Criteria to Assess Cancer Immunotherapy Combinations in Early-Phase Clinical Trials: Types of Clinical Trial Designs Needed for Regulatory Approval

Public Private Partnership Perspective

A collaborative workshop convened by the:
National Cancer Policy Forum
Forum on Drug Discovery, Development, and Translation

November 15, 2022

Roy S. Herbst
Ensign Professor of Medicine
Professor of Pharmacology
Deputy Director, Yale Cancer Center
Assistant Dean for Translational research
Yale School of Medicine

LUNG-MAP

SWOG CANCER RESEARCH NETWORK

YaleNewHavenHealth
Smilow Cancer Hospital

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

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Disclosures: Roy S. Herbst, MD, PhD

Consulting
AstraZeneca; Bolt Biotherapeutics; Bristol-Myers Squibb ; Candel Therapeutics, Inc.; Checkpoint Therapeutics; Cybrexa Therapeutics ; DynamiCure Biotechnology, LLC; eFFECTOR Therapeutics, Inc.; Eli Lilly and Company; EMD Serono; Genentech; Gilead; HiberCell, Inc., ; I-Mab Biopharma; Immune-Onc Therapeutics, Inc.; Immunocore; Janssen; Johnson and Johnson; Loxo Oncology; Mirati Therapeutics; NextCure; Novartis; Ocean Biomedical, Inc. ; Oncocyte Corp; Oncternal Therapeutics; Pfizer; Regeneron Pharmaceuticals; Revelar Biotherapeutics, Inc; Ribbon Therapeutics; Roche; Sanofi; WindMIL Therapeutics; Xencor, Inc

Research Support
AstraZeneca; Eli Lilly and Company; Genentech/Roche; Merck and Company

Board Member (non-executive/ independent)
Immunocore; Junshi Pharmaceuticals

Leadership Role
American Association for Cancer Research; International Association for the Study of Lung Cancer; Society for Immunotherapy of Cancer; Southwest Oncology Group

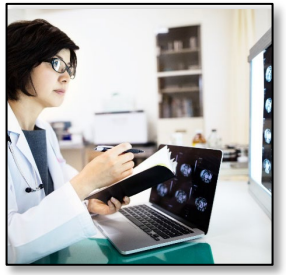
Public-Private Partnership

['pə-blik 'prī-vət 'pärt-nər-,ship]

A collaboration between a government and private enterprise, often on large infrastructure projects that the private partner may finance, plan, or execute.

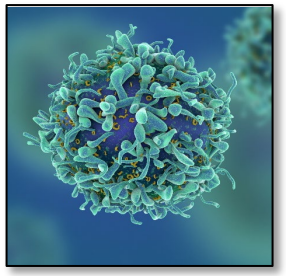
Investopedia

About the FNIH



Mission

The mission of the Foundation for the National Institutes of Health (FNIH) is to support the mission of the NIH. The FNIH creates and leads alliances and public-private partnerships that advance breakthrough biomedical discoveries and improve the quality of people's lives.



Why Collaborate?

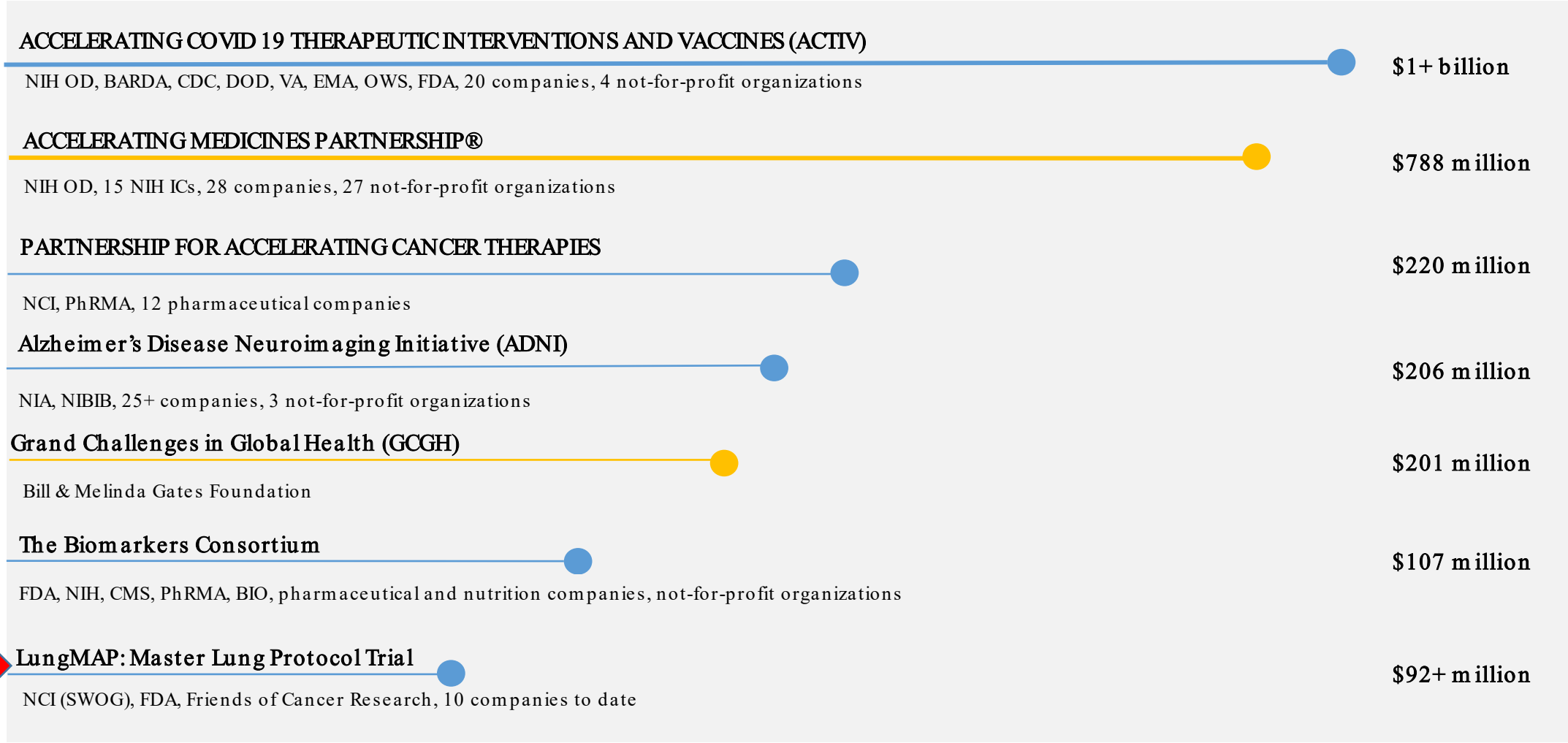
The FNIH was created by Congress in 1990 as a not-for-profit charitable organization. The Foundation began its work in 1996 to facilitate groundbreaking research at the U.S. National Institutes of Health (NIH) and worldwide.

Founded by Congress to:

- Attract and share resources
- Enable insight and innovation
- Establish standards
- Distribute expertise
- Create consensus
- Drive competitiveness in marketplace
- Disseminate knowledge
- Enhance credibility
- Reduce costs
- Support training & education
- Manage complexity

Select FNIH Partnerships

FNIH partnerships span multiple disease areas and include individuals and organizations from a variety of stakeholder groups.



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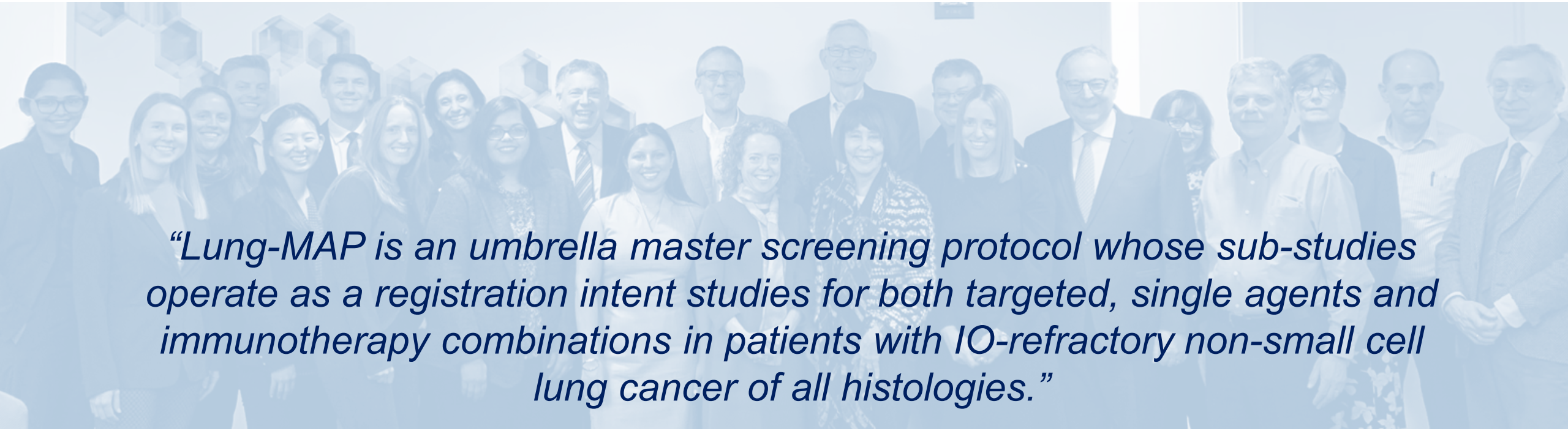
LUNG-MAP Turns 10

Our Partnerships, Achievements, and Lessons Learned



"Lung-MAP is an umbrella master screening protocol whose sub-studies operate as a registration intent studies for both targeted, single agents and immunotherapy combinations in patients with IO-refractory non-small cell lung cancer of all histologies."

FNIH
Foundation for the National Institutes of Health

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Plan For the Talk

1. The Birth of Lung-MAP

2. Top Ten: Partnerships, Achievements, and Lessons Learned

3. Thoughts for the Future

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The Genesis of Lung-MAP

October 2011 – Creativity Inspiration motivated by TCGA and Battle trials at the SWOG Group Meeting

February 2012 – NCI TMSC, FDA, Leading Academicians, Clinicians, Industry, Government representatives

November 2012 – Lung Master Protocol Trial Design Proposal hosted by Friends of Cancer Research

March 2013 – Development of the Lung Master Protocol

June 2014 – Lung-MAP trial launched

- **Public-Private Partnerships - SWOG IND Sponsor**
- **Primary Objective**
  - Overall survival of biomarker-selected patients treated with standard of care (SoC) versus the experimental targeted therapy
- **Drugs and Biomarkers**
  - Steering Committee to evaluate each applicant
- **Study Design**
  - Phase II/III in patients with advanced squamous cell carcinoma as the un-met need
  - Foundation Medicine as the central lab for biomarker testing
  - Targeted treatment based on biomarker results

L-R: M. Redman, J. Abrams, V. Miller, A. Ashby, V. Papadimitrakopoulou, D. Gandara, J. Woodcock, R. Herbst, J. Allen

NCI: National Cancer Institute;
TMSC: Thoracic Malignancies Steering Committee
TCGA: The Cancer Genome Atlas

SPECIAL ARTICLE

OPEN

Consensus Report of a Joint NCI Thoracic Malignancies Steering Committee: FDA Workshop on Strategies for Integrating Biomarkers into Clinical Development of New Therapies for Lung Cancer Leading to the Inception of "Master Protocols" in Lung Cancer

Shakun M. Malik, MD, Richard Pazdur, MD,† Jeffrey S. Abrams, MD,* Mark A. Socinski, MD,‡ William T. Sause, MD,§ David H. Harpole Jr., MD,‖ John J. Welch, MD, PhD,* Edward L. Korn, PhD,¶ Claudio Dansky Ullmann, MD,* and Fred R. Hirsch, MD PhD#*

(*J Thorac Oncol.* 2014;9: 1443–1448)

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Design of a Disease-Specific Master Protocol

2012 Friends of Cancer Research / Brookings Institution
Conference on Clinical Cancer Research

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.

FRIENDS of CANCER RESEARCH http://www.focr.org/events/design-lung-cancer-master-protocol

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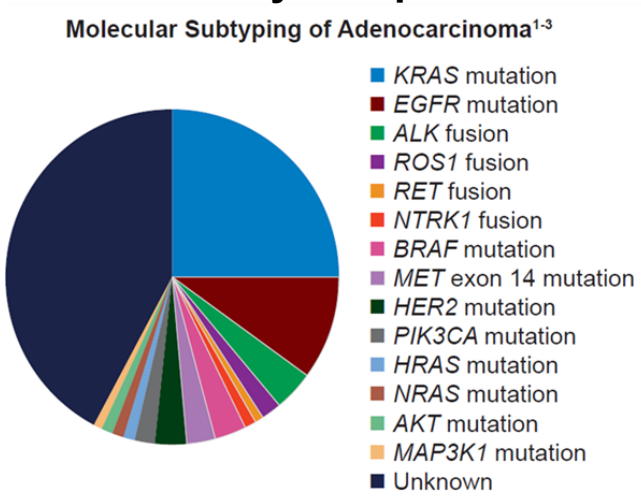
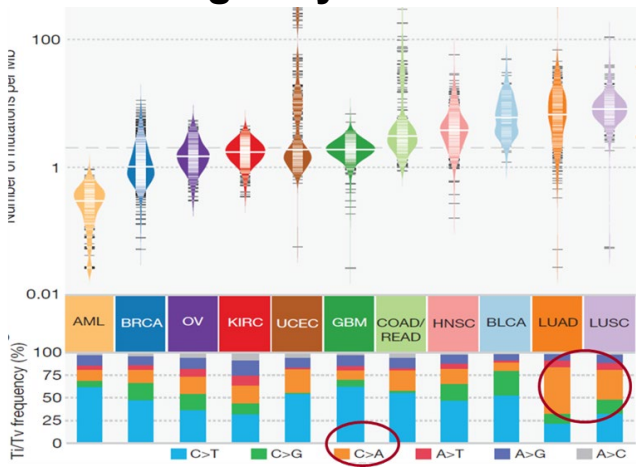
Advanced NSCLC as an Ideal Tumor Type for a Master Protocol

Genomically complex



Immunologically Well Suited



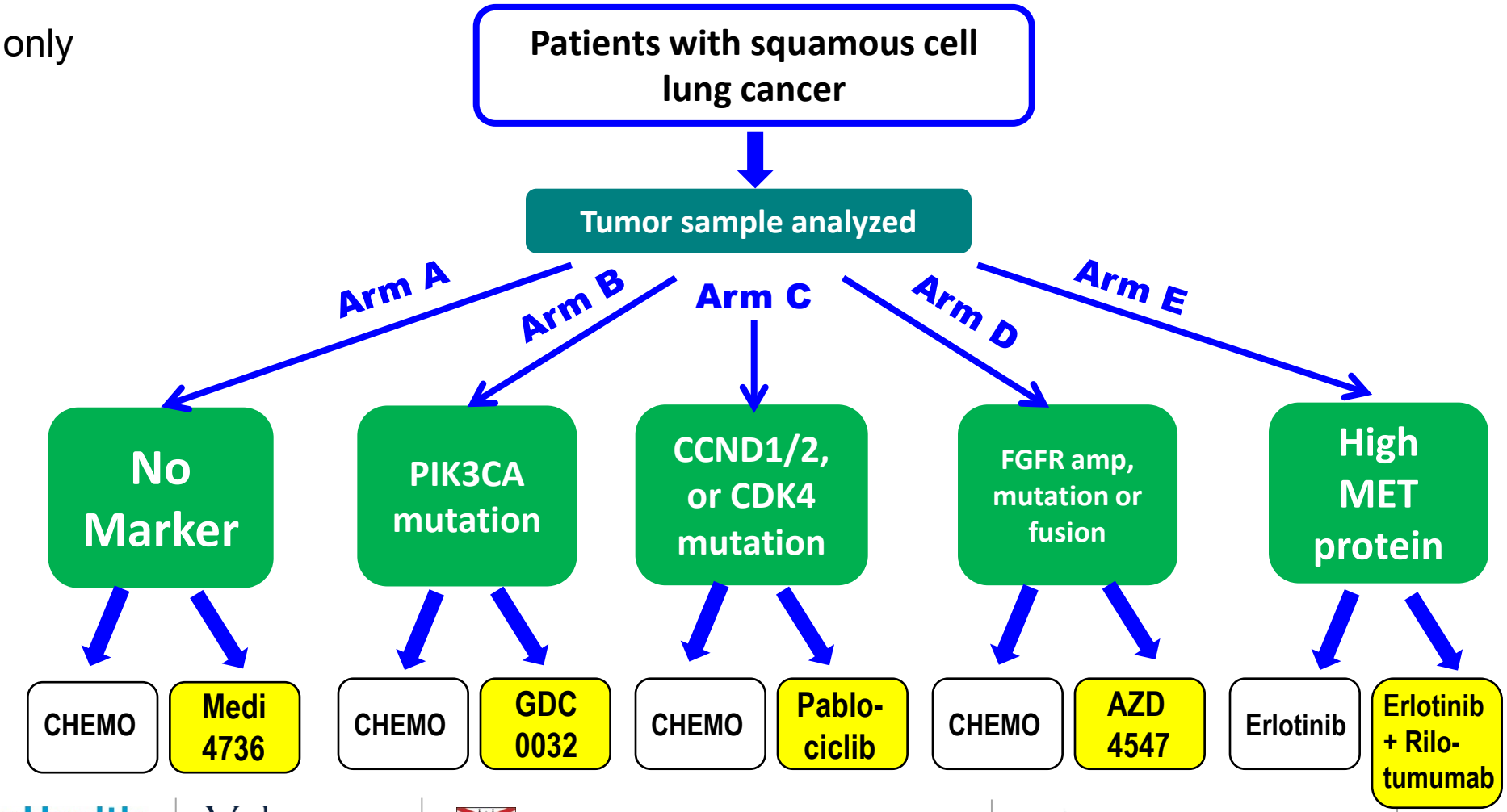
Goals of the Lung MAP Master Protocol:

- Test new anti-cancer therapies in uncommon-rare genotypes of NSCLC?
- Test new anti-cancer therapies in NSCLC patients refractory to IO
- Apply broad-based molecular screening (NGS) in the clinic
- Achieve an acceptable turn-around time for molecular testing in the clinic (<2 weeks)
- Expedite the clinical trials process (through a public-private partnership)
- Bring Lung MAP to NCTN community sites nationwide (“bring the trials to the patient”)
- Create “New Science” from Lung MAP resources

The first open sub-studies

Open June 2014

Squamous only
2nd line
SWOG



AstraZeneca
Genentech BIOONCOLOGY
Pfizer
MedImmune
AMGEN

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Recognized by 21st Century Cures: Modernizing Clinical Trials

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

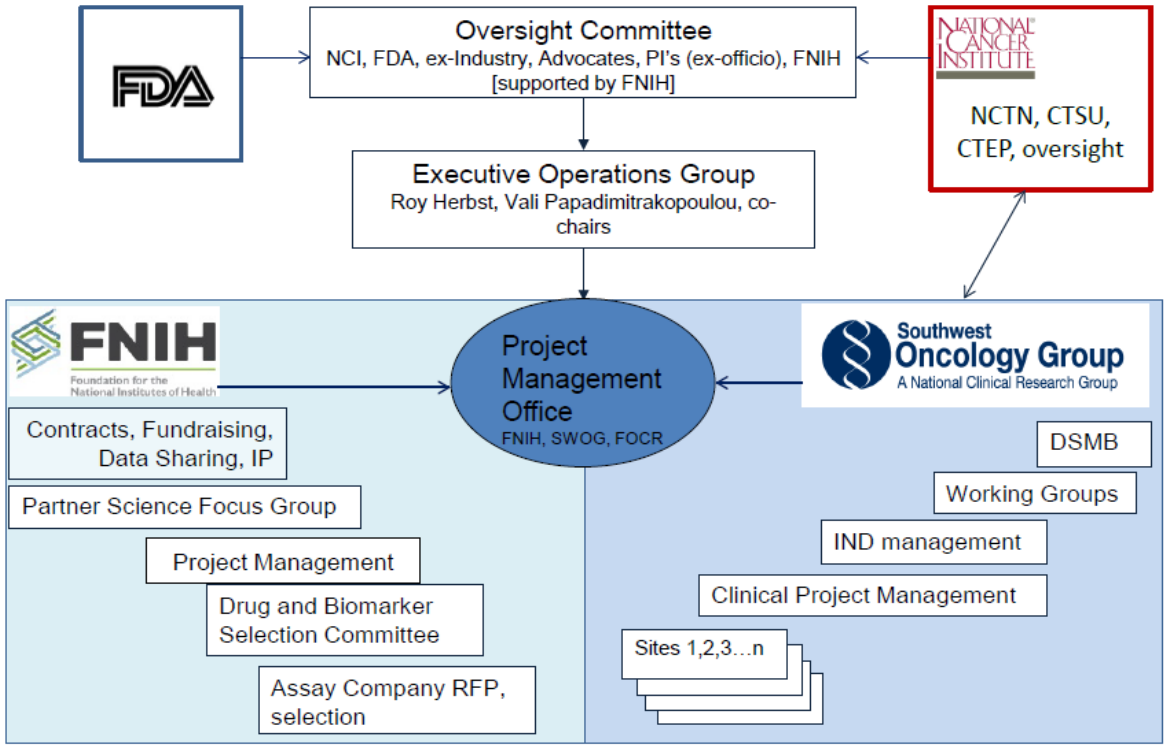
Plan For the Talk

1. The Birth of Lung-MAP

2. Top Ten: Partnerships, Achievements, and Lessons Learned

3. Thoughts for the Future

#1 It takes a Village: Teamwork breeds success



FOUNDATION MEDICINE · AstraZeneca · Bristol Myers Squibb · abbvie · Pfizer · Genentech BIOONCOLOGY · AMGEN · Lilly · MedImmune · MERCK · CLOVIS ONCOLOGY · LOXO ONCOLOGY (Wholly owned subsidiary of Eli Lilly and Company) · ImmunityBio

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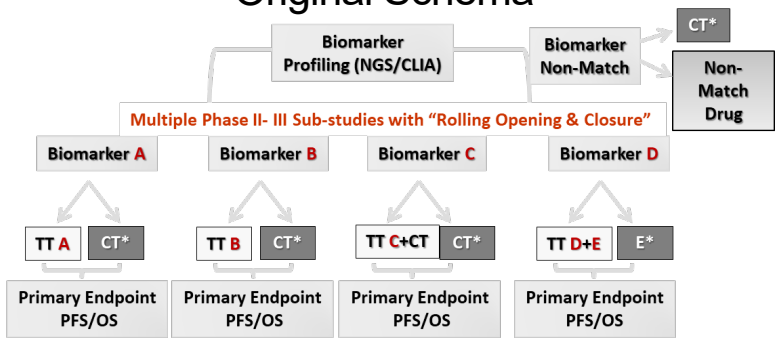
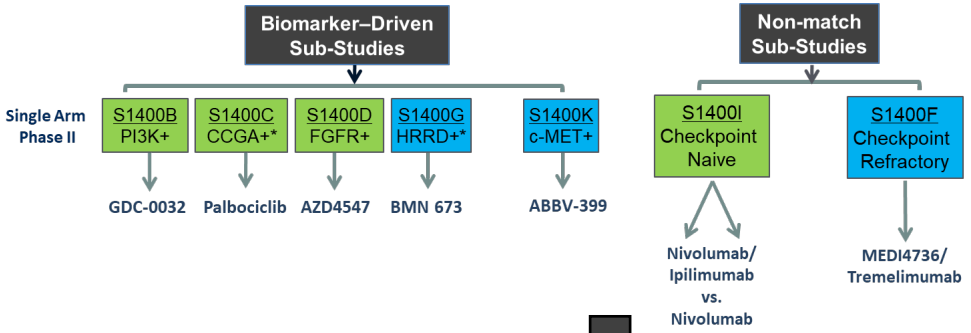
#2 Evolve with the treatment landscape

Original Schema

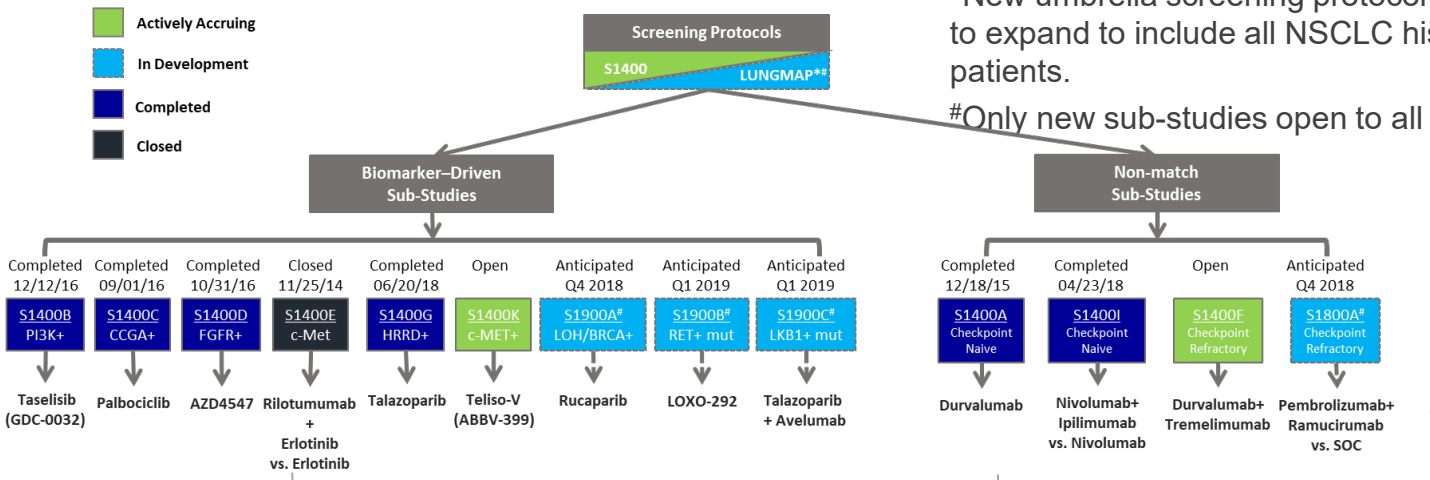


Squamous Only, SWOG, 2014

Revision Responding to Immunotherapy Approval



Current Schema



*New umbrella screening protocol (**LUNGMAP)** will allow the trial to expand to include all NSCLC histologies and include more patients.

#Only new sub-studies open to all NSCLC histologies.

Full intergroup governance

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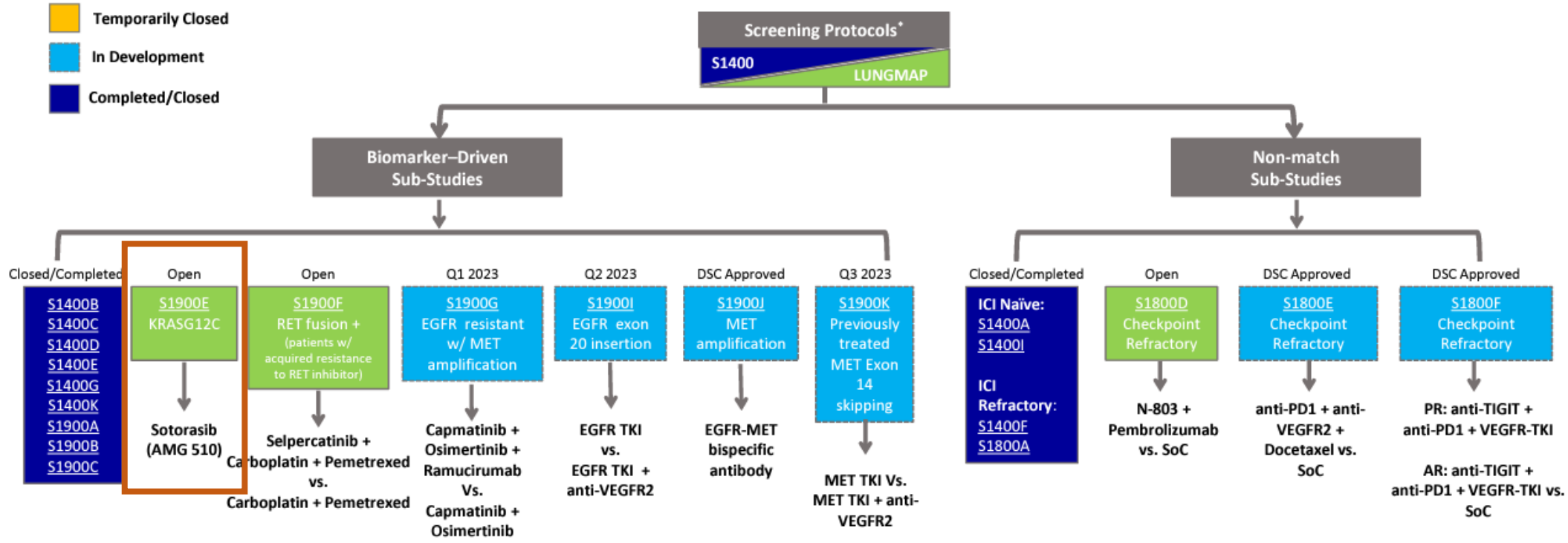
Current Lung-MAP Schema 2022

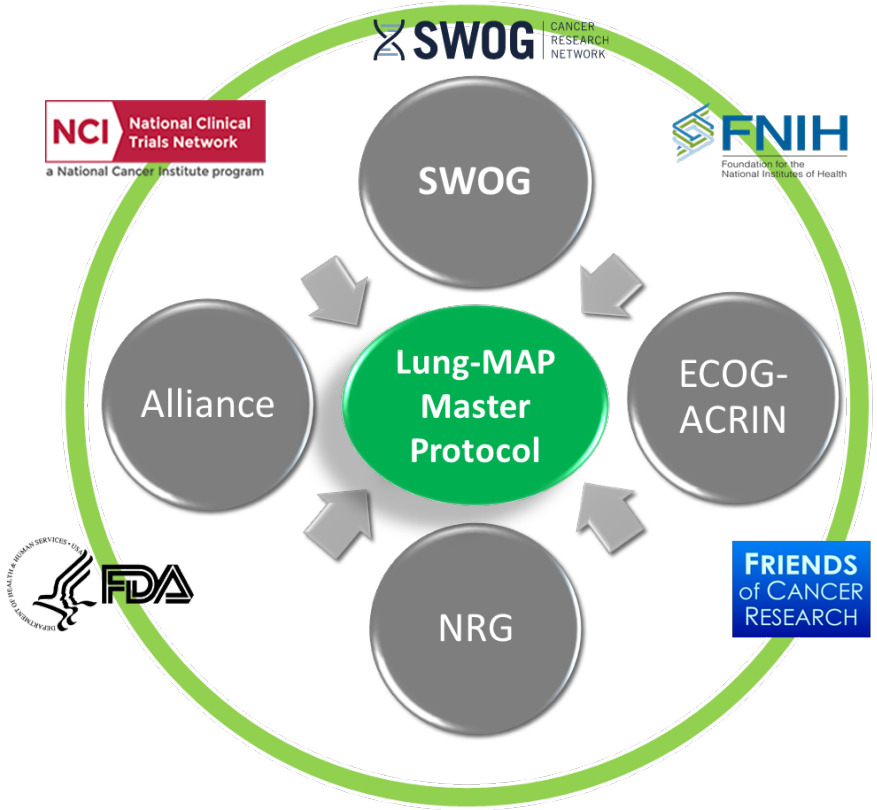


*LUNGMAP screening protocol (activated 1/28/19) allows all histologic types of NSCLC. S1400, the original screening/umbrella protocol included only squamous lung cancer. S1400 accrued patients between 6/16/2014 and 1/28/2019. While S1400 is closed to accrual, patients enrolled to S1400 may participate in sub-studies they are eligible for.

TRIAL POINTS OF INTEREST:

- Each of sub-study operates independently of the others
- Prescreening can be performed while the patient is on any line of therapy for stage IV disease
- Repeat or fresh biopsy necessary for tissue screening is paid 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.**

#3 Cohesive project management is crucial

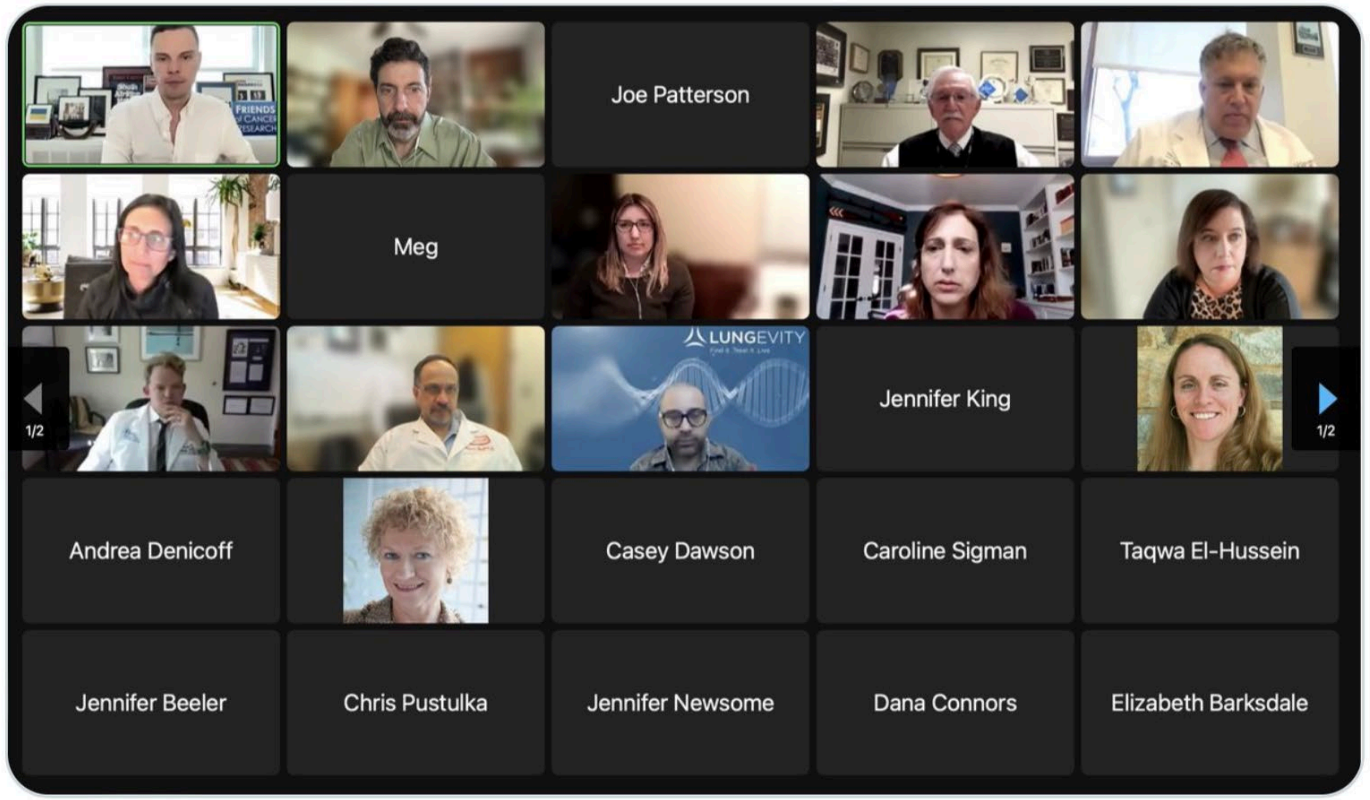


- Neutral third-party purse-holder, project manager, and contractor is beneficial
- Migration to a centralized IRB and introducing other protocol efficiencies is crucial for long-term survival and enrollment in the trial

Accrual E

Lung-MAP @LungMAP · Mar 29

LungMAP team meeting today w leaders of patient #advocacy groups to update them on #NSCLC master protocol and what's in the works for potential future studies. Advocate collaboration is critical to continued success! #NSCLC @LUNGevity @EGFRResisters @GO2Foundation @CrusadersMet



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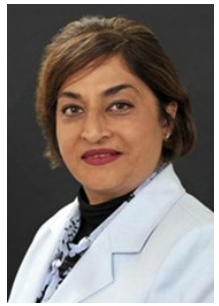
#4 Drug selection is critical with a choice of trial designs

- More than 30 formal drug selection committee meetings since 2013
  - >40 drugs
  - >20 companies engaged in discussions
- Additional ad hoc meetings to discuss pathways and targets
- Monthly internal drug selection committee meetings started in 2017 managed by Beverly Smolich from CCS Associates

Hossein Borghaei, DO, MS
Martin Edelman, MD



Shakun Malik, MD

Targets and combinations evaluated since 2013:

c-MET	KRAS (G12)	PD-L1/TIM-3 ± PARP
EGFR	HDAC	HDAC/PD-1
FGFR	PD-1/CTLA-4	IL-15/PD-1
PI3K	PD-L1/CTLA-4	c-MET/EGFR/VEGFR
CDK4/6	EGFR/PD-1	TIGIT/PD-1/TKI
PD-L1	c-MET, AXL	c-MET/VEGFR
PARP	IL-2 (Prodrug)/PD-1	EGFR/VEGFR
ERBB3	TORC1/2/CTx	PD-1/CTx/VEGFR
TKI	RET	
Glutaminase	PARP/PDL-1	

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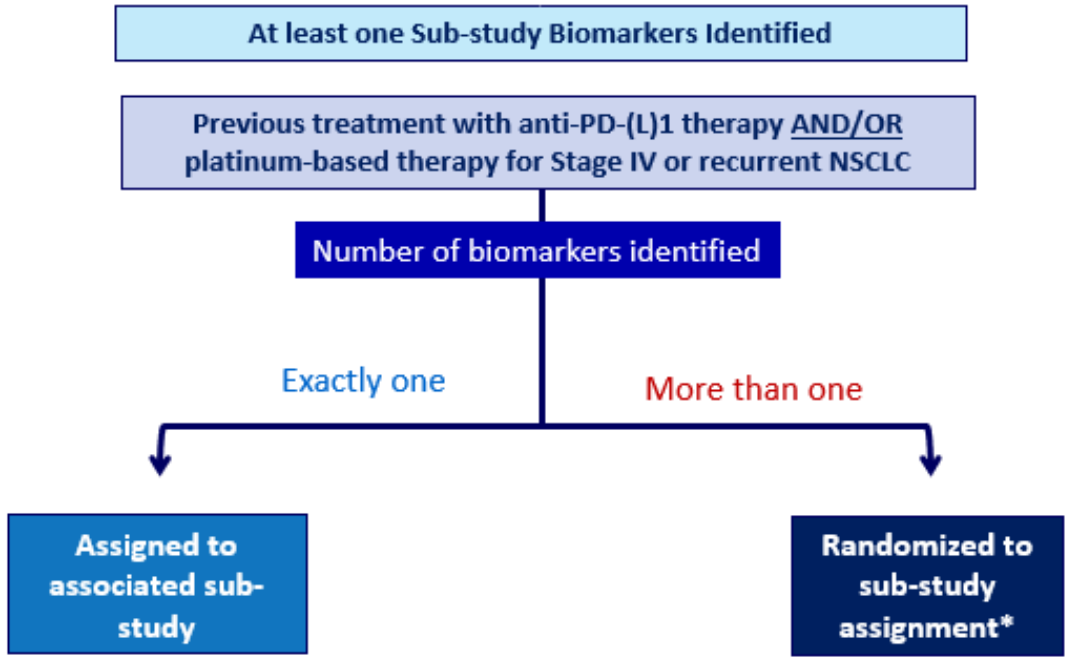
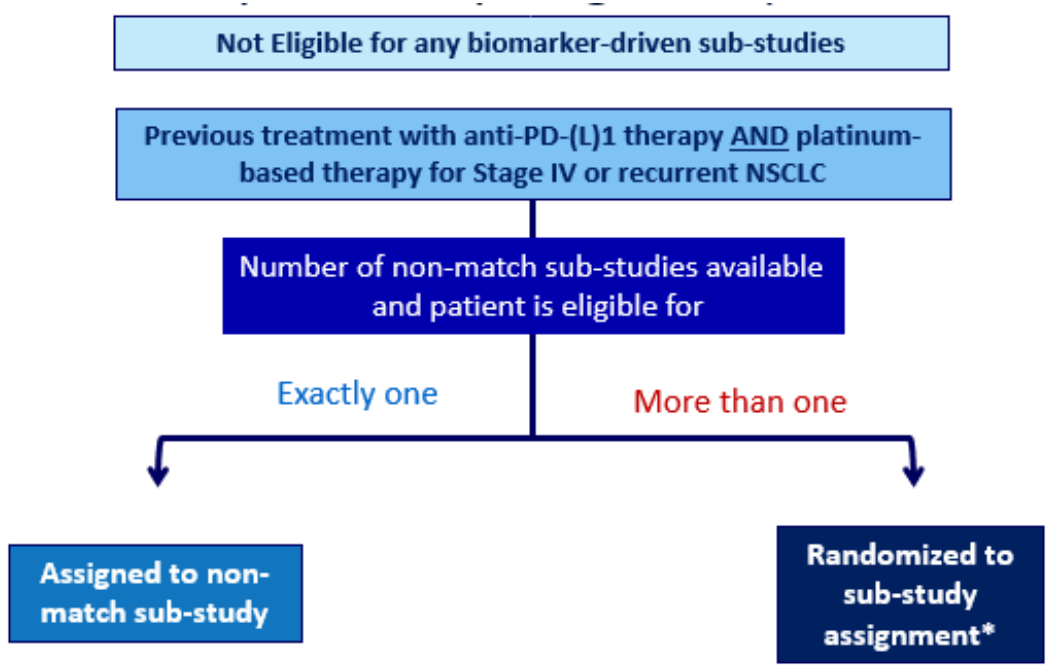
Sub-study design and assignments

Biomarker-driven Sub-study Assignments



Non-match Sub-study Assignments



*Randomization for patients with multiple sub-study biomarkers identified uses a weighted approach which favors assignment to sub-studies with lower estimated prevalence

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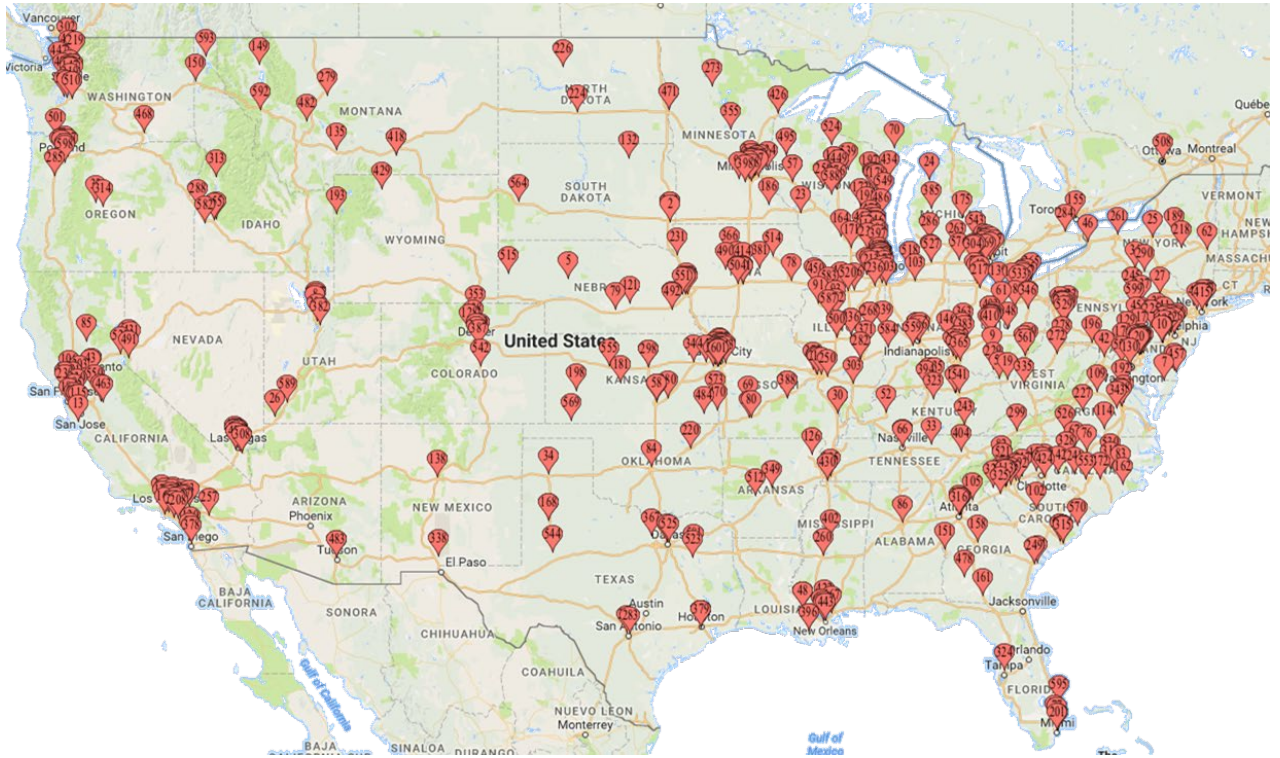
#5 Pre-screening provides access to a large number of patients

As of 09/28/22	Total	S1400	LUNGMAP
Screening Registrations	**4579**	**1864**	**2715**
Screened at PD	2129	1127	1002
Pre-screened*	2450	737	1713
Sub-study Assignments	**2947**	**1484**	**1463**
Among Screened at PD	1830	996	834
Among Pre-screened	995	414	581
Additional Assignments after PD on a Sub-study	122	74	48
Sub-study Registrations	**1078**	**690****	**388**

~4,600 patients screened since 2014



David Gandara, MD

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#6 Improved clinical trial diversity

Riha Vaidya, PhD

Mary Redman, PhD

	Lung-MAP (N=3,556)	SWOG NSCLC (N=2,215)	US NSCLC Population
Age ≥ 65 years	57.2%	46.3% *	69.8% *
Female	38.6%	47.2% *	46.0% *
Race: Black	9.2%	8.2%	14.1% *
Race: Asian/Pacific Islander	2.8%	5.1% *	4.8% *
Race: Native American	0.5%	0.4%	0.5%
Ethnicity: Hispanic	2.4%	3.8% *	5.1% *
Rural residence	17.3%	14.4% *	-- §
Areas with highest social needs	42.2%	36.7% *	-- §
Medicaid/No Insurance (if age < 65 years)	27.6%	17.8% *	-- §

* Difference versus Lung-MAP statistically significant ($p<0.01$)

§ No population-level data available for geographic/SES comparisons

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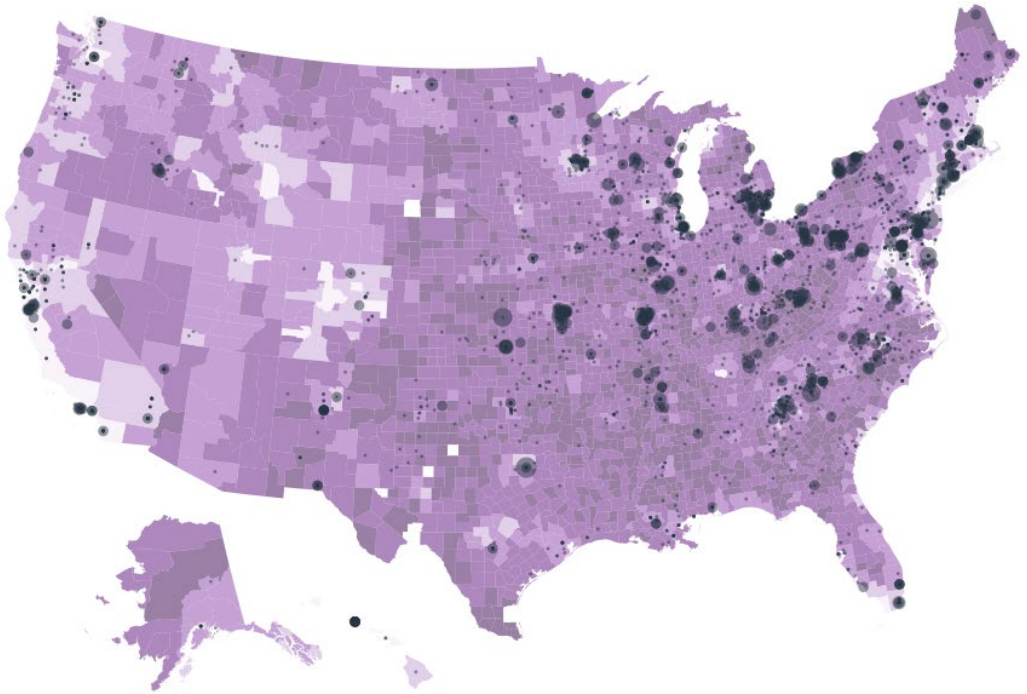
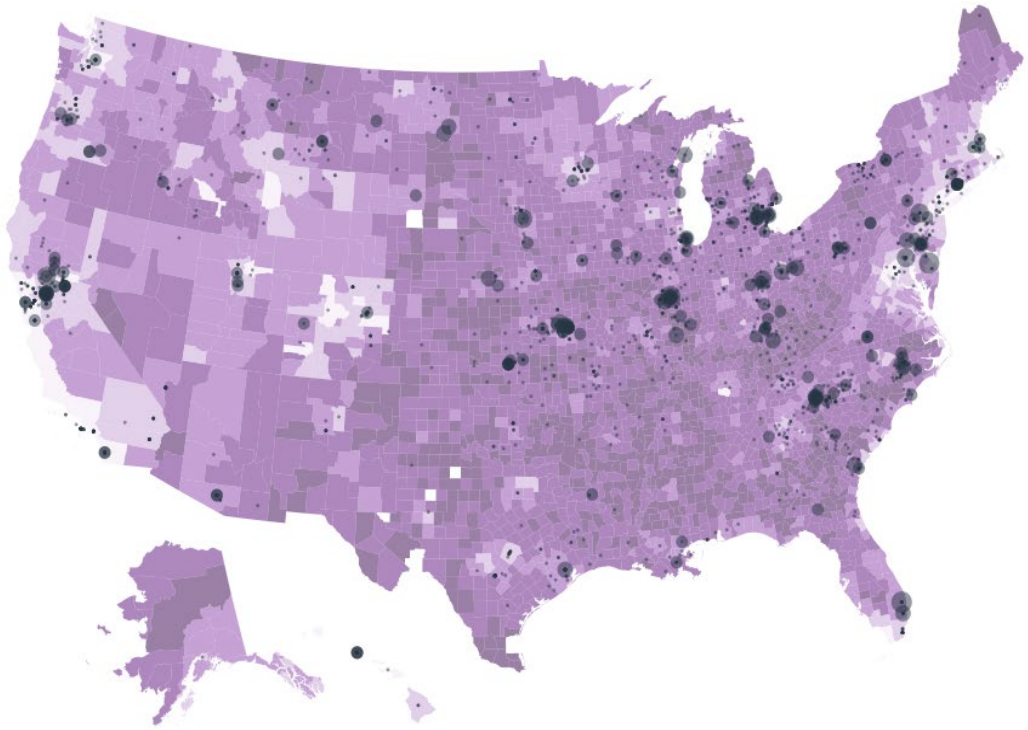
Enrollment by Area Deprivation (Rural)

LUNGMAP Accruals 1/1/2014 - 12/31/2020



NSCLC Studies Accruals 1/1/2001 - 12/31/2020



Lung-MAP DEI Strategies: We have more work to do!

- Formed Lung DEI Sub-Committee
- Supporting Community Sites conducting a DEI Gap Analysis
- Engagement with Lung Cancer Advocacy Group
- GO2 DEI Presentation on Nov 1

Lucy Gansauer, MSN, RN
Lung Committee DEI Champion

Jhanelle Gray, MD

Characteristic	US Census 2021 est.	LungMAP Master*
White	75.8%	86%
Black or African American	13.6%	10%
Asian	6%	2%
Pacific Islander	0.3%	<1%
Native American	1.3%	<1%
Multi-Racial	1.3%	<1%
Unknown	2%	2%
Hispanic or Latino (of any race)	18.2%	2%

*Fall 2022 Lung Committee Report of Studies

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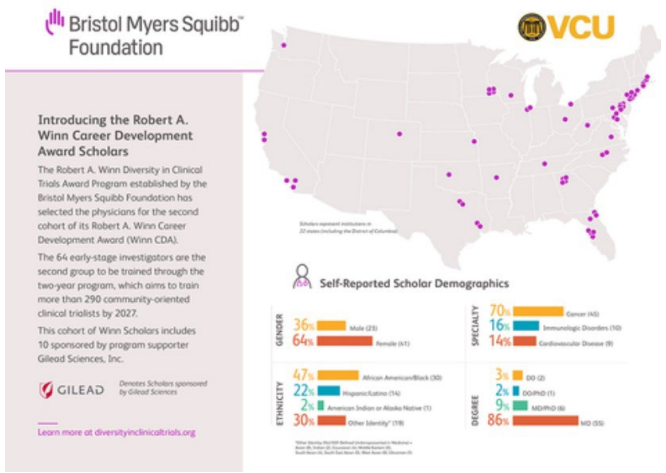
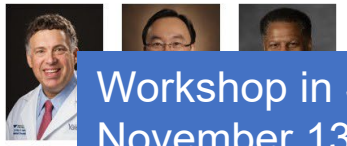
The Robert A. Winn Diversity in Clinical Trials Award Program Announces the Second Group of Physicians to be Trained in the $114 Million Program

64 physicians comprise Cohort II, bringing the total to 116 participants in the program's second year



BMSF-AACR Design and Implementation of Clinical Trials Workshop

Workshop Codirectors
Roy S. Herbst, MD, PhD, Yale University Cancer Center, New Haven, CT
Yu Shyr, PhD, Vanderbilt University Medical Center, Nashville, TN
Robert A. Winn, MD, VCU Massey Cancer Center, Richmond, VA

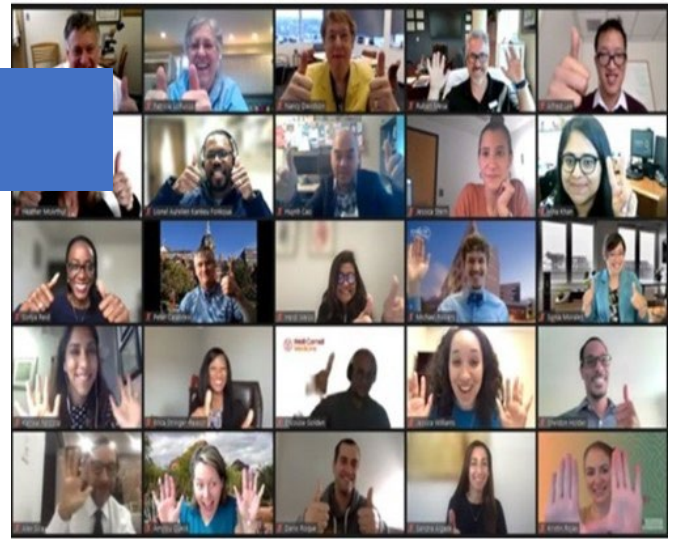


Workshop in Santa Monica
November 13-19 2022

Steering Committee
Elliott M. Antman, MD, Brigham and Women's Hospital, Boston, MA
Peter A. Calabresi, MD, Johns Hopkins University School of Medicine, Baltimore, MD
Marcia R. Cruz-Correa, University of Puerto Rico School of Medicine, San Juan, PR
Nancy E. Davidson, MD, Fred Hutchinson Cancer Research Center, Seattle, WA
Carmen E. Guerra, MD, MSCE, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA
Ruben A. Mesa, MD, Mays Cancer Center at UT Health San Antonio at MD Anderson, San Antonio, TX





2021 virtual mtg

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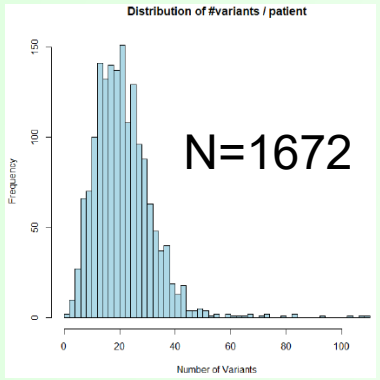
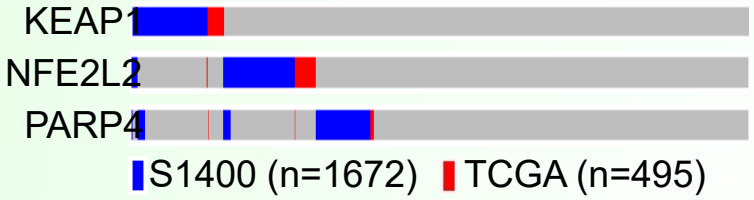
#7 Translational Medicine is Key

S1400: Largest NGS dataset of advanced squa. cell lung cancers of previously treated patients

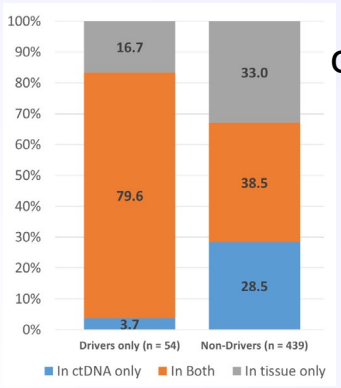


Novel finding: mutual exclusivity of PARP4, KEAP1 & NFE2L2 alterations

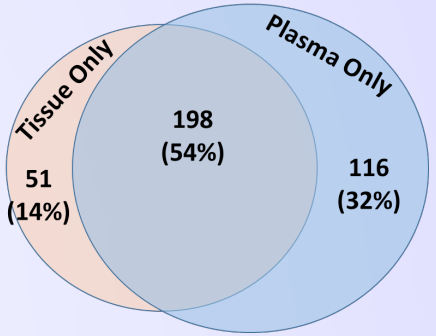


Kozono et al. WCLC 2020

Use of liquid biopsy data in LUNGMAP



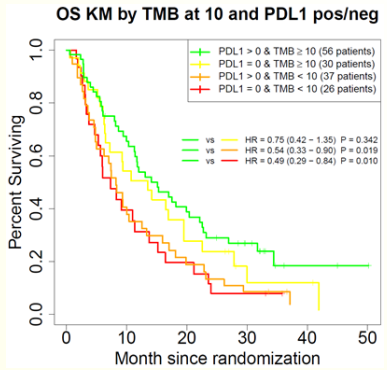
High tumor tissue-ctDNA concordance supports use of mutations found in ctDNA for enrollment onto LUNGMAP sub-studies



Mack et al. WCLC 2020

Immuno-oncology biomarkers in S1400 sub-studies

Combination of higher tumor mutational burden (TMB) and PD-L1 expression impacted survival outcomes in the S1400I randomized study of nivolumab ± ipilimumab



Hirsch et al. WCLC 2020

Upcoming Highlights

- Composite Immune Checkpoint Inhibitor signature for efficacy of ICI therapy in advanced squamous cell lung cancer (Gandara et al.)
- ctDNA analyses in Lung-MAP sub-studies
- Addition of protein biomarkers to Lung-MAP to facilitate novel immuno-oncology and antibody-drug conjugate sub-studies

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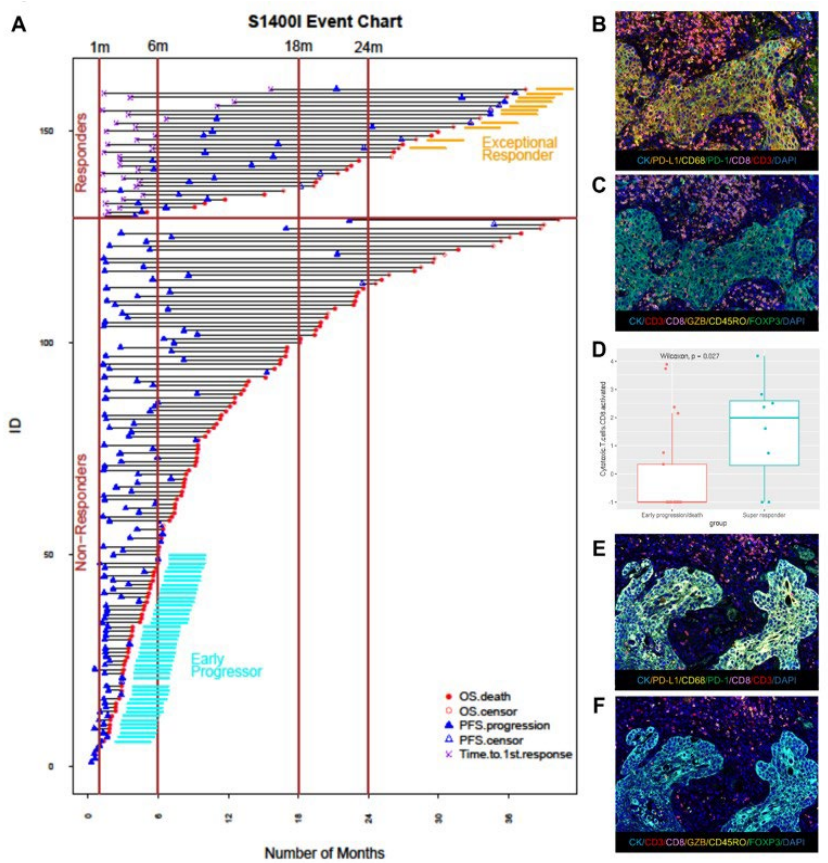
Lung-MAP Translational Medicine

Multi-omics profiling reveals molecular and immune features associated with benefit from immunotherapy for advanced squamous cell lung cancer patients from the phase III SWOG Lung-MAP S1400I trial

CIMAC-CIDC
Immuno-Oncology
Biomarkers Network

Ignacio Wistuba Md, PhD



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#8 1800A: The eagle has landed: ASCO 2022


Karen Reckamp, MD, MS


Konstantin H. Dragnev, MD

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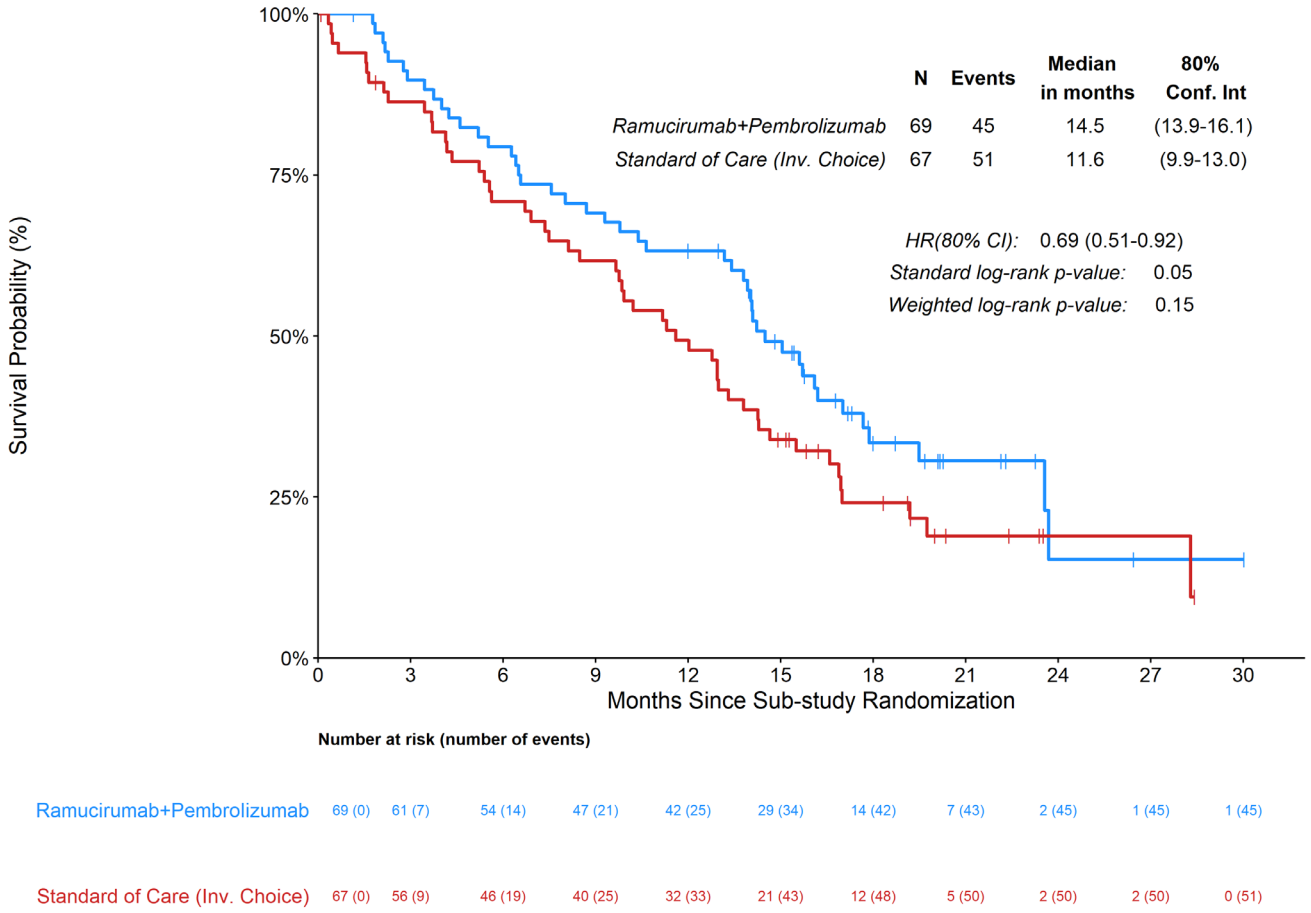
Overall survival: IO Combo hit the endpoint
Ramucirumab and pembrolizumab in previously treated advanced NSCLC



Median OS for RP 14.5 months v. SOC 11.6 months

HR= 0.69; SLR p-value 0.05

Standard of care therapy received:

- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

#9 Pragmatica Lung Trial

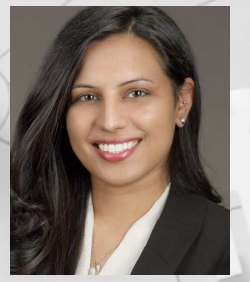
Pragmatica

A real-world clinical trial for patients whose non-small cell lung cancer has returned after immunotherapy

Breakthrough Designation Under Review

Working closely with FDA, NCI and NCTN partners on a Pragmatic trial


Richard Pazdur, MD

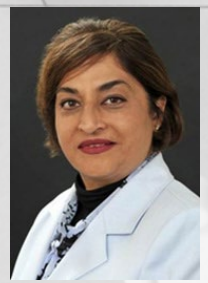

Harpreet Singh, MD


Karen Reckamp, MD, MS


Konstantin Dragnev, MD


Mary Redman, PhD


Ellen Sigal, PhD


Shakun Malik, MD


Jhanelle Gray, MD


Roy Herbst, MD PhD

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Lilly MERCK

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#9 Pragmatica Lung

MERCK Lilly

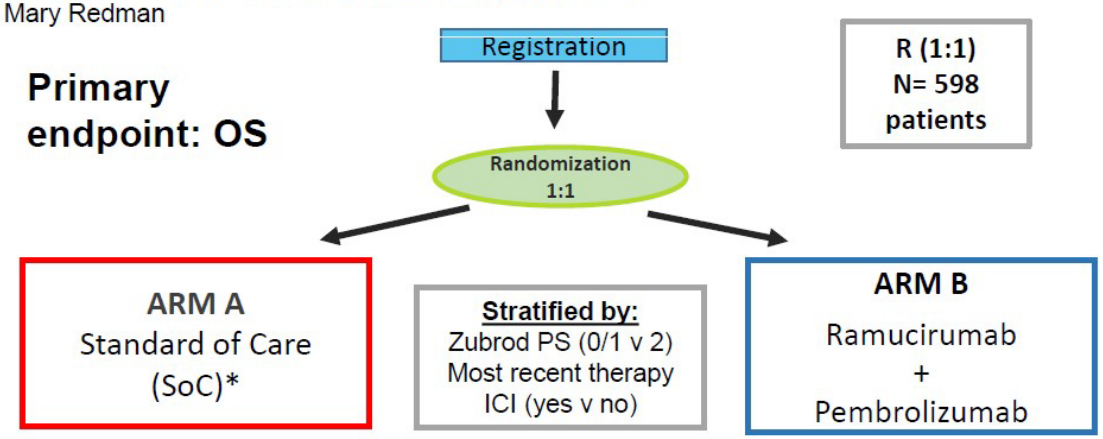
Phase III Rationale

- Effective therapy following frontline ICI for NSCLC is needed with limited FDA-approved options.
- We propose a pragmatic clinical trial design to promote diversity and inclusion in clinical trials.
- The aim of the trial is to validate the improvement in overall survival demonstrated in S1800A.
- The purpose is to empower investigators to treat patients as would be done in real world practice.
- The design is novel and potentially paradigm-changing to decrease barriers to enrollment and minimize the data collection burden.

S2302 Treatment/Schema

S2302, PROJECT PRAGMATICA: A PROSPECTIVE RANDOMIZED STUDY OF RAMUCIRUMAB (NSC 749128) PLUS PEMBROLIZUMAB (MK-3475; NSC 776864) VERSUS STANDARD OF CARE FOR PARTICIPANTS PREVIOUSLY TREATED WITH IMMUNOTHERAPY FOR STAGE IV OR RECURRENT NON-SMALL CELL LUNG CANCER

Chair: Karen Reckamp, MD; Co-chair: Konstantin Dragnev, MD; TBD
Statistician: Mary Redman



*SoC treatment is to be determined by the treating investigator and participant. It is recommended that the choice of SoC drug(s) is based on NCCN guidelines for a "systemic therapy for advanced or metastatic disease-subsequent."

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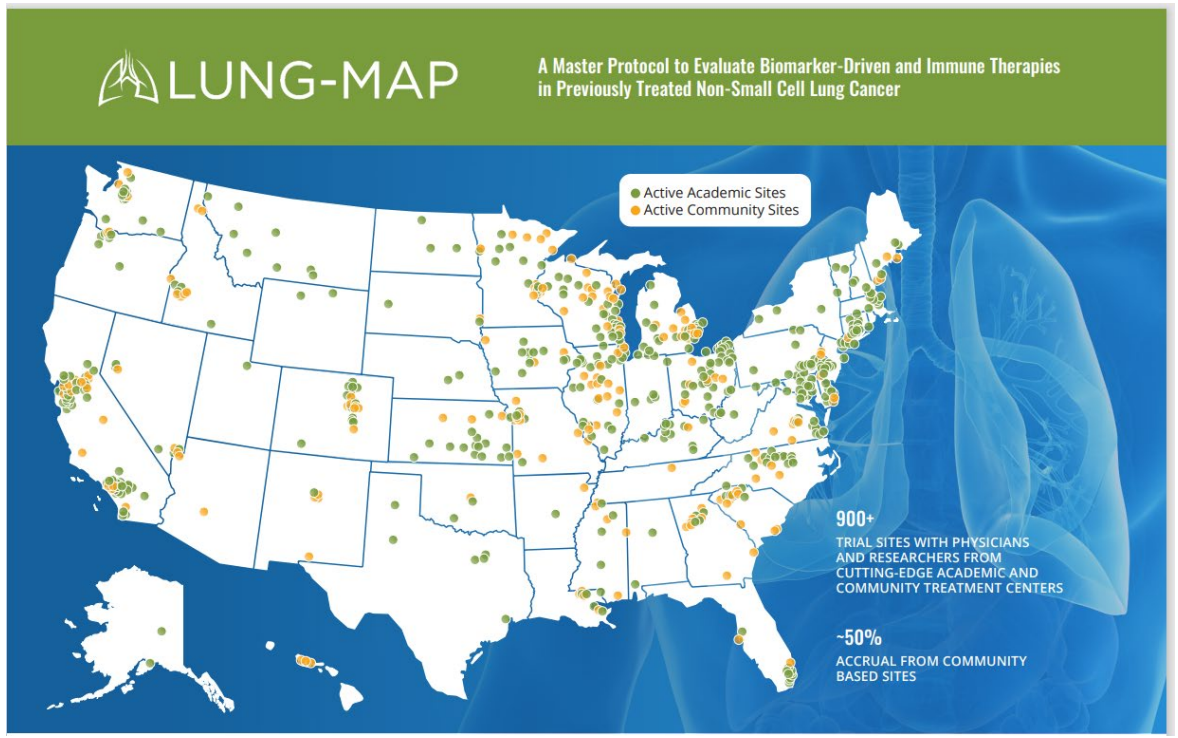
#10 It's about the patient

I am more confident than I have been in a long time. Lung-MAP gave me my life back. *~ Clifford C.*

Most importantly, we are grateful Lung-MAP has helped many patients and we want to amplify our success so far by opening the trial to more patients!

I continue to be so grateful for everyone involved. Even after 48 visits for my opdivo infusion!
~ Annie B.

And We Have Helped Many Patients Lung Map By the Numbers



Nearly 30 Public and Private Collaborators and Supporters in Partnership since 2014

13
PARTNERING PRECISION MEDICINE DIAGNOSTIC COMPANIES AND LEADING PHARMACEUTICAL COMPANIES

15
INVESTIGATIONAL DRUGS OR DRUG COMBINATIONS TESTED

16 Initiated | 14 Completed
SUB-STUDIES CONDUCTED

10
AGENTS AGAINST SPECIFIC TUMOR MUTATIONS/GENETIC SIGNATURES TESTED IN NSCLC

12
MONTH AVERAGE SUB-STUDY STAND UP TIME FROM APPROVAL BY THE LUNG-MAP DRUG SELECTION COMMITTEE TO ACTIVATION

22
MONTH AVERAGE TIME TO TARGET ACCRUAL COMPLETION FOR ~80 PERSON STUDY, DRIVEN BY BIOMARKER PREVALENCE

7
SUPPORTING PATIENT ADVOCACY GROUPS

~4,250 | ~650 Per Year
PATIENTS SCREENED

~2,750
PATIENTS ELIGIBLE FOR A TREATMENT IN A WELL-DESIGNED TRIAL

~1,000 | 150+ Per Year
PATIENTS TREATED WITH CUTTING-EDGE THERAPIES

300+
ALTERED GENES INTERROGATED IN EACH PATIENT'S TUMOR

24%
UNDERSERVED MINORITY PARTICIPANTS ENROLLED

8
ORGANIZATIONS, INCLUDING NCI AND FDA, WORKING TOGETHER TO CONDUCT AND OVERSEE THE STUDY

10,000+
ANNOTATED SPECIMENS IN A TISSUE BANK TO ALLOW DEEPER SCIENTIFIC STUDIES TO influence FUTURE TRIALS

35+
PUBLICATIONS AND ABSTRACTS

Additional Benefits of Lung-MAP

SHARED COSTS AND RISKS OF TESTING THERAPEUTICS FOR COMPANIES

FOSTERING DRUG COMBINATION COLLABORATIONS BETWEEN COMPANIES

ACCELERATED TIMEFRAMES FOR EVALUATION OF TREATMENT EFFICACY DUE TO THE LARGE NETWORK

STRONG SUPPORT FROM THE FDA WITH ABILITY FOR STUDIES TO HAVE REGULATORY INTENT

Highly Motivated Expert Partners for Trial Conduct

FNIH · FRIENDS of CANCER RESEARCH · NCI National Clinical Trials Network · SWOG CANCER RESEARCH NETWORK · ECOG-ACRIN cancer research group · NRG ONCOLOGY · ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

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Thoughts for the Future

- Master protocols provide efficiencies and can be very successful
- Implementation can be complicated: Oversight, conduct, and monitoring are more involved than a single study, or even the same number of independent studies
- A major lesson learned is the need for up-front planning, communication, and specification or roles. Need for constant innovation, aggressive timelines and teamwork
- A major key to success is flexibility within a principled set of constraints
- Let the science drive the trials- learn from translational research
- Promote access and diversity- to help the most patients with NSCLC!!

Thank You





Thank You Team Science At Its Best!