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

Enabling Precision Medicine Workshop
March 8, 2017

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Professor of Pharmacology
Chief of Medical Oncology
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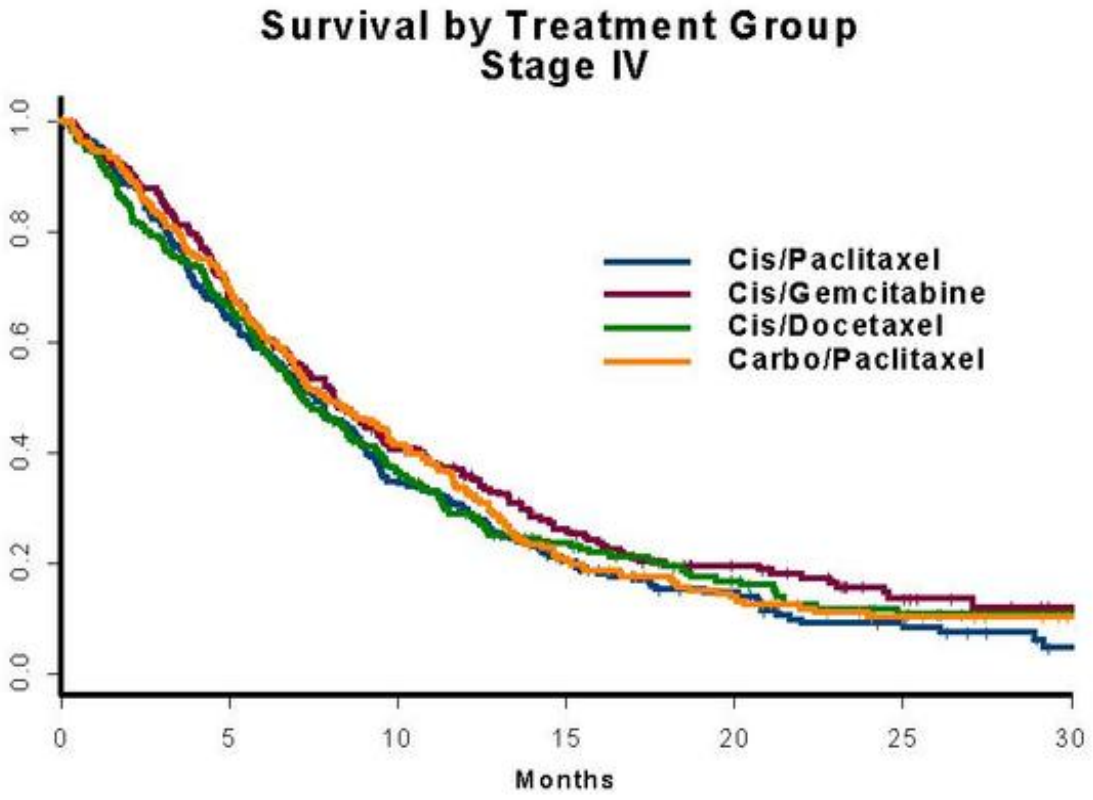
Lung Cancer Therapy in 1997

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

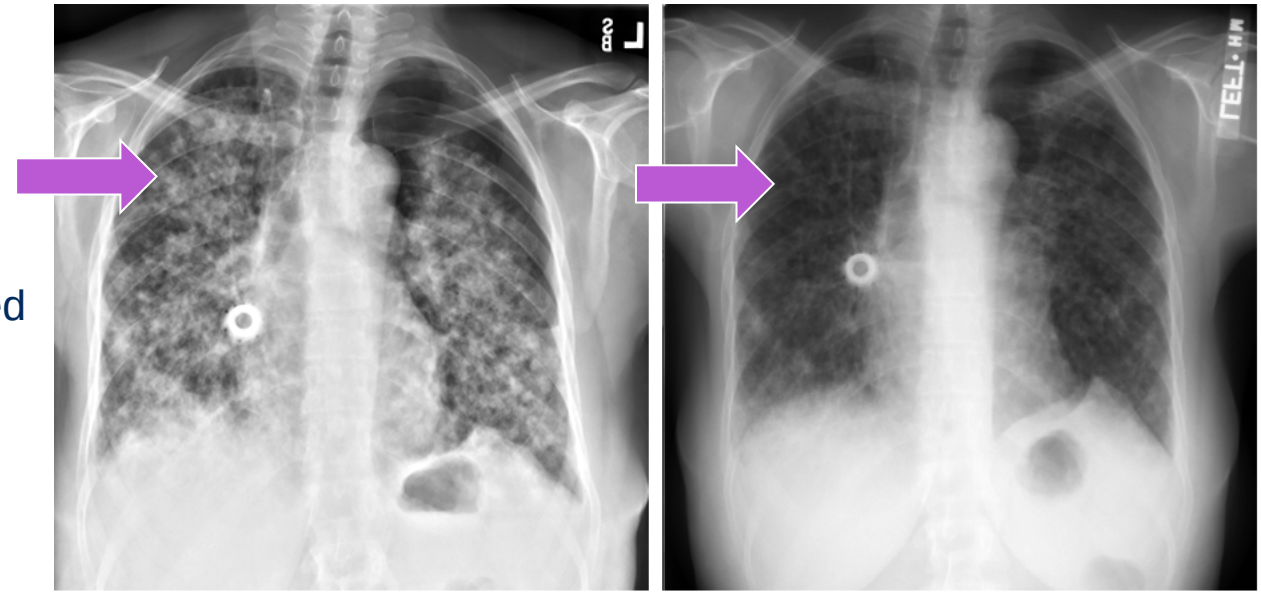


- All randomized studies had similar results
- No clear efficacy benefit for non-platin combinations (or triplets)
- **A paradigm shift was needed!!**

Schiller JH et al. *N Engl J Med* . 2002;346(2):92-8.

The Very First Gefitinib Continuous Phase I Study (1998)

FDA Approved
May 2003



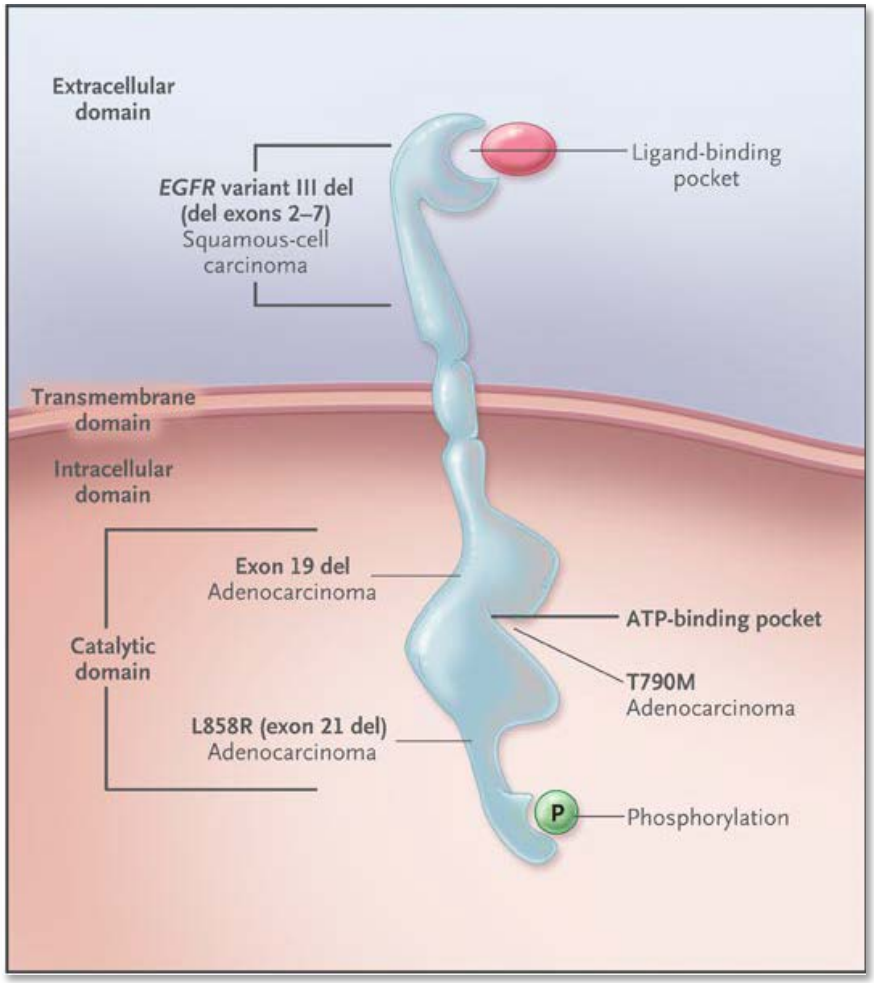
Baseline 1 Week Later

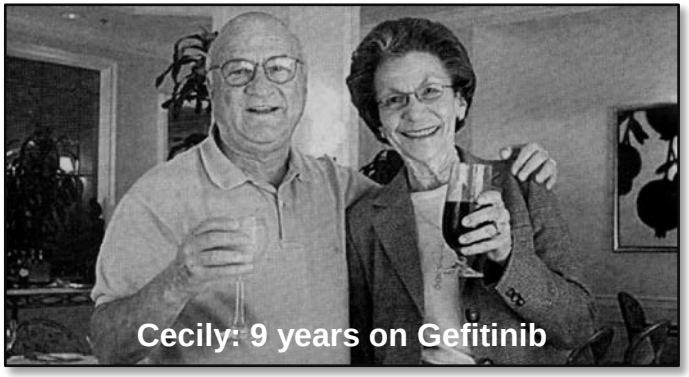
Selective Oral Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor ZD1839 Is Generally Well-Tolerated and Has Activity in Non–Small-Cell Lung Cancer and Other Solid Tumors: Results of a Phase I Trial

By Roy S. Herbst, Anne-Marie Maddox, Mace L. Rothenberg, Eric J. Small, Eric H. Rubin, Jose Baselga, Federico Rojo, Waun Ki Hong, Helen Swaisland, Steven D. Averbuch, Judith Ochs, and Patricia Mucci LoRusso

Herbst RS et al. *J Clin Oncol*. 2002;20(18):3815-3825.

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





A SPECIAL REPORT PERSONAL HEALTH

PERSONAL JOURNAL.

THE WALL STREET JOURNAL.

Why *Curing* Your Cancer May Not Be the Best Idea

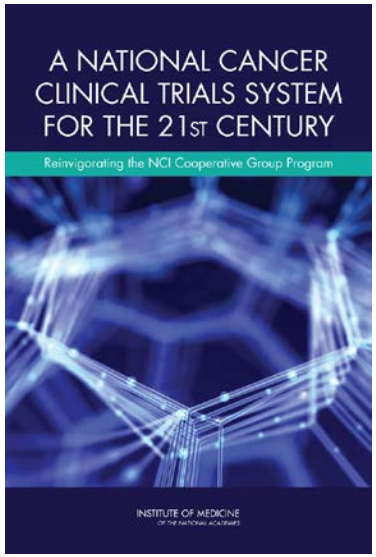
More doctors and patients are starting to view cancer as a chronic illness—something to be treated, not cured

By Tara Parker-Pope

Tara Parker-Pope Wall Street Journal 2003

Paez JG et al. *Science.* 2004;304(5676):1497-500.
Lynch TJ et al. *N Engl J Med.* 2004;350:2129-39.
Herbst RS et al. *N Engl J Med*. 2008;359:1367-80.

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

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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 Wholley, Director, The Biomarkers Consortium, FNIH
Karen Arscott, Patient Advocate, Lung Cancer Alliance
Shakuntala Malik, Medical Officer, FDA

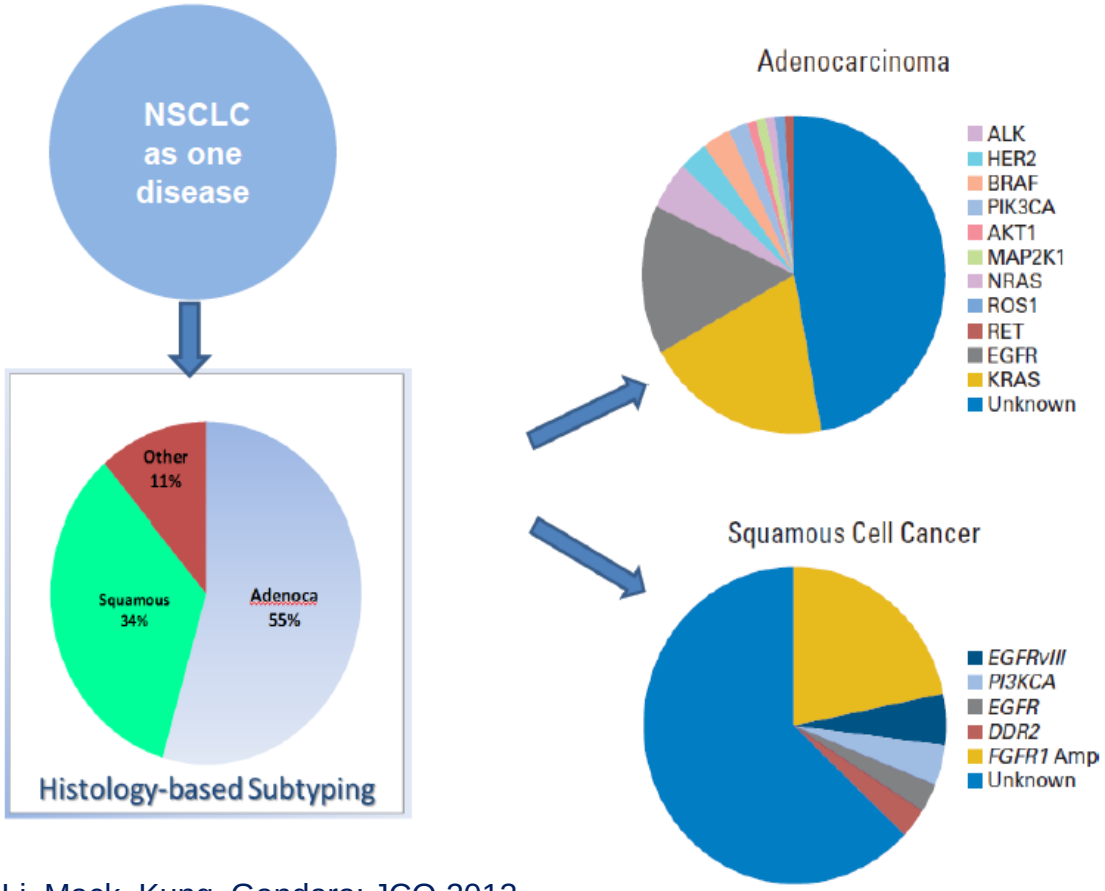
Introduction

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)

Li, Mack, Kung, Gandara: JCO 2013

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

LUNG-MAP S1400

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.

Lessons Learned From Lung-MAP
Choosing the right patient population

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

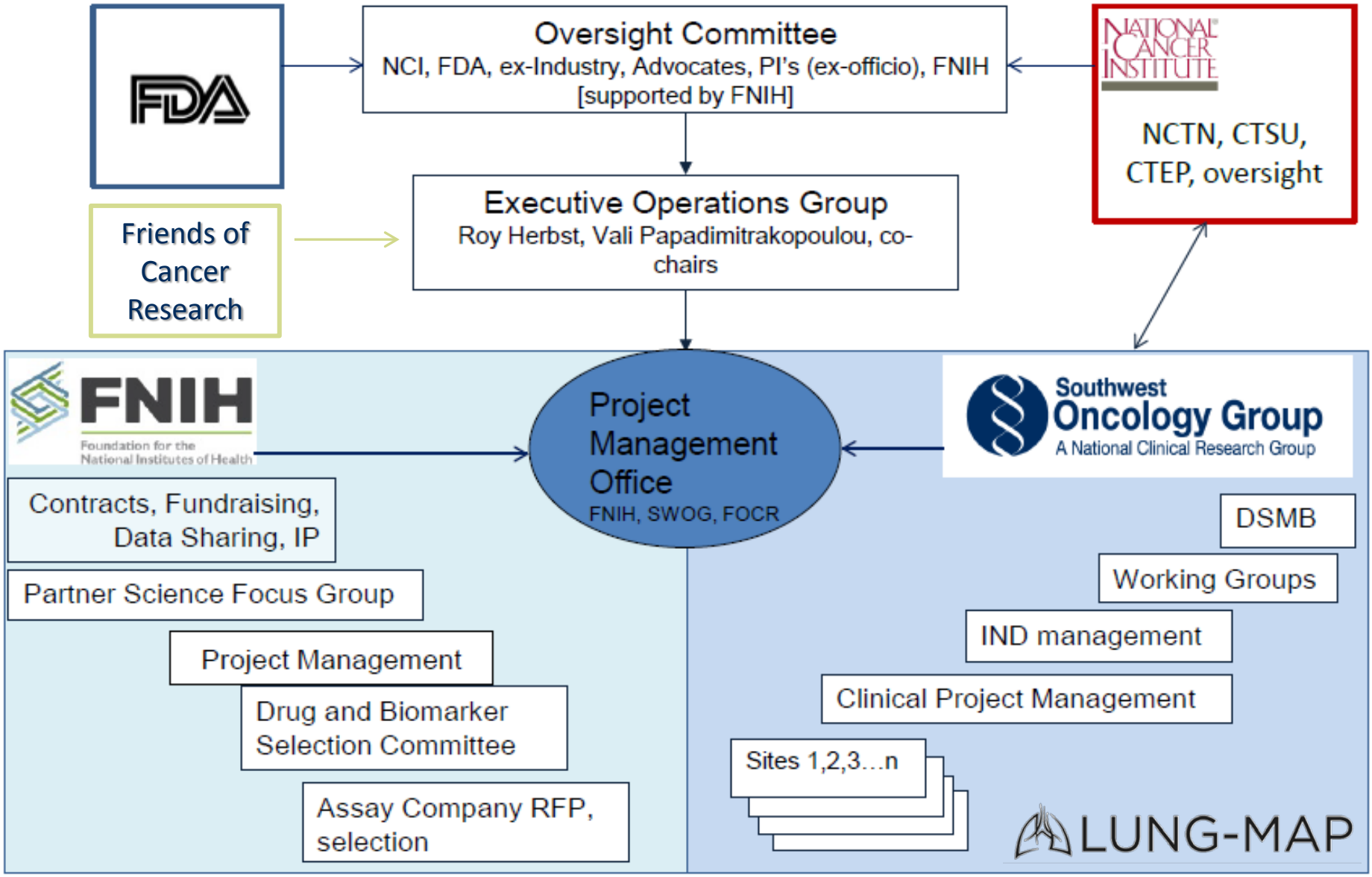
S1400 Master Protocol
Unique Private-Public Partnerships with the NCI

Genetic Alterations Identified

Gene	Event Type	Frequency
FGFR1	Amplification	20-25%
FGFR2	Mutation	5%
PIK3CA	Mutation	9%
PTEN	Mutation/Deletion	18%
CCND1	Amplification	8%
CDKN2A	Deletion/Mutation	45%
CMET	Amplification/Mutation	40%
PDGFRA	Amplification/Mutation	9%
EGFR	Amplification	10%
MCL1	Amplification	10%
BRAF	Mutation	3%
DDR2	Mutation	4%
ERBB2	Amplification	2%

Lessons Learned From Lung-MAP

It takes a village



Lung- MAP Partners and Collaborators

Drug Selection Committee

LUNG-MAP Voting Members

Roy Herbst (Chair), Yale Cancer Center	**Pasi Janne**, Dana Farber Cancer Institute
Kathy Albain, Loyola Medicine	**Gary Kelloff,** NCI
Jeff Bradley, Washington University in St. Louis	**Vali Papadimitrakopoulou,** MD Anderson
Helen Chen, NCI	**Suresh Ramalingam**, Emory Healthcare
Kapil Dhingra, KAPital Consulting	**David Rimm,** Yale Cancer Center
Gwen Fyfe, Consultant	**Mark Socinski,** UPMC Cancer Center
David Gandara, UC Davis Cancer Center	**Naoko Takebe,** NCI
Glenwood Goss, University of Ottawa	**Everett Vokes**, University of Chicago
Fred Hirsch, University of Colorado Cancer Center	**Ignacio Wistuba**, MD Anderson
Peter Ho, QI Oncology	**Jamie Zwiebel,** NCI

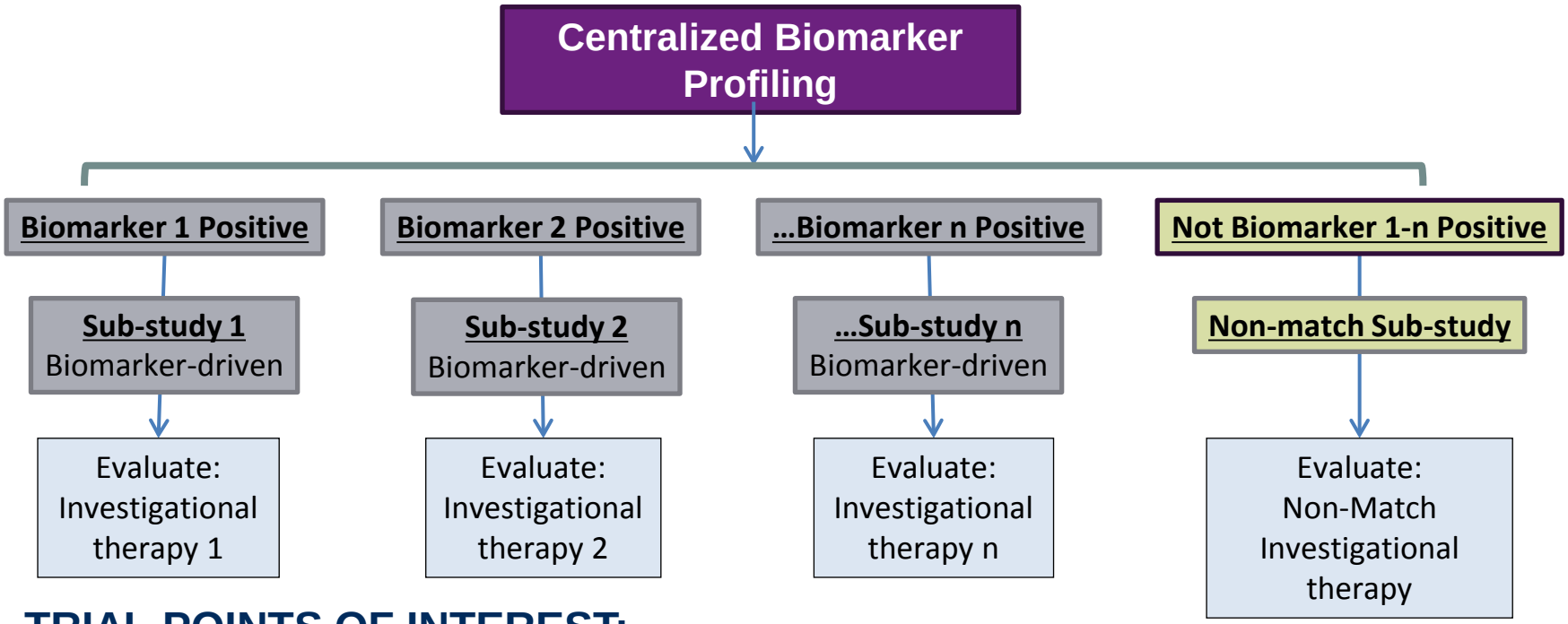
Non-Voting Members

Jeff Allen, Friends of Cancer Research	**Ellen Sigal,** Friends of Cancer Research
Shakun Malik, FDA	**Caroline Sigman**, CCSA/FNIH
Vince Miller, Foundation Medicine	**James Sun,** Foundation Medicine
Mary Redman, Fred Hutchinson Cancer Center	**David Wholley,** FNIH

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

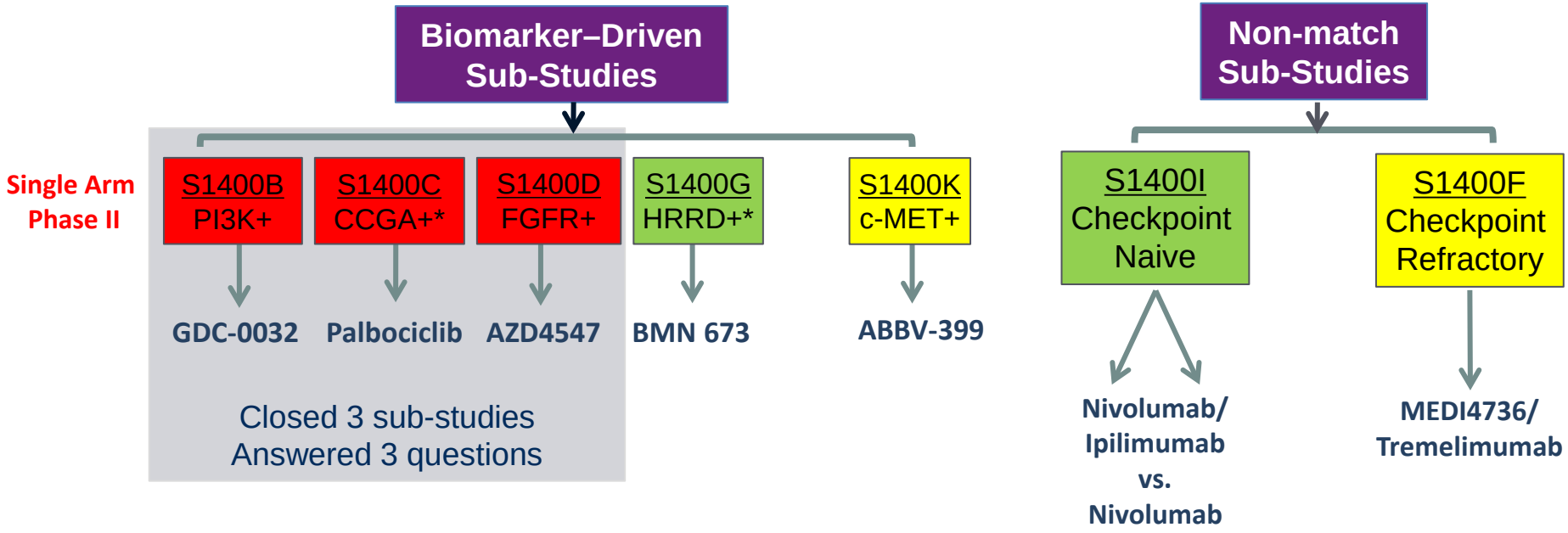


TRIAL POINTS OF INTEREST:

- 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

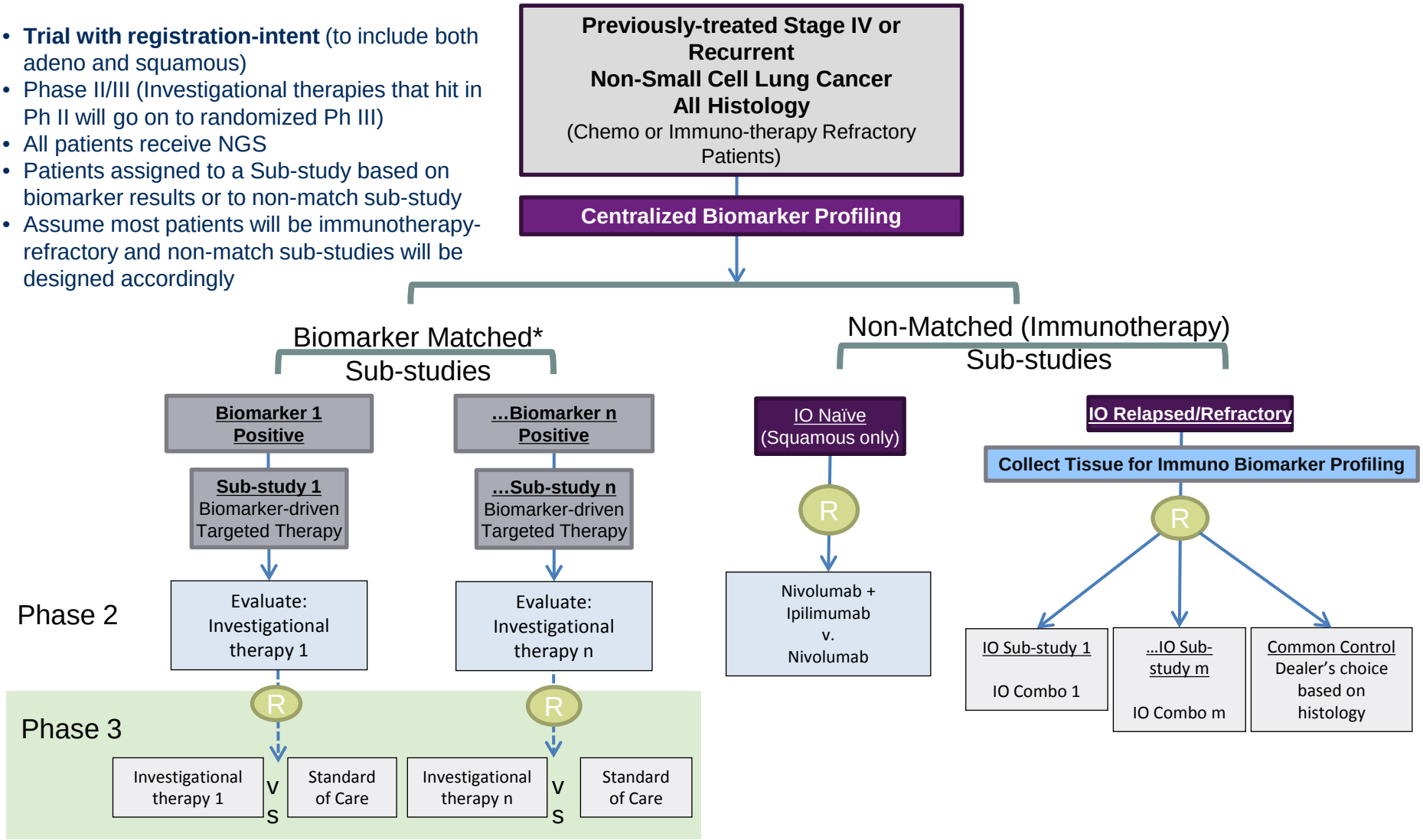


Two new sub-studies – S1400G (2/27/2017) and S1400F (expected Mar 31)
Additional Sub-studies – S1400J and S1400K expected within 6-9 month period

*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

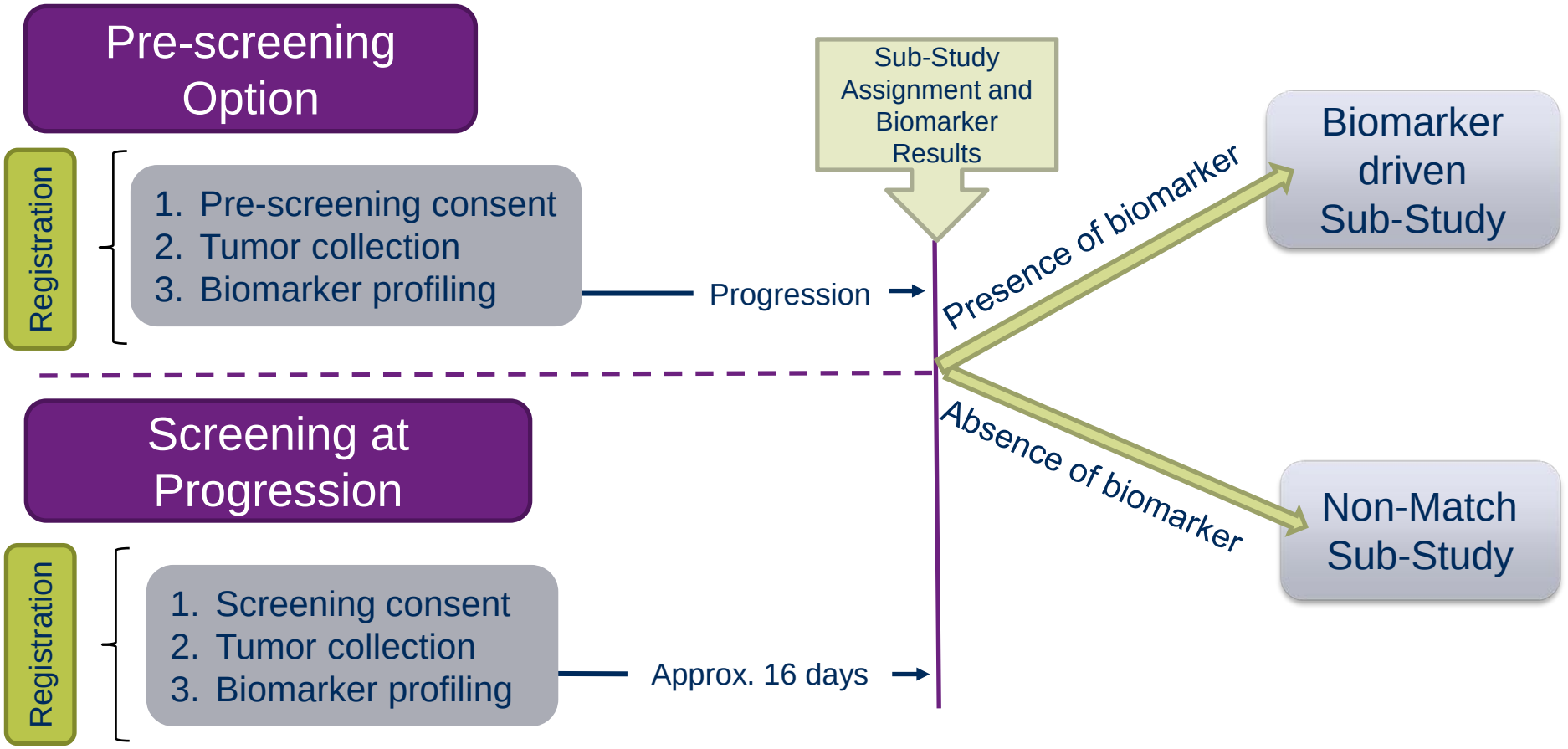


Currently, biomarkers are defined by NGS. Though approaches such as c-MET IHC or Immunotherapy biomarkers may be used

Lessons Learned From Lung-MAP

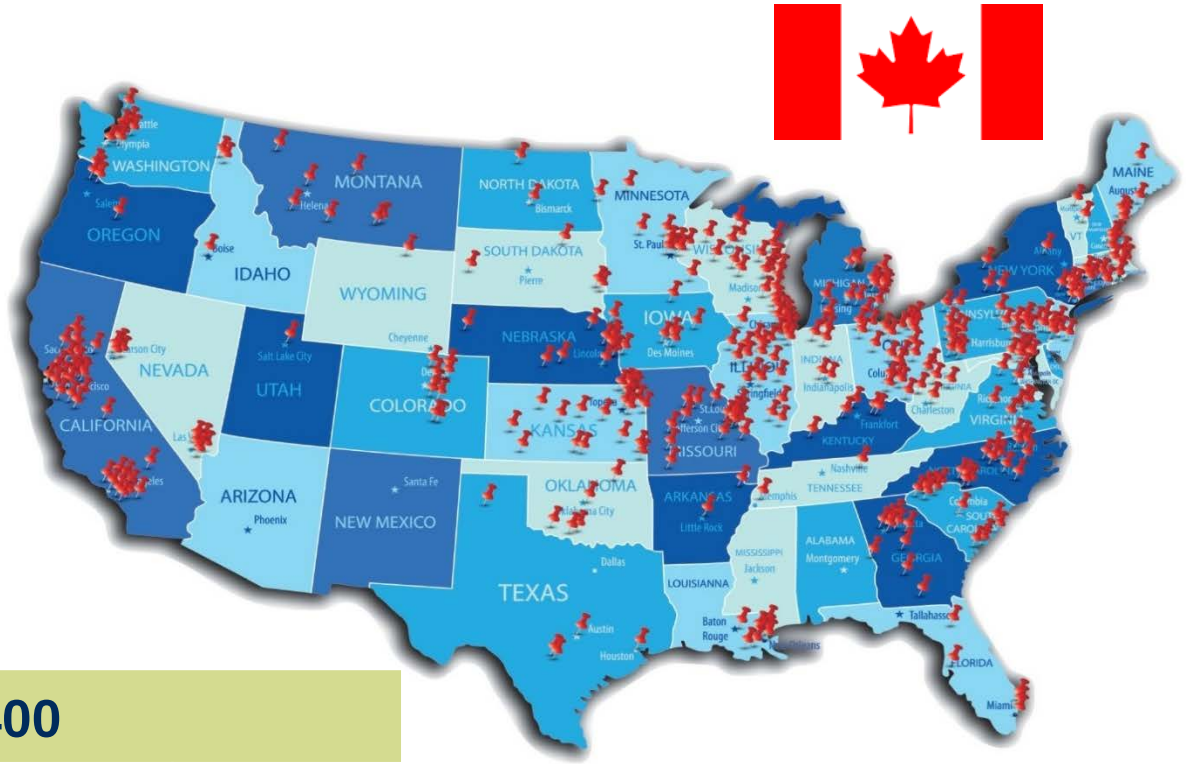
Broad Screening of Patients is Feasible

S1400 Screening Schema



Lessons Learned From Lung-MAP

Sites are interested in the study



Trial Metrics: S1400	
Total sites open for S1400	747
Total pts registered to S1400	1141
Prescreened	406
Screened at PD	765
Total pts assigned to a sub-study	884
Patients registered to sub-study	434

Lessons Learned From Lung-MAP
Adequate Funding is Needed

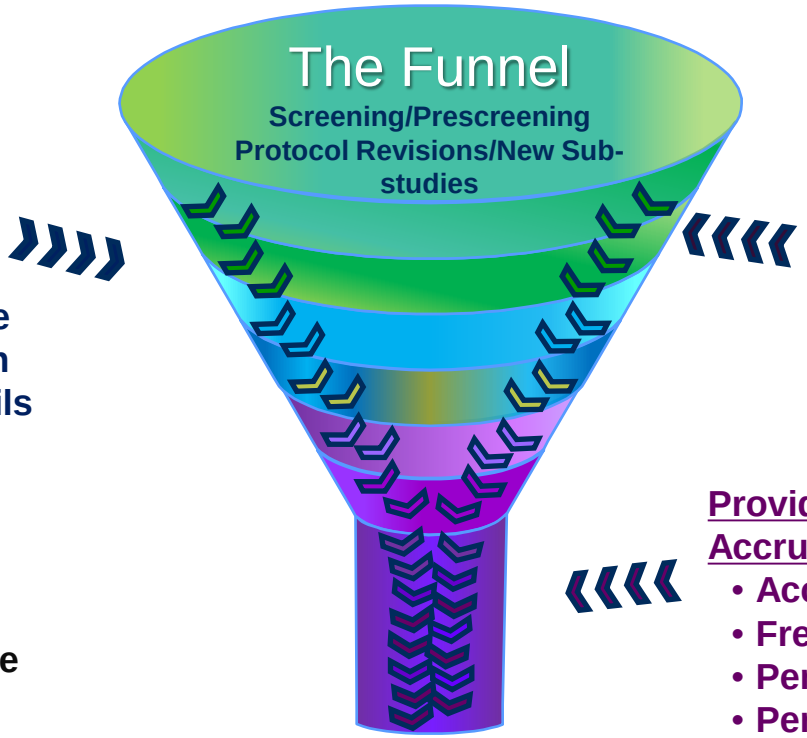
- Sites receive **up to** **$5,869** (**$1,079** screening/**$4,790** registration) for each patient on trial
- Reimbursements of **$3,000** (CT-guided)/**$6,000** (bronchoscopy) for biopsies performed at screening and/or progression after initial response
- Sites will be reimbursed for additional research 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

Our Advisors:

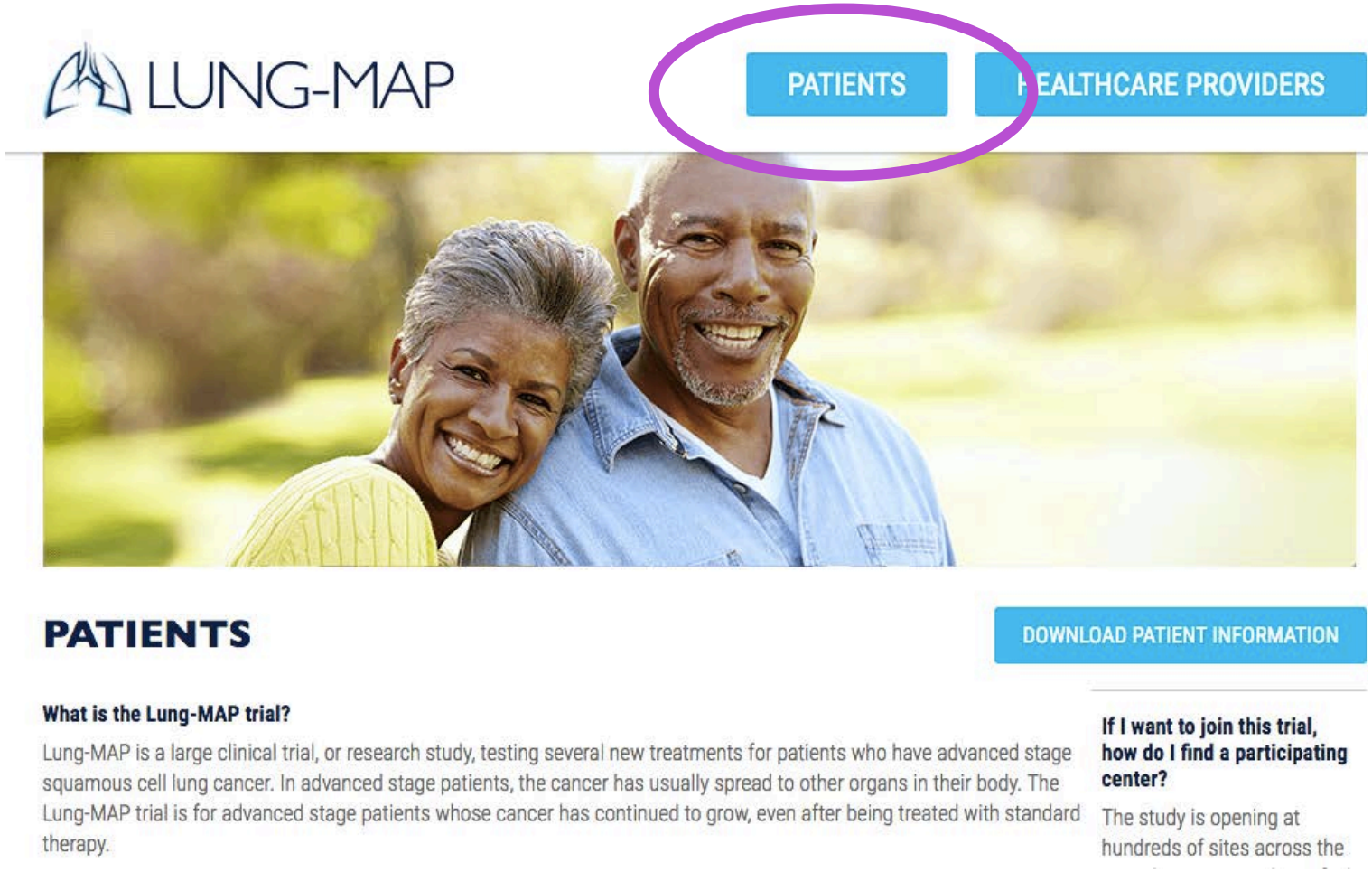
- Trial Oversight Committee
- Trial Leadership Team
- Site Coordinators Committee
- Public Affairs Committee

Provide Extra Support for High Accruing Sites:

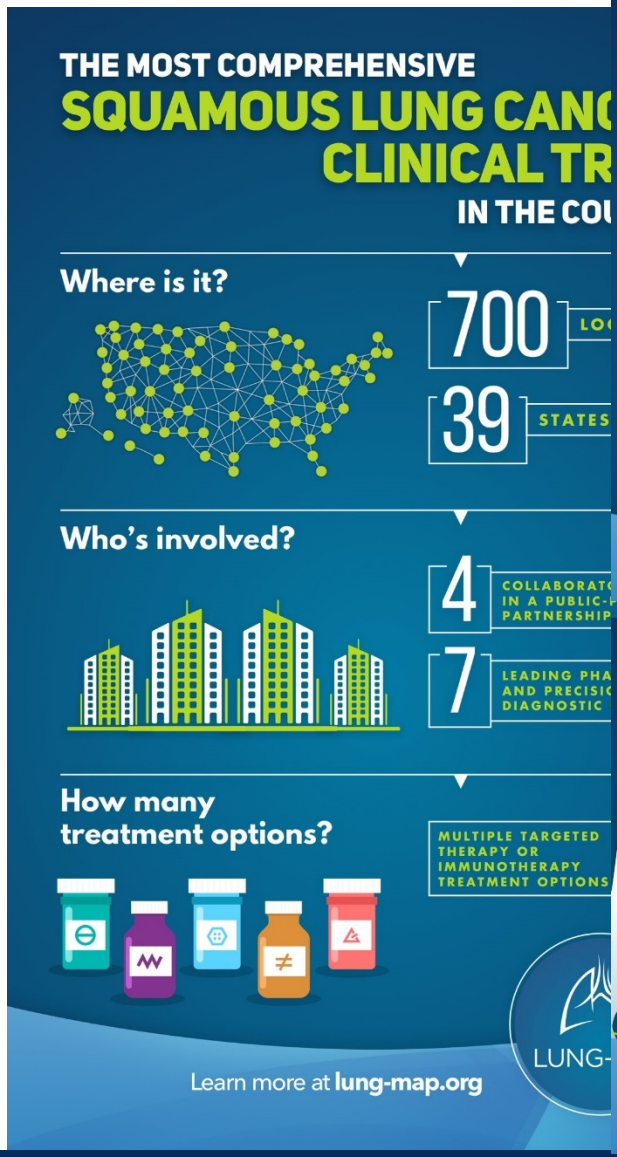
- Accrual Planning
- Frequent Contact with Site Staff
- Personalized Materials
- Personalized Social Media
- Personalized Outreach to Patient Advocates
- Investigator Teleconferences

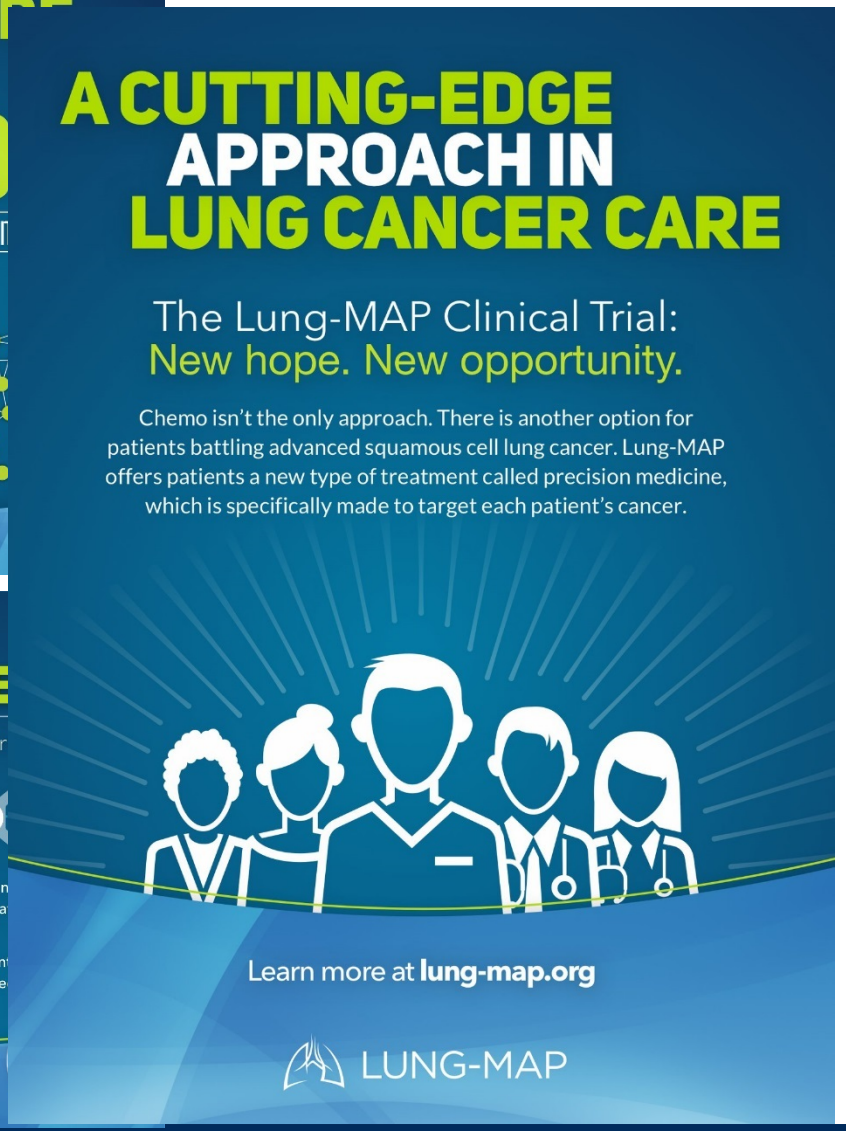
Lessons Learned From Lung-MAP

Speed is of the essence



Getting the word out





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!

www.lung-map.org