Session II: Academic Research in Breast Cancer: Challenges and Opportunities

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ECOG-ACRIN Group Co-Chair

Symposium: Innovation in Breast Cancer 2014
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Cancer Care in the U.S.

Community Practices

NCI-Designated Cancer Centers

Patients

Other Medical Centers
Trial Sponsors in the U.S.

Clinical Trials

- Pharmaceutical Sponsored
- NCI Sponsored
- Investigator Initiated
Stakeholders in U.S. Trials

- Investigators
- Sponsors
- Participating Sites
- Regulatory Agencies
- Patients
Foundations Supporting Breast Cancer Research in the U.S.

- American Cancer Society
- AVON Breast Cancer Foundation
- The Breast Cancer Research Foundation
- Susan G. Komen®
- Stand Up to Cancer (SU2C)
The Clinical Trial *Ecosystem*
## NCI Spending 2010 - 2012

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>2010 Spending (in millions)</th>
<th>2011 Spending (in millions)</th>
<th>2012 Spending (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>$281.9</td>
<td>$296.8</td>
<td>$314.6</td>
</tr>
<tr>
<td>Prostate</td>
<td>300.5</td>
<td>288.3</td>
<td>265.1</td>
</tr>
<tr>
<td>Breast</td>
<td>631.2</td>
<td>625.1</td>
<td>602.7</td>
</tr>
<tr>
<td>Colorectal</td>
<td>270.4</td>
<td>265.1</td>
<td>256.3</td>
</tr>
<tr>
<td>Bladder</td>
<td>22.6</td>
<td>20.6</td>
<td>23.4</td>
</tr>
<tr>
<td>Melanoma</td>
<td>102.3</td>
<td>115.6</td>
<td>121.2</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>122.4</td>
<td>126.4</td>
<td>119.5</td>
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<tr>
<td>Kidney</td>
<td>44.6</td>
<td>46.2</td>
<td>49.0</td>
</tr>
<tr>
<td>Thyroid</td>
<td>15.6</td>
<td>16.2</td>
<td>16.5</td>
</tr>
<tr>
<td>Endometrial (Uterine)</td>
<td>14.2</td>
<td>15.9</td>
<td>19.1</td>
</tr>
</tbody>
</table>
CTEP Accrual Portfolio of Breast Cancer Patients:
Only Randomized Phase 2 and 3 Studies

Accrual to Non-Breast Cancer Studies

Accrual to Breast Cancer Studies

ECOG-ACRIN cancer research group
Reshaping the future of patient care

RL Comis MD, 02-21-14
CTEP Accrual Portfolio of Breast Cancer Patients: Randomized Phase 2 and 3 Studies

- Neoadjuvant (early stage)
- Adjuvant (early stage)
- Metastatic Breast Cancer


Number of Patients: 0-14,000

Image: Bar chart showing the number of patients for each year in the categories of Neoadjuvant, Adjuvant, and Metastatic Breast Cancer.
High Impact Trials in North America

- Screening
  - Digital mammography (DMIST)
  - Sonography (6666)
  - MRI (6697)
- Primary therapy
  - Breast conservation surgery vs. mastectomy (B06)
- Metastatic disease
  - Bevacizumab (E2100)
High Impact Trials in North America

• Adjuvant therapy
  – Chemotherapy and endocrine therapy (E1180, B14)
  – Trastuzumab in HER2-positive disease (N9831, B31)
  – Taxane therapy (C9344, B28)
  – Taxane schedule (E1199)
  – Extended adjuvant endocrine therapy > 5 years (MA17)

• Biomarkers
  – Oncotype DX® validation (B14, S8814)
  – Oncotype DCIS score validation (E5194)
Revised Cooperative Group Structure in the U.S./North America

• ECOG-ACRIN Cancer Research Group
• SWOG
• Alliance for Clinical Trials in Oncology
  – CALGB, NCCTG and ACOSOG
• NRG Oncology
  – NSABP, RTOG and GOG
• NCIC Clinical Trials Group
**ECOG-ACRIN Cancer Research Group**

- 2012 merger combined complementary **therapeutic** and **diagnostic imaging** strengths:
  
- **Eastern Cooperative Oncology Group (ECOG)**
  - Large-scale treatment trials changed the standard of care in numerous cancer types
  - Biomarker-driven trials helped to individualize therapy

- **American College of Radiology Imaging Network**
  - Full range of medical imaging research
    - Surveillance strategies in high risk populations
    - Imaging biomarkers in early phase trials
    - Prevention approaches in landmark screening trials
    - Methodologies in comparative-effectiveness research
NCI Clinical Trials System

- 3,100 Institutions
- 14,000 Investigators
- About 25,000 pts enrolled on tx trials annually

Trials FY2006 | FY2007 | FY2008 | FY2009 | FY2010
--- | --- | --- | --- | ---
All Phases: Treatment Trials | 27,667 | 24,715 | 25,784 | 29,285 | 23,468

Accrual Distribution:
- Phase 3: 83.4%
- Phase 2: 15.1%
- Phase 1/Pilot: 1.5%
How effective is therapy for breast cancer?

<table>
<thead>
<tr>
<th>Years</th>
<th>5 Year Survival</th>
</tr>
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<tbody>
<tr>
<td>1975-1977</td>
<td>75%</td>
</tr>
<tr>
<td>1984-1986</td>
<td>79%</td>
</tr>
<tr>
<td>1990-1992</td>
<td>85%</td>
</tr>
<tr>
<td>2001-2007</td>
<td>90%</td>
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</tbody>
</table>

SEER, 1975-2007

IARC 2008

ECOG-ACRIN cancer research group
Reshaping the future of patient care

RL Comis MD, 02-21-14
Major Survival Benefits Obtained from Incremental Advances

- No surgery
- Local Therapy (surgery and radiation)
- Chemotherapy + hormonal therapy
- Chemotherapy + hormonal + targeted therapy

Relapse-free survival vs. Time in Years
Incremental Benefit

- chemo TX + anti ER + targeted
- mastectomy
- No surgery

Each incremental step assumed that no pt is cured with the previous step

- Significant overtreatment
- Need to conduct large trials to demonstrate small benefit

Slide courtesy of Soon Paik
Molecular Portrait of Breast Cancers

- Basal-like
- HER-2
- “Normal”
- Luminal B
- Luminal A

"Intrinsic" gene set on 78 single tumor samples

Sorlie T et al, PNAS 2001

Slide courtesy of L. Carey
Practice-Changing Results
21-Gene Recurrence Score

• Chemotherapy versus hormonal therapy for node negative breast cancer
• PACCT-Program for the Assessment of Clinical Cancer Tests
• VALIDATION MADE POSSIBLE BY TUMOR BANKING and prospective/retrospective evaluation of banked tumor samples (NSABP B-14 and NSABP B-20)
DFS in Early Stage Breast Cancer by Recurrence Score (NSABP B-20)

- Patients with tumors that have high Recurrence Scores have a large absolute benefit of chemotherapy (similar results with CMF and MF)
- Patients with tumors that have low Recurrence Scores derive minimal, if any, benefit from chemotherapy
Node Neg, ER (+), Breast Cancer

Register Specimen banking FFPE and germ line

21-gene RS n=11,233

RS < 10
Hormone Therapy Registry N=1625

RS 11 – 25
Randomize Hormone Rx vs. Chemotherapy + Hormone Rx N=6908

RS > 25
Chemotherapy + Hormone Rx N=1731

Accrual complete as of 10/06/2010
Can molecular profiling be used to select patients for chemotherapy in lymph node positive breast cancer?

• S1007 RxPONDER asks key scientific question
  – Role of molecular profiling and anatomic staging

• The 21-gene RS will predict the benefit of chemotherapy in node positive (1-3 nodes), HR+ breast cancer patients with RS ≤ 25 treated with state-of-the-art endocrine therapy
  – Chemotherapy benefit (if it exists) will increase as the RS increases
S1007 RESPONDER a clinical trial
Rx for Positive Node, Endocrine Responsive Breast Cancer

Recurrence Score

RS > 25 (N= 3,800 alternative trials)
Refuse
N= 1,600
Record therapy and follow

RS ≤ 25
Randomize
N= 4,000
1. RS
2. Menopausal status
3. ALND vs. SLNB
Accept

N= 2,000
Chemotherapy; appropriate endocrine therapy

N= 2,000
No Chemotherapy; appropriate endocrine therapy

775 of 4000 RANDOMIZED
171% of predicted at quarter 6
ER Positive Breast Cancer

Overcoming Hormonal Resistance: PI3K mTOR Pathway

Muschgrove, *Nat Rev Cancer* 2009
S1207 NSABP Adjuvant Everolimus

- N=3400
  - 3.5 years accrual
- ER pos HER-2 neg
  - LN neg; > 2cm; RS > 25
  - 1-3 + LN; RS > 25
  - >4 pos LN
- HR 0.75 – 90% power
- 5-year DFS of 84.5% (absolute improvement of 4.6%).
New ECOG-ACRIN Scientific Directions

• Role of platinums as post-neoadjuvant therapy in triple negative breast cancer (EA1131)

• Role of HDAC inhibitors in ER-positive metastatic (E2112)

• Imaging as a biomarker
E1113: Randomized Phase III Post-Neoadjuvant Cisplatin in TNBC
PIs: Ingrid Mayer, Vanderbilt University

Localized breast cancer
Subtype:
• TNBC

Completed neoadjuvant chemotherapy including anthracycline and taxane
Residual disease
• Breast >= 1 cm
• Or lymph nodes

Standard care:
No additional therapy

1:1 randomization and stratify:
• PAM50: Basal vs. other
• T: < 2 vs. 2-4 vs. > 4 cm
• N: Pos vs. Neg
• ER/PR: Pos vs. Neg

Primary endpoint: DFS in basal group
80% power to detect 33.3% reduction in DFS hazard rate (median 48 vs. 72 months), assumes 15% non-adherence, 75% basal subtype
N=840 randomized (630 in PAM50 basal group), 12 patients/month, total duration 53 months accrual + 30 months follow up

Cisplatin 75 mg/m² every 3 weeks x 4 cycles
Rationale for HDAC Inhibitors in ER-Positive Breast Cancer

- Most patients develop resistance to endocrine therapy
- HDAC inhibitors sensitive cells to anti-estrogen therapy and reverse treatment resistance
- ENCORE 301 trial suggests adding an HDAC inhibitor to endocrine therapy improves clinical outcomes
Entinostat Overcomes Hormone Resistance

Entinostat restores estrogen receptor sensitivity *in vivo*\(^1, 2\)

![Graph showing tumor volume changes](image)

Weeks

Mean Tumor Volume (mm\(^3\))

1. Control
2. Switch to entinostat
3. Continue letrozole
4. Continue letrozole / add entinostat
5. Switch to exemestane / add entinostat

**Protein expression levels from tumors**

*From xenograft AI resistant model, Sabnis et al.*\(^3\)

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\(^1\) Sabnis, SABCS, 2010 #850523 "HDAC inhibitor entinostat restores responsiveness of letrozole resistant MCF-7Ca xenografts to AIs through modulation of Her-2"

Humanized mouse xenograft ER+ breast cancer model designed to study aromatase inhibitors (N=10 per group)

 Syndax Pharmaceuticals - Molecular Targets 2011
ENCORE Results (OS): Feb 2012

Intent-to-treat population

Exemestane + Entinostat: median OS 28.1 months
Exemestane + Placebo: median OS 19.8 months
Hazard Ratio 0.59 (95% CI: 0.36, 0.97)
P=0.04 (2-sided); P=0.02 (1-sided)
Median Follow-up for OS = 25 months

Improvement in OS has stayed consistent with > 2 yr median follow up
E2112: Phase III trial exemestane + entinostat/placebo

PI: R. Connolly, MD

Eligible:

Advanced breast cancer
ER/PR+, HER2-
Progression on prior non-steroidal AI

Randomize

Exemestane plus
Entinostat

Primary endpoints:
PFS and OS

Exemestane plus
Placebo

N~ 600 total (N-360 for primary PFS analysis)

Pharmacodynamic biomarker validation: Blood at baseline, 2 wks for PBMC lysine acylation

- **PFS**: 88.5% power to detect a 42% reduction in the PFS failure hazard rate with no interim efficacy analysis; corresponds to an improvement in median PFS from 4.1 to 7.1 months (projected at 30 months after activation)
- **OS**: 80% power to detect a 25% reduction in the OS failure hazard rate with interim analysis plan; corresponds to an improvement in median OS from 22 to 29.3 months (projected at 69 months after activation)
Potential biomarker Trial of FES PET:
Endocrine Therapy Recommended as Initial Therapy for ER-Positive Metastatic Breast Cancer

- **Hypothesis:**
  - Low or absent FES uptake (SUV < 1.5) predicts poor response and early progression
  - Negative predictive test

- **Clinical impact:**
  - ER-positive, FES-PET positive: Endocrine therapy
  - ER-positive, FES-PET negative: Chemotherapy
18F-Fluoroestradiol (FES): PET Estrogen Receptor (ER) Imaging

Provides a Quantitative Estimate of ER Expression

\[ \text{ER Concentration (fmoles/mg protein)} \]

\[ \text{Tumor Uptake (%ID/mL x 10^{-4})} \]

\[ \text{vs Radioligand Binding} \]

\[ \text{vs IHC} \]

\[ (\text{Kieswetter, J Nucl Med, 25: 1212, 1984}) \]

\[ \text{Mintun, Radiology 169:45, 1988.} \]

\[ \text{Peterson, J Nucl Med 49: 367, 2008.} \]
FES Uptake Predicts Breast Cancer Response to Endocrine Therapy

Example 1
- Recurrent sternal lesion
- ER+ primary
- Recurrent Dz strongly FES+

Example 2
- Newly Dx’d met breast CA
- ER+ primary
- FES-negative bone mets

Opportunities and Challenges in Molecular Era

• “Precision or personalized therapy”
  - Avoid overtreatment and undertreatment

• Understand biology of molecular subtypes
  - Preoperative setting allows for evaluation of tumor response and molecular markers
  - Identification of targets and co-development of diagnostics
  - North American Breast Cancer Correlative Science committee

• Improvement in survival in metastatic breast cancer
Reshaping the future of patient care

www.ecog-acrin.org