Cancer Biomarkers, Clinical Trials, and New Treatment Options

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Cancer Mortality Rates Declining

- From 2003-2007, incidence rates ↓ 1% & death rates ↓ 1.6 % annually
- For 7 of the top 15 cancers, trends in death rates ↓ during past 10- and 5-year periods
  - For men and women: declines in GI cancers (colorectal, stomach), kidney, brain, & hematologic (NHL, leukemia, myeloma)
  - For men: declines in lung, prostate, and oral cavity
  - For women: declines in breast and bladder cancers, plus ovary, lung, and cervical (during past 5 years)
- Black men and women
  - highest death rates overall, but largest ↓ in rates from 1998-2007
  - For new cancers, black men had the highest overall incidence rates
- Cancer in older Americans (> 65 years)
  - Expected to ↑ 2-fold between 2000 and 2030 due to aging population and higher cancer rates in the aged
Factors Contributing to Declining Cancer Death Rates

- Screening/early diagnosis
- Systemic therapy
- Prevention (eg. smoking cessation)
Black Race and Localized Breast Cancer

• Associated with worse outcomes (DFS, OS)
  – Differences more pronounced in population-based compared with clinical trial populations
  – Suggests disparities and comorbidities are contributing factors
  – Overall decline in breast cancer mortality rates less in blacks, resulting in widening of racial gap

• Other potential explanations
  – More “basal subtype” or “triple negative” disease
  – Later stage at presentation
  – More obesity

Bach et al. JAMA 2002; 287: 2106-2113; Menahse et al. JNCI 2008; 101: 993-1000
Carey et al. JAMA 2006; 295: 2492-2502
Dignam. JNCI 2001; 30:36-43, Hershman et al. JCO 2005; 23: 6639-6646
Objective

*Elucidate influence of race in a clinical trial population treated with contemporary local & systemic adjuvant therapy*

- **Evaluate the effect of black race on outcomes**
  - OS - overall survival
  - DFS – recurrence, death, or contralateral breast cancer (*not* other second primary cancers)
- **Determine effect by breast cancer subtype**
  - Triple negative
  - HER2-positive
  - HR-positive, HER2 negative/unknown
Results - Patient Characteristics:
Characteristics of Black Subjects vs. Others

• **Population** - 405 (8.4%) were black
• **Demographic characteristics**
  – Younger age (median 48 vs. 51 yrs; p<0.0001)
  – Premenopausal status (54% vs. 46%; p=0.0015)
  – Higher median BMI (32 vs. 28 kg/m²) and more obesity
    (≥ 30 kg/m²) (46% vs. 26%) (p<0.0001)
• **Disease characteristics**
  – More TN disease (32% vs. 17%; p<0.0001)
  – More HER2-pos disease (25% vs. 19%; p=0.045)
  – Less ER and/or PR-pos disease (55% vs. 73%; p<0.0001)
  – Larger tumor size (p=0.020) but less nodal involvement
    (p=0.0007)
Results: Treatment Administered
Black subject vs. other subjects

• Surgery
  – Higher breast conservation rates (44% vs. 39%; p=0.025)
  – Comparable RT rates (58% vs. 56%)

• Chemotherapy
  – Similar distribution of taxane treatment arms (p=0.91)
  – No difference in proportion who received all planned cycles of AC or taxane or who required dose reduction
    • Exception: fewer black subjects had dose reduction of q3 week docetaxel (19% vs. 28%; p=0.049)

• Endocrine therapy
  – More use of tam alone (43% vs. 36%) and fewer treated with sequential tam-AI (45% vs. 57%) (p=0.0074)
  – No difference in adherence to endocrine therapy
DFS: HR-Pos/HER2-Neg or Unknown

DFS for race (HR-positive / HER2-negative or unknown)

DFS Probability

Non-black (5-year DFS rate: 84.5%)
Black (5-year DFS rate: 76.7%)

HR=1.58 (95% CI 1.19 to 2.10)
p=0.0015

Patients at risk:
Black 161 145 135 112 36 Black
Non-black 2646 2528 2322 2098 1838 607
OS: HR-Pos/HER2-Neg or Unknown

OS for race (HR-positive / HER2-negative or unknown)

HR = 1.49 (95% CI 1.05 to 2.12)

p = 0.025

Non-black (5-year OS rate: 91.9%)

Black (5-year OS rate: 87.6%)

Patients at risk:

- Black: 161, 153, 146, 129, 114, 43
- Non-black: 2646, 2598, 2464, 2281, 1996, 676
DFS & OS: Triple Negative Disease

DFS for race (Triple negative)

- Non-black (5-year DFS rate: 69.4%)
- Black (5-year DFS rate: 69.0%)

p = 0.89

Patients at risk:
- Black: 129, 109, 91, 76, 68
- Non-black: 757, 632, 544, 483, 413

OS for race (Triple negative)

- Non-black (5-year OS rate: 76.1%)
- Black (5-year OS rate: 79.8%)

p = 0.50

Patients at risk:
- Black: 129, 118, 102, 86, 77
- Non-black: 757, 687, 600, 530, 449
DFS & OS: HER2-Pos Disease

**DFS for race (HER2-positive)**

- **Non-black**: 5-year DFS rate: 77.6%
- **Black**: 5-year DFS rate: 77.1%
- \( p = 0.91 \)

**Patients at risk:**
- Black: 100, 89, 79, 65, 59
- Non-black: 852, 767, 678, 618, 545

**OS for race (HER2-positive)**

- **Non-black**: 5-year OS rate: 86.9%
- **Black**: 5-year OS rate: 84.2%
- \( p = 0.39 \)

**Patients at risk:**
- Black: 100, 93, 87, 72, 64
- Non-black: 852, 820, 766, 694, 605

**Months at risk:**

- 0, 20, 40, 60, 80, 100
Multivariate Model in HR-Pos/HER2-Neg Group: DFS
Covariates included Age (≤ 45 vs. > 45 years), Nodes (1-3 vs. 0, or > 4 vs. 0), Tumor Size (≤2 vs. > 2 cm), Menopausal Status (Pre vs. Post) Surgery Type (BCS vs. Mastectomy)

<table>
<thead>
<tr>
<th>Additional Variables Added to Above Model</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black race only</td>
<td>1.41 (1.00, 2.00)</td>
<td>0.053</td>
</tr>
<tr>
<td>Obesity only</td>
<td>1.26 (1.04, 1.51)</td>
<td>0.016</td>
</tr>
<tr>
<td>Race &amp; Obesity</td>
<td>1.33 (0.93, 1.89)</td>
<td>0.120</td>
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<tr>
<td>Race</td>
<td>1.23 (1.02, 1.49)</td>
<td>0.030</td>
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<tr>
<td>Obesity</td>
<td></td>
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<tr>
<td>Race-Obesity Interaction</td>
<td>1.09 (0.68, 1.74)</td>
<td>0.720</td>
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<tr>
<td>Black &amp; Obesity</td>
<td>1.80 (1.06, 3.03)</td>
<td>0.028</td>
</tr>
<tr>
<td>Black &amp; No Obesity</td>
<td></td>
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</table>

*Cox’s Proportional Hazards Model*
Multivariate Model in HR-Pos/HER2-Neg Group: OS
Covariates included Age (< 45 vs. > 45 years), Nodes (1-3 vs. 0, or > 4 vs. 0), Tumor Size (<2 vs. > 2 cm), Menopausal Status (Pre vs. Post), Surgery Type (BCS vs. Mastectomy)

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<tr>
<th>Additional Variables Added to Above Model</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black race only</td>
<td>1.50 (0.98, 2.31)</td>
<td>0.065</td>
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<tr>
<td>Obesity only</td>
<td>1.45 (1.15, 1.82)</td>
<td>0.001</td>
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<tr>
<td>Race &amp; Obesity</td>
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<tr>
<td>Race</td>
<td>1.36 (0.88, 2.10)</td>
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<tr>
<td>Obesity</td>
<td>1.42 (1.12, 1.78)</td>
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<tr>
<td>Race-Obesity Interaction</td>
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<tr>
<td>Black &amp; Obesity</td>
<td>1.07 (0.6, 1.9)</td>
<td>0.830</td>
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<tr>
<td>Black &amp; No Obesity</td>
<td>2.02 (1.06, 3.84)</td>
<td>0.032</td>
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</table>

*Cox’s Proportional Hazards Model*
DFS: Race and Obesity

DFS for race and obese (HR-positive / HER2-negative/unknown)

- Black, Obese (5-year DFS rate: 79.9%)
- Black, Nonobese (5-year DFS rate: 76.0%)
- Other, Obese (5-year DFS rate: 83.1%)
- Other, Nonobese (5-year DFS rate: 85.6%)
Conclusions

• **Black race associated with**
  – Younger age and more obesity at presentation
  – Higher rates of triple negative and HER2-pos disease
  – Larger tumor size and less nodal involvement

• **Poorer outcomes in HR-pos/HER2-neg disease**
  – Not explained by comorbidities or disparities in care
  – Obesity also appears to be a contributing factor
  – Other confounding variables

• **Findings consistent with some prior reports**
  – clinical trial populations

*Dignam. JNCI 2001; 30:36-43; Albain et al. JNCI 2009; 101:984-002*
Triple-Negative Breast Cancer: Clinical Features and Patterns of Recurrence

- Often present as interval cancers
- Weak relationship between tumor size and node status
- Rapid rise in risk of recurrence following diagnosis
- Peak risk of recurrence at 1-3 years
- Distal recurrence rarely preceded by local recurrence
- Local recurrence not predictive of distal recurrence
- Increased mortality rate first 5 years
- Majority of deaths occur in first 5 years
- Rapid progression from distant recurrence to death
New Treatment Options: Approved or on Horizon

- **Small molecule inhibitors**
  - Erotinib, lapatanib (EGFR, HER2)
  - Sunitinib, sorafenib, pazaponib (angiogenesis)
  - Temsirolimus, everolimus (m-TOR)
  - Imatinib, dasatinib, nirotinib (c-Kit and/or BCR-abl)
  - PLX 4032 (B-RAF)
  - Crizotinib (ALK kinase)

- **Antibodies and other immunologic agents**
  - Bevacizumab (VEGF)
  - Trastuzumab, cetuximab (HER2, EFGR)
  - Ipilimumab (CTLA4)

- **Cytotoxic agents**
  - Carbazitaxel, ixabepilone, eribulin

- **Endocrine agents**
  - Abiratarone
### Hundreds of Potential Therapeutic Targets:
#### Example - HER2-positive Breast Cancer

<table>
<thead>
<tr>
<th>Therapeutic Target</th>
<th>Example</th>
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</thead>
<tbody>
<tr>
<td>HER2 dimerisation inhibitor</td>
<td>Pertuzumab</td>
</tr>
<tr>
<td></td>
<td>Monoclonal antibody that inhibits dimerisation of HER2</td>
</tr>
<tr>
<td>HER2 ADC</td>
<td>T-DM1</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab-based ADC delivering cytotoxic drug (DM1) specifically to HER2-positive tumour cells</td>
</tr>
<tr>
<td>PI3K inhibitors</td>
<td>Lapatinib</td>
</tr>
<tr>
<td></td>
<td>Reversible inhibitor of EGFR and HER2 tyrosine kinase</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>eg Neratinib</td>
</tr>
<tr>
<td></td>
<td>Irreversible inhibitor of EGFR, HER2 and HER4 tyrosine kinase</td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td>eg Everolimus</td>
</tr>
<tr>
<td></td>
<td>Small molecule inhibiting mTOR signal transduction</td>
</tr>
<tr>
<td>HSP 90 inhibitors</td>
<td>eg Tanespimycin</td>
</tr>
<tr>
<td></td>
<td>Antineoplastic antibiotic inhibiting HSP 90</td>
</tr>
<tr>
<td>VEGF receptor inhibitors</td>
<td>eg Bevacizumab</td>
</tr>
<tr>
<td></td>
<td>Monoclonal antibody inhibiting VEGF</td>
</tr>
</tbody>
</table>

*Courtesy of Javier Cortez, MD, PhD*
Open Cancer Clinical Trials
Clinical Trials.Gov Database
(accessed 4/10/11 – search terms: Cancer | Open Studies | Exclude Unknown | Studies Without Results | Interventional Studies | Adult

<table>
<thead>
<tr>
<th></th>
<th>NIH</th>
<th>Industry</th>
<th>Both</th>
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<tbody>
<tr>
<td>Phase I</td>
<td>577</td>
<td>1162</td>
<td>1739</td>
</tr>
<tr>
<td>Phase II</td>
<td>811</td>
<td>1429</td>
<td>2240</td>
</tr>
<tr>
<td>Phase III</td>
<td>200</td>
<td>418</td>
<td>618</td>
</tr>
<tr>
<td>Total</td>
<td>1588</td>
<td>3009</td>
<td>4597</td>
</tr>
</tbody>
</table>

- About 25,000 accruals annually on NCI-sponsored trials
- Only 3% of adult cancer patients are enrolled on therapeutic clinical trials
Phase III clinical trial development and completion
Clin Cancer Res. 2010: 22; 5381-9 & 2011 (17 1947-55)

• **Methods**
  – Adult phase I-III NCI trials between 2000-2007 (n = 764) analyzed accrual performance
  – Subgroup analyzed for trial development process.

• **Results**
  – Accrual
    • 82% did not complete projected accrual rate
    • 37% did not meet accrual goal
  – Development process for cooperative group trials
    • 769 steps, 36 approvals
    • median of ~2.5 years from concept review to study opening
• Novel trial designs
  – Phase 0 trials
  – Better phase II & III designs
  – Faster, more accurate conclusions

• Predictive biomarkers
  – Tandem development
  – Validation
Phase 0 Clinical Trial of the Poly (ADP-Ribose) Polymerase Inhibitor ABT-888 in Patients With Advanced Malignancies


Fig 2. Average plasma concentrations (μM) of ABT-888 in patients before and after administration of a single 10-, 25-, or 50-mg dose of ABT-888 over 24 hours. Plasma C_{max} levels exceeding the target threshold of 0.21 μmol/L were achieved in all patient cohorts. Vertical bars represent standard deviations (SD).
Purpose of Phase II Studies
New Agent or Regimen

• Sufficient efficacy to merit further evaluation
  – Not designed to confirm improved outcomes

• Safety profile

• Predictive biomarkers
  – or subpopulations who benefit
Phase II Trials

• Initially developed as a method for identifying agents with antitumor activity
  – Single cytotoxic agents
  – Response rate usually endpoint
  – Benchmark usually 20% ORR

• Use expanded beyond this initial objective
  – Combinations
  – Comparison with historical data
  – Cytostatic agents
### Randomized Phase II Designs

<table>
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<tr>
<th>Design</th>
<th>Attributes</th>
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</thead>
<tbody>
<tr>
<td><strong>Selection (&quot;pick the winner&quot;)</strong></td>
<td>• Comparison between 2 experimental arms</td>
</tr>
<tr>
<td></td>
<td>• Each compared with historical control</td>
</tr>
<tr>
<td></td>
<td>• ORR usually the endpoint</td>
</tr>
<tr>
<td><strong>Screening</strong></td>
<td>• Experimental vs. control arm</td>
</tr>
<tr>
<td></td>
<td>• Standard therapy +/- investigational agent</td>
</tr>
<tr>
<td><strong>Randomized Discontinuation</strong></td>
<td>• All patients receive experimental agent</td>
</tr>
<tr>
<td></td>
<td>• Randomize non-progressors to continued therapy vs. placebo</td>
</tr>
</tbody>
</table>
• **Endpoint**
  – ORR vs. PFS vs. biomarker (eg, molecular imaging)

• **Study design**
  – ORR
    • Monotherapy: single arm acceptable (if adequate historical data)
    • Combination: randomized trials recommended
  – PFS
    • Randomization required, use placebo control when feasible
    • Consider crossover after primary endpoint reached

• **Patient selection/enrichment**
  – Use biomarker for selection only when well supported (eg, HER2)
  – Predefine exploratory biomarker & adequately power subgroup
  – Consider multi-disease trials

*Seymour et al. Clinical Cancer Research, 2010*
I-SPY 2 Adaptive Trial Design

* HER2 positive participants will also receive Trastuzumab. An investigational agent may be used instead of Trastuzumab.
I-SPY2 TRIAL

Graduate, drop, or add experimental arms in real time during the trial, not at trial completion

Outcome: Complete response at surgery

Population of patients

ADAPTIVELY

RANDOMIZE

Experimental arm 1
Experimental arm 2
Experimental arm 3
Experimental arm 4
Experimental arm 5
Standard therapy

Courtesy of D. Berry
<table>
<thead>
<tr>
<th>Agent</th>
<th>HER2+ / Any HR Cancers</th>
<th>HER2- / HR+ Cancers</th>
<th>HER2 - / HR - Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARP Inhibitor</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>IGFR Inhibitor</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pan ErbB Inhibitor</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>APO/TRAIL Agonist</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Angiopoietin Inhibitor</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Biomarkers in Clinical Practice

• What is a biomarker?
  – “A characteristic that is objectively measured and evaluated as an indicator of normal biologic … or pathogenic processes, or pharmacologic responses to a therapeutic intervention.”
  – Examples
    • ER, PR, HER2 expression – weakly prognostic, predictive for benefit from endocrine and HER2 directed therapy
    • Multiparameter gene expression assays – prognostic, predictive of chemotherapy benefit

• How can it help?
  – Provide Information not otherwise available from clinical features
  – Directing therapy

Impact of Molecular Profiling on Research Paradigm

Hypothesis-Based Research
- evaluate limited number of genes/proteins
- selected based upon a specific hypothesis and rationale

Molecular Profiling – High-Throughput Analysis
- may apply to a variety of “-omic technologies”
  - genomics (DNA, RNA)
  - proteomics (proteins)
  - epigenomics (eg, methylation, acetylation)
  - combinations of above

Discovery-Based Research
- large volumes of data generated without specific hypothesis
- class discovery & class comparison/prediction
Predictive Biomarkers in Oncology Practice

• Breast cancer
  – ER/PR by IHC – endocrine therapy
  – HER2 by IHC/FISH – anti-HER2 therapy

• Metastatic colorectal cancer
  – K-Ras mutation – anti-EGFR directed therapy

• Melanoma
  – B-Raf mutation – B-Raf inhibitors
Clinical Utility and Clinical Practice

• Clinical Utility
  – Treatment change?
  – Do patients benefit from change?

• Clinical Practice & Regulatory Approval
  – CLIA vs. FDA approval of assay/analytes
  – CLIA certification of laboratory
• Biospecimen and assay quality
  – Biospecimens
  – Analytic Performance
  – Harmonization

• Analytic and regulatory standardization
  – Bioinformatics
  – Collaboration and Data Sharing
  – Regulatory

• Stakeholder engagement
  – Stakeholder Education and Communication
  – Science Policy
AACR-FDA-NCI Cancer Biomarkers Collaborative Consensus Recommendations


• Biospecimen quality of research specimens
  – Establish quality standards & promote routine quality assessment
  – Develop a publicly available national oncology resource of reference standards for biospecimen quality assessment and analytic validation
  – Promote an infrastructure and climate supportive of biospecimen research

• Analytic Performance
  – Develop best practices for analytic validation of various analytes and technologies
  – Define and implement quality systems for use in assay validation
  – Develop universal physical reference standards

• Standardization and Harmonization
  – Harmonize biomarker validation and qualification terminology
  – Develop common data standards
  – Define a universal data element set to accompany biospecimens
  – Create a simple, standard, and efficient informed consent process and document
AACC-FDA-NCINCI Cancer Biomarkers Collaborative Consensus Recommendations


- **Bioinformatics**
  - Implement a common workspace in a federated application environment
  - Establish a collection of use cases (i.e., working models) for biomarker development to facilitate the development of appropriate bioinformatics tools

- **Collaboration and Data Sharing**
  - Form a model pre-competitive consortium to facilitate sharing scientific information and research operations
  - Incentives to encourage collaborations (sponsors and regulators)
  - Contribute biospecimen methods data & experimental data to public databases

- **Regulatory Issues – develop best practices**
  - Codevelopment of therapeutics and diagnostics
  - Evidentiary standards for changes in drug labeling & companion diagnostics
  - Biomarker assays based on a composite of multiple individual biomarkers
  - Retrospective-prospective study designs for clinical qualification of biomarkers
  - Adaptive clinical trial designs for using biomarkers in drug development
  - Alternative prospective trial designs for companion diagnostics
**Stakeholder Education and Communication**
- Educate patients and health care providers about the value and need for biospecimen collection
- Increase awareness and understanding of the importance of analytic validation and quality control
- Educate stakeholders in regulatory pathways to accelerate codevelopment of therapeutics and diagnostics

**Science Policy**
- Identify areas and/or processes that could enhance the environment for biomarker development
- Explore ways to improve reimbursement for biospecimen handling and diagnostic tests
- Address the barriers to biomarker research produced by the HIPAA Privacy Rule
## Gene Expression Assays

<table>
<thead>
<tr>
<th>Assay (Company)</th>
<th>Method</th>
<th>Tissue Type</th>
<th>Approval</th>
<th>Patient Population</th>
<th>Prognosis/Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammaprint 70 Gene Assay (Agendia)</td>
<td>DNA Microarray</td>
<td>Fresh or Frozen</td>
<td>Europe and US (FDA)</td>
<td>ER-Pos/Neg stage I-II breast cancer</td>
<td>Prognostic for distant recurrence</td>
</tr>
<tr>
<td>Oncotype DX 21 Gene Assay (Genomic Health)</td>
<td>qRT-PCR</td>
<td>FFPE</td>
<td>Europe and US (CLIA)</td>
<td>ER-Pos stage I-II breast cancer</td>
<td>Prognostic for distant recurrence, Predictive of chemotherapy benefit if RS high</td>
</tr>
<tr>
<td>Theros 2 Gene Ratio (Biotheranotics)</td>
<td>qRT-PCR</td>
<td>FFPE</td>
<td>US (CLIA)</td>
<td>ER-Pos, Lymph node Negative Breast Cancer</td>
<td>Prognostic for distant recurrence</td>
</tr>
<tr>
<td>MapQuantDX 5 Gene Molecular Grade (Ipsogen)</td>
<td>DNA Microarray</td>
<td>Fresh or Frozen</td>
<td>Europe</td>
<td>ER-Pos, Grade 2 tumors</td>
<td>Prognosis–reclassification of tumors from grade 2 to grade 1 or 3</td>
</tr>
</tbody>
</table>
Rationale for TAILORRx
(Trial Assigning Individualized Options for Treatment):

**Who?** (population?)

**What?** (assay?)

**How?** (design?)
Management of ER-Positive, Lymph-Node Negative Breast Cancer

- ~137,000 diagnosed annually in North America
- ~80-85% are adequately treated with
  - surgery +/- irradiation
  - hormonal therapy
- Adding chemotherapy ↓ recurrence by ~25%
  - absolute benefit is small (~3-5% or less)
- Current practice guidelines
  - chemotherapy recommended for most
Concordance among Gene-Expression-Based Predictors for Breast Cancer

Cheng Fan, M.S., Daniel S. Oh, Ph.D., Lodewyk Wessels, Ph.D., Britta Weigelt, Ph.D., Dimitry S.A. Nuyten, M.D., Andrew B. Nobel, Ph.D., Laura J. van’t Veer, Ph.D., and Charles M. Perou, Ph.D.

CONCLUSIONS
Even though different gene sets were used for prognostication in patients with breast cancer, four of the five tested showed significant agreement in the outcome predictions for individual patients and are probably tracking a common set of biologic phenotypes.

Oncotype DX 21 Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

RS = + 0.47 x HER2 Group Score
    - 0.34 x ER Group Score
    + 1.04 x Proliferation Group Score
    + 0.10 x Invasion Group Score
    + 0.05 x CD68
    - 0.08 x GSTM1
    - 0.07 x BAG1

### Category
<table>
<thead>
<tr>
<th>RS (0 – 100)</th>
<th>Low risk</th>
<th>Int risk</th>
<th>High risk</th>
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<tbody>
<tr>
<td>RS &lt; 18</td>
<td>RS 18 –30</td>
<td>RS &gt; 30</td>
<td></td>
</tr>
</tbody>
</table>
Scientific Rationale for Selecting Oncotype DX Assay in TAILORx

1. Validated prognostic test for tamoxifen treated patients
   – predictive of distant recurrence
   – may be used as dichotomous or continuous variable
   – *(Paik et al. NEJM, 2004)*

2. Also validated in population based Kaiser study

3. Lower RS predictive of tamoxifen benefit
   – *(Paik et al. ASCO 2005, abstr 510)*

4. Higher RS predictive of chemotherapy benefit
   – *(Paik et al. JCO 2006)*

5. Correlates more strongly with outcome than Adjuvant!
   – *(Bryant et al. St. Gallen, 2005)*

6. Predictive of local recurrence in tam treated patients
   – *(Mamounas, JCO 2009)*
Rationale for Primary Study Group RS Range of 11-25 Based upon B-20 Results

"Primary Study Group" For Randomization

Recurrence Score

Secondary Study Group 1

Secondary Study Group 2

Benefit from chemo
<table>
<thead>
<tr>
<th>RS</th>
<th>No. (%)</th>
<th>Tam</th>
<th>Tam + Chemo</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11</td>
<td>177 (27%)</td>
<td>98%</td>
<td>95%</td>
<td>1.79</td>
<td>0.47</td>
</tr>
<tr>
<td>11-25</td>
<td>297 (43%)</td>
<td>95%</td>
<td>94%</td>
<td>0.76</td>
<td>0.53</td>
</tr>
<tr>
<td>&gt;25</td>
<td>195 (30%)</td>
<td>63%</td>
<td>88%</td>
<td>0.29</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
CAF Benefit Greatest in Higher RS for Both Nodal Subsets, with No Benefit in Lower RS

Five-Year Probability of Death or Disease Recurrence
Linear model for Recurrence Score and interactions with treatment

- Tam, 4+ nodes (n=54)
- CAF-T, 4+ nodes (n=86)
- Tam, 1-3 nodes (n=94)
- CAF-T, 1-3 nodes (n=133)

Chemo benefit 4+ nodes
Chemo benefit 1-3 nodes

S8814: Courtesy of K. Albain, MD
TAILORx Trial Design

ER-Positive, Node Negative Breast Cancer

- RS<11 Endocrine Therapy
- RS 11-25 Randomize
- RS > 26 Chemotherapy plus Endocrine Therapy

Endocrine Therapy
Chemotherapy plus Endocrine Therapy
## Non-Adherence in Other Seminal Breast Cancer Trials

<table>
<thead>
<tr>
<th></th>
<th>Experimental Arm</th>
<th>Standard Arm</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B06</strong></td>
<td>Lumpectomy +/- RT</td>
<td>Mastectomy</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>7%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td><strong>E2190</strong></td>
<td>High-dose chemo</td>
<td>Standard chemo</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>14%</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

**Practice changing results:**
- B06: Lumpectomy/RT as effective as mastectomy
- E2190: High dose therapy not effective as thought
Effect of Non-Adherence Rate on Sample Size of Randomized Group and Entire Study

- Non-Adherence Rate: 5%, 10%, 15%, 20%, 25%, 30%
- February 2009: 6191
- March 2009: 4390
- April 2009: 7047
- May 2009: 7851
- June 2009: 8802
- July 2009: 9937
- August 2009: 11,306
- September 2009: 12,979

No. Patients:
- 6191
- 4390
- 7047
- 7851
- 8802
- 9937
- 11,306
- 12,979

Non-Adherence Rate:
- 5%
- 10%
- 15%
- 20%
- 25%
- 30%

No. Patients:
- 4390
- 4891
- 5484
- 6191
- 7044
- 8066
- 4711

June 2009: 6191
March 2009: 4390
April 2009: 7047
May 2009: 7851
June 2009: 8802
July 2009: 9937
August 2009: 11,306
September 2009: 12,979

Effect of Non-Adherence Rate on Sample Size of Randomized Group and Entire Study
EORTC-BIG MINDACT TRIAL DESIGN: 6,000 Node negative women

Evaluate Clinical-Pathological risk and 70-gene signature risk

Clinical-pathological and 70-gene both HIGH risk

55%

Discordant

Clin-Path HIGH
70-gene LOW
70% N=1344

Clin-Path LOW
70-gene HIGH
30% N=576

Clinical-pathological and 70-gene both LOW risk

32%

13%

N=1920

H₀: 5y DMFS >92% (80% power)

Use Clin-Path risk to decide Chemo or not

Clin-Path High
70-gene Low: CTx 70% 672
Clin-Path Low
70-gene High: no CTx 30% 288

Use 70-gene risk to decide Chemo or not

Clin-Path High
70-gene Low: no Ctx 70% 672
Clin-Path Low
70-gene High: CTx 30% 288

Supported by the EU framework VI programme
BIG-TRANSBIG Secretariat—Used with permission
No benefit to CAF over time if low RS

Strong benefit if high RS

Disease-Free Survival by Treatment

Low risk (RS < 18)

Stratified log-rank p = 0.97 at 10 years

High risk (RS ≥31)

Stratified log-rank p = 0.033 at 10 years

Intermediate risk (RS 18-30)

Stratified log-rank p = 0.48 at 10 years

TAMOXIFEN (n=55, 15 events)
CAF-T (n=91, 26 events)

TAMOXIFEN (n=47, 22 events)
CAF-T (n=57, 20 events)
Southwest Oncology Group: RxPONDER Trial

Node-positive (1-3 nodes) HR-positive and HER2-negative breast cancer

(N= 600)
RS already Available

RS \leq 25 ?

RS > 25
(N= 4,300)
Discuss alternative trials for high risk patients

RS \leq 25
(N= 6,300)
Physician and patients discuss randomization knowing the RS

Accept

N= 4,500
Randomization stratified by
1. RS
0-13 vs. 14-25
23. Menopausal status

N= 2,250
Chemotherapy; appropriate endocrine therapy

Refuse

N= 1,800
Record chosen therapy and followed for vital status through cancer registry

N= 2,250
No Chemotherapy; appropriate endocrine therapy

(N= 10,000)
Patients consent to study-sponsored RS testing, discussion of potential trials, tumor tissue submission and linkage to cancer registry data
New Treatment Options, Clinical Trials, and Cancer Biomarkers

• New treatment options
  • Scores of new drug targets
  • Dozens of agents for each target
  • Innumerable potential combinations

• Clinical trials
  • New models needed
  • Both larger and smaller trials needed

• Cancer biomarkers
  • Development challenging
  • Critical for defining who benefits