RECENT ADVANCES IN BREAST CANCER THERAPY

Dr. Bhuvaneswari Ramaswamy MD MRCP
Ohio State University
## Breast Cancer – Introduction

<table>
<thead>
<tr>
<th>Incidence of Invasive Breast cancer in the US</th>
<th>230, 480 (~124.3 per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Life time Risk</strong></td>
<td>1 in 8 women</td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>2,747,459</td>
</tr>
<tr>
<td><strong>Median Age of Diagnosis</strong></td>
<td>61</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>39,270</td>
</tr>
</tbody>
</table>

### Race Incidence

<table>
<thead>
<tr>
<th>Race</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>All Races</td>
<td>124.3/100,000</td>
</tr>
<tr>
<td>White</td>
<td>127.3 per 100,000 women</td>
</tr>
<tr>
<td>Black</td>
<td>121.2 per 100,000 women</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>94.5 per 100,000 women</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>80.6 per 100,000 women</td>
</tr>
<tr>
<td>Hispanic b</td>
<td>92.7 per 100,000 women</td>
</tr>
</tbody>
</table>

*Based on Surveillance Epidemiology and End Result Database*

_American Cancer Society, Cancer Facts & Figures. 2006_
## Breast Cancer: Then and Now

### Then
- ~75% of women survived ≥5 years
- Mastectomy was the only surgical option
- Single-agent chemotherapy was standard of care
- Hormonal therapy with tamoxifen was under investigation only
- Genes involved in breast cancer development have not yet been identified

### Now
- ~95% of women survive ≥5 years
- Lumpectomy is available
- Combination chemotherapy is the standard of care
- Hormonal therapy is widely used
- Receptor-based therapy is widely used
- Understanding of genetic components have expanded

Age-adjusted Cancer Death Rates for Females by Site, US, 1930-2005

Adapted from American Cancer Society. Cancer Facts and Figures 2009.
BREAST CANCER
MORTALITY BY STAGE

Stage of Breast Cancer and Five-Year Relative Survival

<table>
<thead>
<tr>
<th>Stage of Breast Cancer</th>
<th>Percent (%) Relative Survival Over Five Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (DMCIS)</td>
<td>100%</td>
</tr>
<tr>
<td>Stage II</td>
<td>100%</td>
</tr>
<tr>
<td>Stage III</td>
<td>86%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>57%</td>
</tr>
<tr>
<td>Stage V</td>
<td>20%</td>
</tr>
</tbody>
</table>
Stages of Breast Cancer

**Localized Disease:**
- Distribution - 60%
- 5-Year Survival – 98%

**Locally Advanced**
- Distribution 33%
- 5-year Survival 84%

**Metastatic Disease**
- Distribution 5-7%
- 5-year survival 23%

Based on Surveillance Epidemiology and End Result Database
Biology of Breast Cancer

Breast Cancer

Hormone Receptor (+) 65-75%

HER2+ 15-20%

TN* 15%

*Triple Negative
"Intrinsic" gene set on 78 single tumor samples

HER-2
Basal-like
"Normal"
Luminal B
Luminal A

476 cDNA clones
85 Arrays

Sorlie T et al, PNAS 2001
Outcomes Based on Molecular Subtype

A

\[
P < .01
\]

Time to Distant Metastasis (months)

B

\[
P < .01
\]

Overall Survival (months)

Sorlie T et al, PNAS 2001
## Molecular-Genetic Profiling

<table>
<thead>
<tr>
<th></th>
<th>Tissue</th>
<th>Patients</th>
<th>FDA</th>
<th>Validation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>MammoPrint</td>
<td>fresh</td>
<td>Node neg ER+, ER-</td>
<td>yes</td>
<td>MindAct</td>
</tr>
<tr>
<td>Wound Healing</td>
<td>fresh</td>
<td>ER+</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td><strong>Oncotype DX</strong></td>
<td>paraffin</td>
<td>Node neg ER+</td>
<td>yes</td>
<td>TAILORx</td>
</tr>
<tr>
<td><strong>HOXB 13/IL-17b Ratio</strong></td>
<td>paraffin</td>
<td>ER+</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td><strong>CYP 2D6</strong></td>
<td>blood</td>
<td>all</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>
ONCOTYPE DX ASSAY

- **Proliferation**
  - Ki67
  - STK15
  - Survivin
  - CCNB1 (cyclin B1)
  - MYBL2

- **HER2**
  - GRB7
  - HER2

- **Estrogen**
  - ER
  - PGR
  - BCL2
  - SCUBE2

- **Invasion**
  - MMP11 (stromelysin 3)
  - CTSL2 (cathepsin L2)

- **GSTM1**

- **CD68**

- **BAG1**

- **Reference**
  - ACTB (β-actin)
  - GAPDH
  - RPLPO
  - GUS
  - TFRC
Table 1. Kaplan–Meier Estimates of the Rate of Distant Recurrence at 10 Years, According to Recurrence-Score Risk Categories.*

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Percentage of Patients</th>
<th>Rate of Distant Recurrence at 10 Yr (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>51</td>
<td>6.8 (4.0–9.6)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>22</td>
<td>14.3 (8.3–20.3)</td>
</tr>
<tr>
<td>High</td>
<td>27</td>
<td>30.5 (23.6–37.4)</td>
</tr>
</tbody>
</table>

* A low risk was defined as a recurrence score of less than 18, an intermediate risk as a score of 18 or higher but less than 31, and a high risk as a score of 31 or higher.
† CI denotes confidence interval.
‡ P<0.001 for the comparison with the low-risk category.
“A lady with growth neoplastic
Thought surgical ablation too drastic.
She preferred that her ill
Could be cured with a pill,
Which today is no longer fantastic.”
ATLAS STUDY

Objective

Tamoxifen x 5 yrs

6846 women with ER+ operable breast cancer who had had ~5 years of adjuvant (N=6846*)

Objectives:
• Recurrence Rate
• Breast Cancer Mortality

*Numbers of Patients for the Analysis:
(1) Patients with ER negative and ER unknown breast cancer (N=6048) were excluded from the analysis of the study’s primary objectives.
(2) All 12,894 patients were included in safety analysis.

SABC 2012, Abstract S1-2; Lancet. 2012 Dec 4 [ahead of print]
ATLAS Study

• After mean of 7.4 woman years of follow up (30,000 w-y in years 5-9, 16,000 in years 10-14, 2000 later)

• Compliance was 80%
**A**

- Continue tamoxifen to 10 years
- Stop tamoxifen at 5 years

5–9 years: RR 0.90 (0.79–1.02)  
≥10 years: RR 0.75 (0.62–0.90)  
All years: log-rank p = 0.002

**B**

5–9 years: RR 0.97 (0.79–1.18)  
≥10 years: RR 0.71 (0.58–0.88)  
All years: log-rank p = 0.01

<table>
<thead>
<tr>
<th></th>
<th>5–9 years</th>
<th>10–14 years</th>
<th>≥15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue tamoxifen to 10 years</td>
<td>2.83% (428/15115)</td>
<td>1.96% (165/8439)</td>
<td>2.54% (24/945)</td>
</tr>
<tr>
<td>Stop tamoxifen at 5 years</td>
<td>3.16% (471/14889)</td>
<td>2.66% (214/8038)</td>
<td>3.03% (268/859)</td>
</tr>
</tbody>
</table>

Log-rank O-E and variance V

<table>
<thead>
<tr>
<th></th>
<th>5–9 years (SE)</th>
<th>10–14 years (SE)</th>
<th>≥15 years (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue tamoxifen to 10 years</td>
<td>-24.8/224.7</td>
<td>-291/947</td>
<td>-21/12.5</td>
</tr>
<tr>
<td>Stop tamoxifen at 5 years</td>
<td>-32/940</td>
<td>-271/775</td>
<td>-25/10.6</td>
</tr>
</tbody>
</table>
BREAST CANCER MORTALITY BY STAGE

Stage of Breast Cancer and Five-Year Relative Survival

- Stage I (axICIS): 100%
- Stage II: 100%
- Stage III: 86%
- Stage IV: 57%
- Stage IV: 20%
Survival Improvement in Metastatic Breast Cancer Patients

- Survival of breast cancer patients presenting with metastases at diagnosis has improved over time, strongly suggesting that improvement is related to treatment

Survival Improvement in Metastatic Breast Cancer Patients

- A recent study from M.D. Anderson Cancer Center that compared length of survival of metastatic breast cancer patients treated at their institution in five-year increments.
- Median survival had doubled to 51 months (range 33-69 months) in 1995-2000 from a median survival of 27 months (range 21-33 months) only five years earlier, 1990-1994.
- Five years after their diagnosis with metastatic disease, 40 percent of these patients were still alive, as compared with 29 percent during 1990-1994.
Metastatic Breast Cancer – Systemic Therapy Options Depend on Tumor Biology

- **Hormone Receptor Positive**
  - Endocrine Therapy

- **HER-2/neu Positive**
  - Chemotherapy
  - Anti-HER-2/neu Agents with chemotherapy or endocrine therapy

- **Triple Negative**
  - Chemotherapy

**Bone Modifying Therapy (Patients with Skeletal Metastases)**
Denosumab (RANKL Inhibitor)

Figure 1: Denosumab and Its Role in the Inhibition of Osteoclast Formation, Function, and Survival

Taken from Robert G. Josse, MD 2009 CGS Annual Scientific Meeting
Denosumab

322 centers:
- Europe
- North & South America
- Japan
- Australia
- India
- South Africa

The primary end point:
- Time to 1st on-study SRE (non-inferiority test).

Secondary end points:
- Time to 1st on-study SRE (superiority test)
- Time to 1st and subsequent SREs.
- Safety

Exploratory end points:
- Overall Survival
- Disease Progression
- Skeletal Morbidity Rate
- Change from baseline to week 13 in uNTx and BSAP

Stage IV Breast Cancer Skeletal Metastases N=2046

Zoledronic Acid 4 mg IV Q28D + Placebo SQ Q28D

Denosumab 120 mg SQ Q28D + Placebo IV Q28D

- Daily supplementation with calcium (>500 mg) and vitaminD (>400U) was strongly recommended.
- Chemotherapy and hormonal therapy were allowed (except for oral or intravenous bisphosphonates or unapproved investigational agents).

Time to First Skeletal Related Event

HR = 0.82 (95% CI, 0.71 to 0.95)
P = .01 (Superiority)*

Proportion Without SRE

Study Month

No. at risk
Zoledronic acid 1,020 829 676 584 498 427 296 191 94 29
Denosumab 1,026 839 697 602 514 437 306 189 99 26

Time to First and Subsequent Skeletal Event

- Zoledronic acid 4 mg Q4W (n = 1,020)
- Denosumab 120 mg Q4W (n = 1,026)

Rate ratio = 0.77 (95% CI, 0.66 to 0.89)

P = .001 (Superiority)*

HER Family: Receptors and Ligands

**Ligand binding domain**

**Transmembrane**

**Tyrosine kinase domain**

- HER1
- HER2
- HER3
- HER4

**Ligands:**
- TGF-α
- EGF
- Epi
- β-cel
- HB-EGF
- EGF
- Amp
- HRG (NRG1)
- Epi
- HB-GF
- NRG1
- NRG2
- NRG3
- NRG4

**References:**
HER2 Overexpression in Breast Cancer

HER2 is overexpressed in ~ 18-25% of breast cancers

Normal (1x)
~ 25,000-50,000 HER2 receptors

- Overexpressed HER2 (10-100x)
- Up to ~ 2,000,000 HER2 receptors

1. Excessive cellular division
2. Increased ability to form tumors in experimental mice
3. Increased ability to form metastases
4. Secretion of vascular endothelial growth factors

Disease Free Survival

Overall Survival

Slamon DJ et al. Science 1987;239: 177-235
## Efficacy in Early Breast Cancer: Summary

<table>
<thead>
<tr>
<th>Trial/Experimental Regimen</th>
<th>N</th>
<th>Med f/u</th>
<th>HR DFS p-value</th>
<th>HR OS p-value</th>
<th>Absol. % diff DFS</th>
<th>Absol % diff OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP/N9831 AC→TH</td>
<td>396</td>
<td>2.9 y</td>
<td>0.48 (&lt;0.00001)</td>
<td>0.65 (&lt;0.0007)</td>
<td>12.8 @ 4 y</td>
<td>3.2 @ 4 y</td>
</tr>
<tr>
<td>HERA Multiple→H</td>
<td>340</td>
<td>2 y</td>
<td>0.64 (&lt;0.0001)</td>
<td>0.66 (&lt;0.0115)</td>
<td>6.3 @ 3 y</td>
<td>2.7 @ 3 y</td>
</tr>
<tr>
<td>BCIRG 006 AC→DH</td>
<td>322</td>
<td>2 y</td>
<td>0.61 (&lt;0.0001)</td>
<td>0.59 (0.004)</td>
<td>6 @ 3 y</td>
<td>4 @ 3 y</td>
</tr>
<tr>
<td>BCIRG 006 DCaH (aka TCH)</td>
<td>322</td>
<td>2 y</td>
<td>0.67 (0.00003)</td>
<td>0.66 (0.017)</td>
<td>5 @ 3 y</td>
<td>2 @ 3 y</td>
</tr>
<tr>
<td>FinHer D/V+H→CEF</td>
<td>232</td>
<td>3 y</td>
<td>0.42 (0.01)</td>
<td>0.41 (0.07)</td>
<td>11.7 @ 3 y</td>
<td>6.6 @ 3 y</td>
</tr>
</tbody>
</table>

It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.
LEVEL OF CROSS TALK FOR ONE PATHWAY
The 6 degrees of separation in drug resistance.

A. Drug-sensitizing mutation
   Drug resistance concomitant mutation

   Tumor regression

   Tumor growth

B. Drug-sensitizing mutation
   Drug resistance mutation

   Resistant subclones

C. Differentiated cells
   Cancer stem cells

   Resistant subpopulations

D. Drug-sensitizing mutation
   Drug-induced inhibition of negative feedback

   Tumor growth

E. Drug-sensitizing mutation
   Tissue-specific negative feedback
   Drug-induced inhibition of negative feedback

   Tumor regression

F. Drug-sensitizing mutation

   Tumor growth

   Growth factors

   Fibroblasts
   Macrophages
   Endothelial cells
Pertuzumab and Trastuzumab Bind to Distinct Extracellular HER2 Epitopes

- Pertuzumab-HER2 Complex
  - Inhibits HER2 dimerization with other HER family receptors (particularly HER3)
  - Activates ADCC
  - Inhibits multiple HER-mediated signaling pathways

- Trastuzumab-HER2 Complex
  - Activates ADCC
  - Inhibits HER-mediated signaling pathways
  - Prevents HER2 domain cleavage

CLEOPATRA

HER2+ MBC
1st line
n = 808

1:1

Placebo
Trastuzumab 6mg/kg q 3 weeks
Docetaxel 75 mg/m2 q 3 weeks

Pertuzumab 420 mg q 3 weeks
Trastuzumab 6mg/kg q 3 weeks
Docetaxel 75 mg/m2 q 3 weeks

Baselga NEJM 2011
<table>
<thead>
<tr>
<th>Control</th>
<th>406</th>
<th>311</th>
<th>209</th>
<th>93</th>
<th>42</th>
<th>17</th>
<th>7</th>
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<th>0</th>
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Cleopatra Baselga NEJM 2011
<table>
<thead>
<tr>
<th>Control</th>
<th>406</th>
<th>383</th>
<th>347</th>
<th>228</th>
<th>143</th>
<th>67</th>
<th>24</th>
<th>2</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
</table>
SMART BOMB
Trastuzumab-DM1: Novel Antibody-Drug Conjugate

- **Target expression:** HER2
- **Monoclonal antibody:** Trastuzumab
- **Cytotoxic agent:** DM1
  - Highly potent cytotoxic agent
- **Linker:** SMCC
  - Systemically stable

MCC (Non-reducible thioether bond to a linker molecule)

EMILIA (TDM4370g) Phase III Study: T-DM1 vs Lapatinib/Capecitabine in HER2+ MBC

Stratification:
- World Region
- Number of Previous Chemotherapy
- Type of prior regimens
- Locally advanced breast cancer
- Presence of visceral disease

Patients with HER2+ locally advanced or metastatic breast cancer following treatment with a taxane and trastuzumab (N = 980)

T-DM1 3.6 mg/kg q3w (n = 495)

Lapatinib 1250 mg daily + Capecitabine 1000 mg/m² 2x/day Days 1-14 every 3weeks (n = 496)

Primary endpoint: PFS by IRF, OS, safety
Secondary endpoints: QoL (FACT B), DOR, PFS by investigator assessment
Verma et al. N Engl J Med. 2012 (Published online on October 1)
Endocrine Therapy Resistance

Aromatase Inhibitors

Tamoxifen, Fulvestrant

Everolimus

IGFR

EGFR/HER2

PI3-K, AKT, mTOR, p90RSK, MAPK

Cell survival

Growth factor
Estrogen

Plasma membrane

Cytoplasm

Nucleus

Tamoxifen, Fulvestrant

ER

ER Target gene transcription

Basal transcription machinery

p160, CBP

ER

**BOLERO-2**

- **Postmenopausal ER/PR+ Advanced Breast Cancer**
- **Progression on nonsteroidal AI in the adjuvant or metastatic setting**
- **n = 724**

**Randomize**

2:1

- **Placebo Exemestane**
- **Everolimus Exemestane**

Baselga NEJM 2011
A Local Assessment

Hazard ratio, 0.43 (95% CI, 0.35–0.54)
P<0.001 by log-rank test

Everolimus plus exemestane
(median PFS, 6.9 mo)

Placebo plus exemestane
(median PFS, 2.8 mo)

No. at Risk

<table>
<thead>
<tr>
<th>Everolimus</th>
<th>458</th>
<th>398</th>
<th>294</th>
<th>212</th>
<th>144</th>
<th>108</th>
<th>75</th>
<th>51</th>
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<th>18</th>
<th>8</th>
<th>3</th>
<th>3</th>
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<tbody>
<tr>
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<td>239</td>
<td>177</td>
<td>109</td>
<td>70</td>
<td>36</td>
<td>26</td>
<td>16</td>
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<td>9</td>
<td>4</td>
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Baselga NEJM 2011
<table>
<thead>
<tr>
<th></th>
<th>Everolimus</th>
<th>458</th>
<th>385</th>
<th>281</th>
<th>201</th>
<th>132</th>
<th>102</th>
<th>67</th>
<th>43</th>
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<th>9</th>
<th>3</th>
<th>2</th>
<th>0</th>
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<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>239</td>
<td>168</td>
<td>94</td>
<td>55</td>
<td>33</td>
<td>20</td>
<td>11</td>
<td>11</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

BOLERO-2

Baselga NEJM 2011
WHY???

- WHY are we still dealing with failures???
- WHY do not we cure 100% of patients with breast cancer?
Age-Adjusted U.S. Mortality Rates
By Cancer Site
All Ages, All Races, Female
2000-2009

Cancer sites include invasive cases only unless otherwise noted.
Mortality source: US Mortality Files, National Center for Health Statistics, CDC.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.5, April 2011, National Cancer Institute.
Age-Adjusted U.S. Mortality Rates
By Cancer Site
All Ages, All Races, Both Sexes
2000-2009

Rate per 100,000

Year of Death

2000 2005 2009

Chronic Myeloid Leukemia

Cancer sites include invasive cases only unless otherwise noted.
Mortality source: US Mortality Files, National Center for Health Statistics, CDC.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.5, April 2011, National Cancer Institute.
STUDY DESIGNS FOR ARRAY-BASED GENE EXPRESSION STUDIES

A

Unselected tumor samples

Identification of tumor classes

Selected tumor samples

A-type: marker genes q, r, s are high
B-type: marker genes x, y, z are high

Index with prognostic or predictive information

Russens et al, JCI, 2011
Planned approaches

Molecular Characterization

- Extract tumor biopsy
- Define "actionable" mutation profile of tumor
- Use genetic alteration profile to choose individualized targeted therapeutic

Cancerous tumor

Tumor traditionally classified by histology, tissue site

Extract DNA from tumor to profile for somatic alterations

Courtesy of N. Wagle
NEW SUBTYPES OF BREAST CANCER

Histopathological types
- Medullary
- Adenoid cystic
- Metaplastic
- IDC NOS
- Lobular carcinoma
- Tubular carcinoma
- Mucinous carcinoma

Subtype defined by IHC markers
- ER^-/HER2^-
- ER^-/HER2^+
- ER^+/HER2^+
- ER^+/HER2^-

Subtypes defined by gene expression
- Claudin low
- Basal like
- HER2 related
- Luminal B
- Luminal A
- Normal like

Structural alterations by NGS

Russens et al, JCI, 2011
MULTILEVEL APPROACH FOR DYNAMIC CLASSIFICATION

Level 1a: tumor
Morphology and clinicopathological characteristics

Level 1b: host
Genotype, age, and hormonal status

Level 2a: molecular subtype
Phenotypic or genomic

Level 2b: prognostic and/or predictive tests
Subtype-specific tests

Or
Level 2: NGS data
Algorithms for subtyping and subtype-specific prognostication and prediction of therapy

Level 2c: serum and bone marrow analyses
Micrometastatic disease
Serum
Bone marrow
Lymph nodes
Monitoring response in advanced disease

Level 3: intratumor heterogeneity
Detection of clones with risk of therapy resistance
Verification of markers for MRD

Level 4: integrated approach to provide...
Diagnosis
Prognostication
Prediction of therapy
Markers for micrometastasis detection
Markers for followup of advanced disease

Russens et al, JCI, 2011
“So in other words, we’re hoping to discover what makes the nitty, gritty.”
THANK YOU