Cancer Clinical Trials in the Era of Personalized Medicine: US Investigator’s Perspective

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US Cancer Mortality Rates are Falling!


- Lung & bronchus
- Stomach
- Colon & rectum
- Prostate
- Leukemia
- Liver


- Uterus
- Breast
- Colon & rectum
- Stomach
- Ovary
- Pancreas

*Age-adjusted to the 2000 US standard population.
National Center for Health Statistics, Centers for Disease Control and Prevention.

2010, American Cancer Society, Inc.
Why is this happening?

- Tobacco control (lung)
- Prevention and early detection (colorectal)
- Improved treatment (breast)
Breast Cancer: A Model for Personalized Medicine

- Hormone receptors
- HER2 amplification
- Biomarkers for prognosis allowing selective use of chemotherapy (Oncotype DX, Mammaprint)
I-SPY 1 Clinical Trial Backbone

CALGB 150007 / ACRIN 6657

Layered Imaging and Molecular Biomarker Studies Onto Standard Clinical Care Neo-adjuvant therapy

- Anthracycline
- Taxane

- Serial MRI Scans
- Serial Core Biopsies

Surgery & RT → Tam if ER+

Courtesy of: Laura van ‘t Veer, et al. I-SPY neoadjuvant trial program
### Total Accrual: 237

<table>
<thead>
<tr>
<th>Institution Name</th>
<th>Accrual</th>
</tr>
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<tbody>
<tr>
<td>University of Pennsylvania Medical Center</td>
<td>36</td>
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<tr>
<td>Georgetown University Hospital</td>
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<tr>
<td>University of North Carolina</td>
<td>36</td>
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<tr>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>22</td>
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<tr>
<td>University of Washington</td>
<td>5</td>
</tr>
<tr>
<td>University of Alabama at Birmingham Medical Center</td>
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<tr>
<td>University of Chicago</td>
<td>2</td>
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<tr>
<td>University of Texas Southwestern</td>
<td>14</td>
</tr>
<tr>
<td>University of California San Francisco</td>
<td>66</td>
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</tbody>
</table>

- 1042 frozen cores from 201 patients
- 1301 paraffin cores from 223 patients
- 948 serum samples from 158 patients.

Courtesy of: Laura van ‘t Veer et al. I-SPY neoadjuvant trial program
I-SPY 1 Biomarker Platforms

Tissue: Core

H&E, IHC, FISH
Expression Arrays

p53 GeneChip

Protein Arrays
(RPMA)

UNC, Penn
UNC, UCSF, NKI
UNC
GMU

CGH

Serum

Id1 proteins
autoantibodies
phospho proteins

Courtesy of Laura van ‘t Veer et al. I-SPY neoadjuvant trial program
Tissue Distribution & Analyses Schema

Paraffin
- UNC: Dressler Lab
- Check for Tumor Presence

Initial H&E
- UNC: Livasy, Dressler Lab
- PENN: DeMichelle Lab
- Her2 Protein Overexpression Amplification
- IHC
- FISH

Sample
- UCSF
- 2 Frozen Cores
- Check for Tumor Presence

1 Frozen Core
- GMU: Liotta/Petrucin Lab
- Tumor Enriched
- Proteomics
- UCSF: Hagg Lab
- MDACC: Pusztai/Symmons Lab
- RNA
- 30%
- 70%

Initial H&E
- Core Remainder
- Storage

Gene Expression
- RNA
- Gene Chip For P53
- DNA
- CGH
- Gene Expression
- UCSF: Gray Lab
- UNC: Carey (Dorsey) Lab
- UNC:Perou Lab
- NKI: vantVeer Lab
- 44K Agilent gene expression array data
- cDNA microarray
- MIP (CGH) array
- p53 sequencing
- RPMA
- IHC/FISH

Data uploaded in
- NCI canintegrator
- NCI: caBIG, Madhavan
- UCSC Cancer Genomics Browser
- UCSC: Haussler, Kent, Zhu, Wang

Courtesy of: Laura van ‘t Veer et al. I-SPY neoadjuvant trial program
ISPY-1: Questions addressed or proposed to date

**Predict/Prognosticate**

- Surgical options (conservation)
- Response to chemotherapy (RCB class)
- Outcome: PFS and OS

**Classification based on combinatorics**

- MRI Classification
- Receptor status
- Gene expression classification
- Pathway activity classification
- Infiltrate classification
- Mutational classification

**MRI patterns**
- ER/PR
- Diffuse
- Lobulated
- ...
- v1, Δv1

**Signatures**
- Wound (Cheng)
- 70-gene (mammaprint)
- 20-gene (OncotypeDX)
- Subtype (Perou)
- MDACC/Greyeb/TFAC
- Mesenchymal, Hypoxia
- Immune: Modules

**Individual genes**
- Id1, OATP1A2
- Drug efflux/metab
- CK5-6, EGFR, GRP78
- MYC, TLR2, GPBB, GREB1, HOXB13, DEAR1

**Mutation status**
- p53
- Infiltrate
- -macrophages
- -T cells

**Infiltrate**
- subtype specific
- -metabolic

**Path**
- grade
- nodes

**Collect samples and data**

**Patient info**
- Tumor
- Stroma
- Lymph
- Blood
- Immune infiltrates

**Classify**

- Correlate
- Extract features

**Ask question**

- Predict
- Classify

Courtesy of: Laura van ‘t Veer et al. I-SPY neoadjuvant trial program
This is complicated!
Clinical trials are fundamental to understanding the value of clinical interventions.
Clinical Trial Stakeholders

- Public
- Investigators
- Industry
- Government
- Academia
Who Supports Clinical Trials?

- government (independent grants, cooperative groups)
- industry (includes investigator initiated trials)
- philanthropy (Foundations, Societies, etc.)
Under siege!

Our US Cooperative Groups have been harshly criticized by the Institute of Medicine.
Why Publicly Funded Trials are Important

• Compare the effectiveness of various treatment options
• Combine/compare drugs developed by different sponsors
• Develop therapies for rare diseases
• Address optimal dosing
• Test multi-modality therapies such as radiation therapy in combination with drugs
Why Publicly Funded Trials are Important

- Identify patient and tumor subsets most likely to benefit from interventions
- Study screening and prevention strategies
- Focus on survivorship and quality of life
- Publish negative results
- Assess cost and cost-effectiveness
- Provide “gold standard” databases for registry studies

Courtesy of Richard L. Schilsky
Time to Activation-Phase III trials 2006-2008

- 2% Less than one year
- 40% 1-2 years
- 58% More than two years

Courtesy of Richard Schilsky
Median Days Per Step

- Protocol approval to trial activation: 94 days
- Protocol receipt to protocol approval: 348.5 days
- Concept approval to protocol receipt: 138.5 days
- Concept receipt to concept approval: 93 days
What Does Success Look Like?

- System provides essential infrastructure for Cooperative Group trials in treatment, control, screening, diagnosis, and prevention; and is major enabler of cutting-edge translational investigation across all of NCI’s clinical research programs.

- System opens trials rapidly and completes accrual quickly by leveraging an integrated national network of performance sites.

- System provides a unified clinical and translational infrastructure for the extramural cancer community: investigators, patients, advocates, and industry.

- System at forefront of translational oncologic discovery; efficiently functions to answer critical questions not well supported in a commercial environment.
Who carries out clinical trials?

Clinical scientists with:
- specialized training
- expansive knowledge of cancer biology
- superb clinical skills

This takes years of training.
Most get their first job around age 34 – 40
Translational Science

- Highest premium for promotion for a clinical scientist
- Requires specialized cores and tissue biorepositories
- Depends on collaboration
- Requires as much protected time as “basic science”
The Academic’s Dilemma in an NCI Designated Cancer Center

- Independent research is expected for promotion
- NCI mandates cooperative group activities
- Patients need to be seen and clinical revenue required for compensation
The Institution’s Dilemma

- Patient care generates revenue
- Grant revenue rarely covers true cost
- Clinical researchers often need to be subsidized
- Unfunded mandates must be carried out
- Competition for patients exist
Developing Tools for Precision Medicine:

- Requires specialized cores and tissue biorepositories
- Depends on team science
This is not easy!
### Sample Listing of Participants Involved in the Opening of an Oncology Clinical Trial

<table>
<thead>
<tr>
<th>Participant</th>
<th>Type</th>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
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<tr>
<td>Principal investigators</td>
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<tr>
<td>Sponsor</td>
<td></td>
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<tr>
<td>Clinical trials office</td>
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<tr>
<td>Regulatory staff</td>
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<tr>
<td>Institutional review board</td>
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<tr>
<td>Scientific review committee</td>
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<td>Contracts and grants office</td>
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<tr>
<td>Division chair</td>
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<tr>
<td>Department head</td>
<td></td>
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<tr>
<td>Core medical team</td>
<td></td>
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<tr>
<td>Clinical research center</td>
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<td>Compliance office</td>
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<tr>
<td>Director, medical affairs/oncology administration</td>
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<tr>
<td>US Food and Drug Administration</td>
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<tr>
<td>Finance department</td>
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<td>General hospital review board</td>
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<td>Human subjects radiation committee</td>
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<td>Institutional biosafety committee</td>
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<td>Legal department</td>
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<td>Medical ethics board</td>
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<td>Office of sponsored research</td>
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<td>Pharmacy</td>
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<td>Radioactive drug research committee</td>
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<tr>
<td>Site coordinator</td>
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<tr>
<td><strong>Secondary</strong></td>
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Table 4. Accruals per Trial for All Phases

<table>
<thead>
<tr>
<th>No. of Accruals per Trial</th>
<th>No. of Studies</th>
<th>Total Studies (%)</th>
<th>Cumulative %</th>
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<tr>
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<td>45</td>
<td>20.6</td>
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<td>1-4</td>
<td>72</td>
<td>33.0</td>
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<td>5-10</td>
<td>42</td>
<td>19.3</td>
<td>72.9</td>
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<tr>
<td>11-15</td>
<td>24</td>
<td>11.0</td>
<td>83.9</td>
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<td>16-20</td>
<td>8</td>
<td>3.7</td>
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<tr>
<td>&gt; 20</td>
<td>27</td>
<td>12.4</td>
<td>100.0</td>
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<tr>
<td>Total</td>
<td>218</td>
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NCI Strategy for Biomarker Discovery and Development

Phase I
- Discovery
  - Genomic
  - Epigenomic
  - Transcriptomic
  - Proteomic
- Assay Development
  - IHC
  - ISH
  - PCR
  - MSP
- Pilot Studies
  - Small Retrospective Cohorts

Phase II
- Retrospective Clinical Analysis
  - Large Independent Retrospective Cohorts
- Multi-institution Prospective Clinical Trials
  - Retrospective analysis of biospecimens from Prospective Clinical Trials

Phase III
- Implementation, Change in Clinical Practice
- Prospective Clinical Trials
- Regulatory Approval
- Policy
Databases

• Clinical annotation is a cumbersome and costly process

• Few “user friendly” data analysis tools have been developed
Biomarker Driven Trials

• require Clinical Laboratory Improvement Amendments (CLIA) capability

• may need many additional sites of services

• demand availability of tissue or relevant biospecimens – cost and capacity?

• may require fewer patients
Technology is Advancing Quickly

- cost declining
- high throughput capability
- use of archival FFPE, small tissue samples
Solutions

• Promote central IRBs and improve cooperative group and institutional infrastructure to make clinical research more nimble
• Formalize and support infrastructure for biorepositories linked to outcomes databases in institutions and cooperative groups
• Alter promotion guidelines to reward “teamwork”
• Establish business models to sustain and support clinical science
• Develop community partnerships with Health Care Organizations
• Build global networks and teams to assure population diversity and relevance to regional / national regulatory agencies
A Collaboration of Stakeholders
Thank you!