Re-thinking clinical trial design for NSCLC: The Lung Master Protocol

A Phase II/III Study for Second Line Therapy of Advanced Squamous Lung Carcinoma

Roy S. Herbst, MD, PhD
Ensign Professor of Medicine
Chief of Medical Oncology
Associate Cancer Center Director for Translational Research

November 10, 2014
Identification of Genomic Alterations for NSCLC

Lung Adenocarcinoma

No known genotype

EGFR
KRAS
BRAF
ALK
PIK3CA
HER2
MET
NTRK1
RET
ROS1

2009

2012

Lung squamous cell cancer

Mutations per Mb

Individuals with mutation

2014

nature

IOM Report

Emphasized critical need for a public clinical trials system

4 goals for modernization with 12 recommendations

- Improve speed & efficiency of trial development & activation
- Incorporate innovative science and trial design
- Improve prioritization, support, and completion of trials
- Incentivize participation of patients and physicians

NCI is implementing a comprehensive approach to transforming its clinical trials system to create a highly integrated network that can address rapid advances in cancer biology based on:

- Recommendations from the IOM Report
- Previous reports (Clinical Trials & Operational Efficiency)
- Current stakeholder input

LUNG-MAP
Natural History of Lung Cancer: Importance of Rebiopsy

Stages I-III
Surgically Resected

Advanced – Stage IV
Untreated

Advanced - Stage IV
Refractory to Chemotherapy

Tissues Available

Frequent
Infrequent
Rare

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
**BATTLE 1 Schema**  
*(Phase 2)*

**Umbrella Protocol**

**Core Biopsy**

**Biomarker Profile**

**Randomization:**

*Equal → Adaptive*

- **EGFR**
- **VEGF**
- **KRAS/BRAF**
- **RXR/CyclinD1**

---

**Primary end point:** 8 week Disease Control (DC)
Developing a New Model for Future Trials

Initial Concept to Modernize the Clinical Trial Process:

• To address the issue of modernizing the process with innovative approaches and new clinical trial designs

• Leaders from FDA, NIH, NCI, academic research centers, patient advocacy organizations and the private sector to reach consensus on the design of a biomarker-driven, multi-drug, multi-arm Phase 2/3 registration trial in lung cancer.

• White paper was published by these leaders as part of the 2012 Friends of Cancer Research – Brookings Institution, Conference on Clinical Cancer Research.

• This paper served as the foundation for the protocol that became LUNG-MAP.
Parallel Efforts in Master Protocol Design for NSCLC

TMSC Task Force
F. Hirsch, Chair

- Early Stage NSCLC (ALCHEMIST)
- Advanced Stage NSCLC
  - Squamous
  - Non-Squamous

Friends of Cancer Research (FOCR) Task Force
R. Herbst, Chair

- Advanced Stage NSCLC
  - Squamous
  - Non-Squamous
Platform Trials Landscape

ALCHEMIST: Ph III: Adjuvant non-sq NSCLC

LungMAP: Ph II/III: 2nd Line SCC Lung

MATCH: Ph II: Solid + Lymphoma

M-PACT: 700 pt pilot; refractory solid tumors

ASSIGN: Colon

2nd gen ALKi
ALK MP
S1400 Master Protocol Unique Private-Public Partnerships with the NCTN
Lung-MAP: Major Goals and Hypothesis

- Establish NCTN mechanism for genomic screening of large, homogeneous cancer populations.

- Assign and accrue simultaneously to a multi-sub-study “Master Protocol” comparing new targeted therapy to SoC based on designated therapeutic biomarker-drug combinations.

- Improved genomic screening for clinical trial entry, and improved time lines for drug-biomarker testing allowing for inclusion of the maximum numbers of otherwise eligible patients in comparison with currently employed “single screen-single trial” approaches.
Lung-MAP: Major Goals and Hypothesis

• **Ultimate goal** is to identify and quickly lead to approval safe and effective regimens (monotherapy or combinations) based on matched predictive biomarker-targeted drug pairs.
Interim Endpoint: PFS
Primary Endpoint: PFS/OS

Genomic Screening

Randomization

Assign treatment Arm by marker

Investigational Targeted Therapy

Tumor Collection

Patient Registration Consent

Treatment

Interim Endpoint: PFS Primary Endpoint: PFS/OS

NGS/IHC (Foundation Medicine)

Standard of Care Therapy
S1400: MASTER LUNG-1: Squamous Lung Cancer- 2\textsuperscript{nd} Line Therapy

**Biomarker Profiling (NGS/CLIA)**

**Non-Match Drug**

Multiple Phase II- III Arms with “rolling Opening & Closure

- **Biomarker A**
  - TT A
  - CT*
  - Endpoint PFS/OS

- **Biomarker B**
  - TT B
  - CT*
  - Endpoint PFS/OS

- **Biomarker C**
  - TT C
  - CT*
  - Endpoint PFS/OS

- **Biomarker D**
  - TT D+E
  - E*
  - Endpoint PFS/OS

**TT=Targeted therapy, CT=chemotherapy (docetaxel), E=erlotinib**

*PI: V. Papadimitrakopoulou (SWOG)*

*Steering Committee PI, Co-Chair: R. Herbst (YALE, SWOG)*

*Lung Committee Chair: D. Gandara*

*Translational Chair: F. Hirsch*

*Statistical Chair: M. Redman*
## Drug Selection Committee

### VOTING Members

<table>
<thead>
<tr>
<th>VOTING Members</th>
<th>Non-Voting Members</th>
</tr>
</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 Dhangra, KAPital Consulting</td>
<td>David Rimm, Yale Cancer Center</td>
</tr>
<tr>
<td>Gwen Fyfe, Consultant</td>
<td></td>
</tr>
<tr>
<td>David Gandara</td>
<td></td>
</tr>
<tr>
<td>Glenwood Goss</td>
<td></td>
</tr>
<tr>
<td>Fred Hirsch, University of Colorado</td>
<td></td>
</tr>
<tr>
<td>Peter Ho, QI Oncology</td>
<td></td>
</tr>
<tr>
<td>Pasi Janne, Dana Farber Cancer Institute</td>
<td>Jamie Zwiebel, NCI</td>
</tr>
</tbody>
</table>

### Discussed with > 20 Companies, multiple agents

### Non-Voting Members

<table>
<thead>
<tr>
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</tr>
</thead>
<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>
</tr>
</tbody>
</table>
Drug Selection Committee Nominations

A selection committee, which includes experts in Lung Cancer, has nominated several molecules for inclusion in the Lung-MAP master protocol initiative, these include:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD4547</td>
<td>AstraZeneca</td>
<td>Fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>GDC-0032</td>
<td>Genentech</td>
<td>PI3K pathway inhibitor</td>
</tr>
<tr>
<td>MEDI4736</td>
<td>MedImmune</td>
<td>Anti-PD-L1 monoclonal antibody</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>Pfizer</td>
<td>CDK 4/6 inhibitor</td>
</tr>
<tr>
<td>Rilotumumab</td>
<td>Amgen</td>
<td>Hepatocyte growth factor receptor/c-met inhibitor</td>
</tr>
</tbody>
</table>
Rationale-Science

Sub-study A

- MEDI4736 anti PD-L1 moAb.
- Prior evidence of activity of anti-PD1 and anti PD-L1 moAbs with a range of RR from 17% to 24% in unselected NSCLC cohorts.
- Promising preliminary clinical activity NSCLC, including SCCA.
- Safety profile favorable.
- Activity within PD-L1+ cohort a secondary objective.
**Rationale-Science**

**Sub-study B**
- GDC—0032 beta isoform-sparing PI3K inhibitor more potent against $PIK3CA^{\text{mut}}$ than wt *in vitro*, interacts with mutant p110a conformation.

- Promising preliminary clinical activity in $PIK3CA$ mutant cancers including SCCA.

- Safety profile c/w other PI3K inhibitors.
Sub-study C

- **PD-0332991** orally active, highly selective inhibitor of cdk4/6.
- *In vitro* activity in Rb+ cell lines and xenografts.
- Best monotherapy activity in unselected population: SD.
- Drug very active in combination with letrozole in ER+, HER2- breast cancer.
Rationale-Science

Sub-study D

- AZD4547 potent and selective inhibitor of FGFR1, 2 and 3.

- *In vitro* activity in FGFR amplified, mut+, gene translocation+ cell lines.

- Best monotherapy activity FGFR amplified SCCA: PR.

- Mucosal dryness, eye, phosphate metabolism.
**Rationale-Science**

**Sub-study E**

- AMG102 Ab against HGF/SF the only ligand of c-Met receptor

- EGFR and Met may cooperate in driving tumorigenesis.

- Met over expressed in up to 50% of NSCLC

- AMG102 in registration trial+CT in gastric cancer.
Squamous Lung Master Protocol Clinical Trial Assay Based On Foundation Medicine NGS Platform

1) DNA extraction
2) Library construction: selected cancer genes
   - Based on FM T5 NGS platform
   - Implemented as “mask” of T5 content and classification rules on called alterations
   - Rules determine biomarker positive/negative status
3) Analysis pipeline
   - Illumina HiSeq 2500
4) Master protocol CTA

Classification rules
- Based on FM T5 NGS platform
- Implemented as “mask” of T5 content and classification rules on called alterations
- Rules determine biomarker positive/negative status

Non-NGS biomarkers:
- Supplementary assays
  - MET IHC (+)
  - MET pathway inhibitor
- Non-match arm
  - All assays (-)
  - Anti-PD-L1 Ab

Classification rules (preliminary)
- PIK3CA mutation
- CCND1 amplification or CDKN2A/B deletion, and RB1 wild-type
- FGFR1/2/3/4 amplification, mutation or fusion
- PI3K inhibitor
- CDK4/6 inhibitor
- FGFR inhibitor
Tissue Flow / Reporting Flow

Tissue Acquisition at Site
Evaluation by Local Pathologist

Ship using Specimen Tracking System (STS)

Foundation Medicine Receives Specimen

FMI NGS

CLARIENT c-Met IHC (daily)

SWOG Statistical Center

Site Notified of Sub-study Assignment with Biomarker reports

Tissue Flow

Assays are run in parallel
Molecular Results (Evolving Ethical Issues)

- **Initially Proposed study:**
  - Pre-screening component
  - Return of molecular results to patients after progression on study treatment

- **NCI Central IRB review of Lung-MAP:**
  - Stipulated that full results of the molecular analysis should be presented to patients prior to enrollment
  - The public is being increasingly aware of the availability of genetic testing and the implications inherent in their family histories related to inherited cancer risk
  - The patient may have privacy/confidentiality concerns regarding the sensitivity of this information

- **Revised study:**
  - Pre-screening removed
  - Results provided to patients and treating physicians prior to enrollment
  - Consulted with leading ethicists on how best to distribute molecular information
  - Document created to assist physicians in communicating to patients that the genetic testing done as part of enrollment in the study is not standard of care for patients
Study Design Within Each Biomarker-defined Subgroup

- **Phase II Analysis**
  - 55 PFS events

- **Phase III Interim Analyses**
  - OS for efficacy
  - PFS/OS for futility

- **Complete Accrual**
  - 256 OS events
  - 290 PFS events

- **Final Analysis**

- **Futility established**

- **Stop**

12 months follow-up

Courtesy of: Mary Redman
### Statistical Design: Phase II Interim Analysis

<table>
<thead>
<tr>
<th></th>
<th>Plan A</th>
<th>Plan B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>PFS</td>
<td></td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>55 progression events</td>
<td></td>
</tr>
<tr>
<td><strong>Target HR (% improvement)</strong></td>
<td>HR = 0.5 2-fold increase</td>
<td>HR=0.4 2.5-fold increase</td>
</tr>
<tr>
<td><strong>Power</strong></td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Type I error</strong></td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Approx. Threshold to continue:</strong></td>
<td>HR= 0.71 41% increase</td>
<td>HR = 0.61 63% increase</td>
</tr>
</tbody>
</table>

Each sub-study can choose between Plan A or Plan B to determine “bar” for continuation past Phase 2 interim analysis.
## Statistical Design: Phase III

### Events

<table>
<thead>
<tr>
<th></th>
<th>PFS and OS Co-primary</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>PFS</td>
</tr>
<tr>
<td>Events</td>
<td>290</td>
</tr>
</tbody>
</table>

### Null Hypothesis (HR)

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null Hypothesis (HR)</td>
<td>0.75* (33% improvement)</td>
<td>1.0 (equivalence)</td>
</tr>
</tbody>
</table>

### Alternative Hypothesis

<table>
<thead>
<tr>
<th></th>
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<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative Hypothesis</td>
<td>0.5 (2-fold increase)</td>
<td>0.67 (50% improvement)</td>
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</tbody>
</table>

### Type I error (1-sided)

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I error (1-sided)</td>
<td>0.014 against HR = 1.33 &lt; 0.00001 against HR = 1</td>
<td>0.025</td>
</tr>
</tbody>
</table>

### Power

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power</td>
<td>90%</td>
<td>90%</td>
</tr>
</tbody>
</table>

*Non HR = 1 null hypothesis encodes clinical significance

Sample size based on OS for all studies

LUNG-MAP
## Sample Size for the Sub-studies

<table>
<thead>
<tr>
<th>Sub-study ID</th>
<th>Prevalence Estimate</th>
<th>Approximate Sample Size</th>
<th>Approximate time of analysis</th>
<th>Sample Size</th>
<th>Approximate time of analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1400A</td>
<td>56.0%</td>
<td>170</td>
<td>8</td>
<td>380</td>
<td>21</td>
</tr>
<tr>
<td>S1400B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GNE-positive</td>
<td>5.6%</td>
<td>78</td>
<td></td>
<td>288</td>
<td></td>
</tr>
<tr>
<td>FMI-positive</td>
<td>8.0%</td>
<td>152</td>
<td>19</td>
<td>400</td>
<td>72</td>
</tr>
<tr>
<td>S1400C</td>
<td>11.7%</td>
<td>124</td>
<td>11</td>
<td>312</td>
<td>45</td>
</tr>
<tr>
<td>S1400D</td>
<td>9.0%</td>
<td>112</td>
<td>11</td>
<td>302</td>
<td>53</td>
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<tr>
<td>S1400E</td>
<td>16.0%</td>
<td>144</td>
<td>9</td>
<td>326</td>
<td>37</td>
</tr>
</tbody>
</table>
## Biomarker prevalence and overlap estimates (based on 108 sqNSCLC)

<table>
<thead>
<tr>
<th></th>
<th>AZ/FGFR</th>
<th>Pfizer/CDK</th>
<th>Genentech/PIK3CA</th>
<th>Amgen/Met*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZ/FGFR</td>
<td>10.2%</td>
<td>2.8%</td>
<td>0.9%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Pfizer/CDK</td>
<td></td>
<td>13.9%</td>
<td>1.9%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Genentech/PIK3CA</td>
<td></td>
<td></td>
<td>9.3%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Amgen/Met</td>
<td></td>
<td></td>
<td></td>
<td>20%</td>
</tr>
</tbody>
</table>

*Assumption of 20% prevalence for Met and random overlap between Met and other biomarkers
TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

◊ Archival FFPE tumor, fresh CNB if needed
Lung MAP Will be Run Throughout the US AND Canada (500+ sites)
Where are we now?

• Study Activated June 16, 2014
• As of October 27, 2014
• IRB Approvals:
  – 353 sites
  – 35 sites with at least 1 patient accrual
• Nearly 100 patients enrolled
• Continuing to Evaluate new drugs and combinations (modular)
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
Tumors contain high levels of c-Met protein.

Tumor DNA has FGFR gene amplification, mutation or fusion.

Tumor DNA has PIK3CA gene mutation.

Tumor DNA has CCND1, D2, CDK4 gene mutation.

Patients with squamous cell lung cancer.

Tumor sample analyzed.

Lung-MAP Trial Arms for Treatment

Patients with squamous cell lung cancer

Tumor DNA has FGFR gene amplification, mutation or fusion

Tumor DNA has PIK3CA gene mutation

Tumor DNA has CCND1, D2, CDK4 gene mutation

Tumor has none of the changes listed here

50% Chemo-therapy

50% MEDI 4736

50% Chemo-therapy

50% GDC-0032

50% Chemo-therapy

50% Palbociclib

50% Chemo-therapy

50% AZD 4547

50% Erlotinib

50% Erlotinib

50% Rilotumab amab+ Erlotinib

50% Chemo-therapy

50% MEDI 4736

50% Chemo-therapy

50% GDC-0032

50% Chemo-therapy

50% Palbociclib

50% Chemo-therapy

50% AZD 4547

50% Erlotinib

50% Erlotinib

50% Rilotumab amab+ Erlotinib

http://lung-map.org/
Real Change, Real Benefits

- **Enrollment Efficiency:** Grouping these studies under a single trial reduces the overall failure rate for patient biomarker screening.

- **Operational Efficiency:** Single master protocol can be amended as needed as drugs enter and exit the study.

- **Consistency:** Every drug entered into the trial will be tested in the identical manner.

- **Predictability:** If pre-specified efficacy and safety criteria are met, the drug and accompanying companion diagnostic will be approved.

- **Patient Benefit:** Brings safe and effective drugs to patients sooner than they might otherwise be available.
Thank you

- Hossein Borghaei, D.O. ECOG-ACRIN, Fox Chase Cancer Center (Sub-study A).
- Jeffrey A. Engelman, MD, Ph.D., ALLIANCE, Massachusetts General Hospital Cancer Center (Sub-study B).
- Corey J. Langer, M.D. NRG, University of Pennsylvania, Hematology Oncology Division, Abramson Cancer Center (Sub-study B).
- Martin J. Edelman, M.D. NRG,The University of New Mexico (Sub-study C)
- Kathy S. Albain, M.D.SWOG,Loyola University Medical Center (Sub-study C )
- Charu Aggarwal, M.D., M.P.H. ECOG-ACRIN , Abramson Cancer Center (Sub-study D)
- Primo N. Lara, Jr., M.D. SWOG,UC Davis Comprehensive Cancer Center (Sub-study D)
- Mark A. Socinski, M.D., ALLIANCE, Pittsburgh School of Medicine (Sub-study E.)
- David R. Spigel, M.D., SWOG, Sarah Cannon Research Institute Sub-study E)