Challenges and opportunities associated with research and development of targeted therapies

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Background

• Increasing # targeted cancer therapies
• Impact on the continuum of cancer research and care.
• Consider further the questions and concerns identified in the targeted therapies panel Oct. 2011.
• Discuss the challenges and opportunities.
• Response of the FDA
• Potential benefits for cancer survivors.
• Consider the necessity for open and complete communication between health providers and patients.
The Researcher, Physician, Regulator, and Patient in an Age of Personalized Medicine

- Note: Researcher = Physician = Regulator!
- Personalization:
  - By tumor site
  - By cell type
  - By cell “profiles”
  - By specific targets on the cell
  - By more complex pathways within cells
  - By “holistic” (background normal tissue) factors

Conventional “Personalization” of Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>ER and/or PR (+)</th>
<th>ER and PR (-)</th>
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</thead>
<tbody>
<tr>
<td>HER2 (+)</td>
<td>“Triple Positive”</td>
<td>“HER2 positive”</td>
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<tr>
<td>HER2 normal</td>
<td>“Hormone sensitive”</td>
<td>“TNBC”</td>
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As presented at the NCCS Cancer Policy Roundtable
March 22-23, 2012

Digging Deeper: Molecular characterization of ER(-) BC

- Unsupervised analysis of ER(-)/PR(-) tumors indicates molecular heterogeneity and distinct disease subtypes

One subtype (Class A) of ER(-) BC is characterized by a hormonally regulated transcriptional program, over expression of the AR, and a proliferative response to androgen

TBCRC011

DFCI, Duke, Georgetown, Mayo, MSKCC, UAB, UCSF, UNC
**Background**

- Breast cancer as an umbrella of phenotypes
  - Diverse natural history and diverse targets
- Trials that are biology-driven
  - Procurement of well annotated biospecimens
  - Access to novel imaging and biological assays
- Too small and too intensive for cooperative groups, too large for any single institution
- Long-standing informal collaborations among breast cancer SPOREs to conduct clinical trials
  - E.g., Avon/NCI Partners in Progress Program
- Need for a nimbler, independent, and ready-on research enterprise

**Mission Statement**

“The TBCRC is a cooperative effort of clinical trialists, translational scientists, and patient advocates from academic medical centers dedicated to innovative, high impact and biologically-driven clinical research. The overarching mission of the Consortium is to lessen the burden of breast cancer by using a collaborative and multidisciplinary approach to improve the understanding of breast cancer biology and test new therapeutic strategies. The Consortium will conduct clinical trials in the preoperative, pre-surgical, metastatic, and preventive settings. Consortium members work together closely to speed completion of clinical trials, share biologic specimens and clinical data, and identify new areas for research.”
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TBCRC Member Institutions

Baylor College of Medicine
Dana-Farber/Harvard CC
Duke University
Georgetown University
Indiana University
Johns Hopkins Kimmel CC
Mayo Clinic
MD Anderson Cancer Center
Memorial Sloan-Kettering CC
University of Alabama, Birmingham
University of California, San Francisco
University of Chicago (2007)
University of Michigan (2009)
University of North Carolina, Chapel Hill
University of Pittsburgh (2009)
Vanderbilt University

Foundation Support
Phase II Study of Bicalutamide for the Treatment of AR(+)/ER(-)/PR(-) MBC

Primary Objective
- Clinical Benefit Rate: CR + PR + SD > 6m

Secondary Objectives
- PFS
- Tolerability
- Correlatives

Study Design

Bicalutamide 150 mg oral daily

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<th>12</th>
<th>24...</th>
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<tbody>
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<td>Tox Eval</td>
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Biostatistics:
- This single-stage design requires 28 patients to discriminate between true response rates of ≤ 5% and ≥ 20% at a Type I error of 5% and a Type II error of 16%
- If ≥ 4 patients have a CR, PR or SD > 6 months, treatment with bicalutamide will have sufficient activity to merit further clinical study
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Screening & Enrollment

Consented for AR testing (n=450)

Screened for AR expression (n=416)

AR (+) (n=49)

On study (n =28)

Eligible on study (n =26)

Ineligible for testing (n=27)

Await testing (n=7)

AR (-) (n=367)

Ineligible for therapy (n=6)

Await enrollment (n=15)

Ineligible post therapy (n=2)

AR in BC: Conclusions

• AR is expressed in ~12% of ER/PR(-) tumors which are largely HER2(-) as well
• Androgen-blockade with bicalutamide is feasible for women with AR(+) ER(-)/PR(-) MBC
• Bicalutamide demonstrated efficacy as defined and pre-specified for this trial
• Bicalutamide is well tolerated
The other side of the coin: Not the cancer

Pathways Linking Obesity with Breast

- Obesity
  - ↑ Estrogen Synthesis
  - Insulin Resistance
    - ↑ Insulin, ↑ IGF-1
    - ↑ Plasma SHBG
    - ↑ Estradiol Bioavailability
    - VEGF Induction
  - Altered Adipokine and Cytokine Production
    - Adipocytes
    - Macrophages
      - ↓ Adiponectin
      - ↑ Leptin
      - ↑ IL-6, IL-1β
      - ↑ TNFα

- Angiogenesis
- Cell Proliferation
- Cell Survival
- Breast Cancer Cell
Obesity Causes An Inflammatory State


Obesity Trends* Among U.S. Adults
BRFSS, 1990, 2000, 2010
(*BMI ≥ 30, or about 30 lbs. overweight for 5’4” person)

Source: Behavioral Risk Factor Surveillance System, CDC.
Diet Induced Obesity: Experimental Design

C57BL/6J ♀ mice (n=40)

4 wks of age (n=20, OVX)

5 wks of age, Begin 10 wk treatment with LF (10 kcal%) or HF (60 kcal%) diets

- LF n=10
- LF, OVX n=10
- HF n=10
- HF, OVX n=10

Diet Induced Obesity Causes Focal Inflammation in the Mammary Gland and Visceral Fat of MICE
Crown-Like Structures are Common in theBreasts of Overweight and Obese Women

![H&E stain](image1) ![CD68 stain](image2)

\[
p = 0.003
\]

<table>
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<tr>
<th>% of cases with CLS</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
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<tbody>
<tr>
<td></td>
<td>1/12</td>
<td>7/10</td>
<td>6/8</td>
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Precision Medicine

Many components and challenges

• Tumor
  • Specific types of markers
  • Variations within tumors is a possible challenge
  • Targeted therapy may not always be transformative
    • Could be just one different chapter in a long book…

• Host factors
  • Socioeconomics
  • Physiology
  • Metabolism/Clearance/Pharmacokinetics

• Societal
  • Funding
  • Commitment
  • Rules/regulations/overhead