LUNG-MAP Kick-Off Training Meeting

S1400 Lung Master Protocol

Friday, May 2, 2014

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Agenda

Welcome	David Gandara, MD
Background	Roy Herbst, MD, PhD
Study Overview	Vassiliki Papadimitrakopoulou, MD
Specimen Requirements	Fred Hirsch, MD, PhD
Statistical Overview	Mary Redman, PhD
Registration and Study Flow	Austin Hamm, BA, CCRP
Imaging	Lawrence Schwartz, MD Michael Knopp, MD, PhD
Informed Consent, Quality Assurance and Monitoring	Elaine Armstrong, MS
Panel Presentation / Questions and Answers	

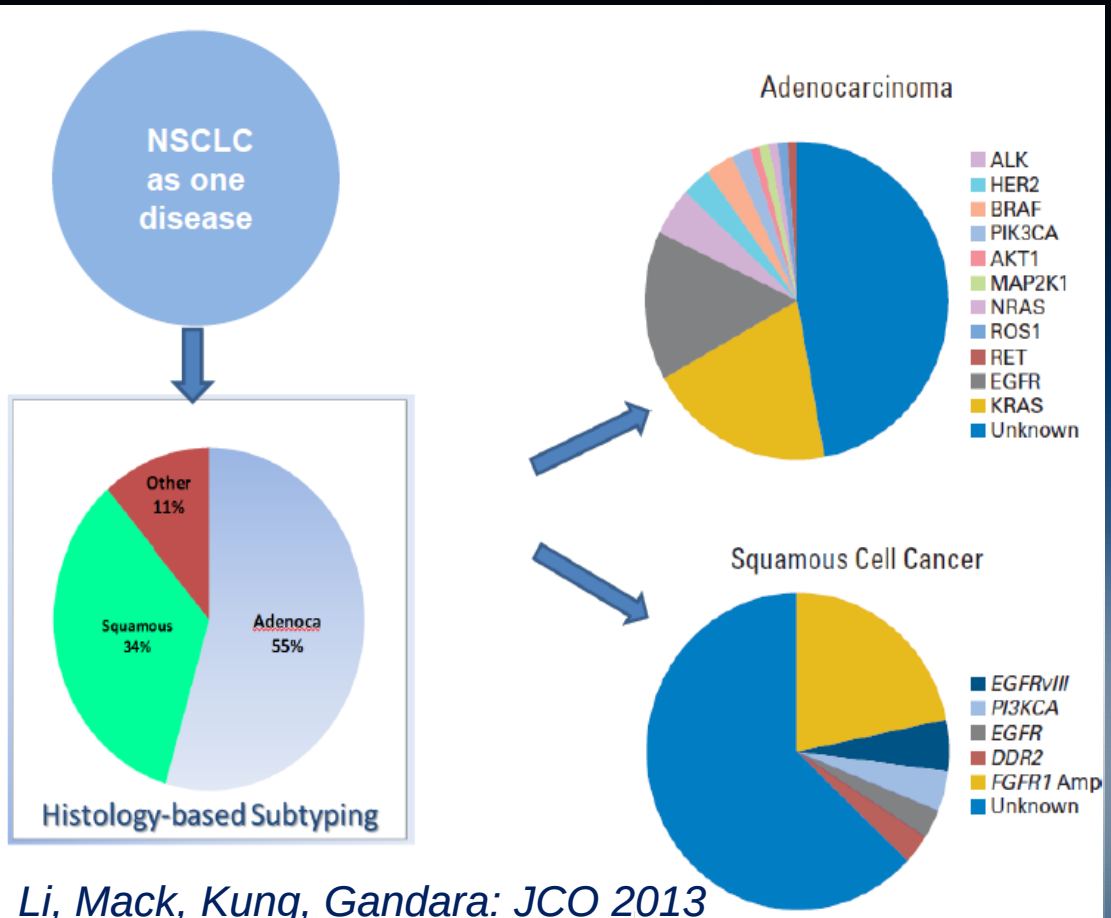
Welcome

David R. Gandara, MD
UC Davis Comprehensive Cancer Center
SWOG Lung Cancer Committee Chair

Addressing unmet needs in Drug-Biomarker Co-Development

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



Li, Mack, Kung, Gandara: JCO 2013

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)

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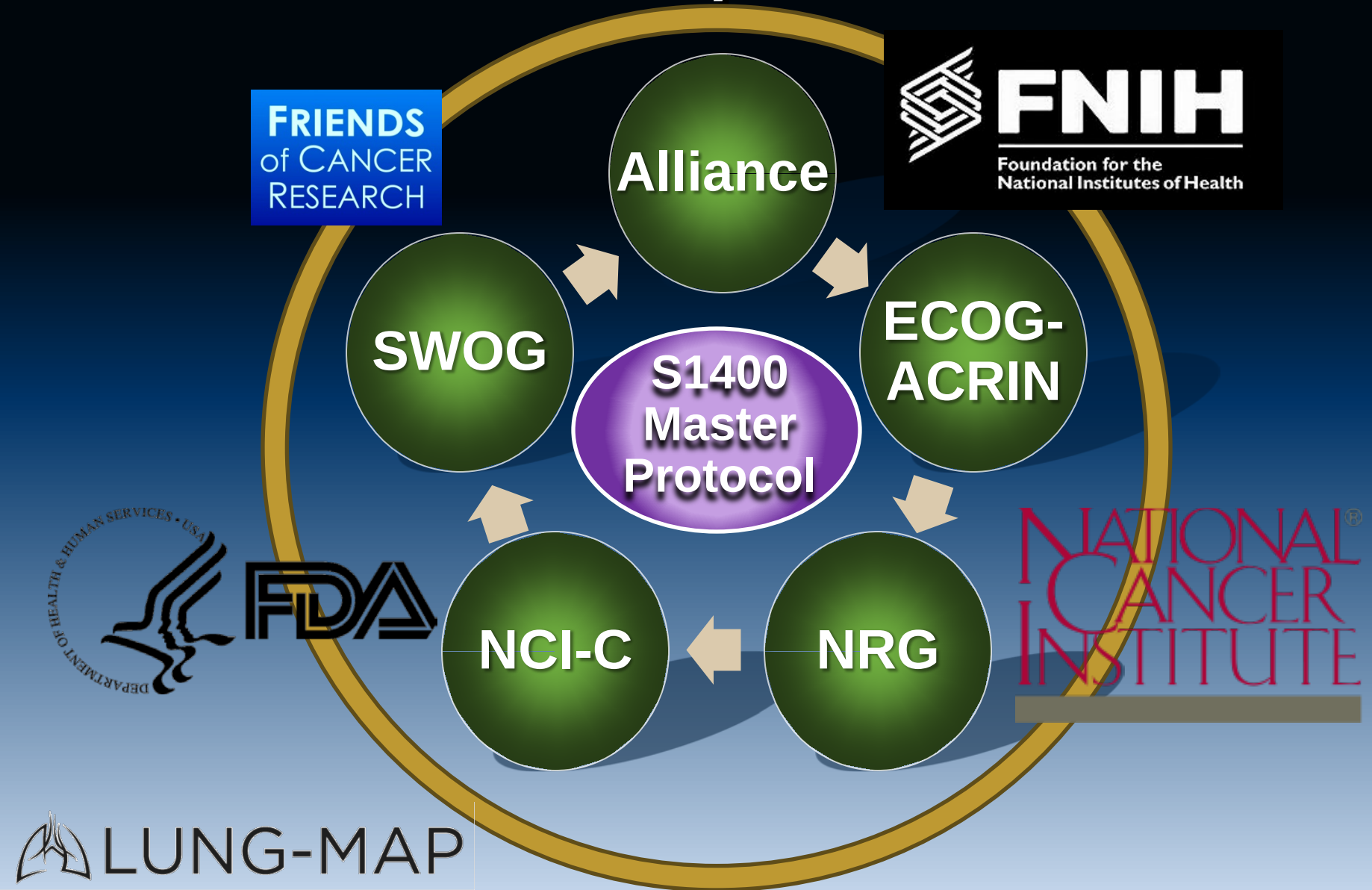
S1400 Master Protocol Unique Private-Public Partnerships with the NCTN



Background

Roy Herbst, MD, PhD

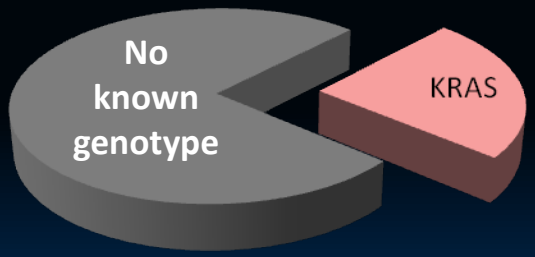
Study Chair, Steering Committee/Targeted Agent Selection Committee Co-Chair

Ensign Professor of Medicine
Professor of Pharmacology
Chief of Medical Oncology
Director, Thoracic Oncology Research Program
Associate Cancer Center Director for Translational Research

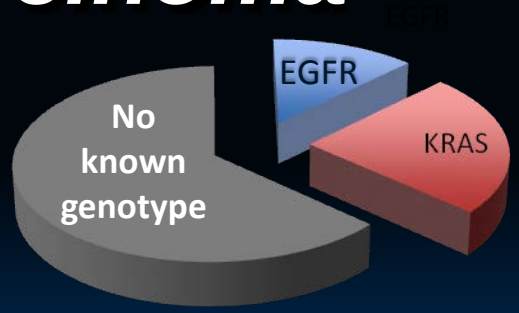
Smilow Cancer Hospital at Yale-New Haven

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

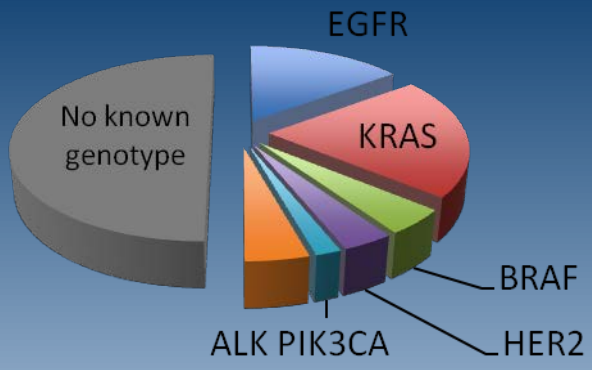
Evolution of Identification of Genomic Alterations in Lung Adenocarcinoma



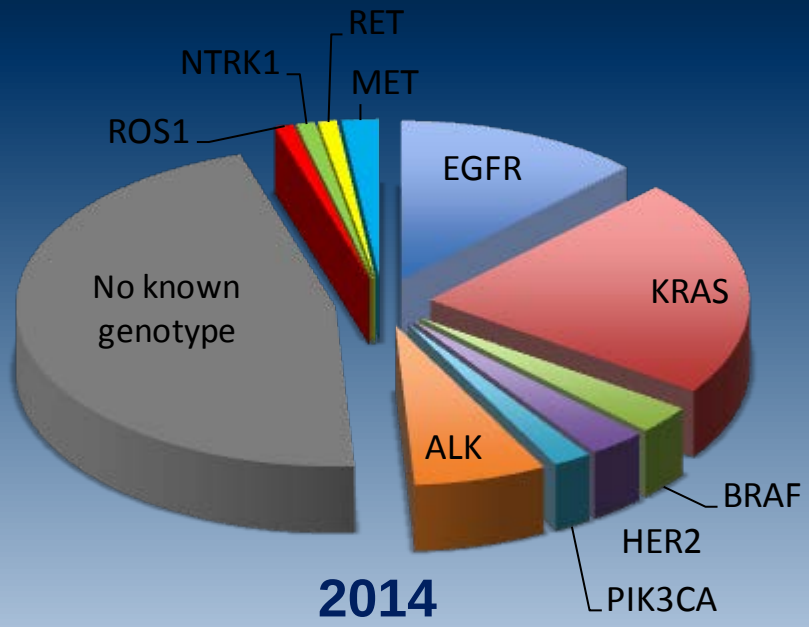
1984 - 2003



2004



2009



2014

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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

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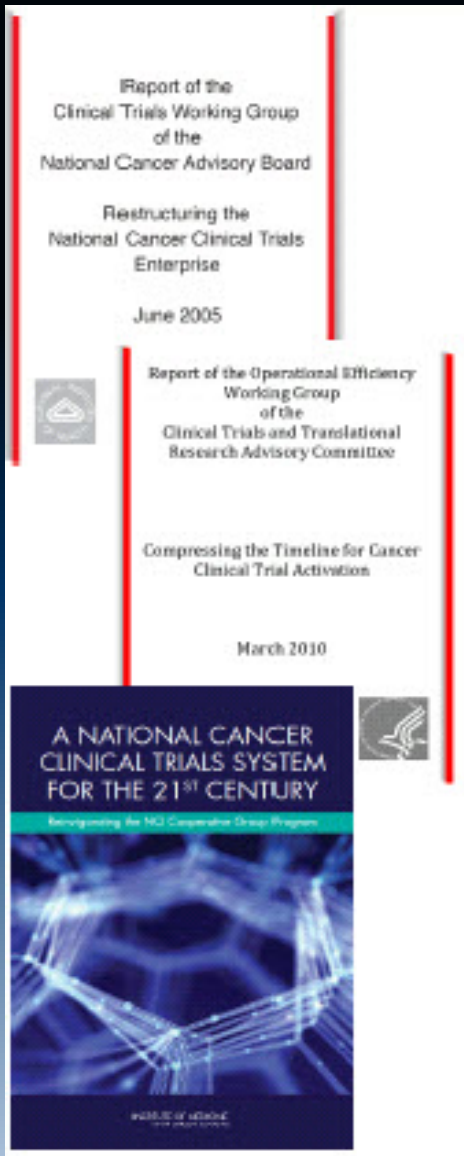
IOM Report on Clinical Trials



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

Detailed genomic analysis of SQUAMOUS cell lung cancers has identified several new potential therapeutic targets

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%
PDGFRA	Amplification/Mutation	9%
EGFR	Amplification	10%
MCL1	Amplification	10%
BRAF	Mutation	3%
DDR2	Mutation	4%
ERBB2	Amplification	2%

- 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

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Peter Hammerman et al. WCLC 2011

Rationale for Master Protocol Design

- **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**

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Parallel Efforts in Master Protocol Design for Non-Small Cell Lung Cancer

Thoracic Malignancies Steering Committee (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

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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, 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	**Jack Welch,** NCI
Peter Ho, QI Oncology	**Ignacio Wistuba**, MD Anderson
Pasi Janne, Dana Farber Cancer Institute	**Jamie Zwiebel,** NCI

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

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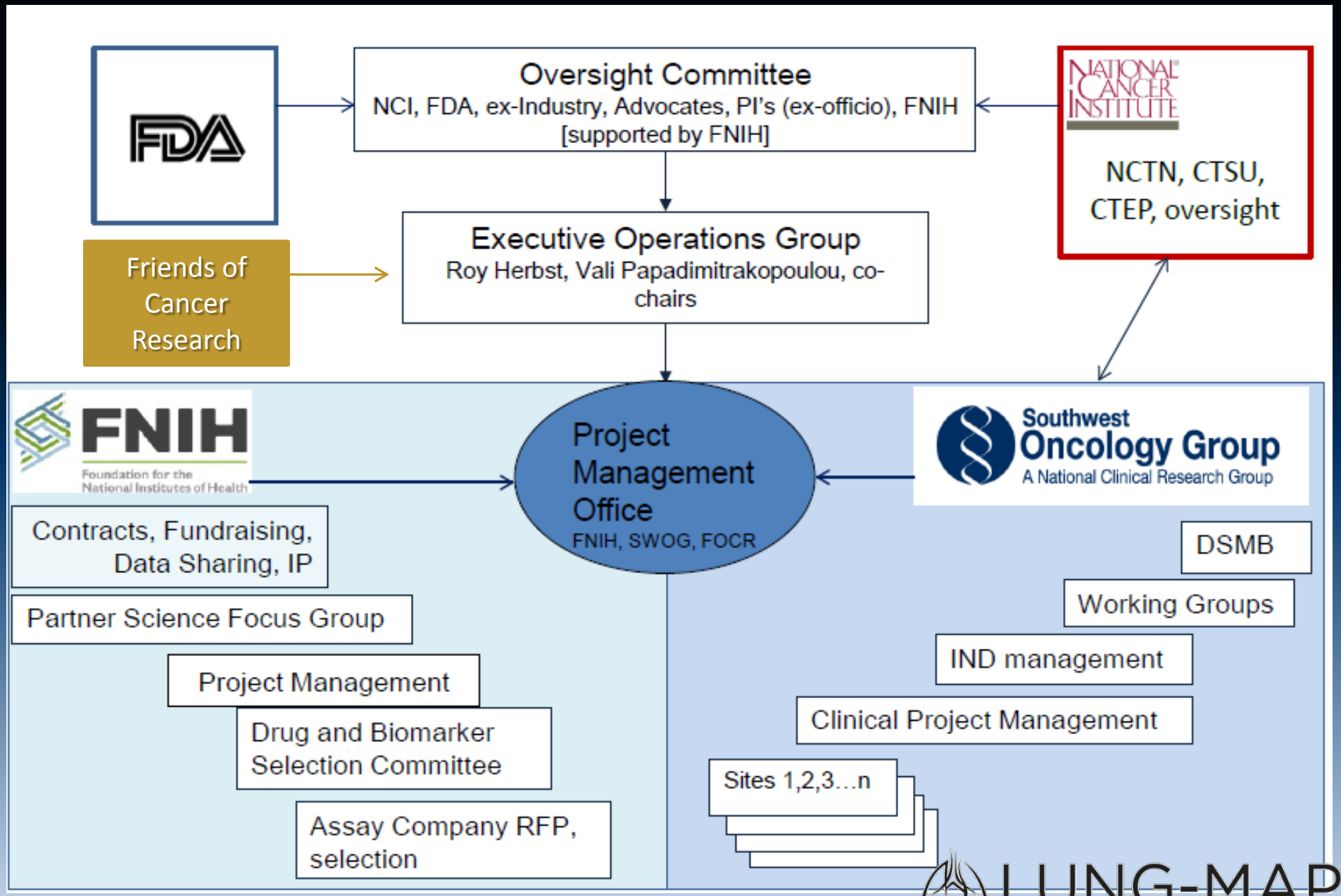
Governance Structure:



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Study Overview

Vassiliki Papadimitrakopoulou, MD
Study Chair, Medical Oncology

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"Phase II/III Biomarker-Driven Master Protocol for Second Line Therapy of Squamous Cell Lung Cancer."

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PHASE II/III BIOMARKER-DRIVEN MASTER PROTOCOL FOR SECOND LINE THERAPY OF SQUAMOUS CELL LUNG CANCER.

NCT #TBD

STUDY CHAIRS:

Vassiliki A. Papadimitrakopoulou, M.D.
(Medical Oncology)
M.D. Anderson Cancer Center
1515 Holcombe Blvd., Unit 432
Houston, TX 77030-4009
Phone: 713/792-6363
FAX: 713/792-1220
E-mail: vpapadim@mdanderson.org

Fred R. Hirsch, M.D., Ph.D.
(Translational Medicine)
University of Colorado Cancer Center
P.O. Box 6511, MS 8117
Aurora, CO 80045
Phone: 303/724-3858
E-mail: fred.hirsch@ucdenver.edu

Philip C. Mack, Ph.D. (Translational Medicine)
UC Davis Cancer Center
Division of Hematology/Oncology
4501 X Street
Sacramento, CA 95817
Phone: 916/734-8022
FAX: 916/734-2361
E-mail: pcmack@ucdavis.edu

Roy S. Herbst, M.D., Ph.D.
(Steering Committee/Targeted Agent Selection Committee Co-Chair)
Yale Cancer Center
Section of Medical Oncology
333 Cedar Street, WWW221
New Haven, CT 06520-8028
Phone: 203/785-6879
FAX: 203/785-4116
E-mail: roy.herbst@yale.edu

Lawrence H. Schwartz, M.D. (Imaging)
Columbia University Medical College
180 Fort Washington Avenue, HP-3-320
New York, NY 10032
Phone: 212/305-8994
FAX: 212/305-4835
E-mail: lschwartz@columbia.edu

David R. Gandara, M.D.
(Lung Committee Chair)
UC Davis Cancer Center
4501 X Street, Suite 3017
Sacramento, CA 95817
Phone: 916/734-3772
FAX: 916/734-7946
E-mail: david.gandara@ucdmc.ucdavis.edu

STUDY AGENTS:

AZD4547 (NSC 765338)
Docetaxel (Taxotere®)(RP56976) (NSC-6285
Erlotinib (OSI-774, Tarceva®) (NSC-718781)
GDC-0032 (NSC 778795)
MEDI4736 (NSC 778709)
Palbociclib (PD-0332991) (NSC 772256)
Rilotumumab (AMG102) (NSC 750009)

Protocol IND#119672

IDE #G120222

BIOSTATISTICIANS:

Mary Redman, Ph.D.
James Moon, M.S.
Shannon McDonough, M.S.
SWOG Statistical Center
1100 Fairview Ave N, M3-C102
P.O. Box 19024
Seattle, WA 98109-1024
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: mredman@fhcrc.org
E-mail: jmoon@fhcrc.org
E-mail: smcdonou@fhcrc.org

SUPPORTING COOPERATIVE GROUPS:

ALLIANCE
Everett Vokes, M.D.
University of Chicago Medical Center

ECOG/ACRIN
Suresh Ramalingam, M.D.
Emory University

NCIC-CTG
Glenwood Goss, M.D.
University of Ottawa

NRG
Jeff Bradley, M.D.
Washington University School of Medicine

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Background

- Non-small cell lung cancer (NSCLC) characterized by multiple and often independent mutations and potential therapeutic targets/ screening is rapidly becoming a part of treatment.

- Lung SCCA remains an “orphan” group/ substantial developments in therapeutics have yet to be seen. Subgroup selection (genotype or phenotype-driven) refined strategy.

- Multi-arm Master Protocol improved operational efficiency: homogeneous patient populations & consistency in eligibility from arm to arm

  Phase II-III design: rapid drug/biomarker testing for detection of “large effects”

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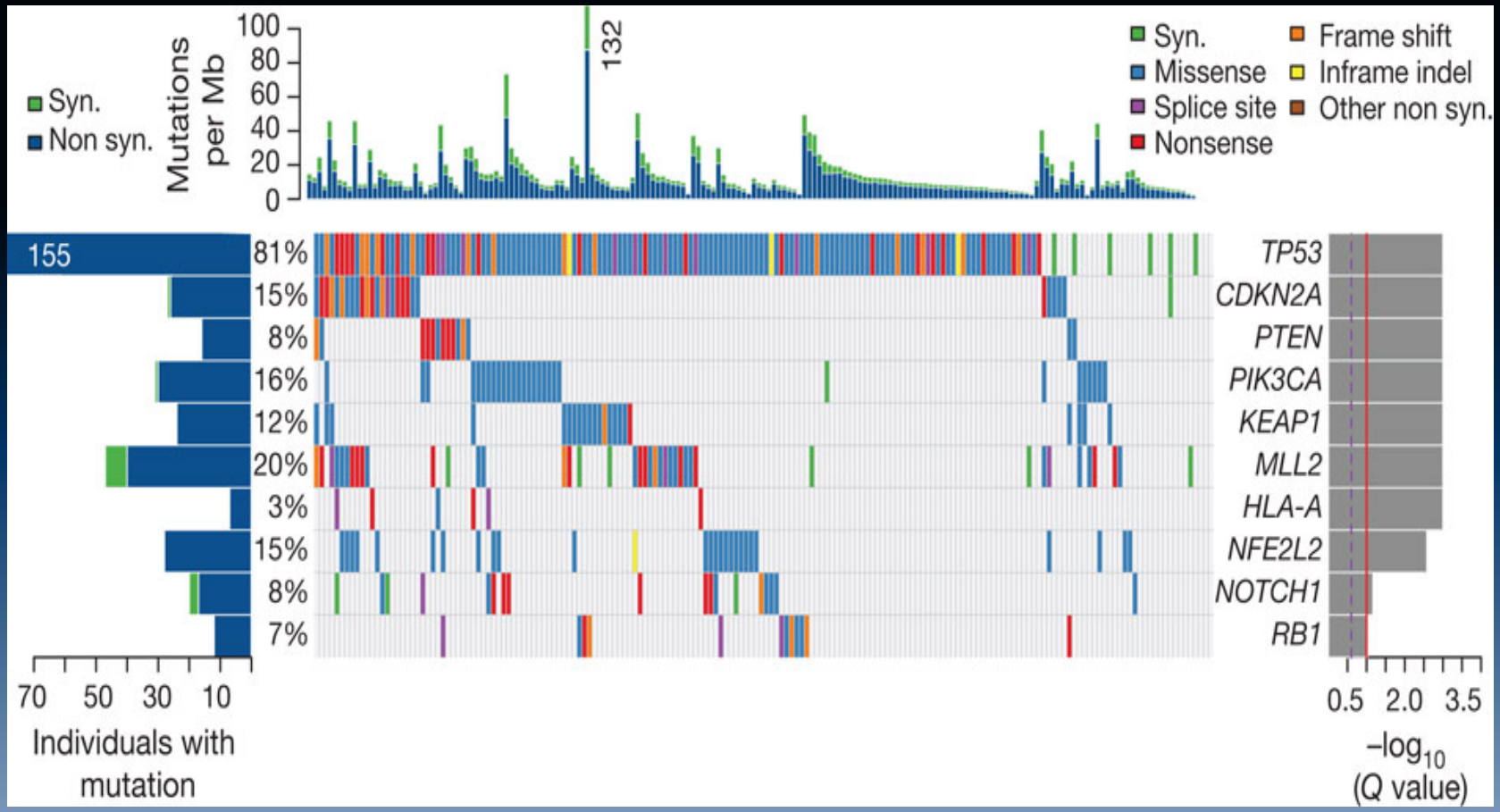
Background (cont.)

- Grouping multiple studies: reduces overall screen failure rate, multi-target screening by broad-based platform: sufficient “hit rate” allowing uninterrupted accrual.

- Potential for bringing safe and effective drugs to patients faster, ineffective drugs are replaced by new improved candidates.

- Designed to allow FDA approval of new therapeutics.

Significantly Mutated Genes in Lung SCCA.



PS Hammerman *et al. Nature* **000**, 1-7 (2012) doi:10.1038/nature11404

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nature

Lung-MAP: Major Goals and Hypothesis

- **To establish an NCTN mechanism** for genomic screening of large but homogeneous cancer populations, assigning and accruing simultaneously to a multi-sub-study **"Master Protocol"** comparing new targeted therapy to SoC based on designated therapeutic biomarker-drug combinations.

- **We hypothesize that Lung-MAP will yield definable and measurable efficiencies in terms of improving genomic screening of cancer patients 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.**

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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.**

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Objectives

- **Primary Objectives:**

A) Phase II Component: To evaluate if there is sufficient evidence to continue to the Phase III component of each biomarker-driven sub-study by comparing progression-free survival (PFS) between targeted therapy (TT) or targeted therapy combinations (TTC) or non-match therapy (NMT) versus standard therapy (SoC) in patients with advanced stage refractory squamous cell carcinoma (SCCA) of the lung.

B) Phase III Component: 1.To determine if there is both a statistically and clinically-meaningful difference in PFS among advanced stage refractory SCCA of the lung randomized to receive TT/TTC versus SoC and NMT versus SoC.
2.To compare overall survival (OS) in patients with advanced stage refractory SCCA of the lung randomized to TT/TTC versus SoC and NMT versus SoC.

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Objectives

- **Secondary Objectives:**

A) Phase II and III : 1. compare response rates among patients with measurable disease randomized to receive TT/TTC/NMT versus SoC. 2.Frequency and severity of toxicities with TT/TTC/NMT versus SoC

- **Exploratory Objectives:**

A) To identify additional predictive tumor/blood biomarkers that may modify response or define resistance to the TT beyond the chosen biomarker

B) To identify potential resistance biomarkers at disease progression

C) To establish a tissue/ blood repository from patients with refractory squamous cell cancer.

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Eligibility

- The patient has a diagnosis of pathologically confirmed lung SCCA by tumor biopsy and/or fine-needle aspiration.
- The patient has a diagnosis of either advanced, incurable stage IIIB or stage IV NSCLC, and failed exactly one front-line metastatic chemotherapy regimen.
- The patient has measurable disease (subjects with active new disease growth in previously irradiated site are eligible).
- The patient's performance status is ≤ 2 at study entry.
- The patient has adequate organ function (will be specified in detail in the full protocol).
- If patient has brain metastasis, they must have been stable (treated and asymptomatic) and off steroids for at least 2 weeks.

- *Drug-specific inclusion and exclusion criteria will be applied as appropriate for each sub-study.

- Central genomic screening (and IHC when applicable) testing will be performed through Foundation Medicine in a CLIA setting using their commercially available NGS platforms.

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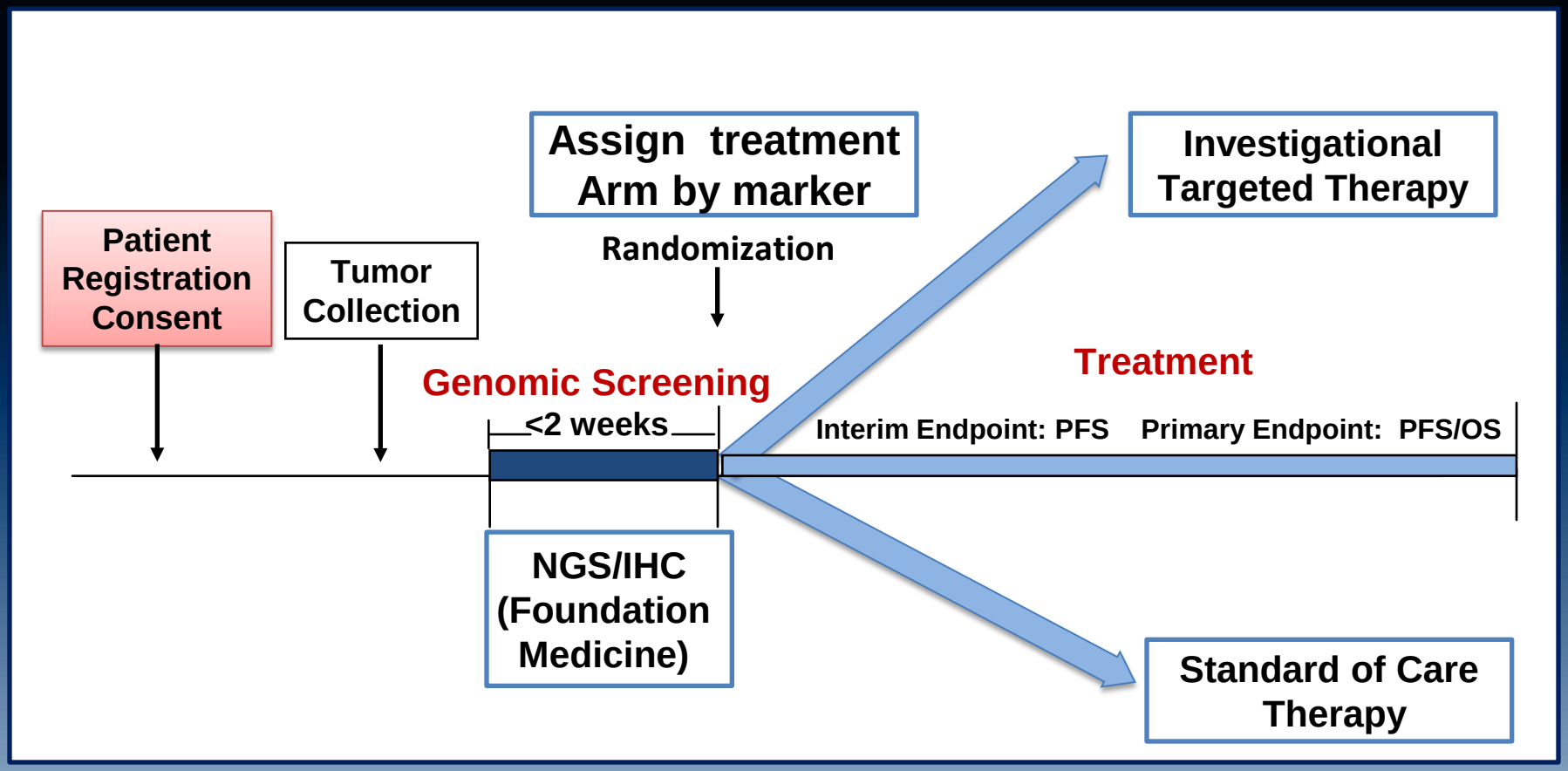
Treatment Schema



Central genomic screening (and IHC) **Foundation Medicine NGS test platform (CLIA/CAP)**.

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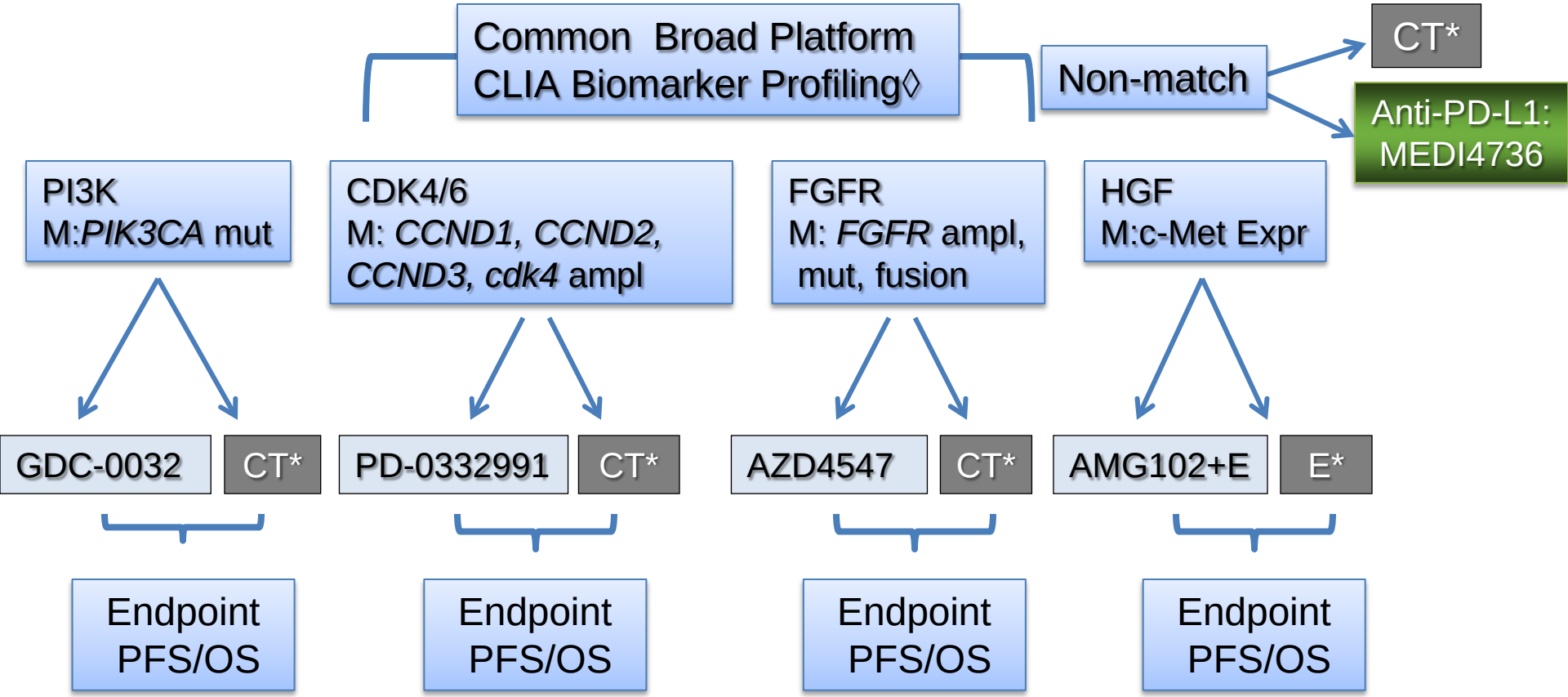

TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

◊ Archival FFPE tumor, fresh CNB if needed

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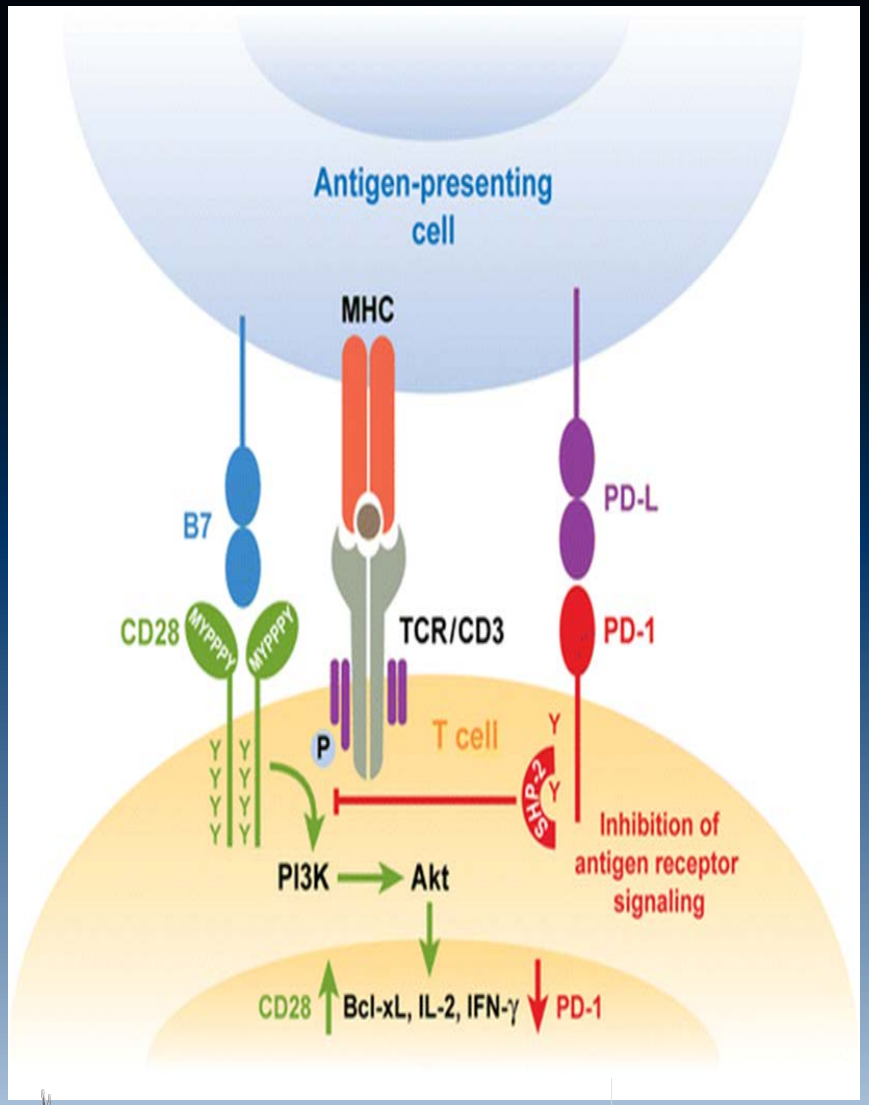
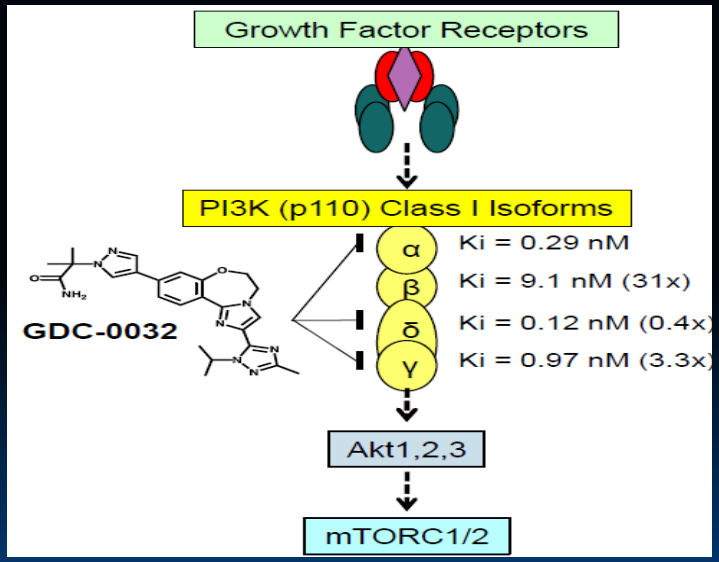
Rationale-Science

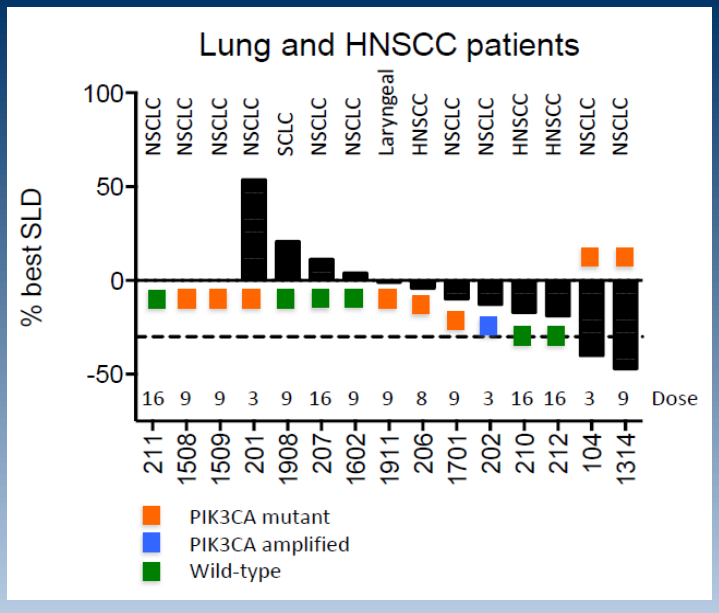


Sub-study A

- 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.

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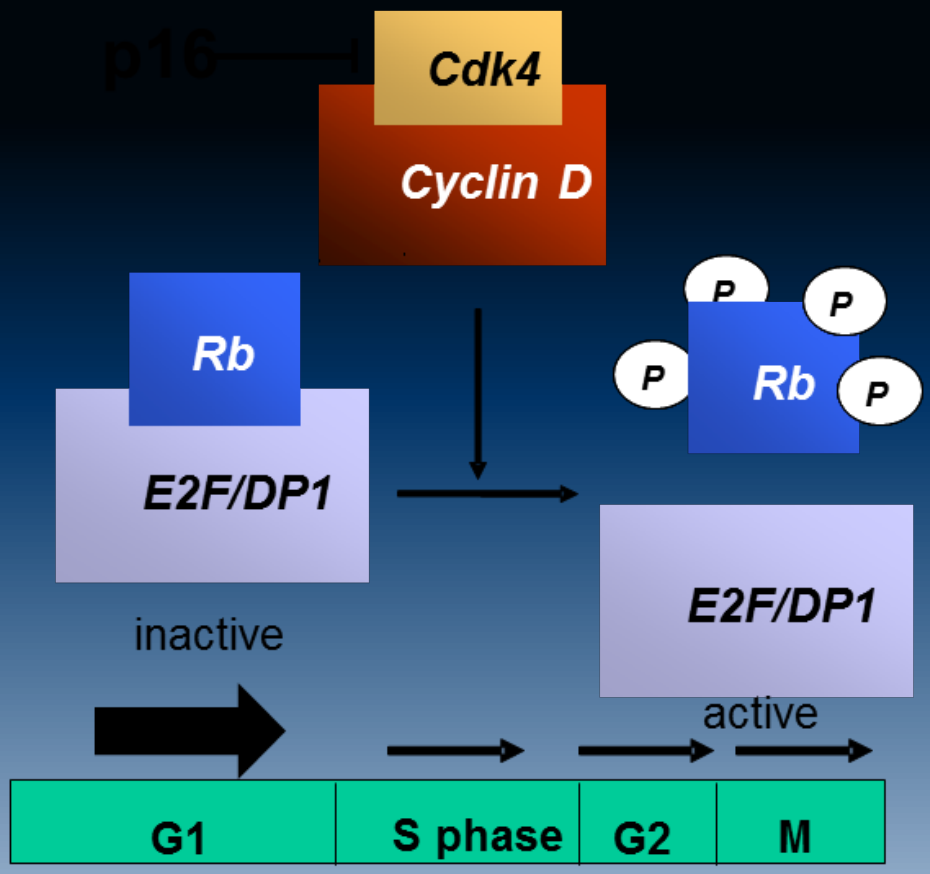
Rationale-Science



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.

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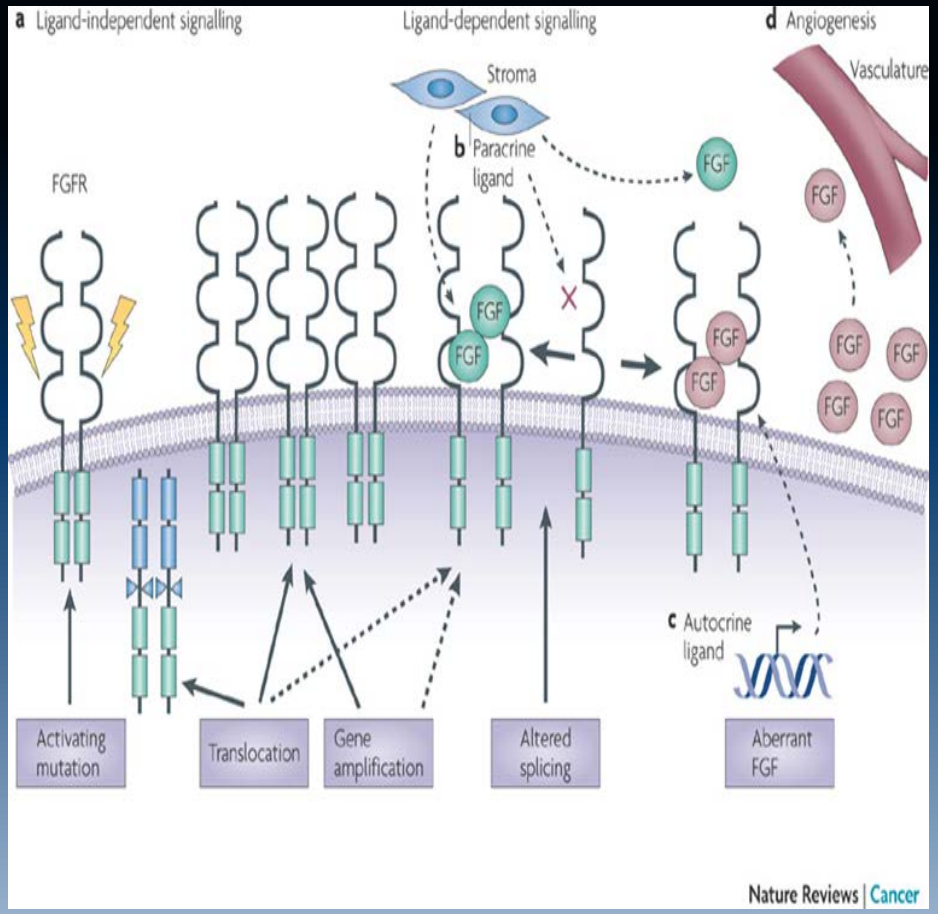
Rationale-Science



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.

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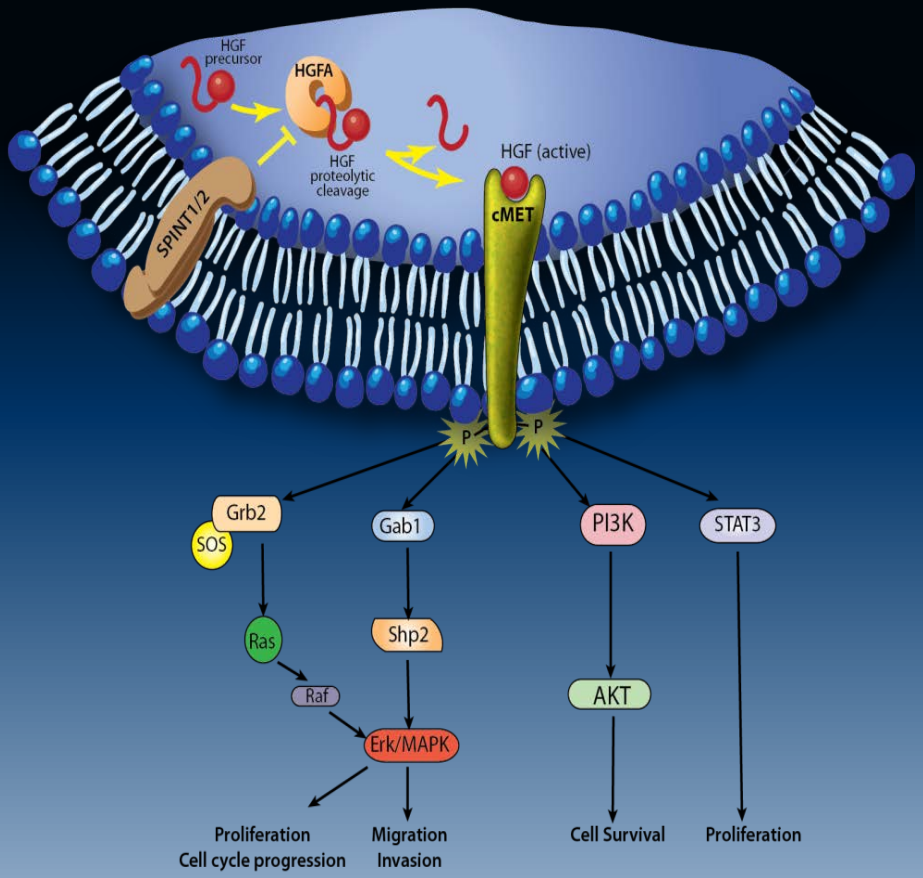
Rationale-Science



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.

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Treatment Plan

SUB-STUDY		Agent	Dose	Route	Schedule	Duration
A	Arm 1	**MEDI4736**	10 mg/kg	IV 60 min	Q 2 weeks	12 months
	Arm2	Docetaxel	75 mg/m^2	IV	Q21 days	Until PD
B	Arm1	**GDC-0032**	4 mg	PO	Continuous	Until PD
	Arm2	Docetaxel	75 mg/m^2	IV	Q21 days	Until PD
C	Arm1	**Palbociclib**	125 mg	PO	Daily (3 wks on/1 wk off)	Until PD
	Arm2	Docetaxel	75 mg/m^2	IV	Q21 days	Until PD
D	Arm1	**AZD4547**	80 mg BID	PO	Continuous	Until PD
	Arm2	Docetaxel	75 mg/m^2	IV	Q21 days	Until PD
E	Arm1	**Rilotumumab +Erlotinib**	15 mg/kg 150 mg	IV 60-120min PO	Q 21days Daily	Until PD
	Arm 2	Erlotinib	150 mg	PO	Daily	Until PD

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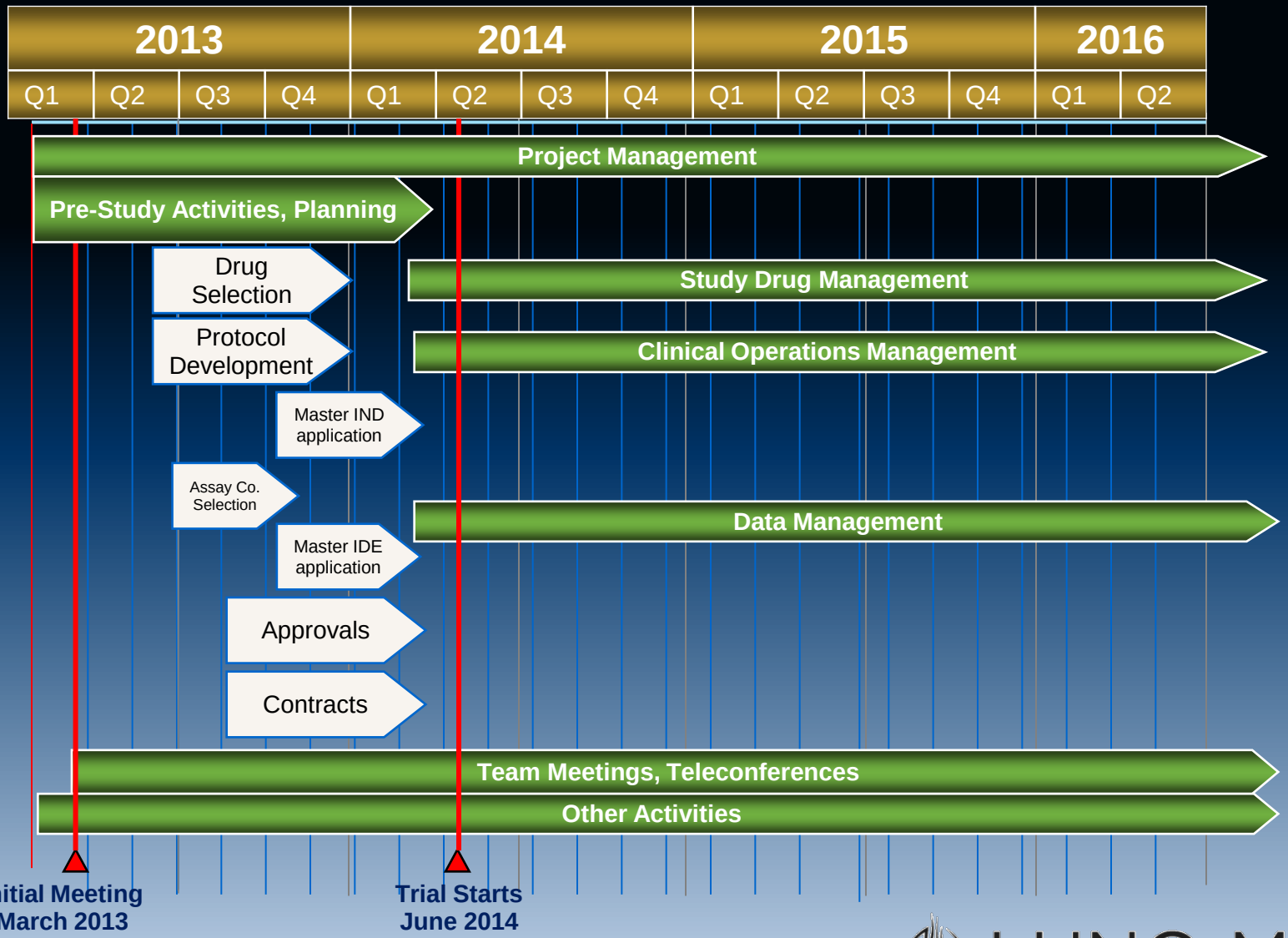
SWOG

FNIH
Foundation for the National Institutes of Health

NATIONAL CANCER INSTITUTE

FRIENDS of CANCER RESEARCH



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Specimen Requirements

Fred Hirsch, MD, PhD
Study Chair, Translational Medicine
Professor of Medicine and Pathology
Univ. of Colorado Cancer Center, Aurora, CO, USA

Tissue Acquisition, Processing and Reporting For the Lung-MAP

Tissue Is the Issue:

At Time of Primary Diagnosis:

Tissue Blocks preferable!

- FNAs acceptable if cell blocks are made!
- 20 FFPE slides (4-5 microns each) sent to FMI
  (12 slides minimum required for eligibility)
- 8 slides (40 microns) will be used for FMI “screening panel”
- 2 slides will be used for C-MET IHC
- 1 H-E slide or Aperio scanned slides should be submitted together with either cell block(s) or unstained slides
- If insufficient tissue: REBIOPSY (30%)

Tissue

Pathology Review - Local Pathologist to Ensure:

1. Squamous Lung Cancer according to WHO, +/- IHC verification: p 40/p63 positive, TTF1 negative.

2. At least 20% viable tumor

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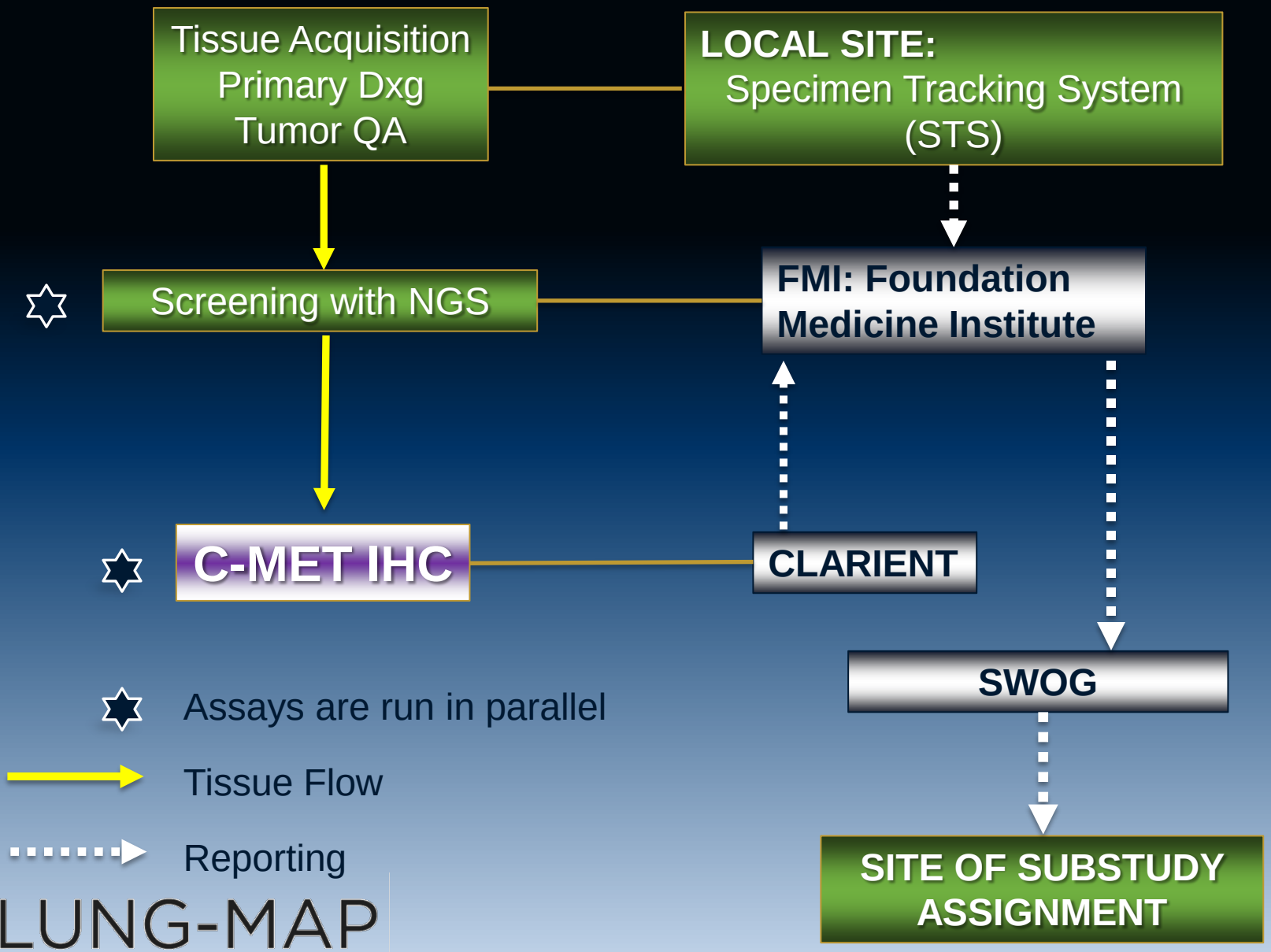
Tissue Flow / Reporting Flow:



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Reporting

- All specimens are to be submitted through the STS.
- FMI will send full report, including MET IHC, to SWOG Stat Center.
- **Sites will be notified of sub-study assignment.**
- Specific results provided upon request following disease progression.

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Tissue: At PD after Response

- It is strongly intended to obtain **biopsy at time of PD** for responding pts in order to study acquired resistant mechanisms,
- Procedure: the same as at Primary Diagnosis!

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Peripheral Blood

- Samples taken at screening (pretreatment / during first line CT/ at PD); at PD (requested)
- 10 ml blood collected in EDTA tubes
- EDTA tubes processed within an hour after vein puncture (otherwise stored in – 4 degrees)
- EDTA tubes will be spun at 800g for 10 minutes at 4 degrees for separating plasma collection
- Plasma will be transferred to 15 ml centrifuge tube for spin 800g in 10 minutes

Peripheral Blood (cont.)

- Plasma will be pipetted into 1ml coded cryovials at 0.5ml aliquots.
- The buffy coats will be transferred from blood tube into 2ml cryovials.
- Samples will be placed immediately into -80 degrees freezer for long term storage.
- Samples shipped in batches to SWOG Repository.

Statistical Overview

Mary Redman, PhD
SWOG Lead Biostatistician
SWOG Lung Committee

FRED HUTCHINSON CANCER RESEARCH CENTER
A LIFE OF SCIENCE

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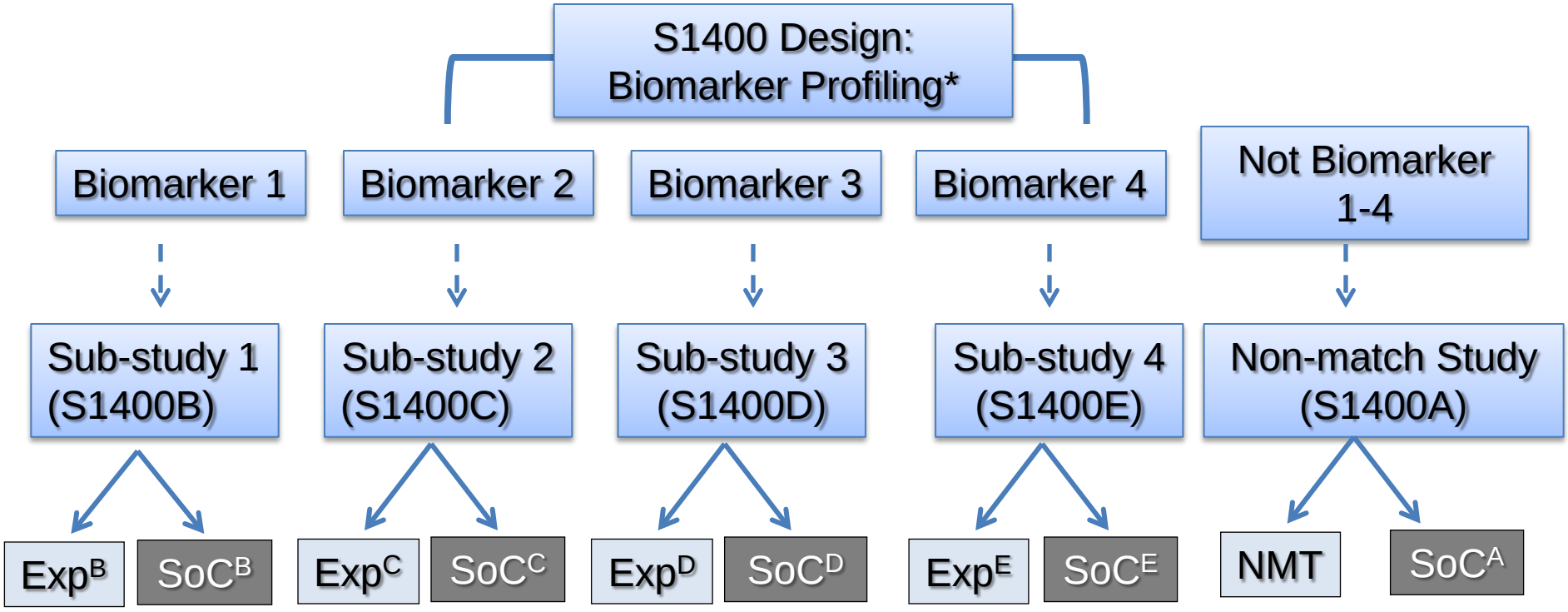

*Sub-studies assigned based on biomarker results, patients with multiple biomarkers randomly assigned to sub-study. Investigators/patients will only be notified of sub-study assignment.
Exp = Targeted therapy or Targeted Therapy combinations
SoC = chemotherapy (docetaxel or gemcitabine) or erlotinib

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Objectives

- **Primary Objectives within each independent sub-study:**

A) Phase II Component:

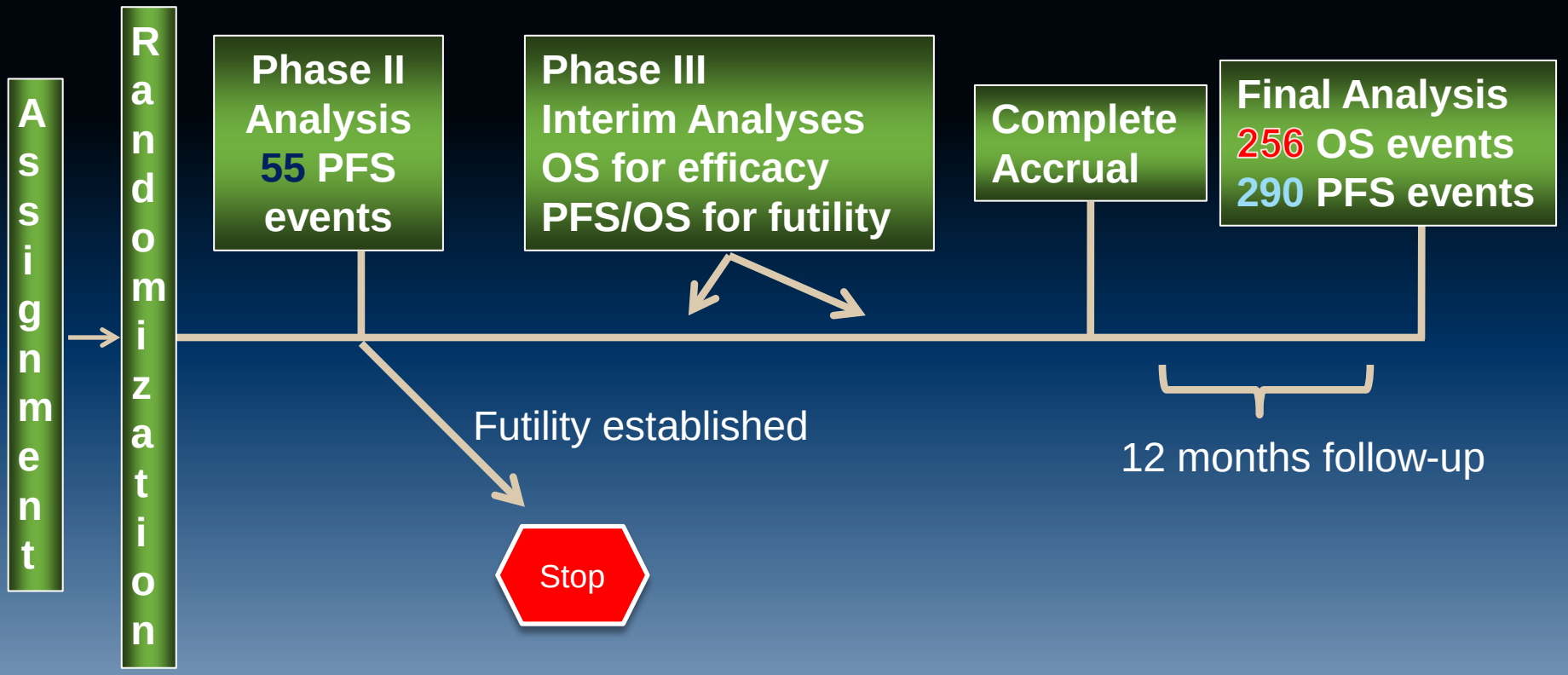
1. To evaluate if there is sufficient evidence to continue to the Phase III component by comparing progression-free survival (PFS) between patients randomized to experimental therapy versus SoC.

B) Phase III Component:

1. To determine if there is both a statistically and clinically-meaningful difference in PFS between the treatment arms.

2. To compare overall survival (OS) between treatment arms.

Study Design Within Each Biomarker-defined Subgroup



LUNG-MAP

Stratification Factors for Treatment Arm Randomization

- **S1400A,C,D,E:**

Patients will be stratified by:

1. **Zubrod Performance Status (0-1 vs. 2)**
2. **Gender (Male vs. Female)**
3. **Smoking Status (Current vs. Former/Never)**

- **S1400B:**

Patients will be stratified by:

1. **Zubrod Perfomance Status (0-1 vs. 2)**
2. **Gender (Male vs. Female)**
3. **Date of diagnosis of metastatic or recurrent squamous cell lung cancer to date of sub-study treatment arm randomization (≤ 6 months vs. > 6 months).**
4. **PIK3CA mutation status per GNE criteria (positive vs. negative as defined in Section 11.1)**

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+	5.6%	78		288	
FMI+	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

LUNG-MAP

The investigator/CRA's role in achieving study goals

Questions on registration, eligibility, or data submission Contact SWOG Data Operations Center at: lungquestion@crab.org

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Importance of Following Disease Assessment Schedule

- **Investigator-Assessed Progression-Free Survival**

From date of randomization to date of first documentation of progression assessed by local review or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

- **Progression-Free Survival by Central Review**

From date of randomization to date of first documentation of progression assessed by central review or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

LUNG-MAP

Importance of Timely and Complete Data Submission

- **Data Submission Schedule**

1. **Data Submission Requirements**
   Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.
2. **Master Forms**
   Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.0.c1 for details.
3. **Data Submission Procedures**
   All participating institutions must submit data electronically via the Web using Medidata Rave® at the following url: https://login.imedidata.com/selectlogin
   a. If prompted, select the 'CTEP-IAM IdP' link.
   b. Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members' web site and OPEN.

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- **Ultimate goal is to identify and quickly lead to approval of safe and effective regimens (monotherapy or combinations) based on matched predictive biomarker-targeted drug pairs.**
- **Achieved through:**
  - Recruitment and registration of appropriate patients
  - Accurate and complete data
  - Timely submission of data

LUNG-MAP

Registration and Study Flow

Austin Hamm, BA, CCRP
SWOG Data Coordinator
SWOG Data Operations Center
Seattle, WA

Pre-Registration

- Recruit/Screen
- Consent
- Eligibility
  - Section 5
- Tissue Availability
  - Tissue blocks preferred, 12-20 slides may be substituted
    - Local pathologist must confirm at least 20% tumor cells in tissue specimen and must sign *Local Pathology Review* form
  - Section 15

LUNG-MAP

Registration

- Use CTSU OPEN for registration to S1400
  - https://open.ctsu.org/open/logonForm.open
  - See Section 13 for details
- Additional info collected during registration
  - Has the patient progressed on front-line therapy?
  - Provide primary and backup email addresses for sub-study assignment notification
- SWOG patient ID will be assigned
  - 6-digits [7xxxxx]
  - Study-specific

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Tissue Submission

- Must be submitted within **ONE DAY** after registration
- Submit to Foundation Medicine, Inc. (FMI)
- Log via SWOG Specimen Tracking System
- Refer to Section 15

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Sub-study Assignment

- Will be emailed to site staff
  - Sent to addresses entered during registration
  - Also displayed in *Sub-study Assignment* form in Rave®
- If patient **screened after progression** on front-line therapy
  - Email sent **within 16 days** after registration

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Sub-study Registration

- Evaluate and confirm sub-study eligibility
  - S1400 main protocol common sub-study eligibility criteria (Section 5.2)
  - Sub-study specific eligibility criteria (Section 5)

- Register in **OPEN** to assigned sub-study
  - **Within 28 days** from receipt of email
  - Patient will be randomized to investigational therapy or standard of care

Sub-study Treatment

- Plan to start therapy **within 5 working days** of sub-study registration
  - Section 3, “Drug Ordering and Accountability”
    - https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
    - Contact NCI Pharmaceutical Management Branch (PMB)
      - Phone: 240/276-6575
      - Email: PMBAfterHours@mail.nih.gov
  - Section 7 for treatment plan
  - Section 8 for dose modifications

*Sub-study Reassignment**

- Meets common sub-study eligibility

AND

- Does **NOT** meet specific sub-study eligibility

THEN

- Submit *Request for Sub-study Reassignment* form

Due to specific sub-study ineligibility **ONLY*

LUNG-MAP

Ineligible for all Sub-studies

- Does **NOT** meet common sub-study eligibility

OR

- Does **NOT** meet assigned specific sub-study eligibility

THEN

- Submit *Notice of Intention Not to Register* form
- Follow and submit forms per S1400 main protocol per Sections 7 and 14

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Additional Information

- Submit data electronically via the web using Medidata Rave®
- Study materials
  - SWOG Institutions
    - http://swog.org → Clinical Trials → Protocol Search → Search "S1400"
  - CTSU Institutions
    - https://www.ctsu.org → Protocols → Search "S1400"
- Questions on registration or data submission?
  - Contact SWOG Data Operations Center at lungquestion@crab.org

LUNG-MAP

Imaging in SWOG 1400

Lawrence Schwartz, MD
Chair, SWOG Imaging Committee

Michael V. Knopp, M.D., Ph.D.
Co-PI IROC

LSchwartz@columbia.edu
Knopp.16@osu.edu

Contact of Imaging Core for the Protocol:
E-Mail: SWOG1400@IROCOhio.org

Coordination of Imaging

- The SWOG Imaging Committee will oversee, guide and consult on all Imaging and Imaging data collection related aspects
- The SWOG Imaging Corelab which now also functions as IROCOhio for the overall NCTN will manage all imaging data collection and support all imaging based assessments

Image Acquisition

- All study participants will have a PET/CT, CT or MRI exam prior to study entry. Participants will then undergo additional imaging every 6 weeks until progression of disease
- The same imaging modality used for the pre-treatment exam must be used for the post-treatment exams
- PET/CT, CT and MRI images will be initially interpreted by the local site radiologist. Imaging exams will then be forwarded to the Imaging and RT Quality Assurance Service Core (IROC) for central review
- Results of the central review will be reported only to the DSMC
- A detailed description of the central radiology PFS review, including image acquisition parameters and image submission instructions will be made available to each site

Imaging Data Upload

- IROC is implementing a IMAGE data upload system which is build upon the ACR TRIAD software
- While this transition is being implemented with the start of the NCTN on 3/1/14, this S1400 master will be the first from the SWOG trials
- IROCOhio is taken the lead to develop the implementation for SWOG

ACRIN Core Lab

RTOG QA Office

Alliance and SWOG Imaging Core Lab at Ohio State

Image Guided Therapy Center at Wash U

Radiological Physics Center (RPC)

Quality Assurance Review Center (QARC)

IROC™

IMAGING AND RADIATION ONCOLOGY CORE

Global Leaders in Clinical Trial Quality Assurance

NCI-NCTN U24 Award

IROC Executive Committee

Co-Directors: Followill (RT)/Knopp (I)

IROC Admin: King/O'Meara/Laurie

Lead Contact for SWOG and S1400

- **IROC Philadelphia Imaging**
- **IROC Philadelphia RT**
- **IROC Ohio**
- **IROC St. Louis**
- **IROC Houston**
- **IROC Rhode Island**

IROC-TRIAD Image Transmission System

- IROC-TRIAD integration with RAVE and RSS provides important advantages for NCTN trials:
  - TRIAD accesses the CTSU to obtain list of studies and sites the user has access to
  - TRIAD will obtain the patient list from Rave for the study and site selected by the user. The user selects the patient
  - TRIAD will obtain the time point information from Rave
  - The user uploads the radiological image for a selected time point
  - Continued refinement to facilitate efficient workflow for the sites

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RADIATION ONCOLOGY CORE
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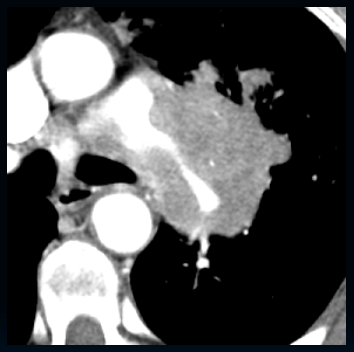
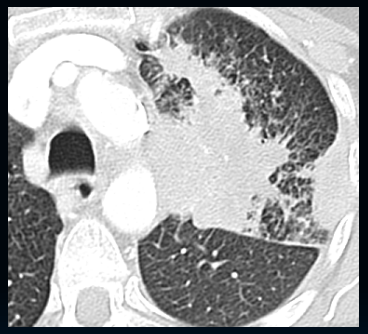
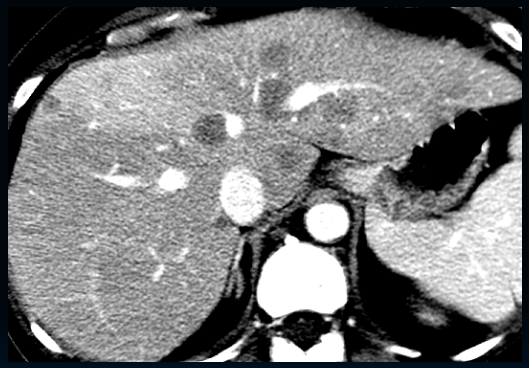
An Imaging Biorepository



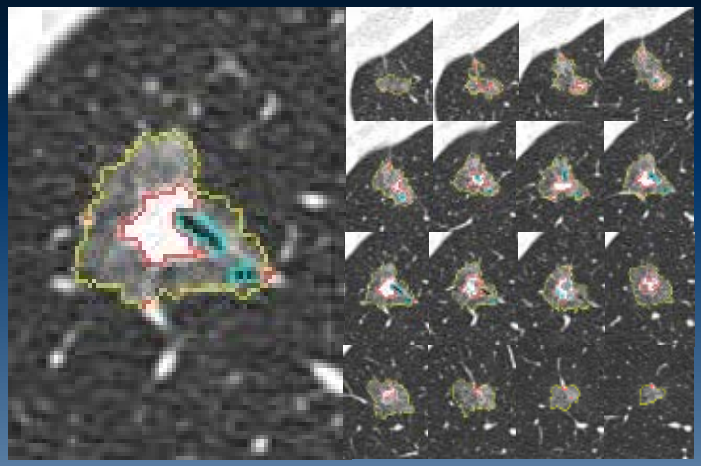


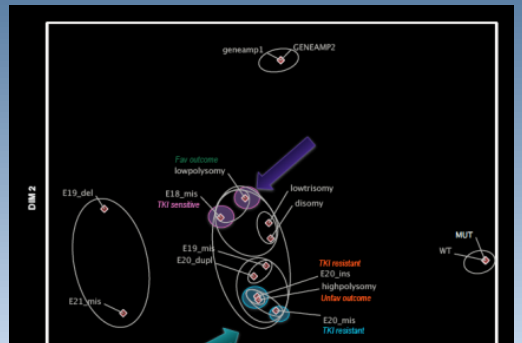


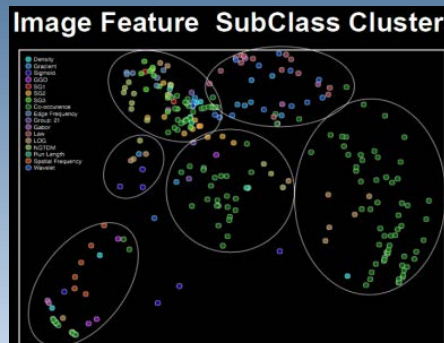
Used to evaluate efficacy of a novel therapy in a clinical trial

Used to determine treatment decisions for an individual patient

Used for correlative analysis to develop predictive tissue biomarkers







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Informed Consent, Quality Assurance and Monitoring

Elaine Armstrong, MS
SWOG Quality Assurance Manager

Consent process: Screening

Screening Consent: After progression

- Allows for submission of tissue specimens and registration for screening
- A new fresh tumor biopsy required if insufficient archival tumor material is available

Consent process: Sub-study Assignment

- Sub-study assignment will not occur until after progression
- Patient must sign targeted treatment consent for the assigned sub-study
- Must register to the assigned sub-study in order to receive the treatment randomization assignment.

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Quality Assurance

- Mandatory training of key site personnel prior to first patient registration.
- Additional mandatory centralized training to be provided if major changes to the protocol occur or common problem areas are identified during monitoring and audits.
- Oversight through routine auditing and monitoring using a risk-based approach to monitoring

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Quality Assurance

- Full time SWOG monitor dedicated 100% to S1400
- Routine monthly communication between monitor and site staff to assess potential problem areas, provide feedback, identify staff turnover, etc.
- Centralized electronic monitoring
- On site monitoring

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Centralized Monitoring (Data Operations)

- Monitoring of data quality through routine review of submitted data
- Verification of critical source documents remotely via the collection and review of pathology, radiology and applicable lab reports
- Analysis of site characteristics and performance metrics to identify trial sites with poor performance or non-compliance through the SWOG IPR and other available reports

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Centralized Monitoring (Operations Office)

- Monitoring timeliness of SAE reporting
- Monitoring timeliness of data submission
- Verification of specimen submission
- Off site review of investigational drug accountability recordkeeping on a biannual basis

On Site Monitoring

- First on site monitoring visit **within 3 months** of first patient registration
- On site monitoring for all sites **twice per year**
- Additional monitoring visits to will be scheduled in response to several factors - rate of accrual, previous monitoring visit results, centralized electronic monitoring outcome, change in staff, etc.

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On Site Monitoring

- Monitoring may be combined with routine audit
- Monitoring reports maintained in NCI-CTMB database
- Corrective and preventative action plans required
- Timely review of all monitoring reports to identify sites that require additional training, monitoring, disciplinary action, etc.