2013 Conference on Clinical Cancer Research

Lung Cancer Master Protocol Activation Announcement
2013 Conference on Clinical Cancer Research

Jeff Allen, PhD
Friends of Cancer Research
Panelists

- Jeff Allen, PhD, Friends of Cancer Research
- Roy Herbst, MD, PhD, Yale Cancer Center
- David Gandara, MD, UC Davis Cancer Center
- Vali Papadimitrakopoulou, MD, MD Anderson Cancer Center
- Ann Ashby, MBA, Foundation for the NIH
- Vince Miller, MD, Foundation Medicine
- Jeff Abrams, MD, Clinical Investigations Branch, NCI
- Janet Woodcock, MD, CDER, FDA
- Mary Redman, PhD, Fred Hutchinson Cancer Center
Governance Structure: S1400 Master Lung-1 Project

Oversight Committee
NCI, FDA, ex-Industry, Advocates, PI's (ex-officio), FNIH [supported by FNIH]

Executive Operations Group
Roy Herbst, Vali Papadimitrakopoulou, co-chairs

Project Management Office
FNIH, SWOG, FOCR

Contracts, Fundraising, Data Sharing, IP
Partner Science Focus Group

Project Management
Drug and Biomarker Selection Committee
Assay Company RFP, selection

DSMB
Working Groups
IND management
Clinical Project Management
Sites 1, 2, 3...n
# Multi-Sector Oversight Committee

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Roy Herbst (co-chair)</td>
<td>Yale Cancer Center</td>
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<tr>
<td>Ellen Sigal (co-chair)</td>
<td>Friends of Cancer Research</td>
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<tr>
<td>Jeff Abrams</td>
<td>NCI</td>
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<tr>
<td>Jeff Allen</td>
<td>Friends of Cancer Research</td>
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<tr>
<td>David Chang</td>
<td>Amgen</td>
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<tr>
<td>Andrea Ferris</td>
<td>LUNGevity</td>
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<tr>
<td>David Gandara</td>
<td>UC Davis Cancer Center</td>
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<tr>
<td>Rich Gaynor</td>
<td>Eli Lilly</td>
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<tr>
<td>Fred Hirsch</td>
<td>University of Colorado Cancer Center</td>
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<tr>
<td>Pasi Janne</td>
<td>Dana Farber Cancer Institute</td>
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<tr>
<td>Vali Papadimitrakopoulou</td>
<td>MD Anderson Cancer Center</td>
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<td>Eric Rubin</td>
<td>Merck</td>
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<td>Regina Vidaver</td>
<td>National Lung Cancer Partnership</td>
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<tr>
<td>Jack Welch</td>
<td>NCI</td>
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<tr>
<td>Janet Woodcock</td>
<td>CDER, FDA</td>
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<tr>
<td>Steven Young</td>
<td>Addario Lung Cancer Medical Institute (ALCMI)</td>
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# Drug Selection Committee

## VOTING Members

<table>
<thead>
<tr>
<th>Member</th>
<th>Institution</th>
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</thead>
<tbody>
<tr>
<td>Roy Herbst (chair), Yale Cancer Center</td>
<td>Gary Kelloff, NCI</td>
</tr>
<tr>
<td>Kathy Albain, Loyola Medicine</td>
<td>Vali Papadimitrakopoulou, MD Anderson</td>
</tr>
<tr>
<td>Jeff Bradley, Washington University in St. Louis</td>
<td>Suresh Ramalingam, Emory Healthcare</td>
</tr>
<tr>
<td>Kapil Dhingra, KAPital Consulting</td>
<td>David Rimm, Yale Cancer Center</td>
</tr>
<tr>
<td>Gwen Fyfe, Consultant</td>
<td>Mark Socinski, UPMC Cancer Center</td>
</tr>
<tr>
<td>David Gandara, UC Davis Cancer Center</td>
<td>Naoko Takebe, NCI</td>
</tr>
<tr>
<td>Glenwood Goss, University of Ottawa</td>
<td>Everett Vokes, University of Chicago</td>
</tr>
<tr>
<td>Fred Hirsch, University of Colorado Cancer Center</td>
<td>Jack Welch, NCI</td>
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<tr>
<td>Peter Ho, QI Oncology</td>
<td>Ignacio Wistuba, MD Anderson</td>
</tr>
<tr>
<td>Pasi Janne, Dana Farber Cancer Institute</td>
<td>Jamie Zwiebel, NCI</td>
</tr>
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## Non-Voting Members

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Jeff Allen, Friends of Cancer Research</td>
<td>Mary Redman, Fred Hutchinson Cancer Center</td>
</tr>
<tr>
<td>Matt Hawryluk, Foundation Medicine</td>
<td>Ellen Sigal, Friends of Cancer Research</td>
</tr>
<tr>
<td>Shakun Malik, FDA</td>
<td>David Wholley, FNIH</td>
</tr>
<tr>
<td>Vince Miller, Foundation Medicine</td>
<td>Roman Yelensky, Foundation Medicine</td>
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</table>
Master Lung Protocol (S1400): Addressing unmet needs in NSCLC

David R. Gandara, MD
University of California Davis
Comprehensive Cancer Center
“Strategies for Integrating Biomarkers into Clinical Development of New Therapies for Lung Cancer”

A Joint NCI Thoracic Malignancies Steering Committee-FDA Workshop
Bethesda MD – February 2-3, 2012

• Trial Design Challenges in the Era of Biomarker-driven Trials
  • Innovative Statistical Designs
  • Challenges for Community Oncology Practice participation
  • The Patient Perspective
• Drug & Biomarker Co-Development in Lung Cancer
  • Failure of “All Comer” designs for drug development in NSCLC
  • Need for Early Co-Development of drugs & associated biomarkers
• Development of Future Lung Cancer Clinical Trials
  • TMSC Master Protocol Task Force in NSCLC
  • Biomarker-driven trial designs in both early stage adjuvant therapy & advanced stage NSCLC
  • Account for inter-patient tumor heterogeneity & genomic complexity of NSCLC
# Classic RCT Design (“All Comer”): Phase III Trials of Chemotherapy +/- Targeted Agent* in 1st-line Therapy of Advanced Stage NSCLC

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Survival Benefit</th>
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<tbody>
<tr>
<td>MMPs</td>
<td>Prinomastat, Others</td>
<td>No</td>
</tr>
<tr>
<td>EGFR TKI</td>
<td>Gefitinib or Erlotinib</td>
<td>No</td>
</tr>
<tr>
<td>Farnesyl Transferase (RAS)</td>
<td>Lonafarnib</td>
<td>No</td>
</tr>
<tr>
<td>PKCα</td>
<td>ISIS 3521</td>
<td>No</td>
</tr>
<tr>
<td>RXR</td>
<td>Bexarotene</td>
<td>No</td>
</tr>
<tr>
<td>VEGFR (TKI)</td>
<td>Sorafenib</td>
<td>No</td>
</tr>
<tr>
<td>VEGF (Mab)</td>
<td>Bevacizumab</td>
<td>Yes</td>
</tr>
<tr>
<td>EGFR (Mab)</td>
<td>Panitumumab</td>
<td>No</td>
</tr>
<tr>
<td>TLR9 Agonist</td>
<td>PF-351</td>
<td>No</td>
</tr>
<tr>
<td>EGFR (Mab)</td>
<td>Cetuximab</td>
<td>Yes**</td>
</tr>
<tr>
<td>IGFR-1</td>
<td>Figitumumab</td>
<td>No</td>
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<tr>
<td>VDA</td>
<td>ASA-404</td>
<td>No</td>
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</tbody>
</table>

*In combination with platinum-based chemotherapy versus chemotherapy

**EGFR IHC positive

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Need for a completely “New Way of Thinking” for development of Targeted Drug/Biomarker Combinations: “Master Protocol”
**Integrated New Drug-New Biomarker Development Paradigm:**

**Phases of Development of a New Drug**
- **Pre-clinical**: ~18 mo.
- **Phase I**: N=30, ~18 mo.
- **Phase II**: N=300, ~18 mo.
- **Phase III**: N=1600, ~36 mos
- **Drug Approval**: Total Time ~90 mos (7.5 years)

**Phase of Development of New Biomarker linked to New Drug**
- **Confirm Target**
- **Assay Development**
- **Integrate Biomarker**
- **Assay Performance**
- **Biomarker Informative?**
- **Assay Validation**
- **Clinical Validation**
- **Co-Primary Endpoint**
- **Clinical Application of Biomarker**

*from Gandara et al: Clin Lung Cancer, 2012*
Strategies for integrating Biomarkers into Clinical Trial Designs for NSCLC when viewed as a Multitude of Genomic Subsets

Evolution of NSCLC → Histologic Subsets → Genomic Subsets

Unmet needs addressed by Master Protocol:
- How to develop drugs for uncommon-rare genotypes?
- How to apply broad-based screening (NGS)?
- How to achieve acceptable turn-around times for molecular testing for therapy initiation? (<2 weeks)
- How to expedite the new drug-biomarker FDA approval process? (companion diagnostic)
Parallel Efforts in “Master Protocol” Design for NSCLC

NCI Thoracic Malignancy Steering Committee (TMSC) Task Force
- Early Stage NSCLC (ALCHEMIST)
- Advanced Stage NSCLC
  - Non-Squamous

Friends of Cancer Research (FOCR) Task Force
- Advanced Stage NSCLC
  - Squamous (SCCA):
    - SCCA represents an Unmet Need
    - All recent new targeted therapies have been in Adenoca (EGFR/ALK)
    - Many new molecular targets have been found in lung SCCA
    - Drugs for each of these targets
S1400 Master Protocol
Unique Private-Public Partnerships with the NCTN

- Alliance
- SWOG
- ECOG-Acin
- NCI-C
- NRG

S1400 Master Protocol

FNIH
Foundation for the National Institutes of Health

NCI
National Cancer Institute

FDA
Food and Drug Administration

Friends of Cancer Research

Department of Health & Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES • U.S.
Phase II/III Biomarker-Driven Master Protocol for Second Line Therapy of Squamous Cell Lung Cancer (SCCA)

Study Chair: Vali Papadimitrakopoulou, MD
UT/MDACC, Dept of Thoracic/Head & Neck Med Oncology

Cooperative Groups Co-chairs:
Alliance: Everett Vokes, MD
ECOG: Suresh Ramalingam, MD
NCI Co-Chair: Jack Welch, MD
NCIC: Glenwood Goss, MD
NRG: Jeff Bradley, MD
SWOG: David R. Gandara, MD

Steering Committee Co-Chair: Roy S. Herbst, MD, PhD
Statistical Co-chair: Mary W. Redman, Ph.D.
Molecular Pathology co-Chair: Ignacio Wistuba, MD
Correlative Science co-Chair: F Hirsch MD, PhD, P Mack PhD
Rationale for Master Protocol Designs

- NSCLC: multiple and often independent mutations and potential therapeutic targets.
- Lung SCCA “orphan” group - substantial developments in therapeutics have yet to be seen.
- Subgroup selection (genotype or phenotype-driven) refined strategy in a Multi-arm Master Protocol with improved operational efficiency: homogeneous patient populations & consistency in eligibility from arm to arm.

Phase II-III design: rapid drug/biomarker testing for detection of “large effects”

- Grouping multiple studies: reduces overall screen failure rate, multi-target screening by NGS platform: sufficient “hit rate” uninterrupted accrual.
- Bring safe and effective drugs to patients faster, ineffective drugs are replaced by new improved candidates.
- Designed to allow FDA approval of new therapeutics.
Significantly mutated genes in lung SQCC.

Assumptions, Major Elements and Objectives

• Each drug clinical data demonstrating biologic activity in a responsive patient group against a measurable target, using predictive biomarker assay that has been analytically validated and is suitable for a pivotal trial.

• Squamous cell carcinoma (SCCA), advanced stage, 2\textsuperscript{nd} line therapy

• Multi-arm randomized, controlled phase II/III registration protocol. Each arm opens/closes independent of other arms, independently powered for OS. Positive results at “rolling” interim analysis determine if a protocol arm proceeds to phase III portion.

• Primary Objectives:
  • **A) Phase II Component:** PFS targeted therapy (TT) vs SOC
  • **B) Phase III Component:** OS for TT vs SOC within each biomarker-defined subgroup.

• Secondary Objectives:
  – **A) Phase II:** Toxicities associated with TT versus SoC.
  – **B) Phase III:** a) PFS b) RR and c) toxicities associated with TT versus SoC.

• Exploratory Objectives: A) Additional predictive tumor/blood biomarkers, B) resistance biomarkers at progression C) tissue/blood repository from patients with refractory SCCA.
• **Organizers:** FOCR, NCI-TMSC, FDA, FNIH
• **Participants:** Entire North American Lung Intergroup (SWOG, Alliance, ECOG-Acrin, NRG, NCI-Canada)
• **Screening:** 500-1,000 patients/year
• **With 4-6 arms open simultaneously, “hit” rate ~70% in matching a patient with a drug/biomarker arm.
**MASTER PROTOCOL**

Biomarker A
- TT A
- CT*
- Endpoint (Interim PFS)
- OS

Biomarker B
- TT B
- CT*
- Endpoint (Interim PFS)
- OS

Biomarker C
- TT C+CT
- CT*
- Endpoint (Interim PFS)
- OS

Biomarker D
- TT D+E
- E*
- Endpoint (Interim PFS)
- OS

Non-match drug

Common Broad Platform CLIA Biomarker Profiling*

Non-match
- CT*

TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib
*Archival FFPE tumor, fresh CNB if needed
TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib
*Archival FFPE tumor, fresh CNB if needed
Statistics

- **Phase II component**
  - Primary outcome: PFS
  - median null PFS = 3 months
  - $HR_{pfs} = 0.5$ (two-fold increase), Power = 90%, 1-sided type I error = 10%
  - Analysis at 55 progression events
  - Threshold to continue to phase III: ~ 41% improvement in PFS
  - RR compared between arms to evaluate if evidence to stop study for early signs of efficacy

- **Phase III Design**
  - Primary outcome: OS
  - median null OS = 8 months
  - $HR_{os} = 0.67$ (50% increase), Power = 90%, 1-sided type I error = 2.5%
  - Interim analyses at 50% and 75% of expected 256 deaths

- **Sample size justification:** approximate patient pool in the US 35,800 -- approx 4% clinical trial participation rate → 625-1250 screened/yr → 500-1,000 enrolled/yr
# Phase II and III sample size and analysis times

<table>
<thead>
<tr>
<th>Marker Prevalence</th>
<th>Phase II Component</th>
<th>Phase III Design</th>
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<tbody>
<tr>
<td>@1,000 accrued/ year</td>
<td>@500 accrued/ year</td>
<td>N</td>
</tr>
<tr>
<td>2.5%</td>
<td>5%</td>
<td>68</td>
</tr>
<tr>
<td>5%</td>
<td>10%</td>
<td>80</td>
</tr>
<tr>
<td>7.5%</td>
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<tr>
<td>10%</td>
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<tr>
<td>12.5%</td>
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<td>104</td>
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<tr>
<td>15%</td>
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<td>110</td>
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<tr>
<td>17.5%</td>
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<tr>
<td>20%</td>
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<tr>
<td>22.5%</td>
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<td>124</td>
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<tr>
<td>25%</td>
<td>50%</td>
<td>136</td>
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<tr>
<td>27.5%</td>
<td>55%</td>
<td>136</td>
</tr>
<tr>
<td>30%</td>
<td>60%</td>
<td>150</td>
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LMP: First Patient In (FPI) -- Q1 2014

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<th>2013</th>
<th>2014</th>
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<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
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**Pre-Study Activities, Planning**
- Drug Selection
- Protocol Development
- Master IND application
- Assay Co. Selection
- Master IDE application
- Approvals
- Contracts

**Project Management**
**Study Drug Management**
**Clinical Operations Management**
**Data Management**
**Team Meetings, Teleconferences**
**Other Activities**

- **Project Starts January 2013**
- **Initial Meeting March 2013**
- **Trial Starts March 2014**
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