Conference on Clinical Cancer Research

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Design of a Disease-Specific Master Protocol
Conference on Clinical Cancer Research

Design of a Disease-Specific Master Protocol

Roy Herbst, MD/PhD
Yale Cancer Center
Modernizing Clinical Trial Process

• Some of the current challenges of drug development
  – Difficulties in recruiting cancer patients to clinical trials
  – Extensive bureaucratic processes required to initiate any clinical trial
  – Lengthy regulatory review

• Modernizing trial process with innovative approaches and new clinical trial designs is of high importance.

• Use novel design strategies combined with biomarker testing
  – to increase trial efficiency
  – improve future phase III clinical trial designs
Phase II Adaptive Screening Trials

• **BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination)**
  - Heavily pretreated refractory non-small cell lung cancer (NSCLC)
  - Determined marker status of 11 biomarkers
  - Randomized patients to four different agents
  - Results were used to design two new BATTLE trials

• **I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2)**
  - Investigates neoadjuvant treatment of new drugs added to traditional chemotherapy in women with locally advanced breast cancer
  - Designed to test multiple novel drugs and biomarkers over five-year timeframe
  - May test up to five drugs simultaneously
  - Add new drugs as existing drugs complete testing
Moving to a Multi-arm Registration Trial

- We propose another alternative to traditional trial design
- Multi-arm, multi-marker/drug “master protocol” Phase III trial
  - Randomized, Controlled
  - No adaptive randomization
  - Multiple new therapies are tested simultaneously in a specific disease setting
  - Designed to allow FDA approval of new therapeutics
  - Assigns patients to experimental treatment vs standard-of-care control arm on the basis of specific biomarkers
Advantages of Master Protocol Multi-drug Registration Trial Design

• Grouping multiple studies reduces the overall screen failure rate
• Single master protocol will result in process and operational efficiency gains
  – Provides consistency
  – Trial infrastructure will be in place
  – Bring safe and effective drugs to patients faster
Master Protocol Multi-Drug Trial Design

Advanced NSCLC patients, multiple experimental drugs with matching predictive biomarker

Interim analysis, PFS (and OS) endpoints

- Meets pre-specified endpoint:
  - Continue experimental arm
  - OS endpoint

- Does not meet pre-specified endpoint:
  - Withdrawn from trial
# Lung Cancer Example

## Squamous Cell Carcinoma Mutation Incidence

<table>
<thead>
<tr>
<th>Gene</th>
<th>Event Type</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>FGFR1</td>
<td>Amplification</td>
<td>20-25%</td>
</tr>
<tr>
<td>FGFR2</td>
<td>Mutation</td>
<td>5%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Mutation</td>
<td>9%</td>
</tr>
<tr>
<td>PTEN</td>
<td>Mutation-Deletion</td>
<td>18%</td>
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<tr>
<td>CCND1</td>
<td>Amplification</td>
<td>8%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Deletion/Mutation</td>
<td>45%</td>
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<tr>
<td>PDGFRA</td>
<td>Amplification-Mutation</td>
<td>9%</td>
</tr>
<tr>
<td>EGFR</td>
<td>Amplification</td>
<td>10%</td>
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<tr>
<td>MCL1</td>
<td>Amplification</td>
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<tr>
<td>BRAF</td>
<td>Mutation</td>
<td>3%</td>
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<tr>
<td>DDR2</td>
<td>Mutation</td>
<td>4%</td>
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<tr>
<td>cMET</td>
<td>High copy-amplification</td>
<td>11%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Amplification</td>
<td>2%</td>
</tr>
</tbody>
</table>
Speakers

• Roy Herbst, MD/PhD, Yale Cancer Center
• David Wholley, M.Phil., FNIH
• Eric Rubin, MD, Merck
• Lisa LaVange, PhD, FDA
• Jeff Abrams, MD, NCI
• Karen Arscott, DO, Lung Cancer Alliance
• Shakuntala Malik, MD, OHOP, FDA

Acknowledgements
Fred Hirsch, Vali Papadimitrakopoulou, David Gandara, Jim Doroshow, Gary Kelloff, Sonia Pearson-White, Keavan Anderson, Sharon Murphy, Lisa McShane
Design of a Disease-Specific Master Protocol
Organizational infrastructure for multi-drug trials

David Wholley
FNIH
The I-SPY 2 trial tests multiple new breast cancer agents using biomarkers and an adaptive trial design.

**Stratifying Biomarkers:**

**Class I/II devices:**
- HER2 (IHC, FISH)
- MammaPrint
- ER, PR

**IDE:**
- MammaPrint44K
- Her2 (RPMA, 44K-microarray)
I-SPY 2 is being conducted as a large-scale public-private partnership managed through the FNIH Biomarkers Consortium

Principal Investigators: Laura Esserman (UCSF) and Don Berry (MD Anderson)

- NCI
- FDA
- ~20 academic cancer centers
- Multiple pharmaceutical companies
  - Contributing agents
  - Funding
- Platform companies
- Laboratories
- Non-profit organizations
- Advocates
- Managed by FNIH and Quantum Leap Healthcare Collaborative
An Independent Agent Selection Committee chooses novel agents based on stringent criteria

- The IASC consists of 5-6 cancer drug development experts without current industry affiliations
  - Phase I testing on candidate agents must be completed
  - Agents must be compatible with standard paclitaxel therapy (no unacceptable additive toxicity)
    - For HER2/neu-directed agents, compatible with paclitaxel plus trastuzumab therapy
  - Known efficacy or rationale for efficacy in breast cancer
  - Targets key pathways/molecules in breast cancer, but only one novel agent per target pathway will be accepted in the trial
  - Fits strategic model for optimizing combinations of single/multiple molecular targeting drugs with or without standard chemotherapy
  - Willingness of company to contribute agent and sufficient availability
I-SPY 2 Organizational Principles, Efficiencies

• FNIH holds a Master IND (developed with FDA and NCI) that incorporates testing of multiple agents
• FNIH negotiates and holds all contracts with sites, pharma companies, biomarker companies, and other entities
• FNIH and QuantumLeap provide centralized co-administration and project management for the trial
• A centralized IT infrastructure (based on caBIG) ensures broad, timely dissemination of data and results
• Formal Data Access and Publication Guidelines ensure transparency and balance company and public health benefit
  – Data and samples are made broadly available to the research community for follow-on research
• FNIH also serves as a trusted 3rd party to manage data and intellectual property coming out of the trial, to maximize the public health benefit
FNIH acts as a trusted third party to ensure fair and appropriate licensing of new inventions arising from I–SPY 2

1. Inventing Organizations grant exclusive licenses to new IP to FNIH

2. FNIH prosecutes and manages resulting patents

3. FNIH markets and licenses IP to interested parties

Medical Center A

Medical Center B

Laboratory C

Drug Co. A

Drug Co. B

Dx Co. C

FNIH returns a fair share of royalties (less expenses) to Inventing Organizations

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Design of a Disease-Specific Master Protocol

Eric H. Rubin, MD
Merck
Proposed Master Protocol Multi-drug Registration Trial Design

- **Disease Model:** Relapsed, refractory non-small cell lung cancer (NSCLC)
- **Sponsor:** A neutral third party
  - e.g., CRO, academic coordinating center
  - Able to establish appropriate firewall procedures
- **Objective:** To compare overall survival (OS) of biomarker-selected patients treated with standard of care (SoC) vs. experimental targeted therapy
- **Standard of Care:** Will be determined prior to trial initiation by the steering committee
Trial Design – Drugs and Biomarkers

• The steering committee will evaluate each application to determine whether a drug/biomarker pair can enter the trial

• **Drugs**
  – Ready to enter a phase III confirmatory trial
  – Each drug must have clinical data demonstrating activity in a responsive patient group
  – Patient group can be identified by assessment of biomarker in patient tumor biopsies
Trial Design – Biomarkers and Screening

• Each compound’s biomarker is based on analytically validated test/platform suitable for a pivotal trial

• This trial could use common screening platform that assays multiple biomarkers
  – If predictive biomarker is in a CLIA-approved platform, it could be considered adequate for patient selection and randomization
    • Would require Investigational Device Exemption (IDE) prior to trial start
    • If new drug shows clinical benefit in selected patient population the biomarker could be analyzed and given FDA clearance
Use of a Multi-marker Platform

• Advantages
  – Conserves tumor samples
  – Testing protocols easier to standardize
  – Sponsors would not be responsible for designing their own diagnostic

• Considerations
  – Have not yet been used in registration trial
  – The process *would require close communication with the FDA* to determine its applicability
Potential Study Design

• At entry, patients will receive a fresh core needle biopsy, with the tissue analyzed with appropriate assay (s)

• Experimental treatment A targets Marker A-positive tumors; Drug B targets Marker B-positive tumors
  – Patients whose tumors are positive for marker A will be randomized to SoC vs drug A
  – Patients whose tumors are positive for marker B will be randomized to SoC vs drug B

• Primary endpoint: Overall Survival (OS)
  – Possible Interim Analysis when 30% of the OS events have occurred
Scenario: Two markers with no marker overlap; one drug per marker.

Advanced NSCLC patients

Core needle biopsy

Stratify by biomarker expression

No marker overlap

Divide in 2 portions:
1) Clinical trial biomarker analysis
2) Save for future analysis

Drugs A1 B1

A+B-

Randomize 1:1

Drug A1 SoC

PFS; OS

A-B+

Randomize 1:1

Drug B1 SoC

PFS; OS

A-B-

SoC
Master Protocol over Time

- Additional drug/biomarker combinations dropped and added to study
Case Study Example

- *PIK3CA* copy number increases or mutations identified in ~ one-third of squamous cell carcinomas
  - Target with PI3K inhibitor, e.g. BYL719

- *DDR2* tyrosine kinase mutations identified in 4% of squamous cell carcinomas
  - Shown to confer sensitivity to dasatinib
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Design of a Disease-Specific Master Protocol

Lisa LaVange, PhD
FDA
Potential Leveraging of Control Subjects

• Leveraging control patients across multiple trials is possible if a neutral 3rd party is running the trial
  – A CRO/Coordinating Center must establish appropriate firewall procedures

• Active drugs would not be compared to each other
  – Approval would be based on meeting pre-specified efficacy and safety criteria compared to SoC

• Which control patients are unique or shared may not need to be disclosed for analysis purposes

• Benefits to sharing control patients
  – Reduced recruitment time
  – Reduced trial costs
Example of Leveraging of Control Subjects

- Marker A/Drug A2’s protocol approved to begin recruitment
  - Randomization of Marker A patients changes to 1:1:1 Drug A1: Drug A2: SoC
  - Use of common protocol with standard procedures, visit schedules, and CRFs allows control patients to contribute data to both trials
- A1 trial completes enrollment while A2 trial is still ongoing
  - Randomization allocation reverts to 1:1 for Drug A2: SoC
  - Shared controls that have completed follow-up in Drug A1 trial
    - Data is unmasked for analysis of the Drug A1 protocol
    - Data remains masked to Drug A2 trial personnel
      - If necessary, data collection on A2 patients continues under the Drug A2 protocol
Scenario: Two markers with no marker overlap; two drugs target marker A.

Advanced NSCLC patients

Core needle biopsy

Stratify by biomarker expression

No marker overlap

A+B-

Randomize 1:1

Drug A1 SoC

PFS; OS

A-B+

Randomize 1:1

Drug B1 SoC

PFS; OS

A-B-

SoC

Drugs
A1 B1

Divide in 2 portions:
1) Clinical trial biomarker analysis
2) Save for future analysis

A+

Randomize 1:1

Drug A2 SoC

PFS; OS

Drug A1 trial arm finishes accruing

A+

Randomize 1:1:1

Drug A1 SoC Drug A2

Drug A1 trial arm finishes accruing

PFS; OS

PFS; OS

+ Drug A2

Attempt to use up all drug: when drug A1 trial arm finishes accruing
Potential Leveraging of Control Subjects

• Leveraging control patients across multiple trials is possible if a neutral 3rd party is running the trial
  – A CRO/Coordinating Center must establish appropriate firewall procedures

• Active drugs would not be compared to each other
  – Approval would be based on meeting pre-specified efficacy and safety criteria compared to SoC

• It may not need to be disclosed for analysis purposes, which controls are unique or shared

• Benefits to sharing control patients
  – Reduced recruitment time
  – Reduced trial costs
Design of a Disease-Specific Master Protocol

Jeff Abrams, MD
NCI
Drug Biomarkers in Lung Adenocarcinoma

TKI-sensitizing EGFR mutations:

- **10%** in Western population
- Up to **50%** in Asian population

Enriched in:
- females
- non-smokers
- younger patients

Multiple tests in clinical use
No FDA-approved clinical assay

ALK Rearrangement

- **5-7%** in Western population
- FDA approved companion diagnostic:
  - Vysis Break Apart FISH probe
National Trial for Molecular Characterization of Early Stage Non-squamous NSCLC

Eligibility:
• Diagnosis of NSCLC (non-squamous)
• Clinical stage I, II, or III deemed resectable
• Pathologic stage I, II, or III that:
  • has been successfully resected
  • adequate tissue available
  • +/- local test for EGFR mutation or ALK rearrangement
• Patient Consent to allow
  • donation of de-identified cancer information for research
  • performance of central testing for adjuvant study referral
  • 5 year follow-up: treatment and outcome
  • contact regarding follow-up biopsy if cancer recurs
  • (optionally) re-contact if no recurrence at end of study
Tissue Flow

Consent & Register: A151216 Screening & Follow-up Protocol

Pre-op Cohort
- SOP-driven FF/FFPE
- After resection, buffy coat

CLIA-approved LAB
- EGFR mutation test (sequencing)
- ALK rearrangement (FISH)

TCGA
- Genomic sequencing
- Transcriptome
- Methylation

E4512: Erlotinib
A081105: Crizotinib

Post-op Cohort
- Assess FFPE
- buffy coat

Other Adjuvant Studies
Data Flow

Consent & Register

Pre-op Cohort

Post-op Cohort

Collect local test info

CLIA-approved Lab
Marker Analysis

EGFR activating mutation

ALK+

E4512

Screen Neg.

A081105

5 year follow-up cohort

TCGA Data

A151216 Registry

Sequencing Database

E4512 Trial Database

A081105 Trial Database
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Design of a Disease-Specific Master Protocol

Karen Arscott, DO
Lung Cancer Alliance
Design of a Disease-Specific Master Protocol

Shakuntala Malik, MD
FDA/CDER/OHOP
Master Protocol Concept


Objective: To bring together leading academicians, clinicians, industry and government representatives to identify challenges and potential solutions in the clinical development of novel targeted therapies for lung cancer

Outcomes: Suggestion to develop Master protocols (by Dr Pazdur) for different stages of Lung Cancer
FDA Perspective

Targeted drug development presents unique opportunities for “personalized medicine”

Master protocols will

- Provide consistency of development approach regardless of intended target
- Better utilize limited resources (including patient resources)
- Bring safe and effective drugs to patients faster

Discussions of trial design and endpoints with FDA to occur once protocol and statistical analysis plan are well developed/near-final
FDA Perspective

FDA Drug approval will, however, depend on

- Integrity of data collected
- Results of the trials
  - Drug effect isolated (clear attribution to drug)
  - Results not only statistically significant but also clinically meaningful
  - Toxicity of the drug.
- Available therapies at the time of approval

Risk: Benefit Ratio
FDA-approved Therapy with Specific Targets in NSCLC

- Erlotinib (EGFR tyrosine kinase inhibitor)
- Bevacizumab (VEGF-A inhibition)
- Crizotinib (ALK inhibitor)

Demonstration of specific molecular abnormalities in patient’s tumor not required in FDA-approved indication for erlotinib and bevacizumab but is required for crizotinib indication
FDA Perspective

Companion diagnostic assay/assay performance sufficient to reliably & reproducibly identify “marker-positive” population

Exploratory studies for “marker-negative” population will need to be conducted to:

- Differentiate between prognostic vs predictive markers
- Support device/test kit claims

CDRH should be involved at initial stages of assay development
New drugs/indications for lung cancer will continue to be approved by FDA based on a demonstrated effect on a surrogate endpoint that is reasonably likely to predict clinical benefit in a population where there is unmet clinical need.

Such approvals are likely to be based on relatively small trials; confirmatory trials will be required to confirm and characterize the actual clinical benefit.
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