Breast Cancer in 2017: New approaches, better outcomes

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Bayhealth Cancer Institute
DBCC Annual Breast Cancer Update
April 4, 2017
Breast cancer—How can we make a difference?

• Identifying who may be at higher risk for developing breast cancer
  • Genetic testing: Who needs it, and what to test for?

• Increasing the chance of cure for early stage breast cancer
  • Adjuvant chemotherapy: Who needs it? and who doesn't?
  • Adjuvant endocrine therapy: How long is long enough?

• Improving the quality...and quantity of life for those with advanced breast cancer
  • Hormone receptor positive
  • Her2 positive
  • Triple negative

References & Slide credits:
• NCCN Guidelines-2017, version 1
• ASCO Annual Mtg-2016
• ASCO University- 2017
• San Antonio Breast Cancer Symposium-2016
• Clinical Care Options-Oncology-2017
Cancer Genetics

Identifying those at higher risk
Understanding genetic testing - Mutations

Germline mutations
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

Mutation in egg or sperm

All cells affected in offspring

Parent → Heritable → Child
When should we think about hereditary cancer?

NCCN Guidelines Version 2.2017
Breast and/or Ovarian Cancer Genetic Assessment

CRITERIA FOR FURTHER GENETIC RISK EVALUATION

- An individual with an ovarian cancer
- An individual with a breast cancer diagnosis meeting any of the following:
  - Early-age-onset breast cancer
  - Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤ 50 y
  - Two breast cancer primaries in a single individual
  - Breast cancer at any age, and
    - ≥1 close blood relative with breast cancer ≤ 50 y, or
    - ≥1 close blood relative with invasive ovarian cancer at any age, or
    - ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age, or
    - Pancreatic cancer at any age, or
    - From a population at increased risk
- Male breast cancer
  - An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age
  - An individual with a personal and/or family history of three or more of the following (especially if early onset and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥ 7), melanoma, sarcoma, adenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polypos of gastrointestinal (GI) tract

- An individual with no personal history of cancer but with
  - A close relative with any of the following:
    - A known mutation in a cancer susceptibility gene within the family
    - ≥2 breast cancer primaries in a single individual
    - ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤ 50 y
    - Ovarian cancer
    - Male breast cancer
    - First- or second-degree relative with breast cancer ≤ 45 y
    - Family history of three or more of the following (especially if early onset and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥ 7), melanoma, sarcoma, adenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polypos of gastrointestinal (GI) tract

Consider referral to cancer genetics professional
BRCA mutation - Cancer risks

**BRCA1-Associated Breast and Ovarian Cancers: Risk to Patients Age 70 Years**
- Breast cancer - mean age 43 (50%-65%)
- Contralateral breast cancer (20%-83%; 27% within 5 years)
- Ovarian cancer - mean age 52 (40%-59%)
- Male breast cancer (1%-3%)
- Prostate cancer

**BRCA2-Associated Breast and Ovarian Cancers: Risk to Patients Age 70 Years**
- Breast cancer - mean age 47 (49%-55%*)
- Contralateral breast cancer (20%-62%; 12% within 5 years)
- Prostate cancer
- Ovarian cancer - mean age 62 (16%-18%)
- Male breast cancer (5%-10%)

*28% in Jewish populations with BRCA2 6174delT
BRCA mutations - What can we do proactively?

- Breast MRI
- Mastectomy
- Oophorectomy
- Endocrine therapy
BRCA 1/2 may be the 'main genes', but not the only genes!

Panel Results - 708 HBOC Patients

- 109/708 (15.3%) had pathogenic mutations
- 59% had mutations in BRCA1 or BRCA2
- 41% had mutations in other genes

# Other Genes Conferring Susceptibility to Breast Cancer

<table>
<thead>
<tr>
<th>Gene name and description</th>
<th>Contribution to hereditary breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTEN (Cowden)</strong> breast, thyroid, colon hamartomas, large head, tricholemmomas</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>STK1 (Peutz-Jegher)</strong>: freckles on lips, small bowel hamartomous polyps</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>TP53 (Li-Fraumeni)</strong>: sarcoma, early breast, brain, adrenal cortical tumors</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>CDH1 (hereditary diffuse gastric cancer)</strong></td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Neurofibromatosis</strong>: café au lait macules, neurofibromas</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>PALB2</strong>: pancreas, early breast, ovary</td>
<td>Rare?</td>
</tr>
</tbody>
</table>
• Think about multi-gene panels when:
  • Multiple or other cancer types in family
  • One or more rare syndromes in differential
  • Results would influence medical management
  • Also can be done later, as 'reflex', if upfront BRCA testing negative
Which genes? For which cancers?
A 'cheat sheet'

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast cancer</th>
<th>Ovarian cancer</th>
<th>Other cancer?</th>
<th>Risk level</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>LOW</td>
<td>Breast cancer, ?pancreatic cancer</td>
</tr>
<tr>
<td>ATR</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>LOW</td>
<td></td>
</tr>
<tr>
<td>BARD1</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>LOW</td>
<td></td>
</tr>
<tr>
<td>CHEK2</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>LOW</td>
<td>Male breast cancer, prostate cancer</td>
</tr>
<tr>
<td>MRE11A</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>LOW</td>
<td></td>
</tr>
<tr>
<td>MUTYH</td>
<td>Y?</td>
<td>N</td>
<td>Y</td>
<td>LOW</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>NBN</td>
<td>Y</td>
<td>N</td>
<td>M</td>
<td>LOW</td>
<td>Hematologic cancers</td>
</tr>
<tr>
<td>PMS1</td>
<td>N</td>
<td>N</td>
<td>N?</td>
<td>LOW</td>
<td>Maybe colon cancer</td>
</tr>
<tr>
<td>PALB2</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>MED</td>
<td>Pancreatic/Breast/Ovarian cancer</td>
</tr>
<tr>
<td>RAD50</td>
<td>N</td>
<td>Y</td>
<td></td>
<td>MED-HIGH</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>RAD51C</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>MED-HIGH</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>CDH1</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>HIGH</td>
<td>Causes Hereditary Diffuse Gastric Cancer &amp; lobular breast cancer</td>
</tr>
<tr>
<td>MLH1</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>HIGH</td>
<td>Causes Lynch syndrome</td>
</tr>
<tr>
<td>MSH2</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>HIGH</td>
<td>Causes Lynch syndrome</td>
</tr>
<tr>
<td>MSH6</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>HIGH</td>
<td>Causes Lynch syndrome</td>
</tr>
<tr>
<td>PMS2</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>HIGH</td>
<td>Causes Lynch syndrome</td>
</tr>
<tr>
<td>PTEN</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>HIGH</td>
<td>Causes Cowden syndrome</td>
</tr>
<tr>
<td>STK11</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>HIGH</td>
<td>Causes Peutz Jegher syndrome</td>
</tr>
<tr>
<td>TP53</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>HIGH</td>
<td>Causes Li Fraumeni syndrome</td>
</tr>
</tbody>
</table>
### Breast and Ovarian Management Based on Genetic Test Results

The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td><strong>Increased risk of BC</strong>&lt;br&gt;• Screening: Annual mammogram and consider breast MRI with contrast starting at age 40 y&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt;• RRM: Consider based on family history</td>
<td><strong>No increased risk of OC</strong></td>
<td>Unknown or insufficient evidence for pancreas or prostate cancer</td>
</tr>
<tr>
<td>BRCA1</td>
<td><strong>Increased risk of BC</strong>&lt;br&gt;• See BRCA Mutation-Positive Management</td>
<td><strong>Increased risk of OC</strong>&lt;br&gt;• See BRCA Mutation-Positive Management</td>
<td>Prostate cancer&lt;br&gt;• See BRCA Mutation-Positive Management</td>
</tr>
<tr>
<td>BRCA2</td>
<td><strong>Increased risk of BC</strong>&lt;br&gt;• See BRCA Mutation-Positive Management</td>
<td><strong>Increased risk of OC</strong>&lt;br&gt;• See BRCA Mutation-Positive Management</td>
<td>Pancreas, Prostate, Melanoma&lt;br&gt;• See BRCA Mutation-Positive Management</td>
</tr>
<tr>
<td>BRIP1</td>
<td><strong>No increased risk of BC</strong></td>
<td><strong>Increased risk of OC</strong>&lt;br&gt;• Consider RRSO at 45–50 y</td>
<td>N/A</td>
</tr>
<tr>
<td>CDH1</td>
<td><strong>Increased risk of lobular BC</strong>&lt;br&gt;• Screening: Annual mammogram and consider breast MRI with contrast starting at age 30 y&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt;• RRM: Consider based on family history</td>
<td><strong>No increased risk of OC</strong></td>
<td>Diffuse gastric cancer&lt;br&gt;• See NCCN Guidelines for Gastric Cancer</td>
</tr>
</tbody>
</table>

**Comments:**
- **ATM**
  - Insufficient evidence to recommend against radiation therapy. The 7271T>G missense mutation may act in a dominant-negative fashion, resulting in a lifetime breast cancer risk as high as 60% by age 80 (which is higher than truncating mutations, where risks are in the range of 30-40%). counsel for risk of autosomal recessive condition in offspring.

- **BRCA1**
  - See BRCA Mutation-Positive Management

- **BRCA2**
  - See BRCA Mutation-Positive Management

- **BRIP1**
  - See BRCA Mutation-Positive Management

- **CDH1**
  - See BRCA Mutation-Positive Management

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**Definitions:**
- BC: Breast cancer
- OC: Ovarian cancer
- RRM: Risk-reducing mastectomy
- RRSO: Risk-reducing salpingo-oophorectomy

**Notes:**
- <sup>c</sup> Age at which screening should start based on the nature of the familial condition and personal risk.

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**References:**
# NCCN Guidelines Version 2.2017

## Genetic/Familial High-Risk Assessment: Breast and Ovarian

### Breast and Ovarian Management Based on Genetic Test Results

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<tr>
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<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHEK2</strong></td>
<td>Increased risk of BC</td>
<td>No increased risk of OC</td>
<td>Colon</td>
</tr>
<tr>
<td></td>
<td>• Screening: Annual mammogram and consider breast MRI with contrast age 40 y≥</td>
<td></td>
<td>• See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
</tr>
<tr>
<td></td>
<td>• RRM: Evidence insufficient, manage based on family history.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments: Risk data are based only on frameshift mutations. The risks for most missense mutations are unclear.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MSH2, MLH1, MSH6, PMS2, EPCAM</strong></td>
<td>Unknown or insufficient evidence for BC riskd</td>
<td>Increased risk of OC</td>
<td>See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
</tr>
<tr>
<td></td>
<td>• Manage based on family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NBN</strong></td>
<td>Increased risk of BC</td>
<td>Unknown or insufficient evidence for OC risk</td>
<td>Unknown or insufficient evidence</td>
</tr>
<tr>
<td></td>
<td>• Screening: Annual mammogram and consider breast MRI with contrast age 40 y≥</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RRM: Evidence insufficient, manage based on family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments: Management recommendations are based on data derived from the 657del5 Slavic truncating mutation. Although risks for other mutations have not been established it is prudent to manage patients with other truncating mutations similarly to those with 657del5. Counsel for risk of autosomal recessive condition in children.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NF1</strong></td>
<td>Increased risk of BC</td>
<td>No increased risk of OC</td>
<td>Malignant peripheral nerve sheath tumors, GIST, others</td>
</tr>
<tr>
<td></td>
<td>• Screening: Annual mammogram starting at age 30 y and consider breast MRI with contrast from ages 30–50 y</td>
<td></td>
<td>• Recommend referral to NF specialist for evaluation and management.</td>
</tr>
<tr>
<td></td>
<td>• RRM: Evidence insufficient, manage based on family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS

The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

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<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
</table>
| PALB2 | Increased risk of BC  
  - Screening: Annual mammogram and consider breast MRI with contrast at 30 y  
  - RRM: Consider based on family history. | Unknown or insufficient evidence for OC risk | Unknown or insufficient evidence |
| Comments: Counsel for risk of autosomal recessive condition in offspring. |
| PTEN | Increased risk of BC  
  - See Cowden Syndrome Management | No increased risk of OC | See Cowden Syndrome Management |
| RAD51C | Unknown or insufficient evidence for BC risk | Increased risk of OC  
  - Consider RRSO at 45–50 y | N/A |
| Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in RAD51C appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer. |
| RAD51D | Unknown or insufficient evidence for BC risk | Increased risk of OC  
  - Consider RRSO at 45–50 y | N/A |
| Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in RAD51D appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer. |
| STK11 | Increased risk of BC  
  - Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal  
  - RRM: Evidence insufficient, manage based on family history. | Increased risk of non-epithelial OC  
  - See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal | See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal |
| TP53 | Increased risk of BC  
  - See Li-Fraumeni Syndrome Management | No increased risk of OC | See Li-Fraumeni Syndrome Management |
Genetic testing-Interpreting results
Not just positive or negative!

**Variant Classes**
- Likely not pathogenic
- Not pathogenic

**Clinical**
- Do not use as predictive test for relatives; counsel as if no mutation detected

**Variant Classes**
- Pathogenic
- Likely Pathogenic

**Clinical**
- Test at-risk relative for the variant and recommend full high-risk surveillance
Multigene panels—beware of VUS (variants of uncertain significance)

• Unclear if variant is undefined deleterious mutation, benign polymorphism, or variant with intermediate risk of cancer
• 2-3% VUS rate with BRCA 1/2
• 15-30% VUS rate with panels
• Many VUS will be reclassified as benign over time
  • Online registry-PROMPT
• VUS do NOT influence patient management or family member testing
  • Treat is as negative result
## Pre-test Genetic Counseling for Panels: Informed Consent

<table>
<thead>
<tr>
<th>1. Information on specific genes being tested, including impact on medical care</th>
<th>10. Confidentiality issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Implications of positive &amp; negative results</td>
<td>11. Possible use of samples in future research</td>
</tr>
<tr>
<td>3. Possibility that test will not be informative</td>
<td>12. Options and limitation of medical surveillance &amp; prevention strategies after testing</td>
</tr>
<tr>
<td>4. Options for risk estimation without testing</td>
<td>13. Importance of sharing test results with at-risk relatives</td>
</tr>
<tr>
<td>5. Risk of passing a genetic variant to children</td>
<td>14. Plans for follow-up after testing</td>
</tr>
<tr>
<td>6. Technical accuracy of the test</td>
<td>*15. Some of the genes included on panels have not been well studied or only contribute modestly to cancer risk</td>
</tr>
<tr>
<td>7. Fees involved in testing &amp; counseling</td>
<td>*16. Higher likelihood of finding a VUS.</td>
</tr>
<tr>
<td>8. Psychological implications of test results</td>
<td>*17. Some results will not affect medical management</td>
</tr>
<tr>
<td>9. Risks &amp; protections against genetic discrimination</td>
<td>* Issues special for NGS cancer panel testing</td>
</tr>
</tbody>
</table>

*ASCO. J Clin Oncol. 2010;893-901.*
Early stage breast cancer

*Increasing chances of cure*
Systemic therapy (drugs) early stage disease—rationale

**Early stage disease (stage I, II, III)**

- Given after (or before) surgery for finite duration
- Kill micro-metastatic disease
- Primary goal is to reduce chances of future breast cancer relapse and reduce chances of eventual death from breast cancer
Adjuvant systemic therapy

Types

• Endocrine therapy
  • Tamoxifen
  • Aromatase inhibitors
  • Ovarian suppression

• Chemotherapy
  • Adriamycin, Cyclophosphamide, Paclitaxel, Docetaxel, 5-FU

• Her2 monoclonal antibodies (Ab)
  • Trastuzumab
  • Pertuzumab

Who gets what? And when?

Breast cancer stage I-III, following surgical resection

If HR+

Endocrine

If High risk?

Chemo

If Her2+

Her2-Ab
Adjuvant chemotherapy: How do we decide who is ‘high risk’?

- Clinical/pathological/genomic factors are best used in combination.
- Responsiveness is a continuum.
- Patient preference!

In favor of adjuvant chemotherapy:
- ER negative
- Ductal histology
- Grade 3
- High proliferation
- High uPA and PAI1
- Basal and HER2 positive
- High MammaPrint® or Oncotype DX® or GGI

Against adjuvant chemotherapy:
- ER positive
- Lobular histology
- Grade 1
- Low proliferation
- Low uPA and PAI1
- Luminal A
- Low MammaPrint® or Oncotype DX® or GGI
Recurrence Score/Oncotype DX®

- A RT-PCR-based gene signature that measures the expression of 21 genes (16 cancer-related genes and 5 reference genes)

- *It uses the Recurrence score (RS) to predict the risk of distant relapse within 10 years*

- Developed in ER+, under tamoxifen treatment

- Extensive retrospective validation; ongoing prospective validation

<table>
<thead>
<tr>
<th>Variable</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis without recurrence score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at surgery</td>
<td>0.004</td>
<td>0.57 (0.39–0.83)</td>
</tr>
<tr>
<td>Clinical tumor size</td>
<td>0.06</td>
<td>1.44 (0.99–2.11)</td>
</tr>
<tr>
<td>Analysis with recurrence score‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at surgery</td>
<td>0.08</td>
<td>0.71 (0.48–1.05)</td>
</tr>
<tr>
<td>Clinical tumor size</td>
<td>0.23</td>
<td>1.26 (0.86–1.86)</td>
</tr>
<tr>
<td>Recurrence score</td>
<td>&lt;0.001</td>
<td>3.21 (2.23–4.61)</td>
</tr>
</tbody>
</table>

Paik, NEJM 2004
Oncotype DX® in Node Negative BC
Paik, JCO 2006

- **NSABP B-20**: ER+, N0, CT (CMF regimen); 651pts (227 TAM /424 TAM+CT)
- **High RS (≥ 31): benefited from CT** (RR 0.26 (95% CI, 0.13 -0.53), relative risk reduction in 10 yrs **27.6%** (SE 8.0%))
- **Low RS (< 18) no significant benefit from CT** (RR 1.31 (95% CI, 0.46 – 3.78), relative risk reduction in 10 yrs **-1.1%** (SE 2.2%))
TAILORx TRIAL

Enrollment period: April 7, 2006 to October 6, 2010 (N=10,273 eligible)

Key Eligibility Criteria
- Node-negative
- ER-pos, HER2-neg
- T1c-T2 (high-risk T1b)
- Age 18-75 years
- No PBI planned

Preregister
Oncotype DX assay
Register
Specimen banking

Statistical Design
- RS 11-25: non-inferiority
  - 90% vs. ≤87% IDFS
  - 835 DFS events
- RS < 11
  - 95% vs. ≤93% DRFI at 10 years
  - 75 DRFI events

Secondary study group 1
RS < 11

ARM A
Hormonal therapy alone

Primary study group
RS 11-25

Randomly Assigned
Stratification factors:
Tumor size, menopausal status, planned chemo, planned radiation

ARM B
Hormonal therapy alone
ARM C
Chemotherapy + hormonal therapy

Secondary study group 2
RS > 25

ARM D
Chemotherapy + hormonal therapy

Recurrence Score = 11
- 7.3% distant recurrence rate at 10 years
- 95% CI 5%, 10%

Recurrence Score = 25
- 16.1% distant recurrence rate at 10 years
- 95% CI 13%, 20%


Presented By Fatima Cardoso at 2016 ASCO Annual Meeting
Results LOW RISK ARM (ET alone)

No. of events: 88 iDFS events and 30 deaths within 5 years of registration, including 18 recurrences (10 distant as first event), 15 second primary breast cancers, 43 other second primary cancers, 12 deaths without another event

5 year iDFS Rate 93.8%  
(95% CI 92.4%, 94.9%)

5 year DRFI Rate 99.3%  
(95% CI 98.7%, 99.6%)

5 year RFI Rate 98.7%  
(95% CI 97.9%, 99.2%)

5 year OS Rate 98.0%  
(95% CI 97.9%, 98.6%)
TAILLORx Low Risk Registry

Summary of Results and Conclusions

• Women with node-negative, ER-positive, HER2-negative EBC and RS < 11 have a 1% risk of distant recurrence at 5 years with endocrine therapy alone
  • Recurrence risk not significantly impacted by age or tumor size
  • Recurrence rates were low irrespective of histologic grade
  • Clinical characteristics could not reliably distinguish patients with a RS <11 vs. 11-25
  • Second primary cancers exceeded cancer recurrence at 5 years

• Since adjuvant CT prevents mostly early recurrences within 5 years\(^1,2\), CT may be spared in this population

• This prospective clinical trial provided the highest level of evidence
  • Supporting the clinical utility of the 21-gene assay in this setting
  • Confirms expert-based clinical guidelines that the RS should be used to risk stratify and assign adjuvant CT \(^3,4\)

• Additional work needed to determine whether more pts may be spared CT
  • TAILORx - node-negative disease with a RS 11-25
  • RxPONDER, OPTIMA - node-positive disease with a RS 25 or lower

---

(1) EBCTCG. Lancet 2005;365 (9472):1687-717
(2) EBCTCG. Lancet 379 (9814):432-44
(3) Harris et al. J Clin Oncol 2007;25:5287-312

Presented By Fatima Cardoso at 2016 ASCO Annual Meeting
Oncotype DX® in node-positive BC
Albain - Lancet Oncol 2010

- **SWOG 8814 trial** – postmenopausal women, ER+, N+, CT (CAF)
- 367 pts (TAM 148/ CAF-TAM 219)
- **No benefit of CT for pts with RS < 18** (p=0.97, HR 1.02 (95%: CI, 0.54–1.93))
- **Better DFS with CT for pts with high RS (≥31)** (p=0.033, HR 0.59 (CI95%: 0.35–1.01))

**Presented By Fatima Cardoso at 2016 ASCO Annual Meeting**

- PlanB phase III
  trial-West Germany N=2449
- Prospective
- Patients with up to 3 LN+ had chemo
  omitted IF RS<12
- For these N1
  patients, 3 yr
  DFS=97.9%
  without chemo!
So how do we use genomic testing for predictive & prognostic benefit currently?

- **Node-NEGATIVE**
  - Low risk score - NO chemo
  - High risk score - YES chemo
  - Intermediate - ? Rely on other factors, await TAILORX trial results

- **Node-POSITIVE (1-3 nodes)**
  - Low risk score - Consider omission of chemo, await RxPONDER trial results
  - Intermed/High risk scores - YES chemo

- **Node-POSITIVE (4+ nodes)**
  - No role for genomic testing, always give chemo
Adjuvant systemic therapy

**Types**
- **Endocrine therapy**
  - Tamoxifen
  - Aromatase inhibitors
  - Ovarian suppression
- **Chemotherapy**
  - Adriamycin, Cyclophosphamide, Paclitaxel, Docetaxel, 5-FU
- **Her2 monoclonal antibodies (Ab)**
  - Trastuzumab
  - Pertuzumab

**Who gets what? And when?**

Breast cancer stage I-III, following surgical resection

- If HR+
  - Endocrine
- High risk?
  - Chemo
- If Her2+
  - Her2-Ab
Substantial risk of delayed breast cancer events beyond 5 years out from initial therapy

Data from 91 trials, looking at 46,000 women who were disease-free after initial 5 yrs of endocrine therapy.  SABCS-2016
Choice of endocrine therapy: AI’s superior to tamoxifen

- EBCTCG: Landmark meta-analysis of individual data on >30,000 women with breast cancer (Lancet, 2015)
- AI’s reduce recurrence rates by 30% compared to tamoxifen
- AI’s reduce risk of breast cancer death by 15% compared with tamoxifen
So how do we best incorporate AI’s?

1. Tamoxifen x 5 years → Tamoxifen x 5 more years
2. Tamoxifen x 5 years → Al x 5 years
3. Tamoxifen x 2-3 years → Al x 5 years
4. Al x 5 years → Al x 5 more years
MA.17R Trial Schema and Design

AI x 5 yrs - Following Prior 5 years of AI - preceded or not by Tamoxifen

Any duration of prior Tamoxifen

4.5-6 yrs of Aromatase Inhibitor

- ER+ and/or PR+ breast cancer
- Postmenopausal and disease-free
- Completed 4.5-6 years of adjuvant AI
- Any time of prior TAM
- Minimum life expectancy ≥5 years (no exclusion for age alone)

n = 1918

Letrozole 2.5 mg po od
Placebo
5 yrs

Presented By Paul Goss at 2016 ASCO Annual Meeting
MA.17R – Improved Outcomes with Letrozole for 10 Years over 5 years

Disease-Free Survival

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Letrozole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>90</td>
<td>90</td>
<td>90</td>
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<td>80</td>
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<td>70</td>
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<tr>
<td>10</td>
<td>10</td>
<td>10</td>
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<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median F/U 6.3 yrs

HR DFS: 0.66
p = 0.01
95% vs 91%

HR Overall Survival: 0.97
P = NS

Contralateral Breast Cancer

<table>
<thead>
<tr>
<th>Cumulative Rate (per 1,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>70</td>
</tr>
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<tr>
<td>20</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

Placebo
HR CBC: 0.42
p = 0.007

Letrozole
Median F/U 6.3 yrs

SUMMARY STATISTICS:
Observed events for Letrozole: 13 (1%)
Observed events for Placebo: 31 (3%)

Presented by: P.E. Goss

Presented By Nancy Davidson at 2016 ASCO Annual Meeting
However, even newer data has 'clouded' the picture somewhat!

- NSABP-B42 trial presented at SABCS-Dec, 2016
- No benefit (statistically significant) from extended AI therapy overall
  - However, 28% reduction in risk of distant metastasis!
  - Greater benefit in high risk patients
- No increase in osteoporotic fractures
So, how do we put this all together?

**Extend AI therapy beyond 5 yrs**
- Good initial tolerance to AI
- Excellent bone health
- Young age
- Higher risk disease by clinical/pathologic features, including high grade, node positive
- Higher risk by genomic testing
- Patient preferences

**Stop AI therapy at 5 yrs**
- Difficult tolerance to AI’s (i.e. poor bone health, musculoskeletal symptoms)
- Lower risk by clinical/pathologic features
- Lower risk by genomic testing
- Patient preferences
Where else can we look in efforts to improve cure rates in early stage disease? Targeted therapy
Advanced breast cancer

Improving quality…and quantity of life through advances in systemic therapy
Treatment Algorithm for Metastatic Breast Cancer

1. Evaluate symptoms, PS, comorbidities
   Establish ER, PR, HER2/neu status
   Review prior treatment history
   Evaluate extent of metastatic disease

2. ER- and/or PR-positive
   - Minimal-moderate symptoms
     - Endocrine therapy
     - Disease progression
     - No or minimal symptoms
       - Endocrine therapy
     - Moderate-severe symptoms
       - Chemotherapy

3. ER-/PR-negative
   - Severe symptoms
     - Chemotherapy
     - Change to endocrine therapy after initial response & symptom relief
   - Chemotherapy (plus trastuzumab if HER2 positive)
     - Continue until disease progression
Breast cancer is many diseases!

### Molecular Classification of Breast Cancer

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<th>Biology/treatment</th>
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<td>• amplification of HER-2 gene and overexpression of HER-2 receptor</td>
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<td>• aggressive&lt;br&gt;• sensitive to anti-HER-2 therapy&lt;br&gt;• sensitive to chemotherapy</td>
</tr>
</tbody>
</table>

**BC subtypes**
- Luminal A/B (65%)
- HER2 positive (20%)
- Basal-like (15%)
Is there an optimal 1st-line endocrine agent for advanced disease?

**FALCON: First-line Fulvestrant vs Anastrozole for Advanced Breast Cancer**

- **Fulvestrant 500 mg IM injection**
  - Days 1, 14, 28, and every 28 days thereafter +
    - Placebo PO daily
  - (n = 232)

- **Anastrozole 1 mg/day PO +**
  - Placebo IM injection
  - Days 1, 14, 28, and every 28 days thereafter
  - (n = 230)

Postmenopausal women with previously untreated hormone receptor-positive advanced breast cancer (N = 462)

- **Primary endpoint:** PFS
- **Secondary endpoints including:** OS, ORR, DoR, CBR, and safety

FALCON: Fulvestrant Extends PFS Compared With Anastrozole

- Median PFS of 16.6 mos with fulvestrant vs 13.8 mos with anastrozole (HR: 0.797; $P = .0486$)
  - No visceral disease ($n = 208$): 22.3 mos with fulvestrant vs 13.8 mos with anastrozole (HR: 0.59; $P < .01$)
  - Visceral disease ($n = 254$): 13.8 mos with fulvestrant vs 15.9 mos with anastrozole (not significant)
- No significant differences in ORR, CBR, or median DoR
- Fulvestrant was associated with an increased incidence of grade $\geq 3$ AEs (22.4 % vs 17.7%) and all-grade arthralgia (16.7% vs 10.3%)
Combining Targeted and Antiestrogen Therapies in HR-Positive Breast Cancer

EGFR HER2

RAS PI3K Akt PTEN mTOR RAS Raf MEK MAPK mTOR

TKI TKI

ER target gene transcription

ER Downregulator
Fulvestrant

Select ER Modulators
Tamoxifen Toremifene

Aromatase Inhibitor
Nonsteroidal Als:
Anastrozole Letrozole
Steroidal Al:
Exemestane

Cell Cycle
Transcription Silencing


Slide credit: clinicaloptions.com
Future Treatment in HR+ ABC: Reversing Resistance with Combination Therapy

**Combination Therapy**

- **2012**: Everolimus + exemestane
- **2015**: Palbociclib + letrozole
- **2016-**: Palbociclib+ fulvestrant
  - CDK 4/6i + letrozole*
  - CDK 4/6i + fulvestrant*
  - Entinostat + exemestane*
  - Taselisib + fulvestrant*
  - Alpelisib + fulvestrant*

**Monotherapy**

- **1977**: Tamoxifen
- **1995**: Anastrozole
- **1999**: Exemestane
- **2002**: Fulvestrant
- **2016**: Fulvestrant* (1L)

*Anticipated approval.

Presented at: ASCO Annual Meeting '16

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**BOLERO-2: Exemestane ± Everolimus in Nonsteroidal AI–Refractory Advanced BC**

- **Postmenopausal women with hormone receptor+/HER2-advanced BC refractory to letrozole or anastrozole**  
  \[N = 724\]

  - Refractory to therapy
    - Recurrence during or within 12 mos of end of adjuvant treatment
    - Progression during or within 1 mo after end of treatment for advanced disease

| Everolimus 10 mg/day + Exemestane 25 mg/day  
\[n = 485\] |
|-----------------|
| Placebo + Exemestane 25 mg/day  
\[n = 239\] |

- **Stratification:**
  - Sensitivity to previous hormonal therapy
  - Presence of visceral disease

- **No crossover allowed**

- **Primary endpoint: PFS**
  - Secondary endpoints: OS, ORR, CBR, safety, QoL, bone markers

---


[Slide credit: clinicaloptions.com]
BOLERO-2: PFS at 18-Mo Follow-up

Median PFS, Mos
Everolimus + exemestane: 7.8
Placebo + exemestane: 3.2
HR: 0.45 (95% CI: 0.38-0.54; $P < .0001$)

## Randomized Trials of Everolimus in Patients with HER2−/ER+ Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Setting</th>
<th>Pre-treatment</th>
<th>Phase</th>
<th>N</th>
<th>Effect on primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole +/- everolimus (Baselga, JCO, 2009)</td>
<td>Neoadjuvant</td>
<td>Endocrine naïve</td>
<td>Phase II randomised</td>
<td>270</td>
<td>Clinical response: 68% vs 59% (P=0.06, pre-spec significance &lt;0.1)</td>
</tr>
<tr>
<td>Tamoxifen +/- everolimus (Bachelot, JCO, 2012)</td>
<td>Metastatic</td>
<td>Resistant to AI</td>
<td>Phase II randomised</td>
<td>111</td>
<td>Clinical benefit rate: 61% (47−74) vs 42% (29−56)</td>
</tr>
<tr>
<td>Exemestane +/- everolimus (Baselga, NEJM 2012 Yardley, Adv Ther 2013)</td>
<td>Metastatic</td>
<td>Resistant to NSAI</td>
<td>Phase III registration</td>
<td>724</td>
<td>Primary endpoint PFS: Local assessment: 7.8 vs 3.2 HR 0.45 (95% CI: 0.38−0.54) P&lt;0.0001 Central assessment: 11.0 vs 4.1 HR 0.38 (95% CI: 0.31−0.48) P&lt;0.0001</td>
</tr>
</tbody>
</table>

Everolimus significantly improves progression-free survival in patients with ER+/HER2− metastatic breast cancer whose cancers are resistant to non-steroidal aromatase inhibitors (FDA/EMA approvals, NCCN/ASCO guidelines)
Background: CDK 4/6

- Cyclin dependent kinases (CDKs) - family of serine-threonine kinases partner with cyclins to regulate cell cycle progression\(^1\)
- Altered expression and activation of various regulators of the cyclin D:CDK-4/6:Rb pathway have been implicated in numerous cancers
- Palbociclib is an oral, highly selective inhibitor of CDK-4/6 that inhibits cell proliferation by prohibiting cell cycle progression from G1 to S phase\(^2\)
- Alterations in the cyclin D:CDK-4/6:Rb pathway have been associated with prognosis, endocrine sensitivity, and growth factor signaling in breast cancer

CDK4/6 Inhibitors in Hormone Receptor–Positive Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target (IC&lt;sub&gt;50&lt;/sub&gt;, nM)</th>
<th>Phase III Trials</th>
<th>Phase I Dose-Limiting Toxicities</th>
</tr>
</thead>
</table>
| Palbociclib (PD0332991) | CDK4 (11) CDK6 (15) | First-line combo:  
  ▪ Letrozole*  
  Second-line combo:  
  ▪ Exemestane  
  ▪ Fulvestrant* | Neutropenia, thrombocytopenia‡ |
| Abemaciclib (LY2835219) | CDK4 (2) CDK6 (10) | First-line combo:  
  ▪ Anastrozole or letrozole  
  ▪ Fulvestrant | Fatigue |
| Ribociclib (LEE011) | CDK4 (10) CDK6 (39) | First-line combo:  
  ▪ Letrozole  
  ▪ Fulvestrant  
  ▪ Tamoxifen or NSAI†  
  Second-line combo:  
  ▪ Fulvestrant | Neutropenia, mucositis, pulmonary embolism, asymptomatic thrombocytopenia, hyponatremia, QTcF prolongation (> 500 ms), increased creatinine |

* Approved. † Premenopausal women; NSAI in combination with goserelin. ‡ Phase II grade 3/4.

PALOMA-2: Study Design (1008)

N=666*

RANDOMIZATION

2:1

Palbociclib (125 mg QD, 3/1 schedule) + letrozole (2.5 mg QD)

Placebo (3/1 schedule) + letrozole (2.5 mg QD)

Primary endpoint
Investigator-assessed PFS

Secondary endpoints
Response, OS, safety, biomarkers, patient-reported outcomes

Stratification factors
- Disease site (visceral, non-visceral)
- Disease-free interval (de novo metastatic; \( \leq 12 \) mo, \( > 12 \) mo)
- Prior (neo)adjuvant hormonal therapy (yes, no)

- Statistical analysis designed to detect an increase in PFS with a true HR of 0.69 (representing a 31% improvement) with 347 events - 90% power with 1-sided \( \alpha=0.025 \)

Assumptions: Median PFS of placebo plus letrozole = 9 mos vs. palbociclib plus letrozole = 13 mos

- Blinded independent central review of efficacy endpoints performed as supportive analysis

*Actual. AI=aromatase inhibitor; HER2=human epidermal growth factor receptor 2; OS=overall survival; PFS=progression-free survival; QD=once daily.
Paloma 2

- Randomized 666 pts 2:1 to Let/palbo vs Let/placebo
- Median age 62 (28 to 89)
- 43% hormone naïve, 49% visceral disease
- PFS (inv)
  - 24.8 vs 14.5 months
  - $p < 0.000001$, HR 0.58
- Confirmed by central review

**PFS: Investigator-Assessed (ITT Population)**

Finn et al, ASCO 2016
### Consistent Clinical Benefit Seen Across PALOMA Studies

<table>
<thead>
<tr>
<th>Design</th>
<th>1003¹ (PALOMA-1)</th>
<th>1008 (PALOMA-2)</th>
<th>1023² (PALOMA-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase 2</td>
<td>Phase 3</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>Open label</td>
<td>Placebo control</td>
<td>Placebo control</td>
</tr>
<tr>
<td>Endocrine partner</td>
<td>Letrozole</td>
<td>Letrozole</td>
<td>Fulvestrant</td>
</tr>
<tr>
<td>Patients on study, N</td>
<td>n=165</td>
<td>n=666</td>
<td>n=521</td>
</tr>
</tbody>
</table>

Efficacy (palbociclib vs control arm)

<table>
<thead>
<tr>
<th>Primary endpoint: PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
</tr>
<tr>
<td>0.49</td>
</tr>
<tr>
<td>0.58</td>
</tr>
<tr>
<td>0.46</td>
</tr>
<tr>
<td>Median PFS, mo</td>
</tr>
<tr>
<td>20.2 vs 10.2 (↑10.0mos)</td>
</tr>
<tr>
<td>24.8 vs 14.5 (↑0.3mos)</td>
</tr>
<tr>
<td>9.6 vs 4.6</td>
</tr>
</tbody>
</table>

**Secondary endpoints, %**

| ORR (ITT, measurable disease) | 43 vs 33, 55 vs 39 | 42 vs 35, 55 vs 44 | 19 vs 9, 25 vs 11 |
| CBR (ITT)                     | 81 vs 58           | 85 vs 70           | 67 vs 40          |

CBR = clinical benefit response; ITT = intent-to-treat; ORR = objective response rate.


Presented By Richard Finn at 2016 ASCO Annual Meeting
CDK 4/6 Inhibitors- Well tolerated, but watch for neutropenia

<table>
<thead>
<tr>
<th>Hematologic AEs — All Causality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Any AE, %</td>
</tr>
<tr>
<td>Neutropenia^a</td>
</tr>
<tr>
<td>Leukopenia^a</td>
</tr>
<tr>
<td>Anemia^a</td>
</tr>
<tr>
<td>Thrombocytopenia^a</td>
</tr>
</tbody>
</table>

AE = adverse event. ^a Includes clustered Medical Dictionary for Regulatory Activity (MedDRA) preferred terms.
**Ribociclib + Letrozole in First-Line MBC: MONALEESA-2 Trial**

- Randomized, double-blind, phase 3 trial

**Patients with hormone receptor-positive, HER2-, ABC w/ no prior systemic therapy for ABC (N = 668)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribociclib + Letrozole</td>
<td>Ribociclib PO 600 mg/d 3-wks-on, 1-wk-off + letrozole PO 2.5 mg/d (n = 334)</td>
<td>0.56 (0.43, 0.72)</td>
<td>3.29 x 10^{-6}</td>
</tr>
<tr>
<td>Placebo + Letrozole</td>
<td>Placebo + letrozole PO 2.5 mg/d (n = 334)</td>
<td>Not reached</td>
<td></td>
</tr>
</tbody>
</table>

Median PFS, mo

Most common grade 3/4 AEs with ribociclib + letrozole:
- Neutropenia, leukopenia, anemia, thrombocytopenia

MONALEESA-2 trial- Improving survival outcomes

![Graph showing survival outcomes comparison between Ribociclib + Letrozole and Placebo + Letrozole.](image)
Breast cancer is many diseases!

### Molecular Classification of Breast Cancer

<table>
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![BC subtypes](image)
Her2 positive breast cancer: the Basics...

- 20% of breast cancers overexpress Her2
  - EGFR with tyrosine kinase activity
- Historically, associated with more aggressive disease and worse prognosis
- Can be tested using FISH or Immunohistochemistry
- Her2 targeted agents have changed the landscape and natural history of this disease
T-DM1 and Pertuzumab Mechanisms of Action

**T-DM1**
- Antibody-drug conjugate
- Induces cell death by inhibiting microtubule polymerization
- Inhibits HER2 signaling
- Activates ADCC
- Inhibits HER2 shedding

**Pertuzumab**
- HER2/HER3 dimerization inhibitor
- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

---

HER 2-Positive MBC Overall Survival

**LEGEND**
- First-Line
- Second-Line Plus
- Third Line-Plus

**ABBREVIATIONS**
- Ana: anastrozole
- Cape: capcitabine
- CT: chemotherapy
- Doc: docetaxel
- Lap: lapatinib
- Let: letrozole
- OS: overall survival
- Pac: paclitaxel
- Pert: pertuzumab
- T-DM1: trastuzumab emtansine
- Tras: trastuzumab

**Source:** Verma et al. The Oncologist 2013
Neoadjuvant Benefit: pCR (%)
Chemo (includes Anthra and Taxane)

Presented by Sunil Verma at 2016 ASCO Annual Meeting
Phase III CLEOPATRA: Trastuzumab and Docetaxel ± Pertuzumab in HER2+ MBC

Stratified by geographic region and previous (neo)adjuvant chemotherapy

- Trastuzumab 6 mg/kg Q3W* + Docetaxel 75-100 mg/m² Q3W† + Pertuzumab 420 mg Q3W‡ (n = 402)
- Trastuzumab 6 mg/kg Q3W* + Docetaxel 75-100 mg/m² Q3W† + Placebo Q3W (n = 406)

*Trastuzumab 8-mg/kg loading dose. †Minimum of 6 docetaxel cycles recommended; < 6 cycles permitted for unacceptable toxicity or PD. ‡Pertuzumab 840-mg loading dose.

- Primary endpoint: PFS (independently assessed)
- Secondary endpoints: PFS (investigator assessed), ORR, OS, safety

Adding Pertuzumab to standard chemo/Trastuzumab improves survival outcomes!

**CLEOPATRA: PFS**

- Pertuzumab (median: 18.5 mos)
- Control (median: 12.4 mos)
- HR: 0.62 (95% CI: 0.51-0.75); \( P < .001 \)

**CLEOPATRA: OS**

- Second interim analysis of OS (median follow-up: 30 mos)
  - Significant, confirmatory, crosses stopping boundary

<table>
<thead>
<tr>
<th>OS</th>
<th>Pertuzumab, trastuzumab, docetaxel</th>
<th>Placebo, trastuzumab, docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>0.66 (0.52-0.84)</td>
<td></td>
</tr>
<tr>
<td>3-yr estimated OS, %</td>
<td>66</td>
<td>50</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>Not reached</td>
<td>37.6</td>
</tr>
<tr>
<td>P Value</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>
TH3RESA: Study Design

Stratified by world region, number of prior tx for MBC, presence of visceral disease

Pts with HER2+ advanced breast cancer, ≥ 2 prior anti-HER2 therapies* (N = 602)

T-DM1 3.6 mg/kg q3w IV (n = 404)

PD

PD
t

Therapy of Physician’s Choice (n = 198)

*Previous treatment with trastuzumab, lapatinib, and a taxane required for eligibility.
†Optional crossover.

- Primary endpoints: PFS by investigator, OS
- Secondary endpoints: ORR by investigator, safety


Slide credit: clinicaloptions.com
TDM-1 as salvage therapy: Extended survival, and manageable toxicity

**TH3RESA: Final OS Analysis**

- Median OS significantly improved with use of T-DM1 vs physician-selected therapy in pretreated pts with HER2+ MBC: HR 0.68 (95% CI: 0.54-0.85; \( P = .0007 \))
- Disposition: discontinuation occurred in 67.1% T-DM1 arm vs 79.3 TPC arm
- 44.9% of TPC arm pts received T-DM1 crossover therapy

**TH3RESA: Grade ≥ 3 AEs**

<table>
<thead>
<tr>
<th>AEs With ≥ 2% Grade ≥ 3 in Either Arm, %</th>
<th>TPC (n = 184)</th>
<th>T-DM1 (n = 403)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>Grade ≥ 3</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13.0</td>
<td>3.8</td>
</tr>
<tr>
<td>Anemia</td>
<td>17.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Increased AST</td>
<td>7.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>5.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Celiitis</td>
<td>3.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>21.7</td>
<td>15.8</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Anemia</td>
<td>11.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>6.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3.8</td>
<td>2.7</td>
</tr>
</tbody>
</table>

*Prespecified crossing boundary = HR < 0.748 (\( P < .012 \)).


Slide credit: clinicaloptions.com
NCCN Guidelines Version 1.2017
Invasive Breast Cancer

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

**Preferred single agents:**

- Anthracyclines
  - Doxorubicin
  - Pegylated liposomal doxorubicin
- Taxanes
  - Paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Other microtubule inhibitors
  - Vinorelbine
  - Eribulin

**Other single agents:**

- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

**Chemotherapy combinations:**

- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab

**Preferred first-line agents for HER2-positive disease:**

- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

**Other agents for HER2-positive disease:**

- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel ± carboplatin
- Trastuzumab + docetaxel
- Trastuzumab + vinorelbine
- Trastuzumab + capecitabine

**Agents for trastuzumab-exposed HER2-positive disease:**

- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents

---

1. There is no compelling evidence that combination regimens are necessary.

---

4. There is no compelling evidence that combination regimens are necessary.
Breast cancer is many diseases!

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Molecular characteristics</th>
<th>Histological characteristics SURROGATES</th>
<th>Biology/treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>• luminal CK expression</td>
<td>• ER+</td>
<td>• indolent behaviour</td>
</tr>
<tr>
<td></td>
<td>• resembles normal epithelium cells</td>
<td>• low grade</td>
<td>• sensitive to hormonal therapy</td>
</tr>
<tr>
<td>Luminal B</td>
<td>• similar than luminal A</td>
<td>• ER+ (lower expression than in luminal A)</td>
<td>• more aggressive behaviour than luminal A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• high grade</td>
<td>• less sensitive to hormonal therapy than luminal A</td>
</tr>
<tr>
<td>Basal-like</td>
<td>• without expression of ER, PR and HER-2 genes</td>
<td>• “Triple negative” (ER-, PR-, HER 2-)</td>
<td>• aggressive behaviour</td>
</tr>
<tr>
<td></td>
<td>• basal CK expression (CK5)</td>
<td>• high grade</td>
<td>• sensitive to chemotherapy</td>
</tr>
<tr>
<td></td>
<td>• expression of growth factors (EGFR, c-kit, HGF, IGF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• BRCA disfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• genetic instability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Her-2 enriched</td>
<td>• amplification of HER-2 gene and overexpression of HER-2 receptor</td>
<td>• HER 2+</td>
<td>• aggressive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• high grade</td>
<td>• sensitive to anti-HER-2 therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• sensitive to chemotherapy</td>
</tr>
</tbody>
</table>

**BC subtypes**

- Luminal A/B (65%)
- HER2 positive (20%)
- Basal-like (15%)
Triple Negative (TNBC): The Basics...

• Defined as negative for ER/PR and Her2/neu
• 20% of breast cancers worldwide
  • 200,000 cases per year
• Higher incidence in age <40, and AA race
• Up to 20% harbor BRCA mutation
• Higher grade, present aggressively with rapid growth
• Worse prognosis compared to other breast cancers
Incidence of TNBC

Estimated Cancer Deaths per year in the USA

Women 270,290

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>26%</td>
</tr>
<tr>
<td>Breast Luminal</td>
<td>10%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7%</td>
</tr>
<tr>
<td>Ovary</td>
<td>5%</td>
</tr>
<tr>
<td>Triple-Negative BC (ER-, PR-, HER2-)</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>2%</td>
</tr>
<tr>
<td>Brain/Other nervous system</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
</tr>
</tbody>
</table>
Triple negative: Natural history

Natural History of TNBC

Recurrence Patterns of TNBC

TNBC recurrences peak at 1 – 3 years; Sharp decline thereafter....
No target to chase? Rely on chemotherapy
Heterogeneity of TNBC: It is not one disease
Different subtypes may have different 'Achilles heels'

Many Approaches Under Evaluation for TNBC in Clinical Trials

<table>
<thead>
<tr>
<th>Pathway/Drug type</th>
<th>Drugs in development</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA repair</td>
<td>PARP inhibitors (olaparib, rucaparib, veliparib), platinum agents (cisplatin, carboplatin)</td>
</tr>
<tr>
<td>PI3K/Akt/mTOR</td>
<td>PI3K inhibitors (buparlisib, taselisib, GDC0941, AZD8186, many others); Akt inhibitors (GDC0068, others), mTOR inhibitors (everolimus, others)</td>
</tr>
<tr>
<td>Androgen (testosterone)</td>
<td>Anti-androgens (bicalutamide, enzalutamide)</td>
</tr>
<tr>
<td>signaling</td>
<td></td>
</tr>
<tr>
<td>Immune</td>
<td>CTLA4 blockade (ipilimumab), PD1/PD-L1 blockade (nivolumab, pembrolizumab, atezolizumab),</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody-drug conjugates</td>
<td>IMMU-132, SGN-LIV1A, PF06647253, CDX-011</td>
</tr>
<tr>
<td>Cell cycle</td>
<td>Dinaciclib, selecliclib</td>
</tr>
<tr>
<td>Chk1</td>
<td>GDC0575</td>
</tr>
<tr>
<td>Bromodomain</td>
<td>TEN-101, GSK525762</td>
</tr>
<tr>
<td>Heat shock (stress)</td>
<td>Ganetespib, others</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>Ramucirumab, cedirinib</td>
</tr>
</tbody>
</table>
Background: The Immune System

**Innate Immunity**
- Nonspecific, activated quickly in response to a pathogen
- Activates the adaptive response

**Adaptive Immunity**
- Specific, activated in response to recognition of a specific pathogen
- Includes T-cell stimulation, B-cell antibody production
- Has a memory component

What should happen: tumor-associated antigens recognized by the immune system and destroyed by both innate and adaptive immune mechanisms (including activation of T cells)

What often happens: Tumors evade detection and destruction by the immune system through immune tolerance and acquiring resistance to killing by activated immune cells.

Evading the immune system: Programmed Cell Death (PD-1) Pathway

- Numerous mechanisms to evade the immune system (immunosuppressive cytokines including TGF-β, IL-4, IL-6, IL-10, etc)
- The PD-1:PD-L1 signaling axis is a mechanism of tumor anti-immunity
- PD-1 receptor on T cells binds PD-L1 and PD-L2 on normal host tissues to down-regulate the immune response to protect host tissues; PD-1:PD-L1 binding leads to T cell suppression
- Cancer cells may usurp this pathway to evade immune killing by expressing PD-L1
- Blocking the PD-1:PDL-1 interaction releases the stop on T cells, leading to T cell mediated immune responses against tumor cells

Amin A and White RL. Oncology. 2013.
Immune checkpoint inhibitors

Pembrolizumab
Nivolumab
Avelumab
Atezolizumab

An engineered anti-PDL-1 antibody

Ipilimumab
### FDA approvals for immune checkpoint antibodies

<table>
<thead>
<tr>
<th>Approval date</th>
<th>Agent</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/25/11</td>
<td>Ipilimumab</td>
<td>met melanoma</td>
</tr>
<tr>
<td>9/4/14</td>
<td>Pembrolizumab</td>
<td>met melanoma</td>
</tr>
<tr>
<td>12/22/14</td>
<td>Nivolumab</td>
<td>met melanoma</td>
</tr>
<tr>
<td>3/4/15</td>
<td>Nivolumab</td>
<td>squamous mNSCLC</td>
</tr>
<tr>
<td>10/2/15</td>
<td>Pembrolizumab</td>
<td>PD-L1 + mNSCLC</td>
</tr>
<tr>
<td>10/9/15</td>
<td>Nivolumab</td>
<td>mNSCLC</td>
</tr>
<tr>
<td>10/28/15</td>
<td>Ipilimumab</td>
<td>Adjuvant melanoma</td>
</tr>
<tr>
<td>11/23/15</td>
<td>Nivolumab</td>
<td>Adv renal cell ca</td>
</tr>
<tr>
<td>5/17/16</td>
<td>Nivolumab</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>5/18/16</td>
<td>Atezolizumab</td>
<td>met urothelial ca</td>
</tr>
<tr>
<td>8/5/16</td>
<td>Pembrolizumab</td>
<td>met H&amp;N ca</td>
</tr>
<tr>
<td>10/19/16</td>
<td>Atezolizumab</td>
<td>met NSCLC</td>
</tr>
</tbody>
</table>

- Merkel cell skin cancer
  - Avelumab, March, 2017
- Hodgkins lymphoma
  - Pembrolizumab, March, 2017
Why is TNBC a good target for immunotherapy?

• High mutation rate, which can produce neoantigens that induce an immune response

• Increased number of tumor-infiltrating lymphocytes, which can facilitate an immune response

• Higher PD-L1 expression levels, which can inhibit T-cell antitumor responses, as compared with other breast cancer subtypes
Efficacy of single agent PDL-1 antibodies in heavily pre-treated TNBC

KEYNOTE-012

TNBC
PD-L1+
Median prior Rx 2

Pembrolizumab 10mg/kg q2w

TNBC
69% PD-L1+ (IHC 2/3)
89% prior Rx ≥ 4#

Atezolizumab q3w*

* 15mg/kg, 20mg/kg or 1200 flat dose
# not all in metastatic setting

Best response | n=27
---|---
Overall response | 19%
Complete response | 4%
Partial response | 15%
Stable disease | 26%
Progressive disease | 48%

Median PFS 2-months
PFS at 6-months 24%

Best response | n=21
---|---
Overall response | 19%
Complete response | 9%
Partial response | 9%
PFS at 24-weeks | 33%

Median DOR: NR
(range: 18 to 56+ weeks)

Nanda et al J Clin Oncol 2016
Emens et al Proc AACR 2015
Checkpoint inhibitors: multiple trials in breast cancer

**IMpassion130**: Atezolizumab in combination with nab-paclitaxel compared with placebo as first-line therapy for metastatic TNBC

**Breast cancer trials using checkpoint inhibitors (clinicaltrials.gov)**

<table>
<thead>
<tr>
<th>Agent</th>
<th># trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>33</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>10</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>9</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>13</td>
</tr>
</tbody>
</table>

**Emens ASCO 2016, (TPS1104)**
PARP (poly adenosine diphosphate-ribose polymerase) Inhibition

PARP Inhibitors Plus Chemotherapy in mTNBC ± BRCA

- Veliparib (ABT-888)
  - Phase I, cisplatin + vinorelbine (N = 45 + 5 expansion)[1]
    - ORR: 35% (CR: 2/48 + PR 15/48); SD: 44% (21/48); median PFS (n = 50): 5.5 mos
    - BRCA+ vs BRCA-: 71% (10/14) vs 30% (8/27) 6-mo PFS; mid-P = .01
    - G3/4 AE: neutropenia (36%), anemia (30%), thrombocytopenia (12%)
  - Phase II, cyclophosphamide (N = 45): ORR, median PFS similar for combination vs cyclophosphamide alone[2]

- Olaparib (AZD2281): phase I, paclitaxel (N = 19)[3]
  - PR: 37% (7/19), 1 without progression
  - G3/4 AE: neutropenia (32%), anemia (22%)


Slide credit: clinicaloptions.com
# PARP Inhibitors in Advanced BC: Ongoing Phase III Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pt Population</th>
<th>Trial</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>BRCA1 or BRCA2 mutation</td>
<td>Olaparib vs physician’s choice of chemotherapy (OlympiAD)(^1)</td>
<td>PFS</td>
</tr>
<tr>
<td>Veliparib</td>
<td>BRCA1 or BRCA2 mutation (suspected/confirmed)</td>
<td>Veliparib + carboplatin/paclitaxel vs placebo + carboplatin/paclitaxel(^2)</td>
<td>PFS</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>BRCA1 or BRCA2 mutation</td>
<td>Talazoparib vs physician’s choice of chemotherapy (EMBRACA)(^3)</td>
<td>PFS</td>
</tr>
<tr>
<td>Niraparib</td>
<td>BRCA1 or BRCA2 mutation (pts with unknown status will be screened if appropriate)</td>
<td>Niraparib vs physician’s choice of chemotherapy (BRAVO)(^4)</td>
<td>PFS</td>
</tr>
</tbody>
</table>

2. ClinicalTrials.gov. NCT02163694.

Slide credit: clinicaloptions.com
Androgen receptor inhibition

**Phase II Trials of Androgen Receptor Inhibitors in mTNBC**

<table>
<thead>
<tr>
<th>Agent</th>
<th>MOA</th>
<th>Pt Population</th>
<th>Efficacy</th>
<th>Drug-Related AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide[1]</td>
<td>Inhibits androgen binding to AR, AR nuclear translocation/DNA binding</td>
<td>AR+ mTNBC</td>
<td>▪ CBR16: 35% (25/75) &lt;br&gt;▪ CBR24: 29% (22/75) &lt;br&gt;▪ CR or PR: 3% (6/75)  &lt;br&gt;▪ mPFS: 14.7 wks</td>
<td>G1: fatigue, nausea, decreased appetite, constipation, diarrhea; G3: fatigue (5%), constipation, back pain, and dyspnea (1% each)</td>
</tr>
<tr>
<td>Abiraterone acetate +</td>
<td>Irreversible inhibitor of androgen-producing enzymes (CYP17)</td>
<td>AR+ mTNBC</td>
<td>▪ CBR (6 mos): 20% (1/34, CR; 5 with SD ≥ 6 mos, 1 pt PR at 12 mos) &lt;br&gt; ▪ mPFS: 2.8 mos</td>
<td>G1: fatigue, nausea; hypertension, hypokalemia; G3: hypertension, adrenal insufficiency, hypokalemia</td>
</tr>
<tr>
<td>Prednisone[2]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicalutamide[3]</td>
<td>Androgen antagonist</td>
<td>AR+ ER/PgR-LA or MBC</td>
<td>▪ CBR (6 mos): 19% (5/26, SD &gt; 6 mos; no CR or PR) &lt;br&gt; ▪ mPFS: 12 wks</td>
<td>G1: limb edema, fatigue, hot flashes, transaminase elevations; G3: 1 pt with liver enzyme abnormalities</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
<table>
<thead>
<tr>
<th>Agent</th>
<th>MOA</th>
<th>Pt Population</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide</td>
<td>Inhibits androgen binding to AR, AR nuclear translocation/DNA binding</td>
<td>AR+ advanced or metastatic TNBC</td>
<td>Phase II: safety, efficacy, biomarker analysis[1]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phase I/II: with taselisib, a PI3K inhibitor; safety, dose, biomarker analysis[2]</td>
</tr>
<tr>
<td>Abiraterone acetate</td>
<td>CYP17A1 inhibitor</td>
<td>Postmenopausal ER+ or AR+ advanced MBC</td>
<td>Phase I/II: safety, dose, biomarker analysis, pharmacogenomic studies[3]</td>
</tr>
<tr>
<td>Bicalutamide</td>
<td>Androgen antagonist</td>
<td>AR+ mTNBC</td>
<td>Phase II: safety, efficacy[4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phase II: safety, efficacy, QoL[5]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phase I/II: with palbociclib, safety, efficacy[6]</td>
</tr>
<tr>
<td>Orteronel (TAK700)</td>
<td>Nonsteroidal CYP17A1 inhibitor</td>
<td>AR+ MBC (TNBC or HR+ BC)</td>
<td>Phase II: safety, efficacy, biomarker analysis[7]</td>
</tr>
<tr>
<td>VT-464</td>
<td>Androgen synthesis inhibitor</td>
<td>AR+ TNBC or HR+ BC</td>
<td>Phase I/II: safety, tolerability, pharmacokinetics, and activity[8]</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
Conclusions: 'Take home' points

• Identifying 'at risk' populations for breast cancer has become increasingly complex...more genes=more questions. Knowledge/research must catch up to technology!

• Increasing use molecular testing-- prognostic and predictive tools, to customize adjuvant therapies to each individual. No two cancers are the same!

• Molecular characterization of metastatic breast cancer has allowed us to identify, and better target, various subtypes of breast cancer. Promising drugs have been approved--with many others on the horizon!
Thank you!