevents HER2 receptor dimerization
- Thought to provide more complete HER2 receptor blockade and to decrease resistance
- Recently approved in combination with trastuzumab and docetaxel as first line therapy for HER2 positive metastatic breast cancer
Cleopatra Study

Patients with HER2-positive MBC (first line)  
N = 808

- pertuzumab + trastuzumab + docetaxel*  
  (≥6 cycles recommended)
- Placebo + trastuzumab + docetaxel*  
  (≥6 cycles recommended)

 Improvement in PFS (6 mos) and OS (HR 0.64)
• <6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion.

T-DM1 (ado-trastuzumab emtansine).

• Antibody drug conjugate
• Trastuzumab linked to a potent antimicrotubule agent (derivative of maytansine)
• After binding to HER2, T-DM1 undergoes receptor-mediated internalization, resulting in intracellular release of DM1
• Delivers highly potent chemotherapy only to HER2 overexpressing cells
• Approved for therapy of metastatic HER2 positive breast cancer previously treated with a taxane and trastuzumab
Receptor T-DM1 complex is internalised into HER2-positive cancer cell

T-DM1 binds to the HER2 protein on cancer cells

Potent antimicrotubule agent is released once inside the HER2-positive tumour cell
EMILIA Study Design

HER2-Positive metastatic breast cancer (N = 980)

- Prior taxane and trastuzumab
- Progression on metastatic tx or within 6 months of adjuvant treatment

T-DM1
3.6 mg/kg IV q3wk

Capecitabine
1000 mg/m² PO bid, Days 1-14, q3wk

+ Lapatinib
1250 mg/day PO qd

Improvement in PFS (30%) and OS (5 months)

Hormone receptor positive breast cancer
Options for hormone positive breast cancer

- **Definition**: Estrogen and/or progesterone receptor >1%
- **SERMS**: tamoxifen or toremifene
- **Aromatase inhibitors**:
  - Letrozole
  - Anastrazole
  - Exemestane
- **Estrogen Receptor Downregulators**:
  - fulvestrant
Latest finding in hormone receptor positive BC

Use of everolimus to reverse endocrine resistance
BOLERO-2: Trial Design

- Stratification:
  1. Sensitivity to prior hormonal therapy
  2. Presence of visceral disease
- No cross-over

BOLERO-2: Addition of everolimus to exemestane improves PFS in HR+ MBC

HR = 0.36 (95% CI: 0.27-0.47)
Log rank $P$ value = $3.3 \times 10^{-15}$

EVE + EXE: 10.6 Months
PBO + EXE: 4.1 Months

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Baselga et al ESMO 2011; NEJM 2012
## BOLERO-2: Most Common G3/4 AEs

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Exemestane (N = 482), %</th>
<th>Placebo + Exemestane (N = 238), %</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
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<tr>
<td><strong>Stomatitis</strong></td>
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<tr>
<td></td>
<td>56</td>
<td>8</td>
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<tr>
<td><strong>Fatigue</strong></td>
<td>33</td>
<td>3</td>
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<tr>
<td><strong>Dyspnea</strong></td>
<td>18</td>
<td>4</td>
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<tr>
<td><strong>Anemia</strong></td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td><strong>Hyperglycemia</strong></td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td><strong>AST</strong></td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td><strong>Pneumonitis</strong></td>
<td>12</td>
<td>3</td>
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Presented by J. Baselga at the 2011 European Multidisciplinary Cancer Congress (ECCO/ESMO), September 26, 2011. Abstract: 9LB

AE: Adverse Event; AST: Aspartate aminotransferase

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

- **Response**
  - Everolimus + Exemestane: 9.5%
  - Placebo + Exemestane: 0.4%
  - \(P < 0.0001\)

- **Clinical Benefit**
  - Everolimus + Exemestane: 33.4%
  - Placebo + Exemestane: 18.0%
  - \(P < 0.0001\)

BOLERO-2: Summary

• Addition of everolimus to exemestane prolongs PFS in patients with ER+ HER2- breast cancer refractory to initial non-steroidal aromatase inhibitors
  – Local: median 6.9 vs 2.8 months, HR = 0.43, \( P < 0.0001 \)
  – Central: median 10.6 vs 4.1 months, HR = 0.36, \( P < 0.00 \)

• Benefit is observed in all subgroups

• Adverse events are consistent with previous experience with everolimus including stomatitis, fatigue and hyperglycemia
Everolimus

• Similar results seen when combined with tamoxifen
• Much smaller benefit when combined with vinorelbine and trastuzumab (herceptin)
New things to watch in clinical trials

• Addition of HDAC inhibitors
Drug Resistance is Multi-factorial

De Novo / Acquired

Genetic
- Histone Demethylases (HDMs)
- Mutations
- Truncations
- Translocations
- DNA Methyltransferases (DNMTs)

Epigenetic
- Target down-regulation
- Tumor suppressor silencing
- DNA damage / repair

Pharmacologic
- Histone Acetyltransferases (HATs)
- Drug efflux
- Drug metabolism
- Histone Methyltransferases (HMTs)

Histone Deacetylases (HDACs)
HDAC Inhibitors Mechanism of Action

HDACi ‘open up’ the structure of DNA

Closed chromatin = Genes off

Open chromatin = Genes on

Histone acetyltransferases (HATs)
Histone deacetylases (HDACs)

HDAC Inhibitors (HDACi)
ENCORE 301 Study Design

Hypothesis: Entinostat re-sensitizes tumors to aromatase inhibitors (AI)

Post-menopausal women with metastatic or locally advanced ER+ breast cancer progressing on a non-steroidal AI (anastrozole or letrozole)

Exemestane + Entinostat (ENT)
5 mg po weekly
N ~ 57

Exemestane + Placebo (PLA)
5 mg po weekly
N ~ 57

Stratification Factors:
• AI disease progression (Adjuvant vs MBC setting)
• Bone only disease (yes / no)
• Geographic region (North America vs EU/Russia)

Randomized, double-blind, placebo-controlled
Endpoints include: 1º PFS, 2º ORR and CBR; Exploratory Endpoint - OS
PFS Greatest in Exemestane+Entinostat in Subjects Who Hyperacetylate

PFS by Treatment and Change in B-cell % Acetylation*

*Similar results in T cells and monocytes
ENCORE 301 Conclusions: Exemestane + Entinostat

- Improved PFS
  – This combination may allow patients to remain on hormonal therapy longer, delaying the need for chemotherapy

- Trend in OS benefit
  – An exploratory endpoint with data that is still maturing

- Well tolerated
  – Safety profile consistent with previous studies

- Increased PFS in subjects who hyperacetylate
  – First randomized study to demonstrate an association between an HDAC inhibitor induced acetylation and clinical outcomes

- These results support plans for the global, pivotal Phase 3 study due to begin enrollment in early 2012
Triple negative breast cancer
Triple negative

- Definition: Lack ER, PR and HER 2 neu
- What we know:
  - Not all created equal
  - Some overlap: basaloid and TNBC
- Is BRCA 1 associated TNBC different?
  - Maybe, not sure yet
  - Differential response to PARP inhibitors
Drugs in clinical trials
PARP inhibitors

- Exploit vulnerability of cells that lack the machinery to repair themselves
- Explored in TNBC and BRCA1/2 mutation carrier
- Still finding its way TNBC but BRCA1/2 look excellent
- Examples: iniparib, olaparib and velaparib
The antibody-drug conjugate CR011-vcMMAE is a fully-human IgG$_2$ antibody to the extracellular domain of GPNMB conjugated to the tubulin inhibitor MMAE.

GPNMB is a glycoprotein expressed in 85% of melanomas and 25 - 40% of breast cancers:
- promotes migration, invasion, and metastasis in preclinical models.

MMAE: monomethylauristatin
Randomized Phase II trial of CDX-011 (CR011-vcMMAE) in Patients with Advanced GPNMB-expressing Breast Cancer

- Stage 4 breast cancer
  - Measurable disease
  - GPNMB +
  - 145 patients enrolled

CDX-011 IV Q3weeks

2:1

Crossover allowed at POD

Physician’s Choice (monotherapy)

Trial completed in January 2012 and WCMC was the lead institution
EMERGE: Correlation of Response and GPNMB Expression

% Patients with Partial Response*

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<td>&lt; 10%</td>
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<td>5%</td>
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<td>≥25%</td>
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Tumor Cells Expressing GPNMB

* Including confirmed and unconfirmed PR
EMERGE: Triple-Negative Patients
Correlation of Response and GPNMB Expression

Tumor Cells Expressing GPNMB

% Patients with Partial Response*

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* Including confirmed and unconfirmed PR
Glembatumumab vedotin:

- Promising activity in patients with TNBC
- Next trial soon.....
New Strategies

Work in Progress:
To understand why BC spreads
Strategy to influence the microenvironment and prevent relapse
Research question

• Why can a tumor be dormant and occult for years in BC and then recur?
  – What are the processes that facilitate this process?
  – Are there any strategies that can interrupt this process pre-clinically that can be replicated clinically?

Maintaining dormancy = cure
Preclinical models of metastatic progression

Primary Tumor Niche

VEGFR1+ hematopoietic progenitor cells (HPC)

Bone Marrow Niche

Distant Site

Premetastatic Niche

Avascular Micrometastases

Preclinical models of metastatic progression

**Primary Tumor Niche**

- VEGF
- bFGF
- PDGF
- + others

**VEGFR2+ endothelial progenitor cells (EPC)**

**Bone Marrow Niche**

**Distant Site**

- Premetastatic Niche

**Avascular Micrometastases**

**Angiogenic switch**

**Vascular Macrometastasis**

Does what happen in mice happen in women with breast cancer?
Are these pre-clinical models relevant to patients with breast cancer?

- What is the natural history of EPCs and HPCs in adjuvant BC patients and metastatic cancer response and progression over time
- Decrease EPCs in women with BC at high risk of relapse

EPCs- CD45^{dim}, CD133+, VEGFR2+ cells; HPCs- CD34+, VEGFR1+
Results

• Study group 132 patients
• There was a surge in VEGFR1+ cells followed by a surge in VEGFR2+ cells followed by a clinical relapse
• Targets for therapy
Identical pattern of HPC surge preceding EPC surge prior to overt relapse in only relapsed patients.

- **PREMETASTATIC NICHE**
  - VEGFR1+ HPC
  - EPC

- **ANGIOGENIC SWITCH**
  - VEGFR2+ EPC

**CLINICAL RELAPSE**

Median: 4 months

2 months
Completed Clinical Study:

- Metastatic measurable Breast Cancer
- Capecitabine
- Capecitabine + VEGF-R1 ab
- Capecitabine + VEGF-R2 ab
- Endpoint: PFS
- Lots of correlatives

Opportunity:
To understand the role of VEGFR 1 and VEGFR2 bone marrow derived cells in metastatic breast cancer
Potential translation: maintenance of tumor dormancy...
Does what happen in mice happen in women with breast cancer? I think so!
Can we impact the EPCs (microenvironment) in a high risk population?

TM study

( phase II study of tetrathiomolybdate in BC pts at high risk of relapse)
Tetrathiomolybdate (TM)

- TM is an oral copper chelator
- Copper is required for angiogenesis, endothelial cell migration and proliferation
- Copper deficiency inhibits angiogenesis and shrinks tumors
- Clinical trials of TM (phase I and II) show that TM is safe. Efficacy has been variable.
Preclinical models of metastatic progression

VEGFR2+ endothelial progenitor cells (EPC)

Primary Tumor Niche

VEGF
bFGF
PDGF + others

Bone Marrow Niche

Distant Site

Premetastatic Niche

Avascular Micrometastases

Angiogenic switch

Vascular Macrometastasis

Identical pattern of HPC surge preceding EPC surge prior to overt relapse in only relapsed patients.

PREMETASTATIC NICHE

VEGFR1+ HPC

ANGIOGENIC SWITCH

VEGFR2+ EPC

Median: 4 months

2 months

CLINICAL RELAPSE
Phase 2 study of TM

Open-label, single-arm phase II trial

Breast cancer at high risk of relapse with NED:
- Stage 3 and 4, any subtype
- Stage 2 triple neg
- Adjuvant tx completed ≥ 6 w
- Hormone therapy allowed
- Target N = 55

Daily oral TM for 2 years, relapse, or toxicity to achieve Cp target < 17 mg/dL

Primary endpoint:
- EPCs

Secondary endpoints:
- PFS
- HPCs
- Adverse events
- Circulating markers of angiogenesis

- Exam & labs monthly
- Imaging every 6 months

Stratification
- Copper depletion
- Molecular subtype

Accrual: June 2007 - ongoing

Jain et al. ASCO Annual Meeting 2011, abstract 1054.
Preliminary results

- TM is safe and well tolerated
- TM copper depletes most patients
- If copper depleted, reduces EPCs
- Went back into lab and figured out additional effects
- Will hopefully continue to move forward
The End!
Thanks for listening