Personalized Medicine for Advanced Non-Small Cell Lung Cancer: From the Battle Trial to Master Protocols

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

September 29, 2014
Lung Cancer Therapy 2000
We Reached A Ceiling for Cytotoxic Chemotherapy

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

Schiller, 2002
Goals of This Presentation

- NSCLC: The Clinical Problem
- Present Innovative Trial Designs for Drug Discovery
  - BATTLE 1
  - BATTLE 2
- Rebiopsy Protocols/Precision Medicine Tumor Boards
- The Future: The Lung Cancer Master Protocol
Gefitinib Antitumor Activity: Initial Phase I Study (2002)

- Response Rate = 10%
- One third of NSCLC patients treated with ZD1839 had SD for ≥3 months
- More responses seen in Asian patients and never smokers
Effect of Deletions and Mutations in the Epidermal Growth Factor Receptor Gene (EGFR) on Disease Development and Drug Targeting

- 1997: First oral EGFR TKI drugs entered the clinic (gefitinib and erlotinib)
- Responses seen in never smokers, Asian patients
- 2004: EGFR gene mutations identified
- 2014: All patients with NSCLC have their tumors profiled for EGFR mutation

Herbst, Heymach, Lippman NEJM 2008
Evolution of Identification of Genomic Alterations in Lung Adenocarcinoma

What about the other 80% or those who become resistant?
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Natural History of Lung Cancer: Importance of Rebiopsy

- **Stages I-III**
  - Surgically Resected
  - Tissues Available: Frequent

- **Advanced – Stage IV Untreated**
  - Bone
  - Brain
  - Liver
  - Adrenal
  - Tissues Available: Infrequent

- **Advanced - Stage IV Refractory to Chemotherapy**
  - Bone
  - Brain
  - Liver
  - Adrenal
  - Tissues Available: Rare

The BATTLE PROGRAMS

Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination

• Platform for integrated translational research
  – Clinical trial program
  – Novel trial design
  – Biomarker discovery

• Scientific Hypotheses
  – Real time biopsies are possible to more accurately reflect aberrant signaling pathways of lung cancer
  – Matching targeted agents with abnormal pathways will improve disease control in lung cancer patients
  – 8-week disease control is an acceptable surrogate for efficacy (OS) in patients with pretreated lung cancer

Kim, Herbst, Wistuba, Lee et al, Cancer Discovery 2011
Primary end point: 8 week Disease Control (DC)

- Erlotinib
- Vandetanib
- Erlotinib + Bexarotene
- Sorafenib

Randomization:

Equal $\rightarrow$ Adaptive

Umbrella Protocol

Core Biopsy

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

Biomarker Profile
BATTLE Eligibility Criteria

• 2\textsuperscript{nd} + Line non-small cell lung cancer
  • Heavily treated population
• Adequate performance status
  • ECOG PS 0-2
• Biopsy-amenable disease
  • Required 2 fresh core biopsies
• Stable brain metastases allowed
**Individual Biomarkers for Response and Resistance to Targeted Treatment: Exploratory Analysis**

<table>
<thead>
<tr>
<th>Drug Treatment</th>
<th>Biomarker</th>
<th>P-value</th>
<th>DC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td><em>EGFR</em> mutation</td>
<td>0.04</td>
<td>Improved</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>High VEGFR-2 expression</td>
<td>0.05</td>
<td>Improved</td>
</tr>
<tr>
<td>Erlotinib + Bexarotene</td>
<td>High Cyclin D1 expression</td>
<td>0.001</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td><em>EGFR</em> FISH Amp</td>
<td>0.006</td>
<td>Improved</td>
</tr>
<tr>
<td>Sorafenib</td>
<td><em>EGFR</em> mutation</td>
<td>0.012</td>
<td>Worse</td>
</tr>
<tr>
<td></td>
<td><em>EGFR</em> high polysomy</td>
<td>0.048</td>
<td>Worse</td>
</tr>
</tbody>
</table>
BATTLE-2 Study Rationale

- BATTLE-1 – adaptively randomized to treatments based on pre-specified biomarkers and outcome data.

- BATTLE-2 - Novelty
  - MK-2206 (AKT i) + erlo-, MK-2206+ AZD6244 (MEK i)
  - Two-Stage Design: Identify predictive markers in Stage 1 and further validate in Stage 2.

- More emphasis and focus on KRAS targeting.

- Find predictive markers and therapies for NSCLC subsets with gene driver mutations beyond the currently approved targeted therapies and those with resistance to targeted therapy and chemotherapy.

- Discover targets.
KRAS and NSCLC: Significant Unmet need!

Vasen, Boyer, Herbst CCR 2014
Pathways targeted

- EGFR TKI (erlotinib)
- AKTi (MK-2206)
- MEKi (AZD6244)
- RAF-VEGFRi (sorafenib)
EML4-ALK Fusion or EGFR Mut exclusion

Stage 1: (n=200)
Adaptive Randomization by KRAS mut status

Stage 2: (n=200)
Refined Adaptive Randomization “Best” discovery markers/signatures

Primary endpoint: 8-week disease control (N = 400)

**Discovery Markers:**

- **Protein expression (IHC):** p-AKT (Ser473), PTEN, HIF-1α, LKB1
- **Mutation analysis (Sequenom):** PI3KCA, BRAF, AKT1, HRAS, NRAS, MAP2K1 (MEK1), MET, CTNNB1, STK11 (LKB1)
- **mRNA pathways activation signatures:** Affymetrix®
  - BATTLE-1: WT-EGFR- Erlotinib, EMT, and Sorafenib
  - BATTLE-2: new “discovery” signatures
- **Protein profiling – RPPA** (n=174)
- **NGS - Foundation Medicine**
- **RNA sequencing**
10/11/2011
Treatment: Arm 3 MK-2206+AZD6244
KRAS mut in codon 12 (GGT to TGT) Gly to Cys (G12C).

12/21/2011
Battle-2 Preparation And Activation Steps

- **Initial clinical trial concept development by PI+ team March-April 2009**
- **Preparation PO1 application**
- **IRB protocol +PO1 submission May-June 2009**
- **IRB approval July 2009**
- **Protocol revisions: Remove IGF1R+ add sorafenib**
- **PO1 resubmit IRB approval July 2010**
- **FDA IND application Dec 2010**
- **FDA Safe to proceed Jan 2011**
- **Sponsor site visit**
- **Drug shipping**
- **Protocol activation + 1st patient on June 2 2011**

- **Phase I dose finding + POC studies by sponsor Q3-4 2009**
- **BATTLE-1 results April 2010**
- **RPTD combination arms Q2 2011**

**Timeline:**
- July 2009: Initial clinical trial Concept development by PI+ team March-April 2009
- July 2009: Preparation PO1 application
- May-June 2009: IRB protocol +PO1 submission
- July 2009: IRB approval
- July 2010: Protocol revisions: Remove IGF1R+ add sorafenib
- July 2010: PO1 resubmit IRB approval
- July 2010: FDA IND application
- July 2010: FDA Safe to proceed Jan 2011
- June 2011: Protocol activation + 1st patient on June 2 2011

**Contract and Agreements:**
- AZ
- Merck
- OSI /Astellas
- Bayer/Onyx
- MDACC

**Budgeting and IP /contract negotiations:**
- Initiated
- Merck /OSI contract negotiations
- Bayer contract negotiations
- AZ contract negotiations
- Merck/OSI contract execution Dec 2010
- Bayer contract execution April-May 2011

**Monthly biomarker conference**
- Biweekly clinical conference
BATTLE-2 Team
Collaboration Among Multiple Departments/Divisions/Institutions/Industry/NCI

Bioinformatics and Computational Biology
- Wang Jing
- Coombes, Kevin R
- L.Diao, P. Tong, L. Shen

Biostatistics
- Lee, J. Jack
- Jeff Lewis, C. Wei

Cancer Medicine
- Hong, Waun Ki

Hamon Center for Therapeutic Oncology Research
- Minna, John J
- Girard, Luc

Pathology
- Kahlor, Neda
- Moran, Cesar

Molecular Diagnostics
- Luthra, Rajyalakshmi

Thoracic/Head and Neck Medical Oncology
- Papadimitrakopolou, V PI
- Thoracic Section faculty (Tsao, A co-PI)
- Research Nursing: White Ashley, Anderson Martha
- Alden, Christine; Gil, James; Casey, Denise
- Regulatory: Thierry Alisha, Bristow Suzanne, Price Mellanie, Ferguson, Jennifer

Interventional Radiology
- Gupta, Sanjay

Diagnostic Radiology
- Erasmus, Jeremy

Tissue Biomarkers
- Wistuba, Ignacio (Dept Molecular Pathology)
- Izzo, Julie
- C.McDowell, N. Hanson

Serum Biomarkers
- Tran, Hai, Heymach, John

Signature Development
- Byers, Lauren
- Skoulidis, Ferdinandos

Thoracic and Cardiovascular Surgery (preclinical data)
- Dai, Bingbing, Fang, Bingliang
- Roth, Jack

IND office
- Hatten Chiq, Tsai Stella
- Buzdar, Aman

NCI RO1
Yale
- Herbst R, Boyer J, Emily Duffield, Peter Koo.

Sanford-Burnham
- Powis Garth

Merck
- Rubin E, Mauro D, Yan L

Bayer

Foundation Medicine: V. Miller, S. Subramanian, G.Frampton

NCI
BATTLE-2 Schema

 ¡BATTLE - Coming Soon!

EML4-ALK Fusion or EGFR Mut exclusion

BATTLE-2 Schema

Primary endpoint: 8-week disease control (N = 400)

Sorafenib E+MK-2206 (AKTi)
MK-2206+ AZD6244 (MEKi)

Stage 2: (n=200)
Refined Adaptive Randomization
"Best" discovery markers/signatures

Erlotinib

Statistical modeling and biomarker selection

Discovery Markers:
• Protein expression (IHC): p-AKT, PTEN, HIF-1α, LKB1
• Mutation analysis (Sequenom): PI3KCA, BRAF, AKT1, HRAS, NRAS, MAP2K1 (MEK1), MET, CTNNB1, STK11 (LKB1)
• mRNA pathways activation signatures: Affymetrix®
W T EGFR - Erlotinib, EMT, and Sorafenib - BATTLE-2: new "discovery" signatures
• Protein profiling – RPPA (n=174)
• NGS - Foundation Medicine
• RNA sequencing

iBATTLE – Coming Soon!
Goals of This Presentation

- NSCLC: The Clinical Problem
- Present Innovative Trial Designs for Drug Discovery
  - BATTLE 1
  - BATTLE 2
- Rebiopsy Protocols/Exceptional responders/Precision Medicine Tumor Boards
- The Future: The Lung Cancer Master Protocol
Acquired Resistance to EGFR TKIs

- Secondary mutations in the drug target
- Activation of bypass signaling pathways
- Mutations in downstream pathways
- Phenotypic changes in the tumor

Adapted from Ohashi et al. J.Clin.Onc. 2013
Yale Lung Rebiopsy Program

Yale Thoracic Oncologist

Anna Wurtz

Study Coordinator

Consent

Coordinates Procedure

- Thoracic surgeon, IP, IR
- Cytopathology (Dr. Guoping Cai)
- Molecular Pathology (Dr. Zenta Walther)

Formalin, Flash frozen, RNA later

To the Politi lab

Cell culture, PDXs

Blood

Patient
<table>
<thead>
<tr>
<th>Treatment</th>
<th>All (n=75*)</th>
<th>EGFR (n=54)</th>
<th>ALK (n=13)</th>
<th>Other (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>34 (46%)</td>
<td>34 (62%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>3 (4%)</td>
<td>3 (6%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Erlotinib + Hydroxychloroquine</td>
<td>7 (9%)</td>
<td>7 (13%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Afatinib + Cetuximab</td>
<td>7 (9%)</td>
<td>7 (13%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>10 (13%)</td>
<td>0 (0%)</td>
<td>10 (77%)</td>
<td>0 (0%)</td>
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<tr>
<td>AP26113</td>
<td>4 (5%)</td>
<td>2 (4%)</td>
<td>2 (15%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>LDK378</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anti-PD1</td>
<td>5 (7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Regorafinib</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Bevacizumab (+ Chemo)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

*7 Subject sampled serially (at initial development of acquired resistance and again at acquired resistance to subsequent therapy). Range: 2-3 collections.
Goals of This Presentation

- NSCLC: The Clinical Problem
- Present Innovative Trial Designs for Drug Discovery
  - BATTLE 1
  - BATTLE 2
- Rebiopsy Protocols/Precision Medicine Tumor Boards
- The Present/Future: The Lung Cancer Master Protocol
LUNG-MAP

S1400 Lung Master Protocol
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
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
NCI and Friends Collaboration 2012

F. Hirsch
S. Malik
C.D. Ulman
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
Detailed genomic analysis of SQUAMOUS cell lung cancers has identified several new potential therapeutic targets

<table>
<thead>
<tr>
<th>Gene</th>
<th>Event Type</th>
<th>Frequency</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>CCND1</td>
<td>Amplification</td>
<td>8%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Deletion/Mutation</td>
<td>45%</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>Amplification/Mutation</td>
<td>9%</td>
</tr>
<tr>
<td>EGFR</td>
<td>Amplification</td>
<td>10%</td>
</tr>
<tr>
<td>MCL1</td>
<td>Amplification</td>
<td>10%</td>
</tr>
<tr>
<td>BRAF</td>
<td>Mutation</td>
<td>3%</td>
</tr>
<tr>
<td>DDR2</td>
<td>Mutation</td>
<td>4%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Amplification</td>
<td>2%</td>
</tr>
</tbody>
</table>

In 63% of lung SCCs we can now identify a possible therapeutic target

Targets need to be validated in pre-clinical models

FGFR1/2, PIK3CA and DDR2 inhibitor trials are planned or ongoing

Peter Hammerman et al. WCLC 2011
Lung-MAP: Major Goals and Hypothesis

• Establish mechanism (within NCTN) 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.
Patient Registration Consent

Tumor Collection

Genomic Screening

Assign treatment Arm by marker
Randomization

Investigational Targeted Therapy

Treatment
Interim Endpoint: PFS
Primary Endpoint: PFS/OS

NGS/IHC (Foundation Medicine)

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

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

Biomarker Profiling (NGS/CLIA)

Biomarker A

Biomarker B

Biomarker C

Biomarker D

Non-Match Drug

Non-Match Drug

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

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

PI: V. Papadimitrakopoulou (SWOG)
Steering Committee 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><strong>Roy Herbst (chair), Yale Cancer Center</strong></td>
<td><strong>Jeff Allen, Friends of Cancer Research</strong></td>
</tr>
<tr>
<td><strong>Kathy Albain, Loyola Medicine</strong></td>
<td><strong>Mary Redman, Fred Hutchinson Cancer Center</strong></td>
</tr>
<tr>
<td><strong>Jeff Bradley, Washington University in St. Louis</strong></td>
<td><strong>Matt Hawryluk, Foundation Medicine</strong></td>
</tr>
<tr>
<td><strong>Kapil Dhingra, KAPital Consulting</strong></td>
<td><strong>Shakun Malik, FDA</strong></td>
</tr>
<tr>
<td><strong>Gwen Fyfe, Consultant</strong></td>
<td><strong>Vince Miller, Foundation Medicine</strong></td>
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<tr>
<td><strong>David Gandara, UC Davis Cancer Center</strong></td>
<td><strong>Roman Yelensky, Foundation Medicine</strong></td>
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<tr>
<td><strong>Glenwood Goss, University of Ottawa</strong></td>
<td><strong>Non-Voting Members</strong></td>
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<tr>
<td><strong>Fred Hirsch, University of Colorado Cancer Center</strong></td>
<td><strong>Jeff Allen, Friends of Cancer Research</strong></td>
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<tr>
<td><strong>Peter Ho, QI Oncology</strong></td>
<td><strong>Matt Hawryluk, Foundation Medicine</strong></td>
</tr>
<tr>
<td><strong>Pasi Janne, Dana Farber Cancer Institute</strong></td>
<td><strong>Shakun Malik, FDA</strong></td>
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</table>

## Non-Voting Members

<table>
<thead>
<tr>
<th>Non-Voting Members</th>
<th>Non-Voting Members</th>
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</thead>
<tbody>
<tr>
<td><strong>Gary Kelloff, NCI</strong></td>
<td><strong>Mary Redman, Fred Hutchinson Cancer Center</strong></td>
</tr>
<tr>
<td><strong>Vali Papadimitrakopoulou, MD Anderson</strong></td>
<td><strong>Matt Hawryluk, Foundation Medicine</strong></td>
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<tr>
<td><strong>Suresh Ramalingam, Emory Healthcare</strong></td>
<td><strong>Shakun Malik, FDA</strong></td>
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<tr>
<td><strong>David Rimm, Yale Cancer Center</strong></td>
<td><strong>Vince Miller, Foundation Medicine</strong></td>
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<tr>
<td><strong>Mark Socinski, UPMC Cancer Center</strong></td>
<td><strong>Roman Yelensky, Foundation Medicine</strong></td>
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<tr>
<td><strong>Naoko Takebe, NCI</strong></td>
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<tr>
<td><strong>Everett Vokes, University of Chicago</strong></td>
<td></td>
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<tr>
<td><strong>Jack Welch, NCI</strong></td>
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<tr>
<td><strong>Ignacio Wistuba, MD Anderson</strong></td>
<td></td>
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<tr>
<td><strong>Jamie Zwiebel, NCI</strong></td>
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</table>
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>
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
   - 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
4) Master protocol CTA

Classification rules (preliminary)

- PIK3CA mutation
- CCND1 amplification or CDKN2A/B deletion, and RB1 wild-type
- FGFR1/2/3/4 amplification, mutation or fusion

Non-NGS biomarkers:

- MET IHC (+)
- MET pathway inhibitor
- Anti-PD-L1 Ab
- Non-match arm
- All assays (-)
- PI3K inhibitor
- CDK4/6 inhibitor
- FGFR inhibitor
TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib
◊ Archival FFPE tumor, fresh CNB if needed
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
# 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>
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<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>
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<tr>
<td>FMI-positive</td>
<td>8.0%</td>
<td>152</td>
<td>19</td>
<td>400</td>
<td>72</td>
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<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>
</tr>
<tr>
<td>S1400E</td>
<td>16.0%</td>
<td>144</td>
<td>9</td>
<td>326</td>
<td>37</td>
</tr>
</tbody>
</table>

- **S1400A**: Lung-MAP Substudy A: Non-Match, MEDI4736 vs. Chemo
- **S1400B**: Lung-MAP Substudy B: PI3K – GDC-0032 vs. Chemo
- **S1400C**: Lung-MAP Substudy C: CDK4/6 - Palbociclib vs. Chemo
- **S1400D**: Lung-MAP Sub-Study D: FGFR - AZD4547 vs. Chemotherapy
- **S1400E**: Lung-MAP Sub-Study E: HGF - Rilotumumab plus Erlotinib vs. Erlotinib
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
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

- **Friends of Cancer Research**

- **FDA**

- **NCTN, CTSU, CTEP, oversight**

- **FNIH**
  - Contracts, Fundraising, Data Sharing, IP
  - Partner Science Focus Group
  - Project Management
    - Drug and Biomarker Selection Committee
    - Assay Company RFP, selection

- **Southwest Oncology Group**
  - DSMB
  - Working Groups
  - IND management
  - Clinical Project Management
  - Sites 1, 2, 3…n
Lung MAP Will be Run Throughout the US- 500+ sites
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.
OK! So Now Are We Ready to Select Drugs for Patients in an even more Personalized Way?

Hello- here is my tumor sequence