A Biomarker-Driven Protocol for Accelerating Therapeutic Development for Squamous Cell Lung Cancer

Enabling Precision Medicine Workshop
March 8, 2017

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Ensign Professor of Medicine
Professor of Pharmacology
Chief of Medical Oncology
Director, Thoracic Oncology Research Program
Associate Cancer Center Director for Translational Research
Lung Cancer Therapy in 1997

We Had Reached A Ceiling for Cytotoxic Chemotherapy
All New Therapies Were the Same!

- All randomized studies had similar results
- No clear efficacy benefit for non-platin combinations (or triplets)
- A paradigm shift was needed!!

The Very First Gefitinib Continuous Phase I Study (1998)

Baseline 1 Week Later

FDA Approved May 2003

Selective Oral Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor ZD1839 Is Generally Well-Tolerated and Has Activity in Non-Small-Cell Lung Cancer and Other Solid Tumors: Results of a Phase I Trial


Effect of Deletions and Mutations in the Epidermal Growth Factor Receptor Gene (EGFR) on Disease Development and Drug Targeting

Development of a Master Protocol for NSCLC

IOM Report 2010

- Emphasized critical need for a public clinical trials system
- Four goals for modernization with 12 recommendations
  1. Improve speed & efficiency of trial development & activation
  2. Incorporate innovative science and trial design
  3. Improve prioritization, support, and completion of trials
  4. Incentivize participation of patients and physicians

Concurrent Efforts

NCI Thoracic Malignancy Steering Committee
Chair: F. Hirsch

Friends of Cancer Research/ Brookings Institute Task Force
Chair: R. Herbst
Development of a Master Protocol for NSCLC

ISSUE BRIEF
Conference on Clinical Cancer Research
November 2012

Design of a Disease-Specific Master Protocol
Roy Herbst, Chief of Medical Oncology, Yale Cancer Center
Eric Rubin, Vice President, Clinical Research Oncology, Merck
Lisa LaVange, Director, Office of Biostatistics, CDER, FDA
Jeffrey Abrams, Associate Director, Cancer Therapy Evaluation Program, NCI
David Whelley, Director, The Biomarkers Consortium, FNIH
Karen Arscott, Patient Advocate, Lung Cancer Alliance
Shakuntala Malik, Medical Officer, FDA

Introduction
Despite several impressive therapeutic advances in recent years, cancer remains the second-leading cause of death in the United States, and effective new therapies are still desperately needed. Developing a

L-R: Mary Redman, Jeff Abrams, Vince Miller, Ann Ashby, Vali Papadimitrakopoulou, David Gandara, Janet Woodcock, Roy Herbst, Jeff Allen
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)
Umbrella
Test impact of different drugs on different mutations in a **single type of cancer**
• BATTLE
• I-SPY2
• SWOG Squamous Lung Master

Basket
Test the effect of a **drug(s)** on a single mutation(s) in a variety of cancer types
• Imatinib Basket
• BRAF+
• NCI MATCH
**Title:** A Biomarker-driven Master Protocol For Previously Treated Squamous Cell Lung Cancer (LUNG-MAP)

**Overall Study Goal:**
- Quickly identify and test new targeted treatments and immunotherapies for squamous cell lung cancer, and, if effective, move those drugs to FDA approval.
Why Squamous Cell Lung Cancer?

- Screening for potential therapeutic targets is rapidly becoming a standard part of treatment of NSCLC
- In 63% of lung squamous cell cancer (SCCA) we can now identify a possible therapeutic target
- Lung SCCA remains an “orphan” group where substantial developments in targeted therapeutics have yet to be seen.
- In 2015, two immunotherapy agents were approved by the FDA for the treatment of squamous lung cancer. Immunotherapy is a major component of the Lung-MAP trial.
- Research is still needed to identify who will respond to immunotherapies and if responses can be enhanced by combinations of immunotherapy + chemo or immunotherapy + targeted agents
Lessons Learned From Lung-MAP
Unique Public-Private Partnership

S1400 Master Protocol
Unique Private-Public Partnerships with the NCI

Genetic Alterations Identified

<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>
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<tr>
<td>FGFR2</td>
<td>Mutation</td>
<td>5%</td>
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<tr>
<td>PIK3CA</td>
<td>Mutation</td>
<td>9%</td>
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<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>
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<tr>
<td>CDKN2A</td>
<td>Deletion/Mutation</td>
<td>45%</td>
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<tr>
<td>CMET</td>
<td>Amplification/Mutation</td>
<td>40%</td>
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<tr>
<td>PDGFRA</td>
<td>Amplification/Mutation</td>
<td>9%</td>
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<tr>
<td>EGFR</td>
<td>Amplification</td>
<td>10%</td>
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<tr>
<td>MCL1</td>
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<tr>
<td>BRAF</td>
<td>Mutation</td>
<td>3%</td>
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<td>DDR2</td>
<td>Mutation</td>
<td>4%</td>
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<tr>
<td>ERBB2</td>
<td>Amplification</td>
<td>2%</td>
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</table>
Lessons Learned From Lung-MAP

It takes a village
Lung- MAP Partners and Collaborators
# Drug Selection Committee

## Voting Members

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

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<tr>
<td>Jeff Allen</td>
<td>Friends of Cancer Research</td>
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<tr>
<td>Ellen Sigal</td>
<td>Friends of Cancer Research</td>
</tr>
<tr>
<td>Shakun Malik</td>
<td>FDA</td>
</tr>
<tr>
<td>Caroline Sigman</td>
<td>CCSA/FNIH</td>
</tr>
<tr>
<td>Vince Miller</td>
<td>Foundation Medicine</td>
</tr>
<tr>
<td>James Sun</td>
<td>Foundation Medicine</td>
</tr>
<tr>
<td>Mary Redman</td>
<td>Fred Hutchinson Cancer Center</td>
</tr>
<tr>
<td>David Wholley</td>
<td>FNIH</td>
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Lessons Learned From Lung-MAP
Master Protocols are Feasible

- Multi-arm Master Protocol
  - Homogeneous patient populations & consistent eligibility from arm to arm
  - Each arm independent of the others
  - Infrastructure facilitates opening new arms faster
  - Phase II-III design allows rapid drug/biomarker testing for detection of “large effects”
- Screening large numbers of patients for multiple targets by a broad-based NGS platform reduces the screen failure rate
- Provides a sufficient “hit rate” to engage patients & physicians
- Bring safe & effective drugs to patients faster
- Designed to facilitate FDA approval of new drugs
Generic Lung-MAP Design

TRIAL POINTS OF INTEREST:
- Each of sub-study operates independently of the others
- Prescreening can be performed while the patient is still on 1st line therapy for Stage IV disease
- If fresh biopsy necessary, new biopsy is paid for by the trial
- Biomarker-driven sub-studies may progress to Phase III if study meets endpoint and Phase III is feasible, at which point the standard of care arm will be determined.
Lessons Learned From Lung-MAP
Need to Keep up with Evolving Treatment Landscape

Biomarker–Driven Sub-Studies

- **S1400B**
  - PI3K+
  - GDC-0032
- **S1400C**
  - CCGA+
  - Palbociclib
- **S1400D**
  - FGFR+
  - AZD4547
- **S1400G**
  - HRRD+
  - BMN 673
- **S1400K**
  - c-MET+
  - ABBV-399

Closed 3 sub-studies
Answered 3 questions

Non-match Sub-Studies

- **S1400I**
  - Checkpoint Naive
  - Nivolumab/Ipilimumab vs. Nivolumab
- **S1400F**
  - Checkpoint Refractory
  - MEDI4736/Tremelimumab

Two new sub-studies – **S1400G** (2/27/2017) and **S1400F** (expected Mar 31)
Additional Sub-studies – **S1400J** and **S1400K** expected within 6-9 month period

*CCGA = Cell Cycle Gene Alternation, HRRD = Homologous Recombinant Repair Deficiency,*
Proposed Lung-MAP Re-Design

- **Trial with registration-intent** (to include both adeno and squamous)
- Phase II/III (Investigational therapies that hit in Ph II will go on to randomized Ph III)
- All patients receive NGS
- Patients assigned to a Sub-study based on biomarker results or to non-match sub-study
- Assume most patients will be immunotherapy-refractory and non-match sub-studies will be designed accordingly

Currently, biomarkers are defined by NGS. Though approaches such as c-MET IHC or Immunotherapy biomarkers may be used
Lessons Learned From Lung-MAP
Broad Screening of Patients is Feasible

S1400 Screening Schema

Pre-screening Option
1. Pre-screening consent
2. Tumor collection
3. Biomarker profiling

Registration

Screening at Progression
1. Screening consent
2. Tumor collection
3. Biomarker profiling

Registration

Sub-Study Assignment and Biomarker Results

Progression

Approx. 16 days

Presence of biomarker

Biomarker driven Sub-Study

Absence of biomarker

Non-Match Sub-Study
Lessons Learned From Lung-MAP

Sites are interested in the study

**Trial Metrics: S1400**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Total sites open for S1400</td>
<td>747</td>
</tr>
<tr>
<td>Total pts registered to S1400</td>
<td>1141</td>
</tr>
<tr>
<td>Prescreened</td>
<td>406</td>
</tr>
<tr>
<td>Screened at PD</td>
<td>765</td>
</tr>
<tr>
<td>Total pts assigned to a sub-study</td>
<td>884</td>
</tr>
<tr>
<td>Patients registered to sub-study</td>
<td>434</td>
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</tbody>
</table>
Lessons Learned From Lung-MAP

Adequate Funding is Needed

• Sites receive **up to $5,869** ($1,079 screening/$4,790 registration) for each patient on trial

• Reimbursements of **$3,000** (CT-guided)/**$6,000** (bronchoscopy) for biopsies performed at screening and/or progression after initial response

• Sites will be reimbursed for additional research based procedures

• Additional reimbursement for research-based procedures and on-site visits (**$1,333**) outside the regular audit schedule
Lessons Learned From Lung-MAP
Accrual may need Enhancement

Help Sites Already Accruing:
• Phone Outreach
• Tracking Data
• Troubleshooting
• Materials
• Training
• Lung-MAP.org Website
• Medical Affairs Liaison
• Leadership Calls/Emails to PIs

Recruit New Participants
• Social Media Campaigns
• Webinars
• Press/Media
• Promotional Video
• Outreach to Lung Cancer Advocacy Groups
• Outreach to Lung Cancer Physicians

Provide Extra Support for High Accruing Sites:
• Accrual Planning
• Frequent Contact with Site Staff
• Personalized Materials
• Personalized Social Media
• Personalized Outreach to Patient Advocates
• Investigator Teleconferences

Our Advisors:
• Trial Oversight Committee
• Trial Leadership Team
• Site Coordinators Committee
• Public Affairs Committee

The Funnel
Screening/Prescreening
Protocol Revisions/New Sub-studies
Lessons Learned From Lung-MAP
Speed is of the essence

PATIENTS

What is the Lung-MAP trial?
Lung-MAP is a large clinical trial, or research study, testing several new treatments for patients who have advanced stage squamous cell lung cancer. In advanced stage patients, the cancer has usually spread to other organs in their body. The Lung-MAP trial is for advanced stage patients whose cancer has continued to grow, even after being treated with standard therapy.

If I want to join this trial, how do I find a participating center?
The study is opening at hundreds of sites across the...
Getting the word out

The most comprehensive squamous lung cancer clinical trial in the country.

Where is it?

700 locations in 39 states.

Who's involved?

4 collaborations in a public-private partnership.

How many treatment options?

7 leading pharma and precision diagnostics.

A cutting-edge approach in lung cancer care.

The Lung-MAP Clinical Trial: New hope. New opportunity.

Chemo isn’t the only approach. There is another option for patients battling advanced squamous cell lung cancer. Lung-MAP offers patients a new type of treatment called precision medicine, which is specifically made to target each patient’s cancer.

Learn more at lung-map.org

The Lung-MAP clinical trial is offered at more than 70 locations.

Learn more at lung-map.org

Learn more at lung-map.org

Yale Cancer Center
Smilow Cancer Hospital at Yale-New Haven
Lessons Learned From Lung-MAP
Need to Modernize Clinical Trials

- Public private partnership
- Leverages NCTN Network
- 500 Patients/year screened
- Biomarker selected trials
- >100 million of industry support
- FDA collaboration- seeks to get drugs approved and to patients!
- Genomic profiling delivered to the community
- A new paradigm for drug development and scientific discovery

21st Century Cures: Changing treatment and policy

Recommendations to the committee:

Biomarkers: Increase rate of per patient reimbursement to support and incentivize studies that evaluate biomarkers

Diagnostics: Develop a framework of policies to govern advanced diagnostics

Partnerships: Examine incentive structures and processes to help establish more multi-stakeholder partnerships to accelerate the clinical trials process

Resources: Sustained funding for NIH and FDA and a diminution of the constraints on education, travel and paperwork that complicate the process
Thank you!

Lung-MAP clinical trial
A groundbreaking collaborative approach that uses multidrug, targeted screening to match patients with studies of investigational new treatments.

HOW IT WORKS.

FOR PATIENTS
Patients are assigned to sub-studies using a comprehensive process that looks at over 200 cancer-related genes.

FOR HEALTHCARE PROVIDERS
Any institution within the National Cancer Institute’s National Clinical Trials Network (NCTN) may open the Lung-MAP study at their site.

www.lung-map.org