What’s New in Breast Cancer Care

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Assistant Professor
Thomas Jefferson University
Outline

• Epidemiology

• Advances in Targeted Therapies by Breast Cancer Type
  • Endocrine responsive
  • Her-2 overexpressed
  • Triple Negative Breast Cancer
### Lifetime Probability of Developing Cancer, Women, US, 2003-2005*

<table>
<thead>
<tr>
<th>Site</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites†</td>
<td>1 in 3</td>
</tr>
<tr>
<td>Breast</td>
<td>1 in 8</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>1 in 16</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>1 in 20</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>1 in 40</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 in 53</td>
</tr>
<tr>
<td>Urinary bladder‡</td>
<td>1 in 84</td>
</tr>
<tr>
<td>Melanoma§</td>
<td>1 in 58</td>
</tr>
<tr>
<td>Ovary</td>
<td>1 in 72</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1 in 75</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>1 in 145</td>
</tr>
</tbody>
</table>

*For those free of cancer at beginning of age interval.
†All Sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.
‡Includes invasive and in situ cancer cases
§Statistic for white women.
2009 Estimated US Cancer Deaths*

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>30%</td>
<td>26%</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>25%</td>
<td>25%</td>
</tr>
</tbody>
</table>

ONS=Other nervous system.
Source: American Cancer Society, 2009.
The chance of developing invasive breast cancer at some time in a woman's life is a little less than 1 in 8 (12%).

In 2013, 232,340 new cases of invasive breast cancer will be diagnosed in women.

64,600 new cases of carcinoma in situ (CIS) will be diagnosed.

39,620 women will die from breast cancer.

After increasing for more than 2 decades, female breast cancer incidence rates decreased by about 2% per year from 1998 to 2007.
Figure 5. Trends in Female Breast Cancer Incidence Rates* by Race and Ethnicity, US, 1975-2004

*Rates are age-adjusted to the 2000 US standard population.

Data source: Surveillance, Epidemiology, and End Results (SEER) Program, 1973-2004, Division of Cancer Control and Population Science, National Cancer Institute, 2007. Data for whites and African Americans are from the SEER 9 registries. Data for other races/ethnicities are from the SEER 13 registries. For Hispanics, incidence data do not include cases from the Alaska Native Registry, Hawaii, and Seattle. Incidence data for American Indians/Alaska Natives are based on Contract Health Service Delivery Area (CHSDA) counties.

American Cancer Society, Surveillance Research, 2007
Figure 6. Trends in Female Breast Cancer Death Rates* by Race and Ethnicity, US, 1975-2004

- African American
- White
- Hispanic/Latina
- American Indian/Alaska Native
- Asian American/Pacific Islander

*Rates are age-adjusted to the 2000 US standard population.

Information is included for all states except Connecticut, Louisiana, Maine, Maryland, Minnesota, New Hampshire, New York, North Dakota, Oklahoma, Virginia, and Vermont.

Data source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2007

American Cancer Society, Surveillance Research, 2007
Breast Cancer Treatment

• Surgery
• Radiation
• Chemotherapy
• Targeted Therapy
Chemotherapy kills growing cells
Targeted Therapy
Types of Breast Cancer

- **ER/PR +, Her-2/neu +** (luminal B)
- **ER/PR +, Her-2/neu -** (luminal A)
- **ER/PR -, Her-2/neu +** (Her-2 overexpressing)
- **ER/PR -, Her-2/neu -** (Basal-like)
Breast Cancer Subtypes

ER+/HER2- 60%

ER-/HER2- 20%

ER+/HER2+ 15%

ER-/HER2+ 5%


Atlas & aTTom Trial Results

Atlas-15,000 women randomized, 13,000 included in final analysis. Ten years of treatment with Tamoxifen compared to five years decreased breast cancer mortality and overall mortality in years 10-15.

Atlas-Ten years of treatment with Tamoxifen decreased breast cancer recurrence in years 10-15.

aTTom-Fifteen percent reduction in risk of recurrence starting at year 10.

aTTom-Twenty-five percent reduction in breast cancer mortality starting at year 10.

Pooled analysis of both trials-9% reduction in mortality risk, 16% starting at year 10.

Side effects, feasibility of ten year regimen, adherence
Hormone Responsive Breast Cancer

BOLERO-2 trial, Baselga et al.

Based on mechanisms of resistance in endocrine response breast cancer.

Seven hundred twenty-four patients randomized to receive either exemestane plus placebo or everolimus with exemestane. All patients were metastatic and had previously progressed on endocrine therapy.

Six month improvement in progression free survival in the arm with both therapies.

Mechanisms of endocrine resistance are a topic of active research. Multiple clinical trials currently accruing with combination therapies.
Types of Breast Cancer

- ER/PR +, Her-2/neu +  (luminal B)
- ER/PR +, Her-2/neu -  (luminal A)
- ER/PR -, Her-2/neu +  (Her-2 overexpressing)
- ER/PR -, Her-2/neu -  (Basal-like)
Human Epidermal Growth Factor Receptor (HER) Family of Receptors and Therapeutic Agents Currently Available or in Development.
Targeted Therapies

• Tumors which overexpress Her-2/neu-family of EGFR receptors

• Introduction of Trastuzumab resulted in prognosis for Her-2/neu + patients being equal to others.

• Used for early and late stage patients.

• Side effects-allergic reaction, decreased heart function

• Lapatinib

• Pertuzumab, TDM-1
Study Overview

• Pertuzumab, an anti-HER2 antibody, recognizes a different epitope of HER2 than does trastuzumab and behaves differently.

• In patients with metastatic breast cancer, the combination of the two antibodies plus docetaxel significantly increased progression-free survival.
Overall Survival.

Hazard ratio, 0.64
(95% CI, 0.47–0.88)

P=0.005

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Pertuzumab</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>402</td>
<td>387</td>
</tr>
<tr>
<td></td>
<td>406</td>
<td>383</td>
</tr>
</tbody>
</table>
Conclusions

- The combination of pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel, when used as first-line treatment for HER2-positive metastatic breast cancer, significantly prolonged progression-free survival, with no increase in cardiac toxic effects.
Pertuzumab in Neoadjuvant Treatment

Use of pertuzumab in neoadjuvant patients (prior to surgery)

Neosphere trial randomized 417 patients to one of four treatment arms.

One treatment arm consisted of Pertuzumab, trastuzumab, and docetaxel in addition to chemotherapy. This arm had the best outcomes compared to the other 3 arms (pathologic complete response). (45.8% v 29%, 24%, and 16.8%).
Study Overview

• Women with metastatic breast cancer that had progressed during treatment with trastuzumab plus a taxane were assigned to lapatinib plus capecitabine or to trastuzumab emtansine.

• The response rate and survival were significantly better with trastuzumab emtansine.
Progression-free Survival, as Assessed by an Independent Review Committee.

- **Lapatinib–Capecitabine**
  - Median No. of Months: 6.4
  - No. of Events: 304

- **T-DM1**
  - Median No. of Months: 9.6
  - No. of Events: 265

Stratified hazard ratio, 0.65 (95% CI, 0.55–0.77)
P < 0.001

**No. at Risk**

| Treatment          | 496 | 404 | 310 | 176 | 129 | 73  | 53  | 35  | 25  | 14  | 9   | 8   | 5   | 1   | 0   | 0   |
|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lapatinib–capecitabine | 495 | 419 | 341 | 236 | 183 | 130 | 101 | 72  | 54  | 44  | 30  | 18  | 9   | 3   | 1   | 0   |

Objective-Response Rate and Duration of Response, as Assessed by the Independent Review Committee.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lapatinib plus Capecitabine (N=389)</th>
<th>T-DM1 (N=397)</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete or partial response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>120</td>
<td>173</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent (95% CI)</td>
<td>30.8 (26.3–35.7)</td>
<td>43.6 (38.6–48.6)</td>
<td>12.7 (6.0–19.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete response — no. (%)</td>
<td>2 (0.5)</td>
<td>4 (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response — no. (%)</td>
<td>118 (30.3)</td>
<td>169 (42.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of complete or partial response — mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>6.5</td>
<td>12.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>5.5–7.2</td>
<td>8.4–20.8</td>
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</tbody>
</table>

* The total number of patients in each group is the number with measurable disease at baseline, as determined by independent review. CI denotes confidence interval.

Conclusions

• T-DM1 significantly prolonged progression-free and overall survival with less toxicity than lapatinib plus capecitabine in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane.
TDM-1 in Early Stage Patients

Katherine Trial-currently accruing patients

Randomizes patients to continue trastuzumab after neoadjuvant treatment or receive TDM-1 for a total of one year.

Sites open worldwide currently, including TJU.
Advances in Her-2/neu overexpressed breast cancer

- Trastuzumab in adjuvant, neoadjuvant, and metastatic setting
- Lapatinib in neoadjuvant and metastatic settings
- Pertuzumab, TDM-1 (Katherine trial) in neoadjuvant, adjuvant and metastatic settings
- Combinations of Her-2/neu inhibitors
Types of Breast Cancer

- ER/PR +, Her-2/neu + (luminal B)
- ER/PR +, Her-2/neu - (luminal A)
- ER/PR -, Her-2/neu + (Her-2 overexpressing)
- ER/PR -, Her-2/neu - (Basal-like)
### Table 1
Summary of clinical features of triple-negative tumours.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Younger age at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>African origin</td>
</tr>
<tr>
<td></td>
<td>BRCA1 mutation carrier</td>
</tr>
<tr>
<td>Tumour characteristics</td>
<td>Ductal invasive carcinoma</td>
</tr>
<tr>
<td></td>
<td>Rare histologies (medullary, metaplastic)</td>
</tr>
<tr>
<td></td>
<td>High-grade</td>
</tr>
<tr>
<td></td>
<td>Negativity for ER, PgR and HER-2</td>
</tr>
<tr>
<td></td>
<td>Elevated mitotic count</td>
</tr>
<tr>
<td></td>
<td>Tumour necrosis</td>
</tr>
<tr>
<td></td>
<td>Pushing margin of invasion</td>
</tr>
<tr>
<td></td>
<td>Larger tumour size</td>
</tr>
<tr>
<td></td>
<td>Axillary node involvement</td>
</tr>
<tr>
<td>Treatment/prognosis</td>
<td>Chemosensitive</td>
</tr>
<tr>
<td></td>
<td>No known targets</td>
</tr>
<tr>
<td></td>
<td>Poorer prognosis (trend of relapse first 3 years)</td>
</tr>
<tr>
<td></td>
<td>Aggressive relapse</td>
</tr>
</tbody>
</table>
Chemotherapy

- Despite poorer prognosis, TNBC is more responsive to chemotherapy than other breast cancer subtypes.

- Neoadjuvant setting (larger tumors treated with chemotherapy before surgery - response to chemotherapy assessed at the time of surgery). Best outcome is pathologic complete response (no tumor left in surgical specimen).

- Three studies of anthracycline and taxane chemotherapy in the neoadjuvant setting showed the highest rate of path CR in triple negative subset (45%).

- Adjuvant setting (chemotherapy after surgery), addition of taxane to anthracycline showed most benefit in TNBC.
Chemotherapy

- Platinum agents are being investigated as chemotherapy backbone for TNBC based on the similarity of TNBC to BRCA mutated cancers.

- Particular sensitivity to the DNA damaging effects of platinum agents.

- Cisplatin has been studied in the neoadjuvant setting and found to be efficacious in TNBC (22% path CR rate).

- Platinum agents (cisplatin and carboplatin) have also been combined with anthracycline and taxane and found to have pathologic CR rates of 40-62%.

- Platinum agents are also being tested as the chemotherapy “backbone” for newer, targeted agents.
Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*

We analysed primary breast cancers by genomic DNA copy number arrays, DNA methylation, gene sequencing, messenger RNA arrays, microRNA sequencing and reverse-phase protein arrays. Our ability to integrate information across platforms provided key insights into previously defined gene expression subtypes and demonstrated the value of multi-omicsonal breast cancer clones when combining data from five platforms, each of which shows significant molecular heterogeneity. Somatic mutations in only three genes (TP53, PIK3CA and CDH1) occurred in >5% of incidence across all breast cancers, however, there were numerous uncommonly associated single nucleotide mutations (including the inactivation of specific mutations in GATA3, PRR5L and MAP2K1 with the basal-like A subtype. We identified two novel protein expression-defined subgroups, possibly produced by stringent selection of tumours that share subtypes in which multiple subtypes including a HER2-negative/1, HER2/ERBB3phosphorylated/EGFR signature within the HER2-enriched expression subtype. Comparison of basal-like breast tumours with high grade ovarian tumours showed many molecular similarities, indicating a related ancestry and similar therapeutic opportunities. The biological findings of the four basal-like breast cancer only caused by different subsets of genetic and epigenetic alterations raise the hypothesis that much of the clinically observable parallelism and heterogeneity occurs within, and not across, these major biological subtypes of breast cancer.

Breast cancer is one of the most common cancers with greater than 200,000 cases and 60,000 deaths per year worldwide. Currently, the heterogeneity of disease is recognized as one of the chief challenges in the development of adequate targeted therapy. The identification of genes with cancerous implications is a major step in the development of targeted therapy. We identified a group of genes with cancerous implications that have significant clinical implications for the development of targeted therapy.

Many studies have focused on the identification of genes with cancerous implications. The identification of genes with cancerous implications has been a major step in the development of targeted therapy. We identified a group of genes with cancerous implications that have significant clinical implications for the development of targeted therapy.

We used a combination of genomic, epigenomic, and transcriptomic data to identify a set of genes that were significantly associated with breast cancer. The genes identified included TP53, PIK3CA, and CDH1, which are known to be involved in breast cancer. We also identified a set of genes that were significantly associated with breast cancer that included GATA3, PRR5L, and MAP2K1, which are known to be involved in the basal-like subtype of breast cancer.

We also identified two novel protein expression-defined subgroups within the breast cancer population. The first subgroup was characterized by high levels of expression of genes involved in the HER2-negative/1 subtype, while the second subgroup was characterized by high levels of expression of genes involved in the HER2/ERBB3phosphorylated/EGFR subtype.

We also compared the basal-like breast cancer subgroup with high-grade ovarian cancer, which showed many molecular similarities, indicating a related ancestry and similar therapeutic opportunities. The biological findings of the four basal-like breast cancer only caused by different subsets of genetic and epigenetic alterations raise the hypothesis that much of the clinically observable parallelism and heterogeneity occurs within, and not across, these major biological subtypes of breast cancer.

Samples and clinical data

Tumour and germline DNA samples were obtained from 425 patients. Differences in patients were assessed on each platform.

* From the Cancer Genome Atlas Network.
• Genetic expression found in basal-like tumors was similar to previously described mutations in ovarian cancers.

• Comparisons were made between basal-like and ovarian, luminal and ovarian and luminal and basal-like cancers.

• Basal-like cancers were found to be most similar to ovarian tumors.

• Mutations in TP53, RB1, MYC1 and BRCA1 were observed in both basal-like and ovarian cancers.

• Suggests that chemotherapy used in ovarian cancers should be explored in basal-like cancers.

• Platinum agents and taxanes are used in ovarian cancer and are under investigation in TNBC.
Parp Inhibitors-Mechanism of Action

Figure 1: Schematic Illustration of Synthetic Lethality—BER = base excision repair (including single-strand break repair); HR = homologous recombination repair.
Kaplan–Meier Estimates of Progression-free and Overall Survival Rates, According to Treatment Group.

Phase III Iniparib Trial

- 519 patients randomized to GC v. GCI
- Co-primary endpoints of overall survival (OS) and progression free survival (PFS)
- No significant difference in OS (11.1 v 11.8 mos)
- No significant difference in PFS (4.1 v 5.1 mos)
- Increased PFS among patients receiving 2^{nd} or 3^{rd} line therapy
- TNBC heterogeneity, chemotherapy backbone, lack of Parp inhibition

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Phase of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iniparib (BSI-201)</td>
<td>BiPar/sanofi-aventis</td>
<td>III</td>
</tr>
<tr>
<td>BSI-401</td>
<td>BiPar/sanofi-aventis</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Olaparib (AZD2281)</td>
<td>KuDOS/AstraZeneca</td>
<td>III</td>
</tr>
<tr>
<td>Veliparib (ABT-888)</td>
<td>Abbot</td>
<td>II</td>
</tr>
<tr>
<td>CO-338</td>
<td>Clovis</td>
<td>II</td>
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<tr>
<td>INO-1001</td>
<td>Inotek</td>
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<tr>
<td>MK-4827</td>
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<td>E7016</td>
<td>Eisai</td>
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</tr>
<tr>
<td>BMN-673</td>
<td>BioMarin</td>
<td>I</td>
</tr>
</tbody>
</table>

• Ongoing studies of Parp inhibitors in neoadjuvant and metastatic settings

• Appropriate chemotherapy backbone

• Efficacy of parp inhibitor

• Jefferson trial-platinum chemotherapy with true parp inhibitor for neoadjuvant treatment
Neoadjuvant Chemotherapy (NACT)

- Goal is to optimize surgical outcomes
- Standard for larger, Stage 3 tumors
- Marginally resectable tumor
- Inflammatory breast cancer
- Best outcome is pathologic complete response path CR
- Surgery is ALWAYS performed, regardless of outcome of chemotherapy
Advantages

• Clinical evaluation of effectiveness of regimen

• Tissue samples before, during, and after treatment-useful for biomarker research.

• Pathologic CR adds to prognostic information.

• May change chemotherapy or perform surgery earlier than planned if patient is not clinically responding.
Path CR by subtype

- Hormone responsive cancers are least likely to have path CR. Response rates generally < 10%

- Her-2 + patients have rates of path CR ranging form 39% without Herceptin to 60% with Herceptin in I-SPY 1.

- Path CR rates for triple negative breast cancer (TNBC) range from 27-60%.

- TNBC is among the most responsive to chemotherapy, but has the highest relapse rates. Anthracycline & taxane containing regimens are most effective.

- Development of new chemotherapy regimens incorporating platinum agents for TNBC is ongoing.
Jefferson Trial

• Platinum agents
• Parp inhibitor
• Neoadjuvant Trial
• Biomarker studies
• Circulating Tumor Cells
Screening

Randomize

On Study

Paclitaxel + Carboplatin (12 weekly cycles)

Paclitaxel + Carboplatin + Veliparib (12 weekly cycles)

AC (4 x 3-week cycles)

AC (4 x 3-week cycles)

Ultrasound

Investig. Biopsy A

CTC sample

MRI

PET/CT

Biopsy

MRI

PET/CT

Ultrasound

Investig. Biopsy B

CTC sample

MRI

Ultrasound

Investig. Biopsy C

CTC sample

MRI

PET/CT

Ultrasound

CTC sample

Surgical Tissue

CTC sample

Consent

0 1 2 3 4 5 6

Time (months)
Advances in TNBC

- Ongoing studies of Parp inhibitors in neoadjuvant and metastatic settings
- Appropriate chemotherapy backbone
- Efficacy of parp inhibitor
- Jefferson trial-platinum chemotherapy with true parp inhibitor for neoadjuvant treatment
Future Directions

• Different subsets within the basal-like subtype have been identified

• Intense infiltration of immune cells

• Expression of genes involved in immune response

• Genetic expression that may correspond with response to anthracycline

• Genetic expression of androgen receptors

• Further characterization of subtypes within TNBC will likely lead to new targets
Future Directions

• Further identification of genetic expression will guide future targets

• Ovarian cancer chemotherapy

• Further exploration of appropriate chemotherapy backbone for use with parp inhibitors

• One Phase II study of inhibitor of proto-oncogene, src, (dasatinib) showed modest benefit in TNBC.

• Inhibitors of the MEK/ERK pathway may be effective therapy for TNBC. MEK inhibitors are in Phase 1 studies.

• EGFR inhibitors
Summary

• Hormone responsive breast cancer-duration of adjuvant endocrine therapy, combination therapies exploiting pathways of resistance.

• Her-2/neu overexpressed-newly approved agents pertuzumab, TDM-1. Ongoing studies of combinations of targeted therapies in all settings.

• TNBC-platinum chemotherapy, parp inhibitors, molecular subtypes