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

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Ensign Professor of Medicine
Chief of Medical Oncology
Associate Cancer Center Director for Translational Research

November 10, 2014

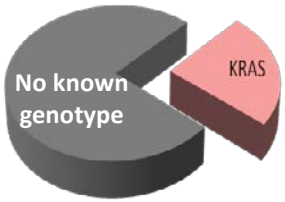
Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

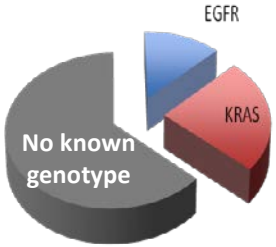
SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

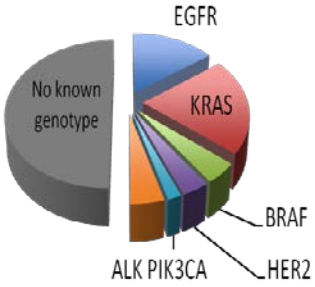
LUNG-MAP

Identification of Genomic Alterations for NSCLC

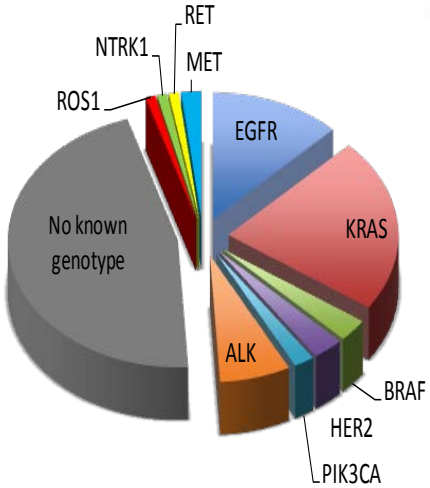
Lung Adenocarcinoma





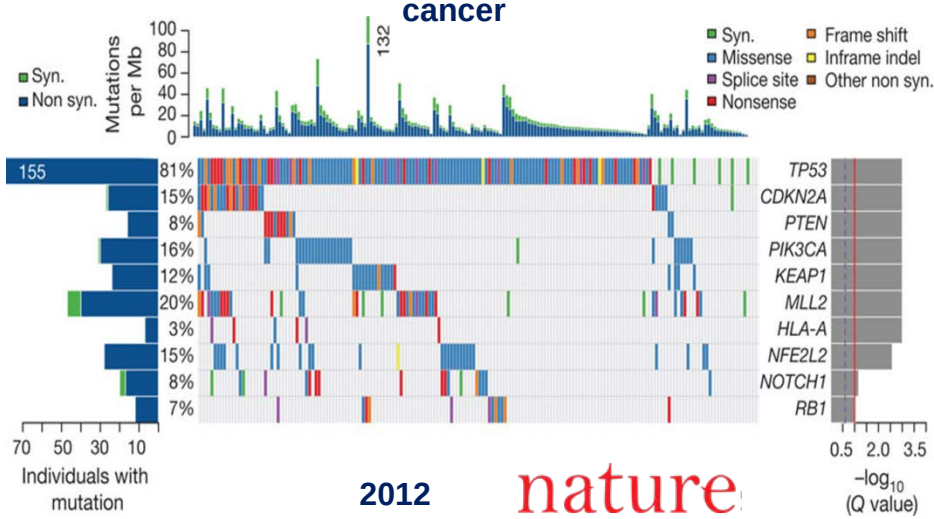


2009



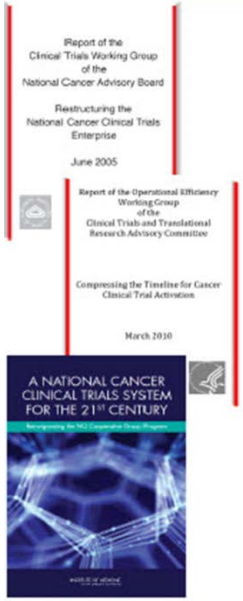
2014

Lung squamous cell cancer



2012 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

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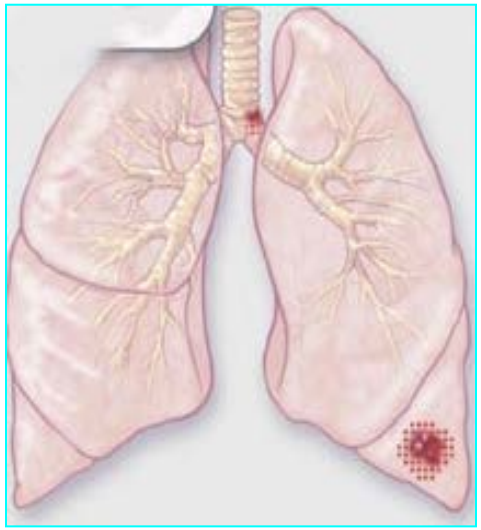
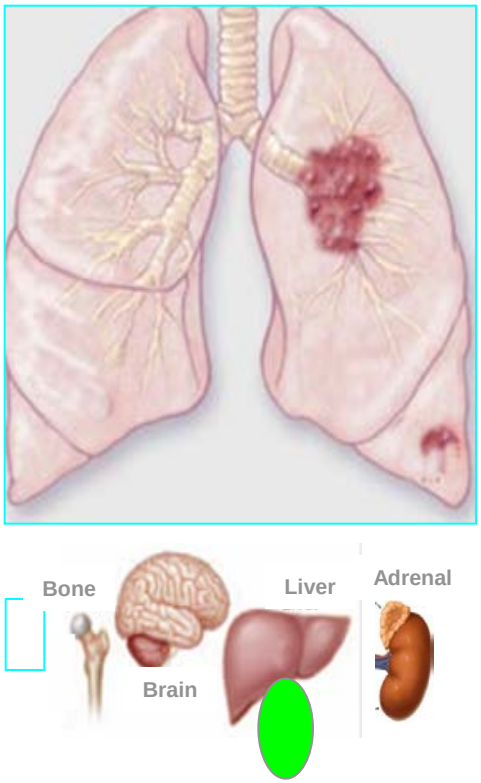
Natural History of Lung Cancer: Importance of Rebiopsy

Stages I-III Surgically Resected	Advanced – Stage IV Untreated	Advanced - Stage IV Refractory to Chemotherapy





Tissues Available	Frequent	Infrequent	Rare

Adapted from Herbst and wistuba N Engl J Med 359:1367, 2008

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

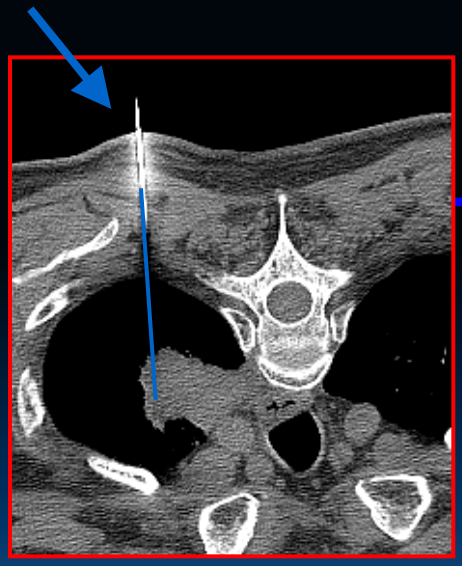
- **Imatinib Basket**
- **BRAF+**
- **NCI MATCH**

LUNG-MAP

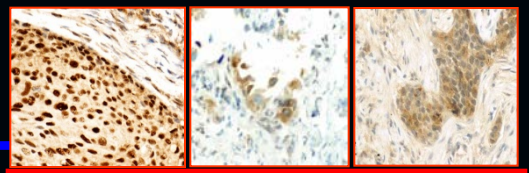
BATTLE 1 Schema

(Phase 2)

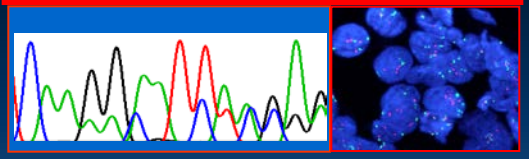
Umbrella Protocol



Core Biopsy



Biomarker Profile



EGFR KRAS/BRAF
VEGF RXR/CyclinD1

Randomization:
Equal → *Adaptive*

Erlotinib | Vandetanib | Erlotinib + Bexarotene | Sorafenib

Primary end point: 8 week Disease Control (DC)

Cancer Discovery, 2012

LUNG-MAP

Developing a New Model for Future Trials

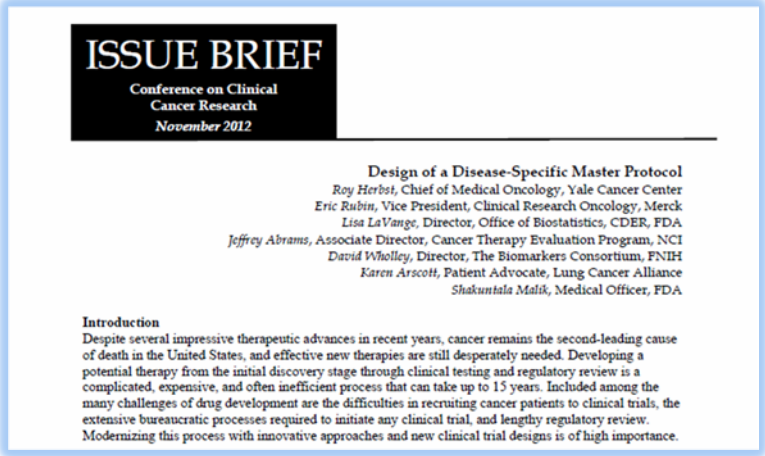
Initial Concept to Modernize the Clinical Trial Process:

- 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 for the protocol that became Lung-MAP.



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

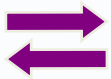
Despite several impressive therapeutic advances in recent years, cancer remains the second-leading cause of death in the United States, and effective new therapies are still desperately needed. Developing a potential therapy from the initial discovery stage through clinical testing and regulatory review is a complicated, expensive, and often inefficient process that can take up to 15 years. Included among the many challenges of drug development are the difficulties in recruiting cancer patients to clinical trials, the extensive bureaucratic processes required to initiate any clinical trial, and lengthy regulatory review. Modernizing this process with innovative approaches and new clinical trial designs is of high importance.

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

National Cancer Institute

Platform Trials Landscape

ALCHEMIST: Ph III: Adjuvant non-sq NSCLC

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

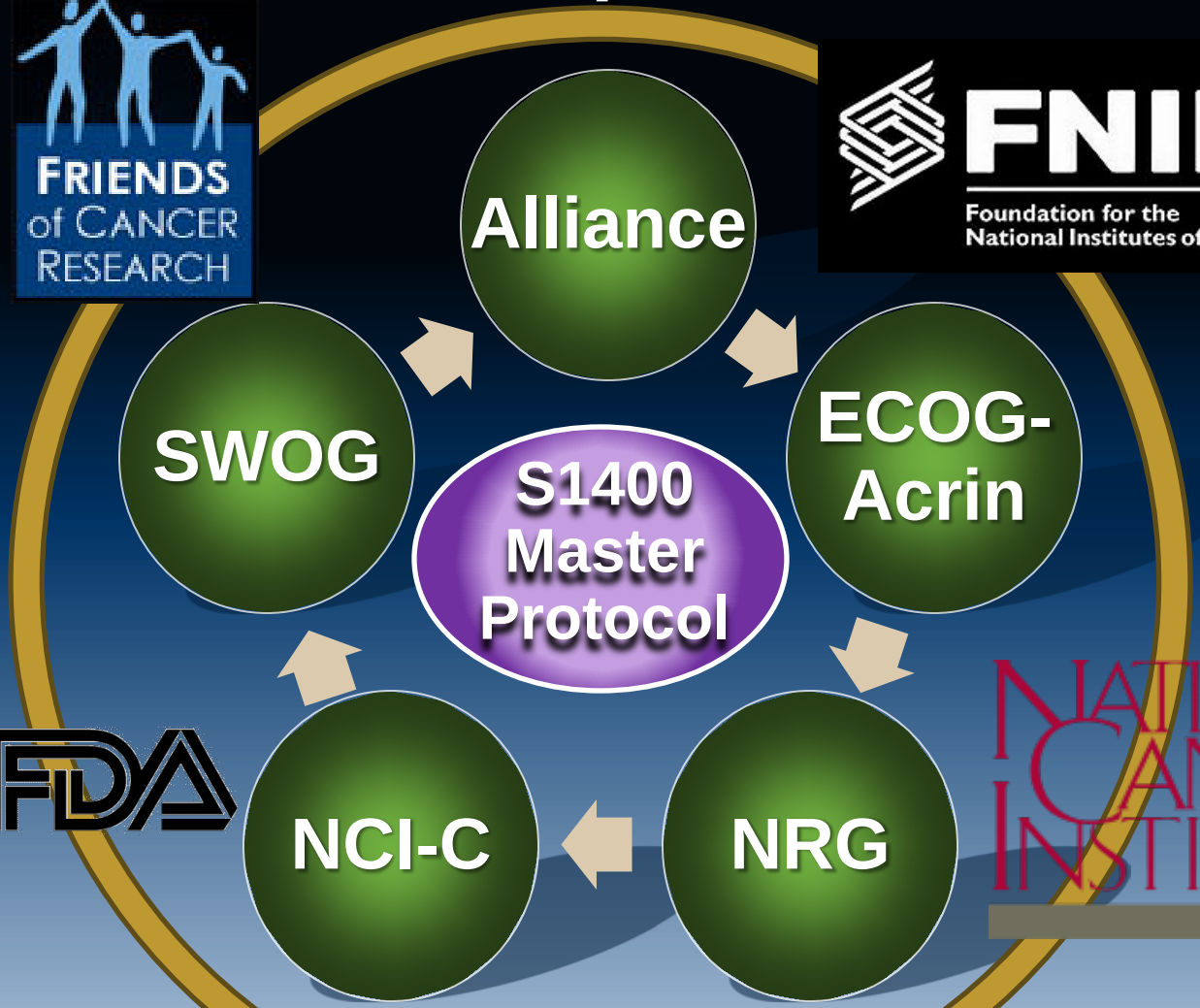
MATCH: Ph II: Solid + Lymphoma

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



FRIENDS of CANCER RESEARCH

FNIH
Foundation for the National Institutes of Health

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA
FDA

NATIONAL CANCER INSTITUTE

LUNG-MAP

Lung-MAP: Major Goals and Hypothesis

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

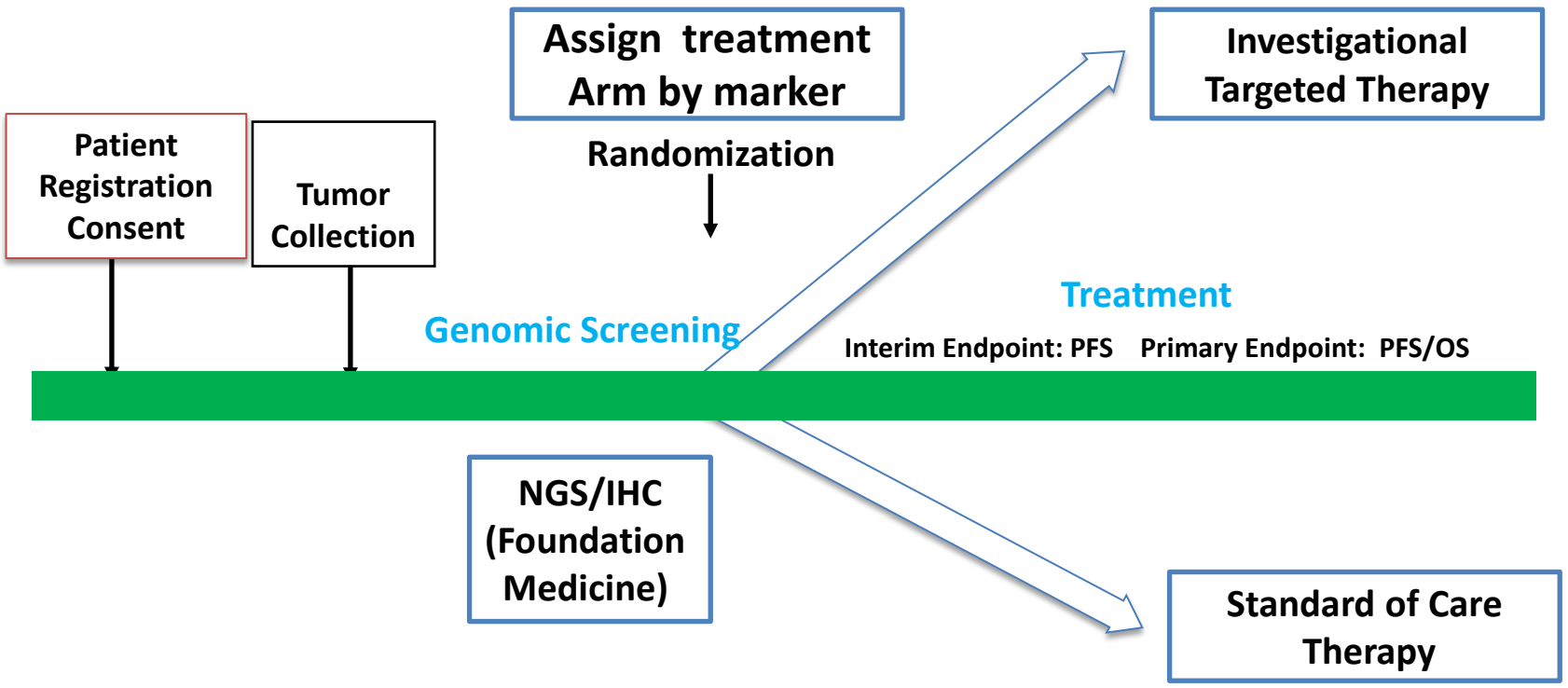
- **Assign and accrue simultaneously to a multi-sub-study "Master Protocol" comparing new targeted therapy to SoC based on designated therapeutic biomarker-drug combinations.**

- **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.**

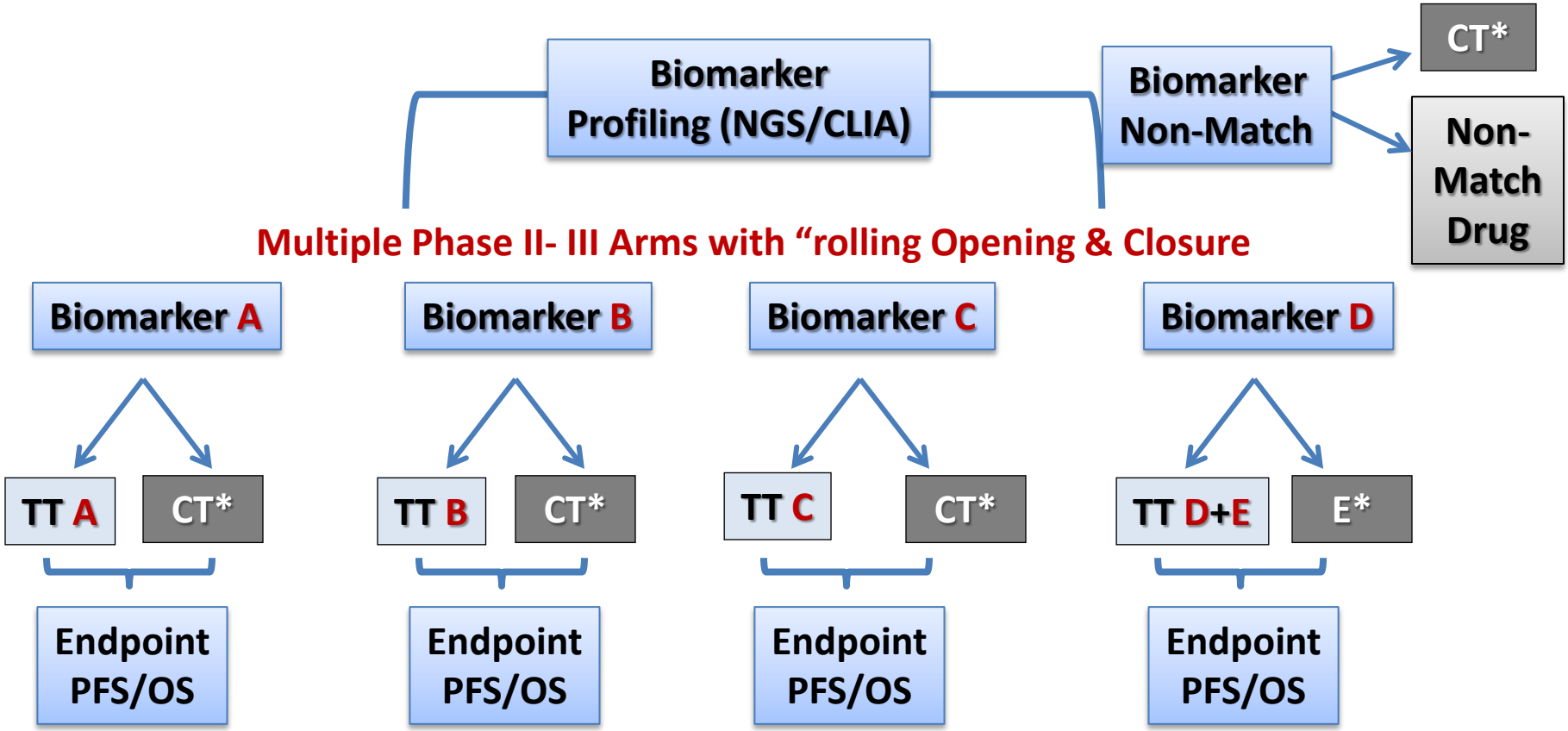
Lung-MAP: Major Goals and Hypothesis

- **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.**

LUNG-MAP


Assign treatment Arm by marker
Randomization
Investigational Targeted Therapy
Patient Registration Consent
Tumor Collection
Genomic Screening
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



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

Roy Herbst (chair), Yale Cancer Center	**Gary Kelloff,** NCI
Kathy Albain, Loyola Medicine	**Vali Papadimitrakopoulou,** MD Anderson
Jeff Bradley, Washington University in St. Louis	**Suresh Ramalingam**, Emory Healthcare
Kapil Dhingra, KAPital Consulting	**David Rimm,** Yale Cancer Center
Gwen Fyfe, Con	
David Gandara	
Glenwood Goss	
Fred Hirsch, Ur	
Peter Ho, QI On	
Pasi Janne, Dana Farber Cancer Institute	**Jamie Zwiebel,** NCI

Discussed with > 20 Companies, multiple agents

Non-Voting Members

Jeff Allen, Friends of Cancer Research	Mary Redman, Fred Hutchinson Cancer Center
Matt Hawryluk, Foundation Medicine	Ellen Sigal, Friends of Cancer Research
Shakun Malik, FDA	David Wholley, FNIH
Vince Miller, Foundation Medicine	Roman Yelensky, Foundation Medicine

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:

Drug	Company	Target
AZD4547	AstraZeneca	Fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor
GDC-0032	Genentech	PI3K pathway inhibitor
MEDI4736	MedImmune	Anti-PD-L1 monoclonal antibody
Palbociclib	Pfizer	CDK 4/6 inhibitor
Rilotumumab	Amgen	Hepatocyte growth factor receptor/c-met inhibitor

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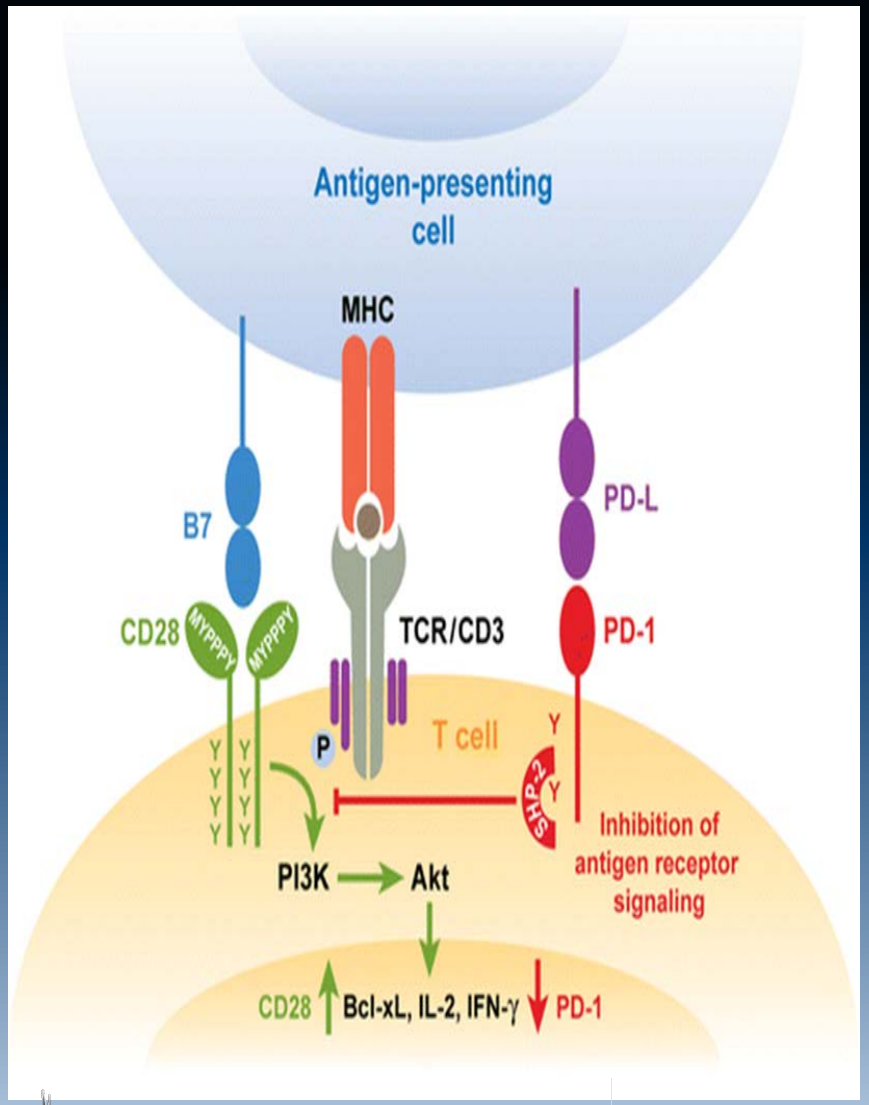
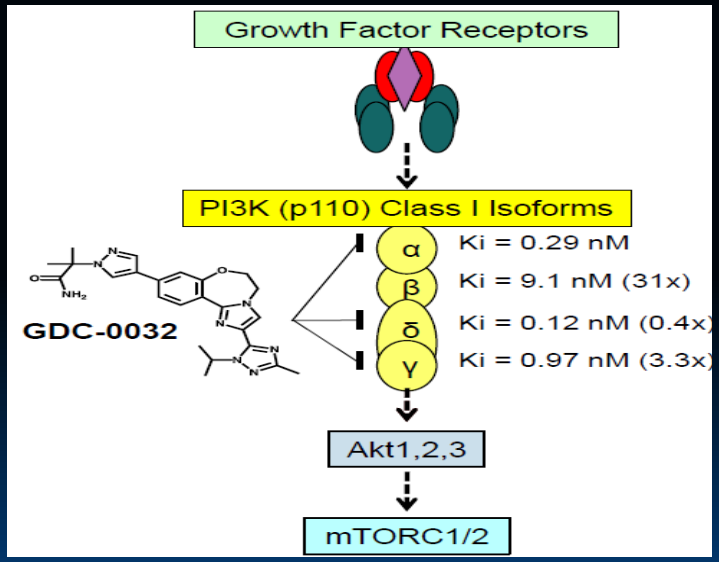
Rationale-Science

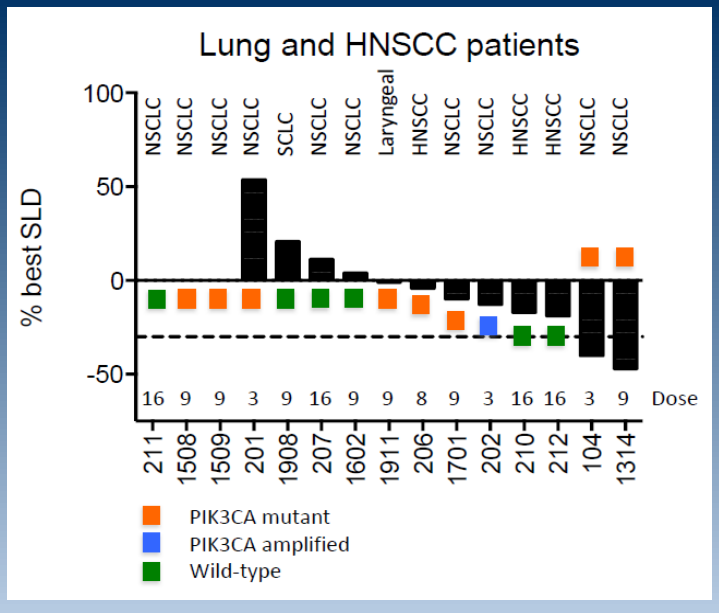


Sub-study A

- 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



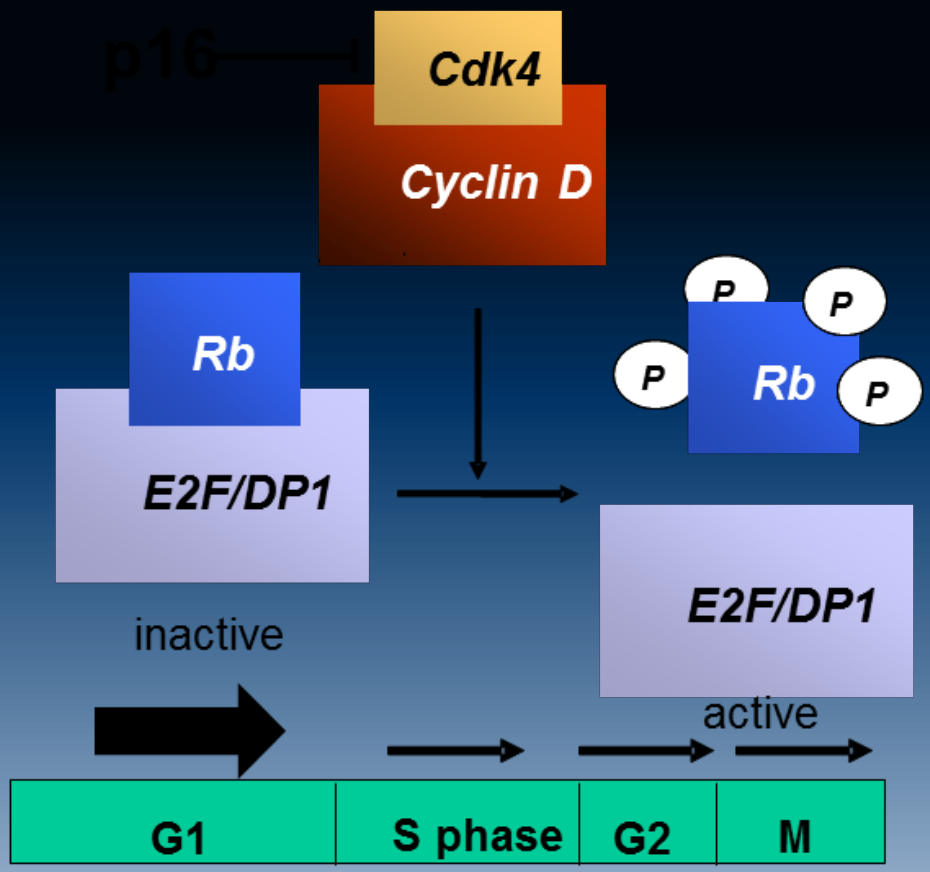


Sub-study B

- GDC—0032 beta isoform-sparing PI3K inhibitor more potent against *PIK3CA*^{mut} than wt *in vitro,* interacts with mutant p110*a* conformation.
- Promising preliminary clinical activity in *PIK3CA* mutant cancers including SCCA.
- Safety profile c/w other PI3K inhibitors.

LUNG-MAP

Rationale-Science

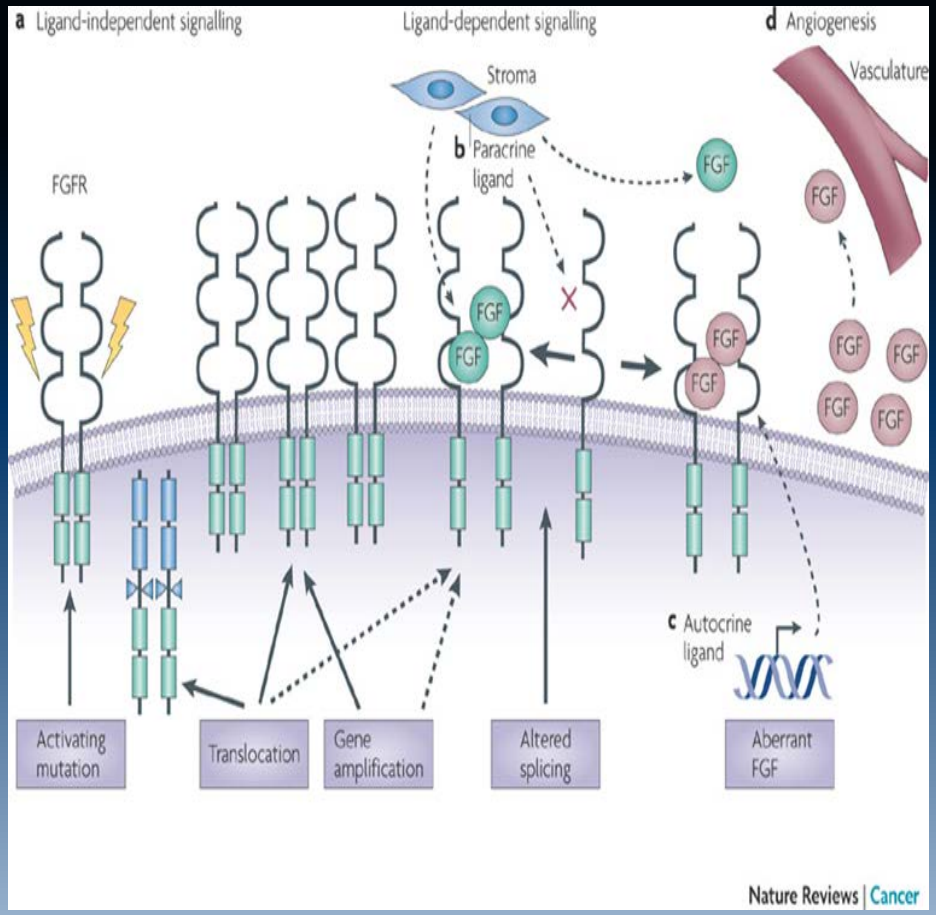


Sub-study C

- 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.

LUNG-MAP

Rationale-Science

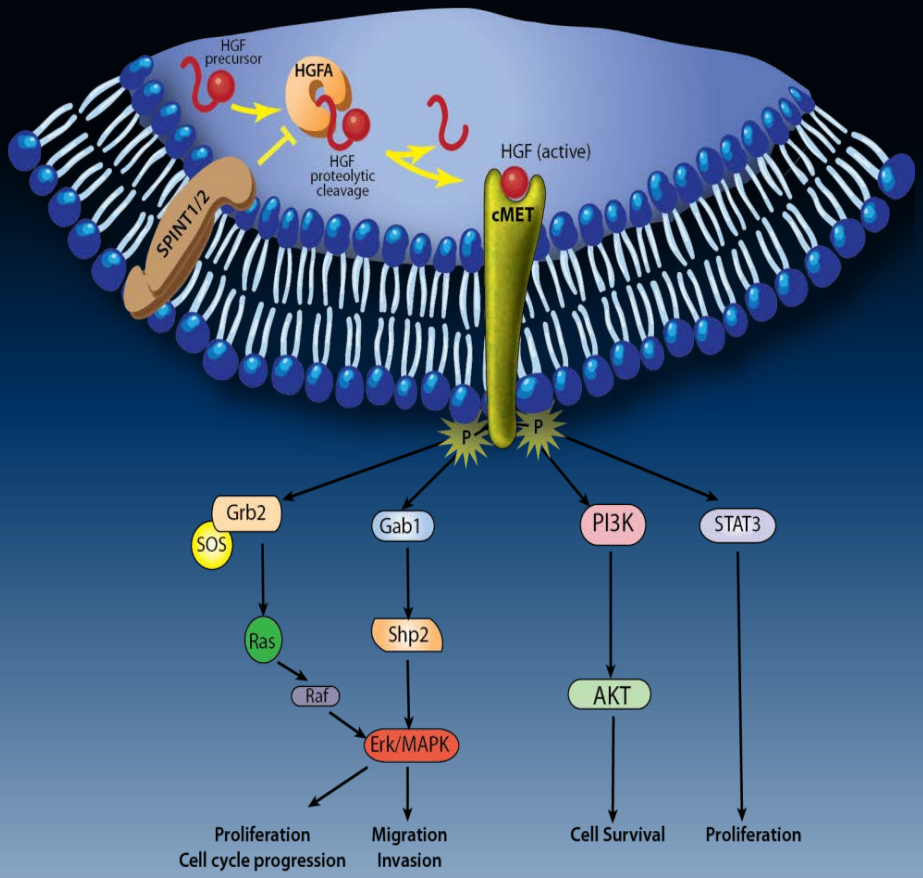


Sub-study D

- 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.

LUNG-MAP

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.

LUNG-MAP

Squamous Lung Master Protocol Clinical Trial Assay Based On Foundation Medicine NGS Platform

Foundation Medicine NGS test platform (CLIA/CAP)

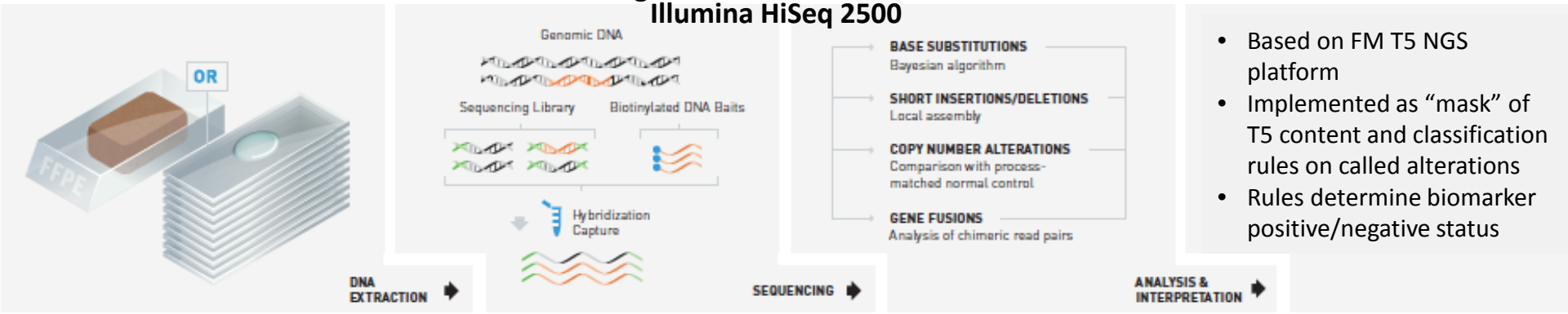
Classification rules

1) DNA extraction

2) Library construction: selected cancer genes

3) Analysis pipeline

4) Master protocol CTA



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

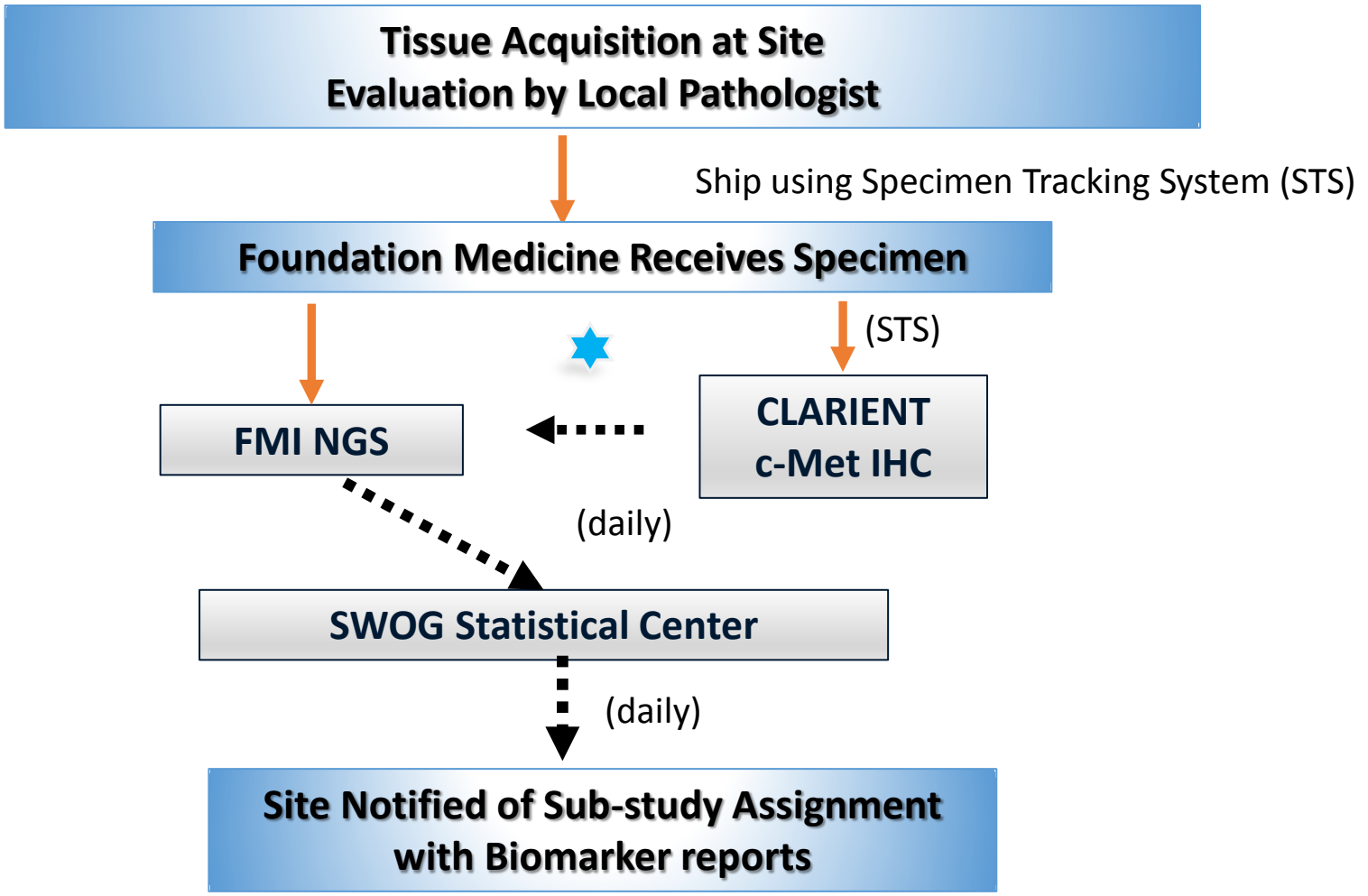
Non-NGS biomarkers:

Supplementary assays	Non-match arm
MET IHC (+)	All assays (-)
↓	↓
MET pathway inhibitor	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



LUNG-MAP

Molecular Results (Evolving Ethical Issues)

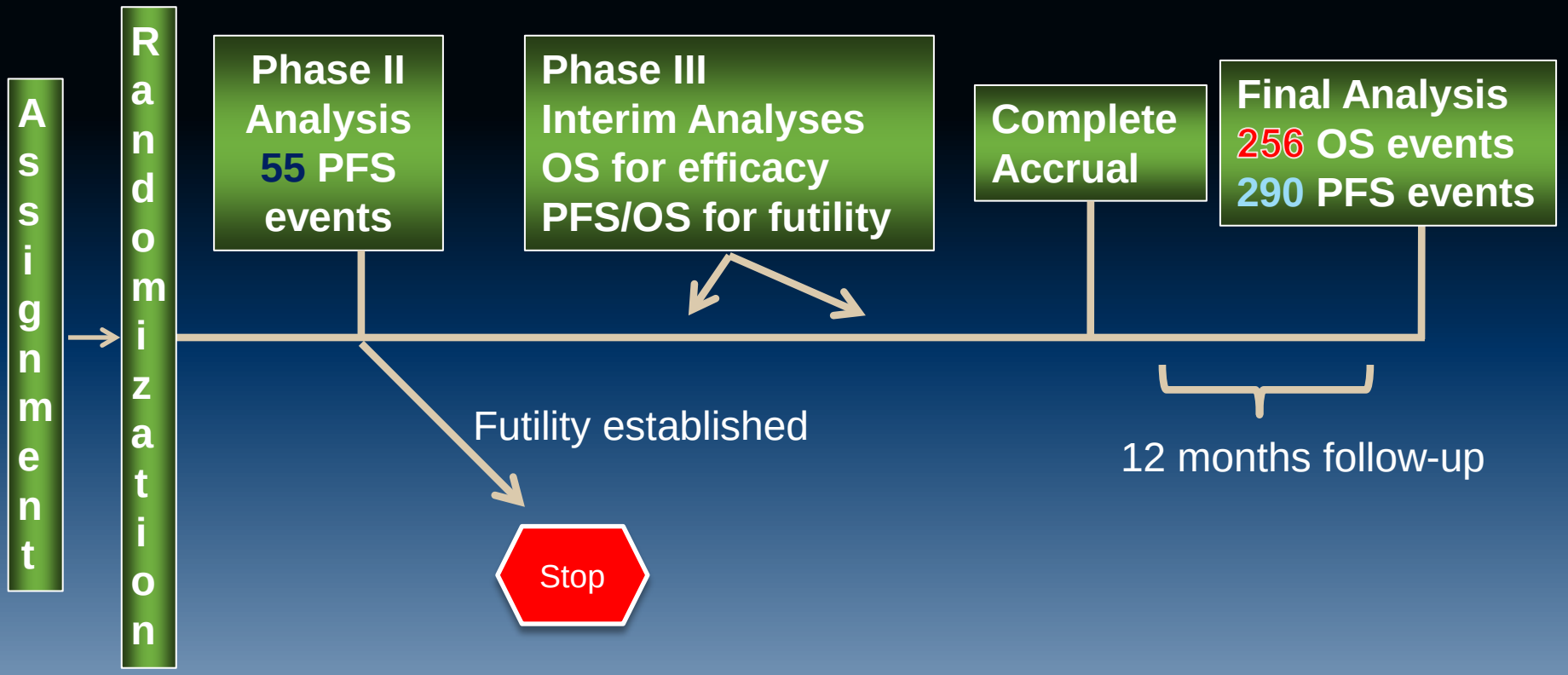
- Initially Proposed study:
  - Pre-screening component
  - Return of molecular results to patients after progression on study treatment

- 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

LUNG-MAP

Study Design Within Each Biomarker-defined Subgroup



LUNG-MAP

Courtesy of: Mary Redman

Statistical Design: Phase II Interim Analysis

	Phase II Design	
	Plan A	Plan B
Primary Outcome	PFS	
Sample Size	55 progression events	
Target HR (% improvement)	HR = 0.5 2-fold increase	HR=0.4 2.5-fold increase
Power	90%	95%
Type I error	10%	4%
Approx. Threshold to continue:		
HR % improvement	HR= 0.71 41% increase	HR = 0.61 63% increase

Each sub-study can choose between Plan A or Plan B to determine “bar” for continuation past Phase 2 interim analysis

LUNG-MAP

Statistical Design: Phase III

	PFS and OS Co-primary	
	PFS	**OS**
Events	**290**	**256**
Null Hypothesis (HR)	**0.75* (33% improvement)**	**1.0 (equivalence)**
Alternative Hypothesis	**0.5 (2-fold increase)**	**0.67 (50% improvement)**
Type I error (1-sided)	**0.014 against HR = 1.33 < 0.00001 against HR = 1**	**0.025**
Power	**90%**	**90%**

** Non HR = 1 null hypothesis encodes clinical significance*

Sample size based on OS for all studies

LUNG-MAP

Sample Size for the Sub-studies

		Phase 2		Phase 3	
Sub-study ID	**Prevalence Estimate**	**Approximate Sample Size**	**Approximate time of analysis**	**Sample Size**	**Approximate time of analysis**
S1400A	56.0%	170	8	380	21
S1400B					
GNE-positive	5.6%	78		288	
FMI-positive	8.0%	152	19	400	72
S1400C	11.7%	124	11	312	45
S1400D	9.0%	112	11	302	53
S1400E	16.0%	144	9	326	37

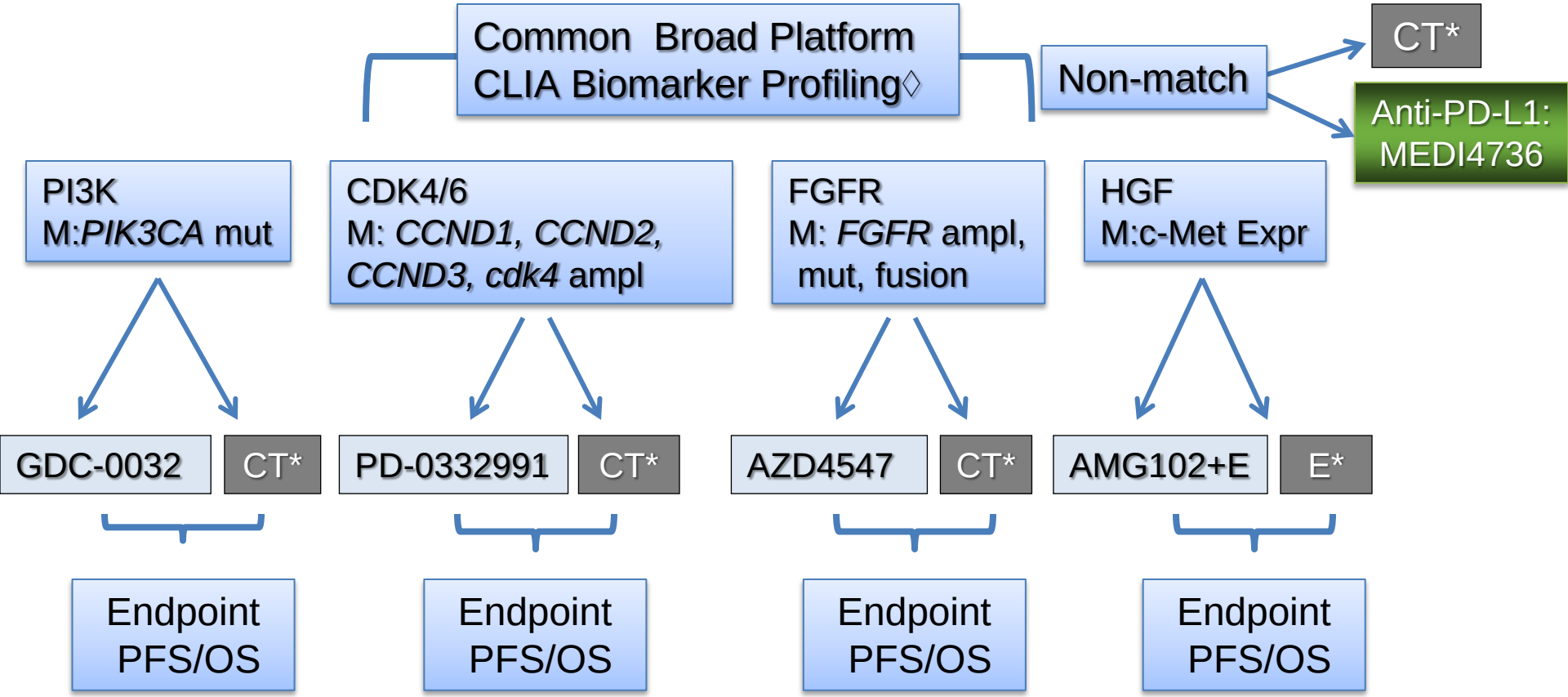
Biomarker prevalence and overlap estimates (based on 108 sqNSCLC)

	AZ/FGFR	Pfizer/CDK	Genentech/PIK3CA	Amgen/Met*
AZ/FGFR	10.2%	2.8%	0.9%	2.0%
Pfizer/CDK		13.9%	1.9%	2.8%
Genentech/PIK3CA			9.3%	1.9%
Amgen/Met				20%

***Assumption of 20% prevalence for Met and random overlap between Met and other biomarkers**

S1400

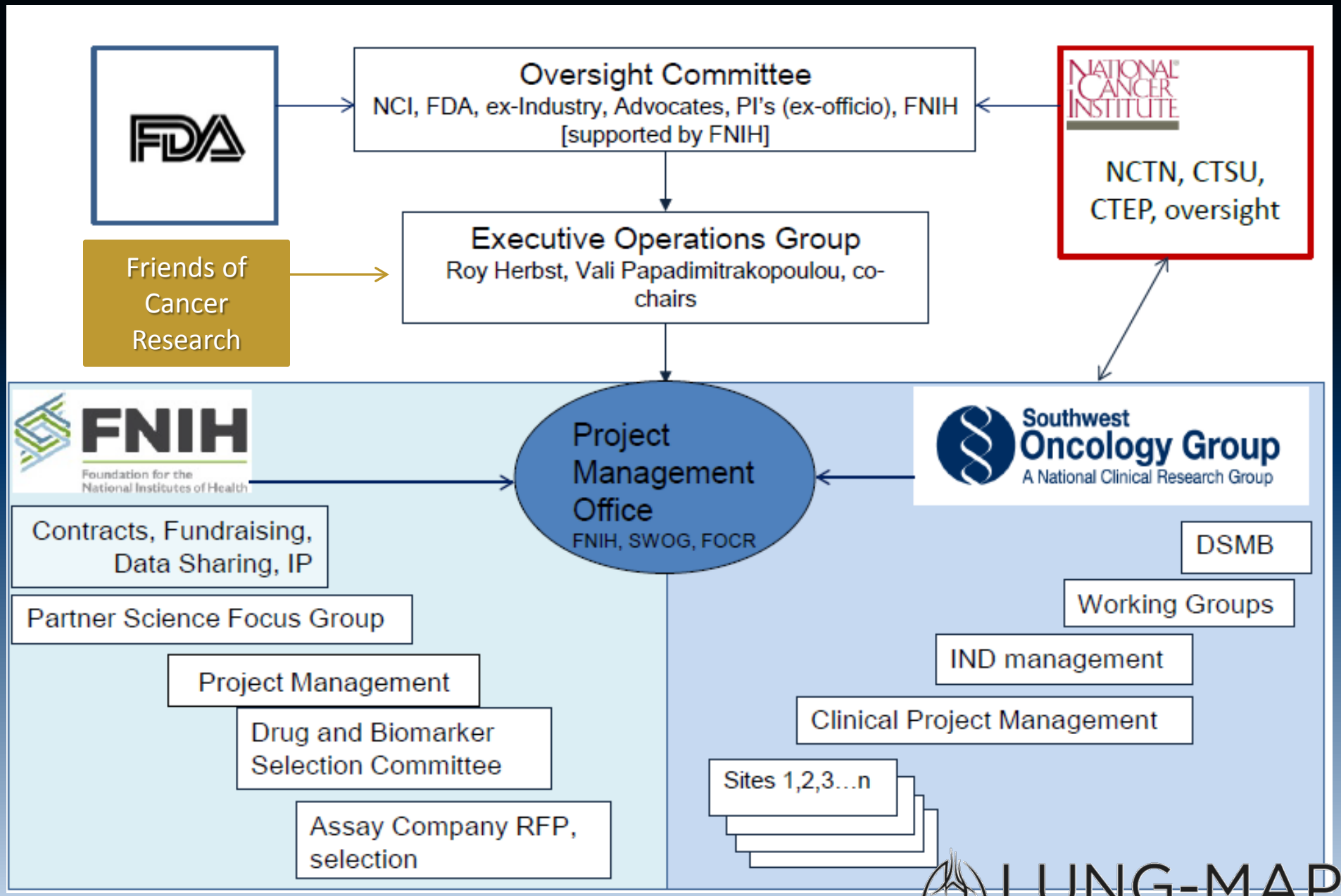
LUNG-MAP

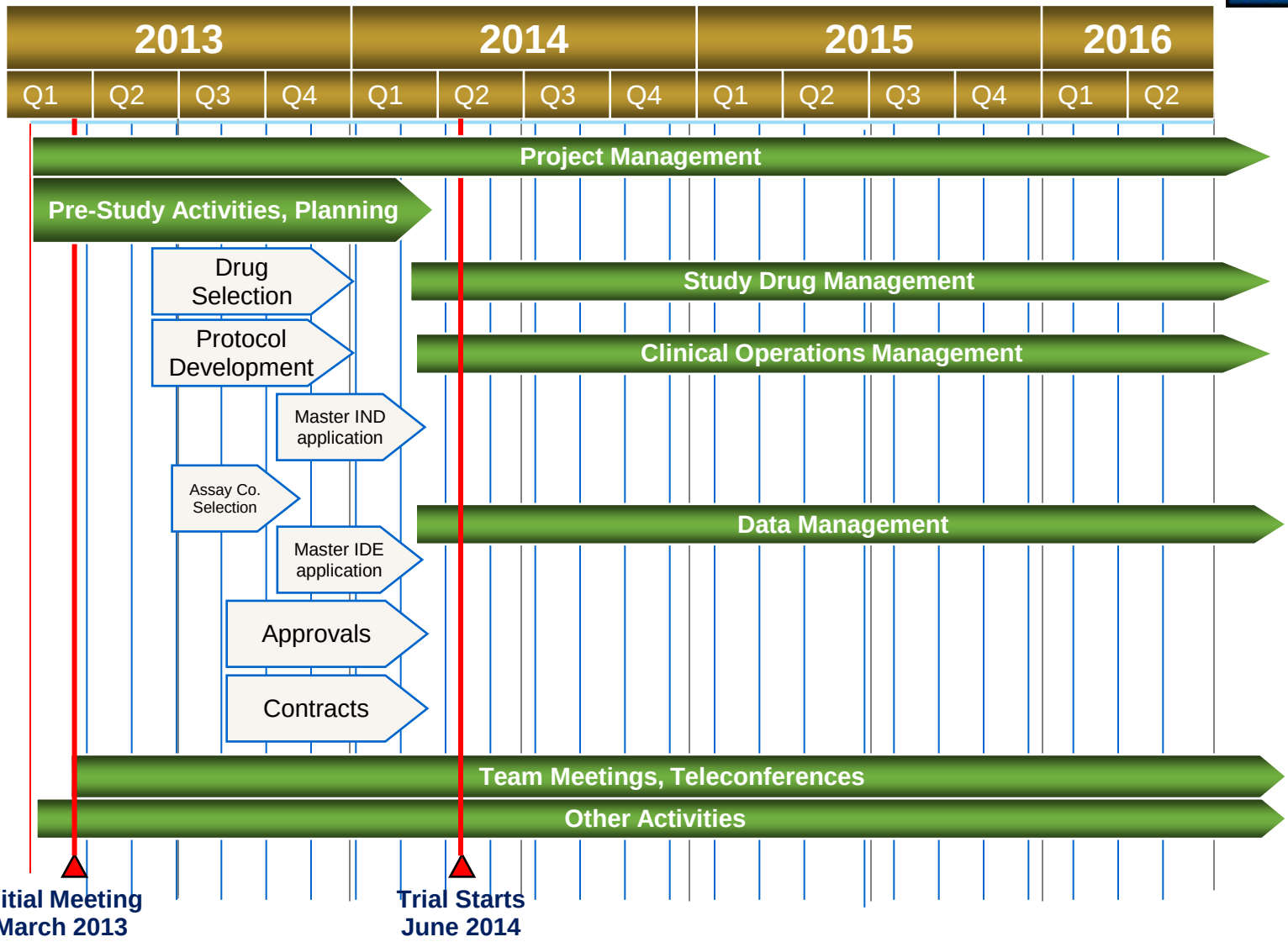


TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

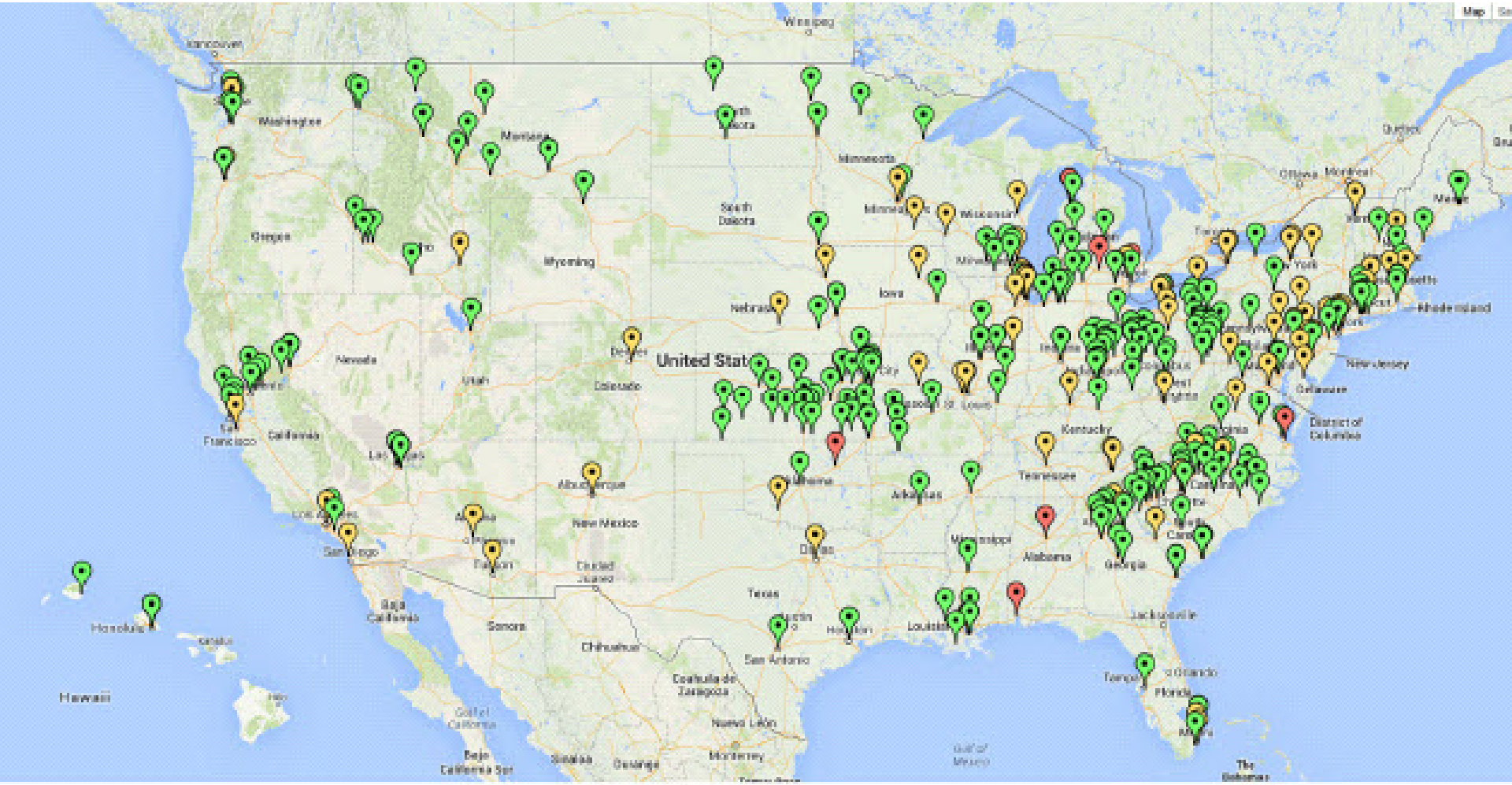
◊ Archival FFPE tumor, fresh CNB if needed

Governance Structure:




2013
2014
2015
2016
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
Q1
Q2
Project Management
Pre-Study Activities, Planning
Drug Selection
Protocol Development
Master IND application
Assay Co. Selection
Master IDE application
Approvals
Contracts
Study Drug Management
Clinical Operations Management
Data Management
Team Meetings, Teleconferences
Other Activities
Initial Meeting
March 2013
Trial Starts
June 2014

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)

21st Century Cures: Modernizing Clinical Trials
July 9, 2014

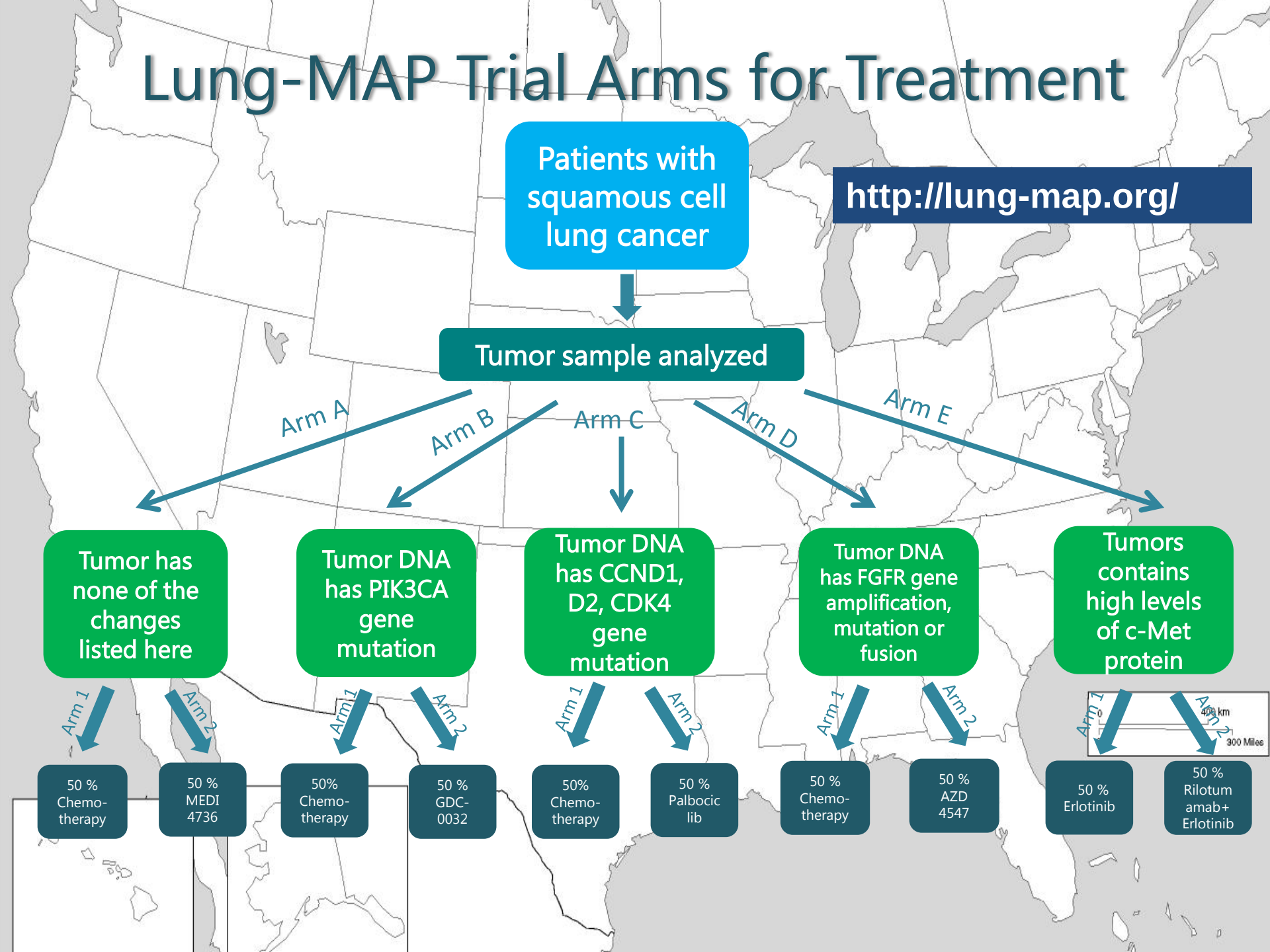
Recommendations to the committee:

- **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

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

Lung-MAP Trial Arms for Treatment



LUNG-MAP

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.

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