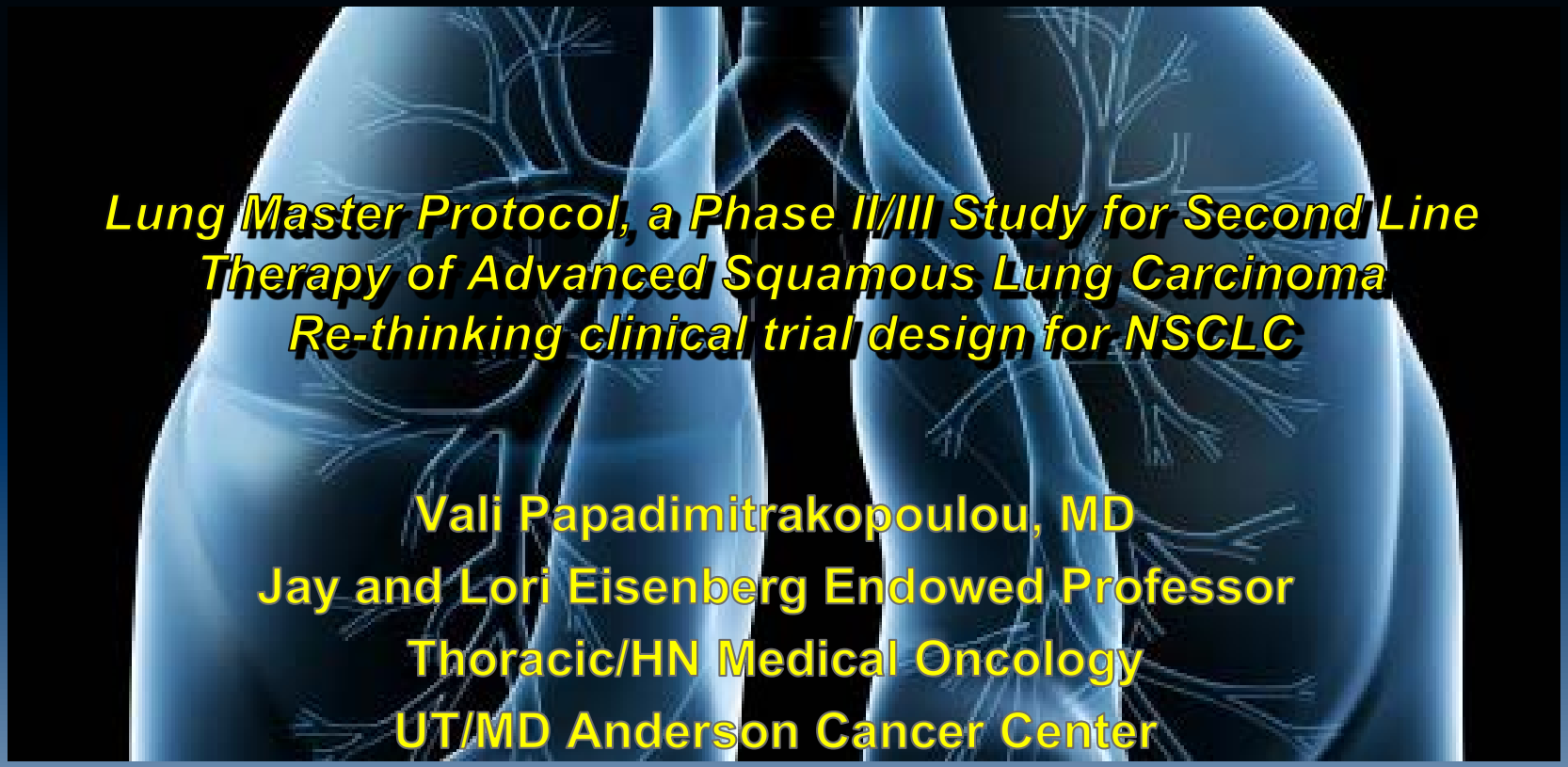
SWOG



Lung Master Protocol, a Phase II/III Study for Second Line Therapy of Advanced Squamous Lung Carcinoma Re-thinking clinical trial design for NSCLC

Vali Papadimitrakopoulou, MD

Jay and Lori Eisenberg Endowed Professor

Thoracic/HN Medical Oncology

UT/MD Anderson Cancer Center

Strategies for Integrating Biomarkers into Clinical Trial Designs for NSCLC

Evolution of NSCLC →Histologic Subsets → Biomarker subsets

Improving the drug development process

- **Less than 5-10% of drugs for oncologic diseases that enter phase 1 clinical trials successfully reach the end of phase 3 trials.**
- **How can we improve these rates?**

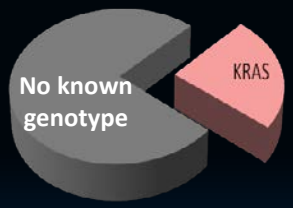
- **Adopt rigorous experimental randomized designs at the animal testing phase.**
- **Smaller uncontrolled phase I clinical trials, consider early randomized studies at phase 1 and phase 2 phases.**
- **Choose smaller biomarker-driven groups with higher plausibility that a match biomarker-drug pair will be confirmed.**
- **Apply power of genomics in patient selection.**

- **Expedite companion diagnostic development with more flexible and broad platforms.**

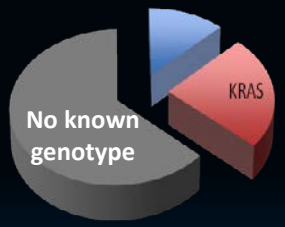
Evolution of Identification of Genomic Alterations

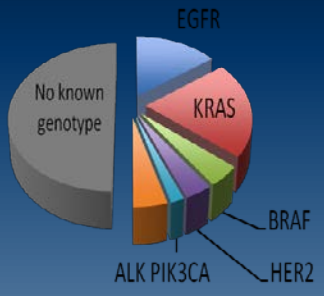
Lung Adenocarcinoma

1984 - 2003

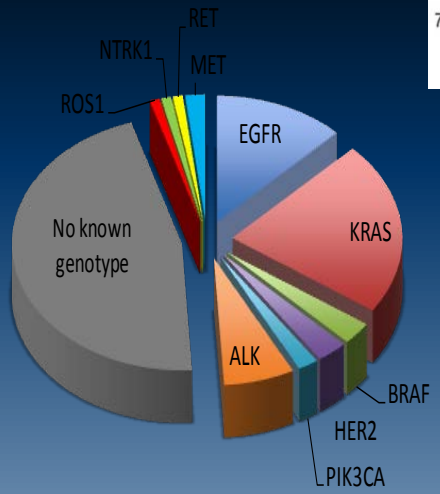


2004



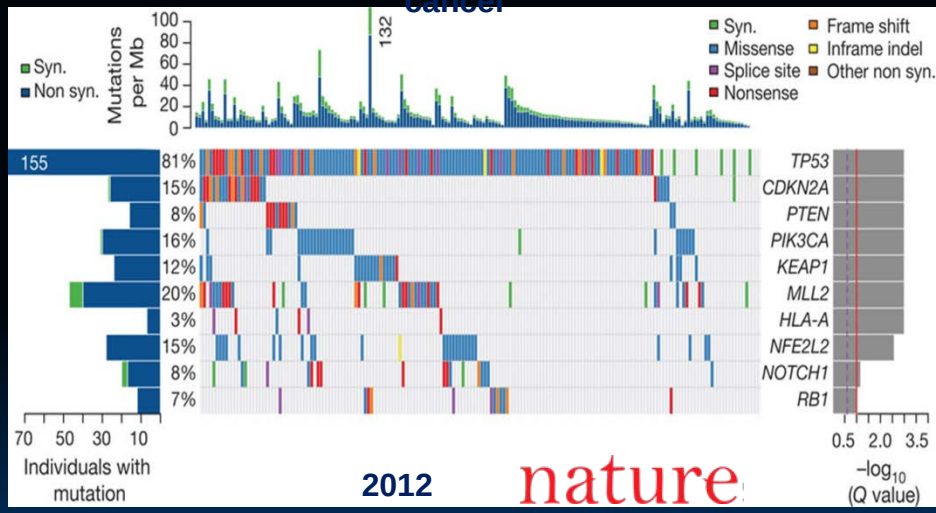


2009

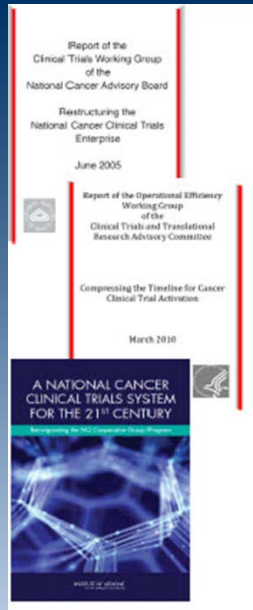


2014

Lung squamous cell cancer



2012 nature



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

LUNG-MAP

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

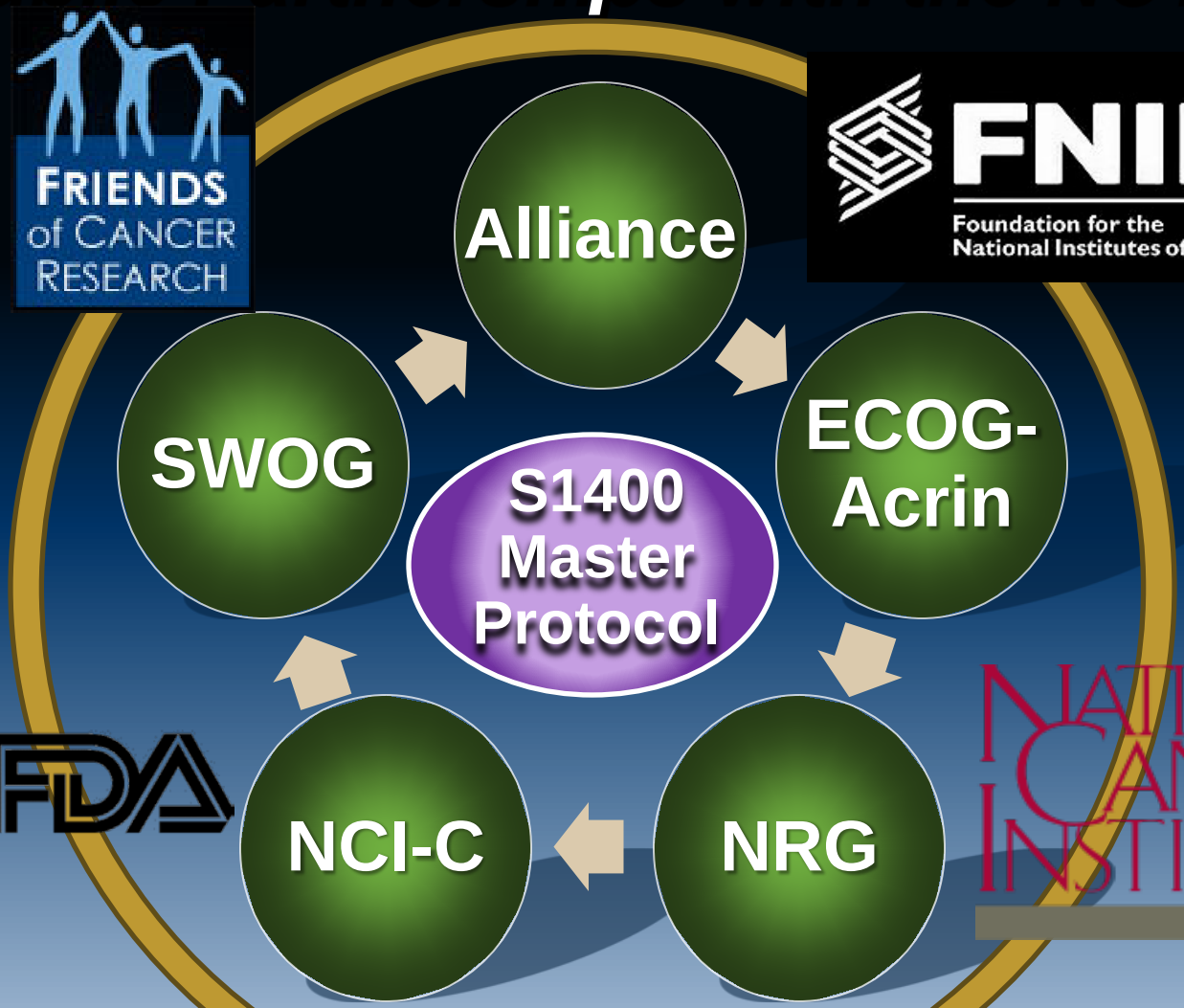
Rationale for Master Protocol Design

- **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**
  - **Rolling phase II (PFS)/phase III (PFS/OS) design allows rapid drug/biomarker testing for detection of "large effects" –bringing safe and effective drugs to patients faster**
  - **FDA registartion potential**
- Screening **large numbers of patients for multiple targets by a broad-based NGS platform reduces the screen failure rate and allows a sufficient "hit rate" to engage physicians and patients-a treatment for almost every patient.**

LUNG-MAP


LUNG-MAP
S1400 Lung Master Protocol

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

SWOG

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

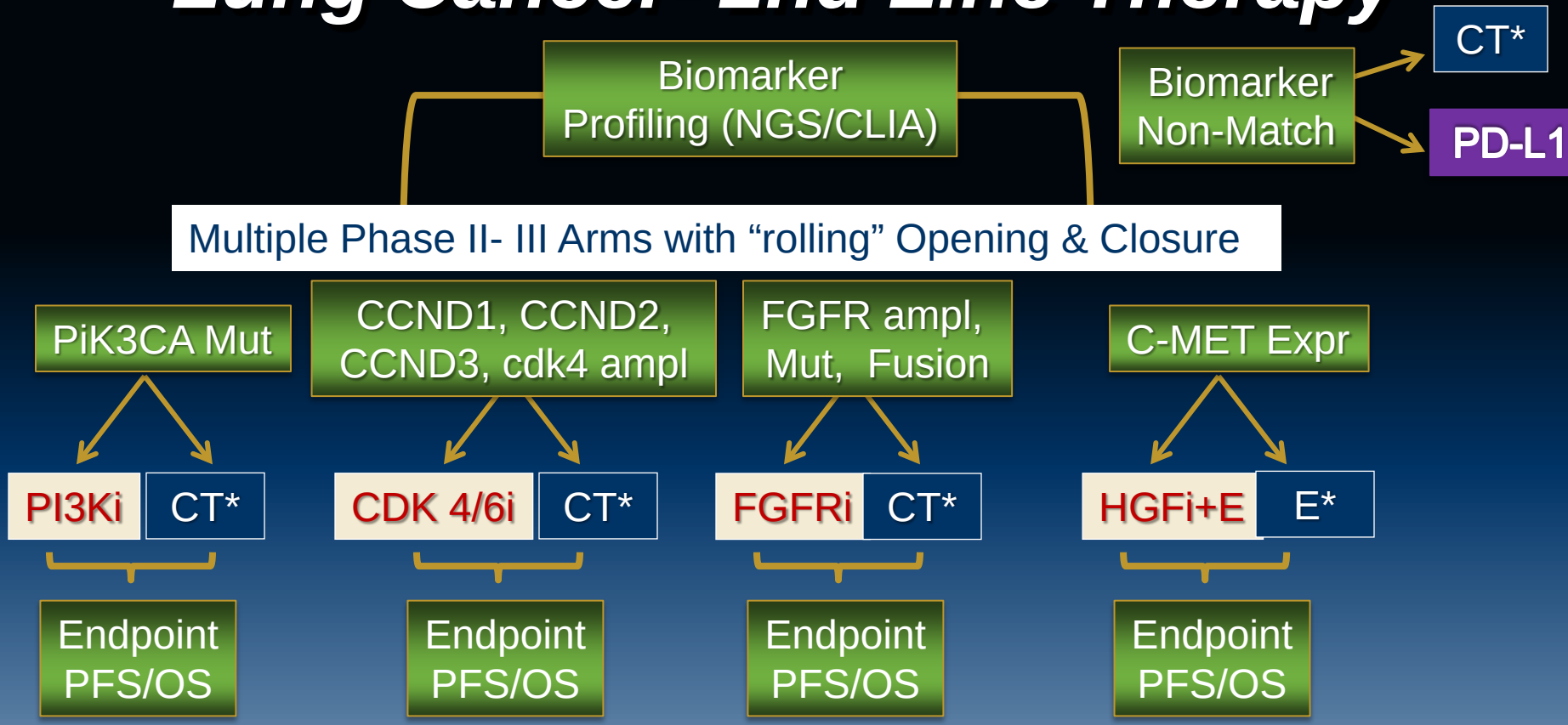
ECOG/ACRIN
Suresh Ramalingam, M.D.
Emory University

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

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

LUNG-MAP

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



CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

PI: V. Papadimitrakopoulou (SWOG)
Steering Committee Chair: R. Herbst (YALE, SWOG)
Lung Committee Chair: D. Gandara
Translational Chair: F. Hirsch
Statistical Chair: M. Redman

LUNG-MAP

Lung-MAP: Major Goals and Hypothesis

- **Hypothesis: Lung MAP will improve genomic screening and 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.**
- **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

Study Design and Objectives

Design:

Independently conducted and analyzed parallel Phase II/III studies

Primary Objectives within each sub-study:

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 investigational therapy versus SoC.

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.

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.

LUNG-MAP

Eligibility

- The patient has a diagnosis of pathologically confirmed lung SCCA by tumor biopsy and/or fine-needle aspiration.
- Patients must have progressed after receiving a platinum-based chemotherapy regimen.

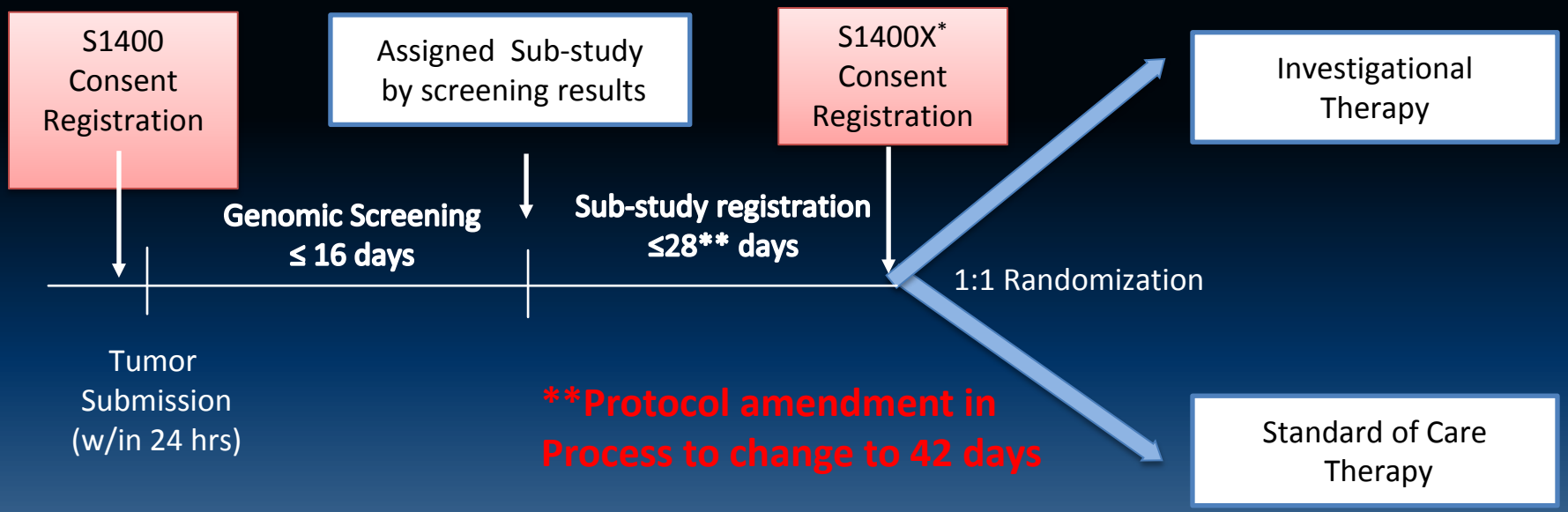
  -Patients who received platinum-based chemotherapy for Stage I-IIIB disease may have received at most one additional chemotherapy regimen for Stage IV disease and must have progressed after receiving this regimen for Stage IV disease.

  -Patients who progressed after chemotherapy for Stage IV disease must not have received any additional chemotherapy.
- 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.

Eligibility Updates

Original	Revised
Disease setting	
Incurable stage IIIB or Stage IV	Only Stage IV
Mixed Histology ≥50% allowed	Mixed histology not allowed
Prior Treatment	
No restrictions on prior radiation	Prior radiation within 28 days before S1400 registration not allowed
Exactly one platinum-containing chemotherapy regimen	Platinum-based chemotherapy required. • Can be regimen for Stage I-IIIB • 2nd for Stage IV allowed after progression of Stage I-IIIB
	• If initial chemo given for Stage IV, exactly one allowed
Other	
Register to assigned sub-study within **28** days	Register to assigned sub-study within **42** days
SGOT/SGPT <= 2.5	ALT/AST <= 2.0

Patient-level Schema

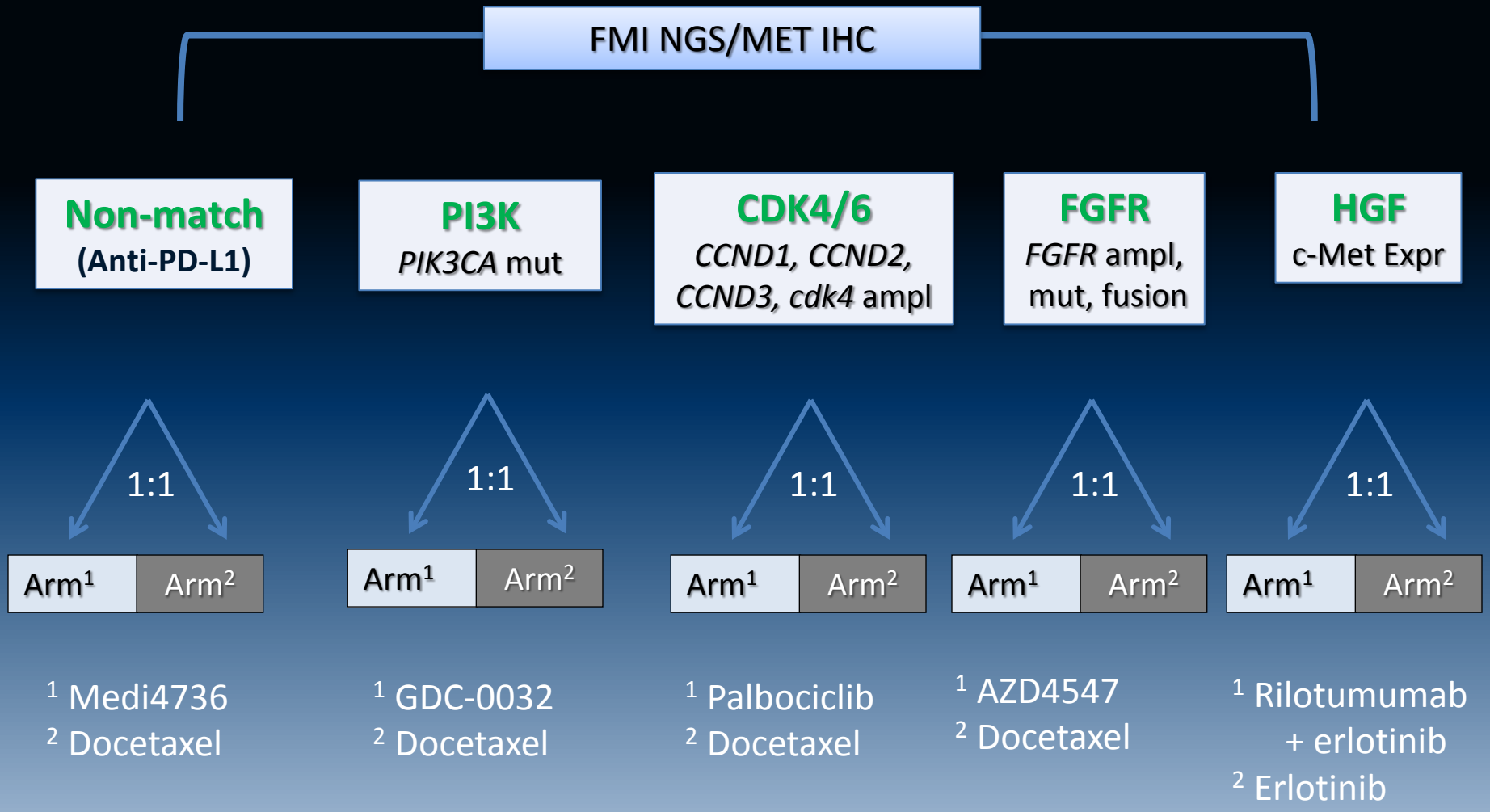


* X = A, B, C,D, or E

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

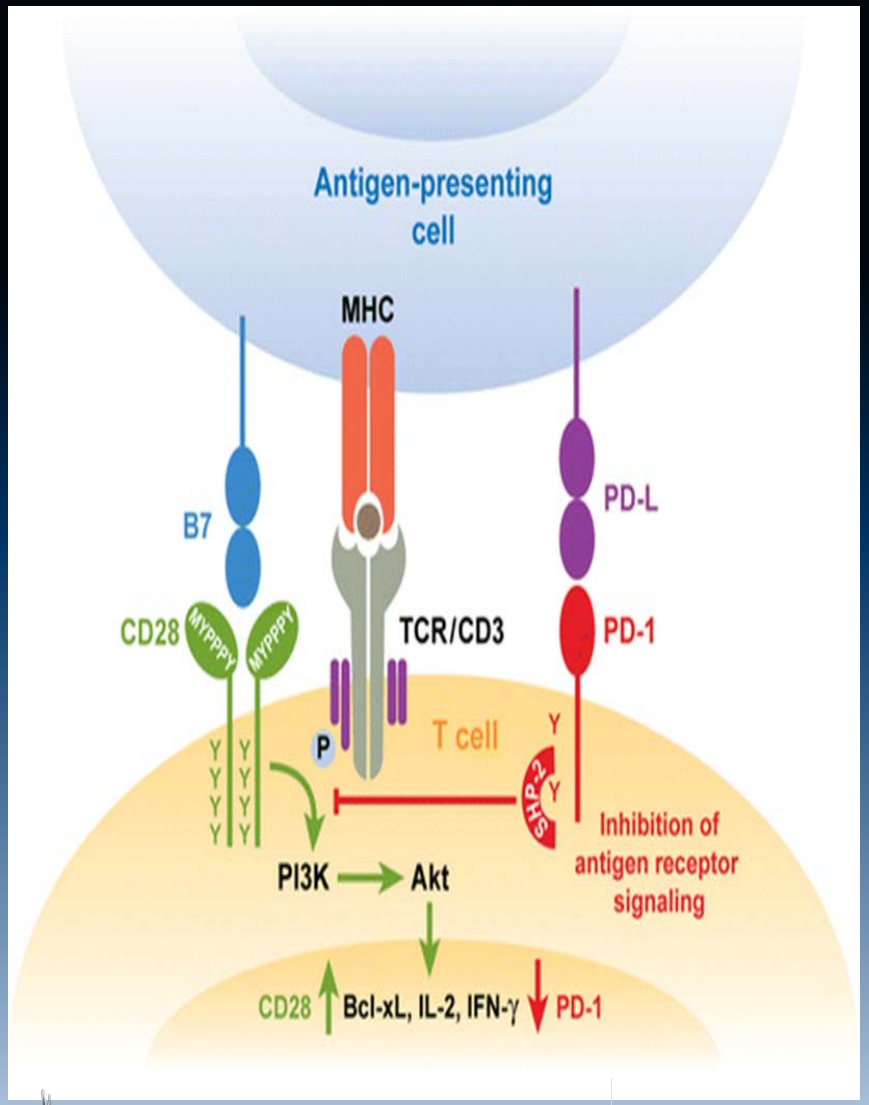
LUNG-MAP

Lung-MAP Trial Schema



LUNG-MAP

Rationale-Science

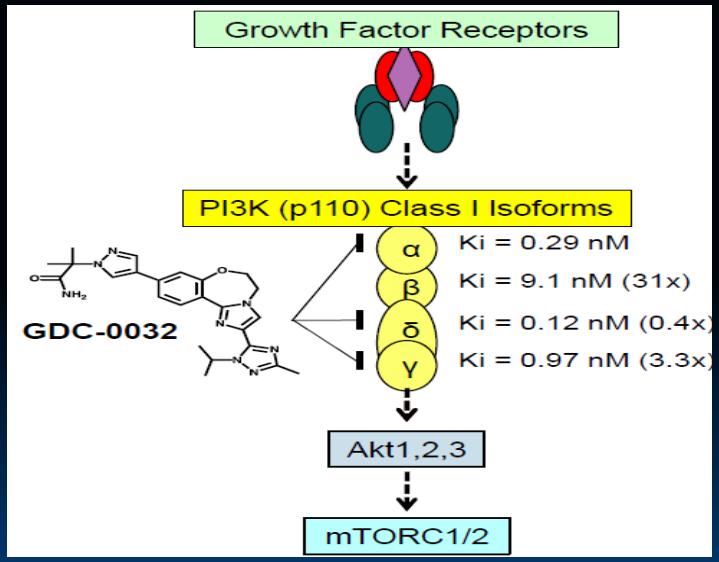


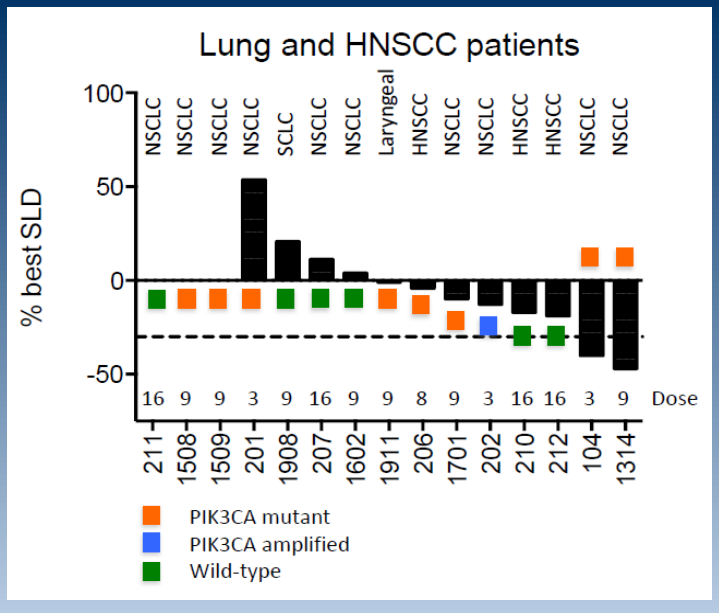
Sub-study A

- 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.

LUNG-MAP

Rationale-Science



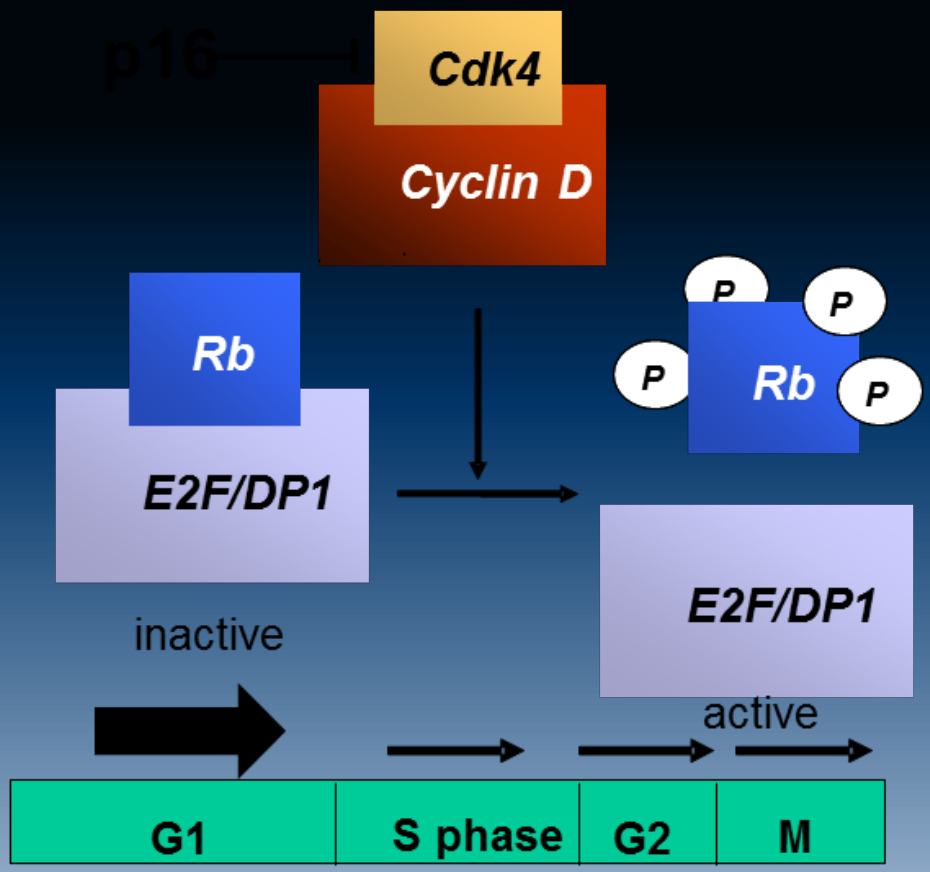


Sub-study B

- 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

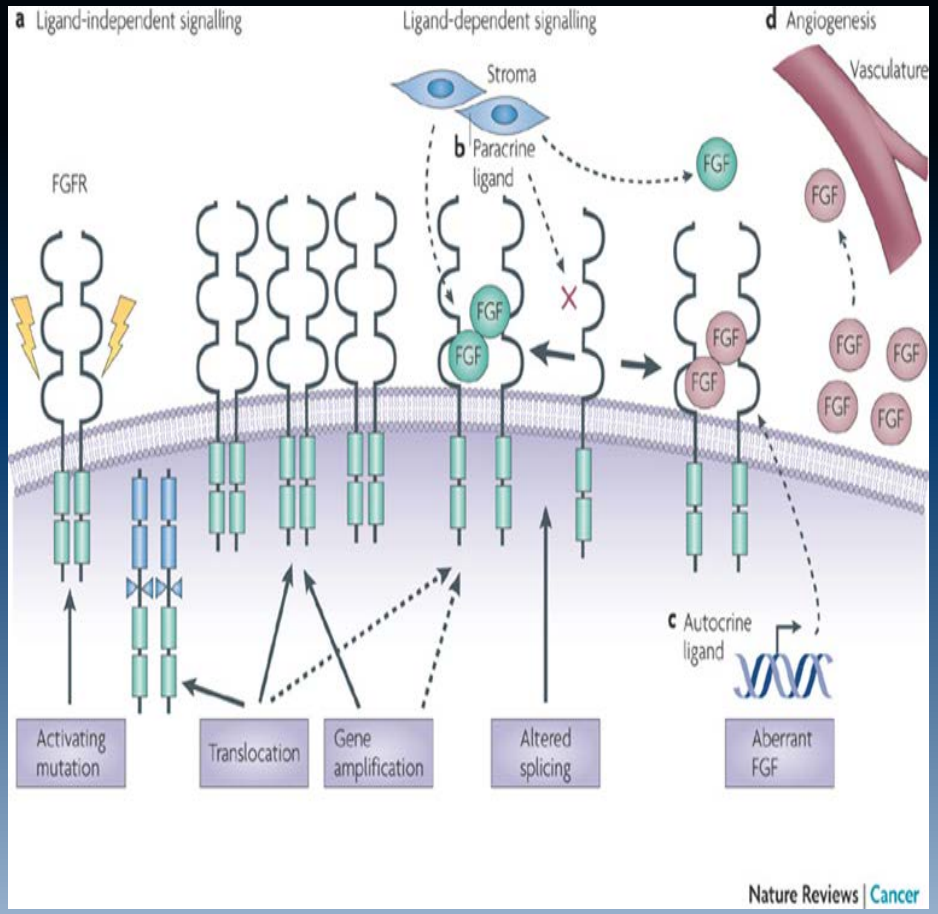


Sub-study C

- 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

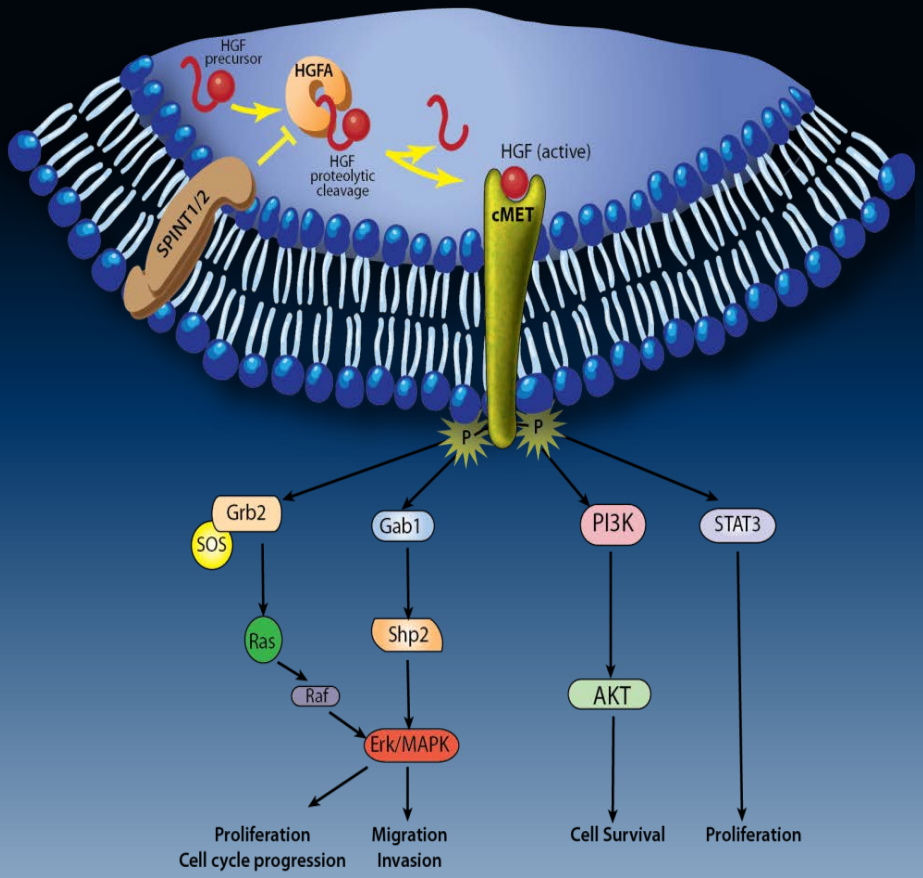
Rationale-Science



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.

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

Tissue Requirements

1. Tissue block (preferred) or at least 12 five-micron unstained slides (20 slides are strongly recommended). – must contain 20% tumor cells.
2. Hematoxilyn-eosin (H&E)-stained slide or Aperio H&E-stained slide
3. Local pathology report from initial diagnosis
4. **S1400** Local Pathology Review Form:

   Tumor material must be reviewed by a local pathologist to ensure sufficient tumor cells are present in the sample. The local pathologist must review and sign off on the **S1400** Local Pathology Review form noting that the tumor tissue contains at least 20% viable tumor cells.

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

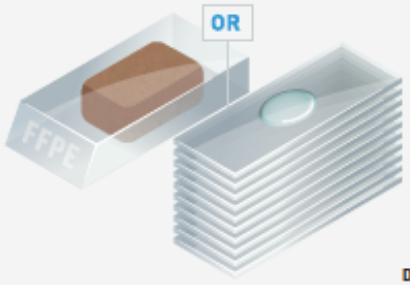
- It is strongly intended to obtain **biopsy at time of PD** for responding pts in order to study acquired resistance mechanisms,
- Peripheral blood at screening and follow-up (plasma and buffy coat).

- EXPLORATORY STUDIES: Applications through regular SWOG TM mechanisms. (www.swog.org)

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

Foundation Medicine NGS test platform (CLIA/CAP)

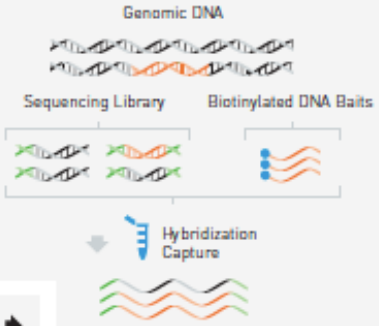
1) DNA extraction



DNA EXTRACTION

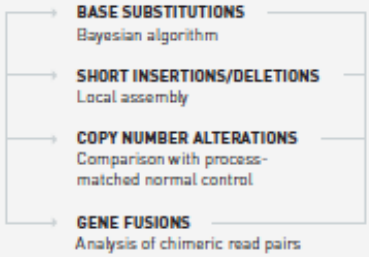
2) Library construction: selected cancer genes

Illumina HiSeq 2500



SEQUENCING

3) Analysis pipeline



ANALYSIS & INTERPRETATION

Classification rules

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

Non-NGS biomarkers:

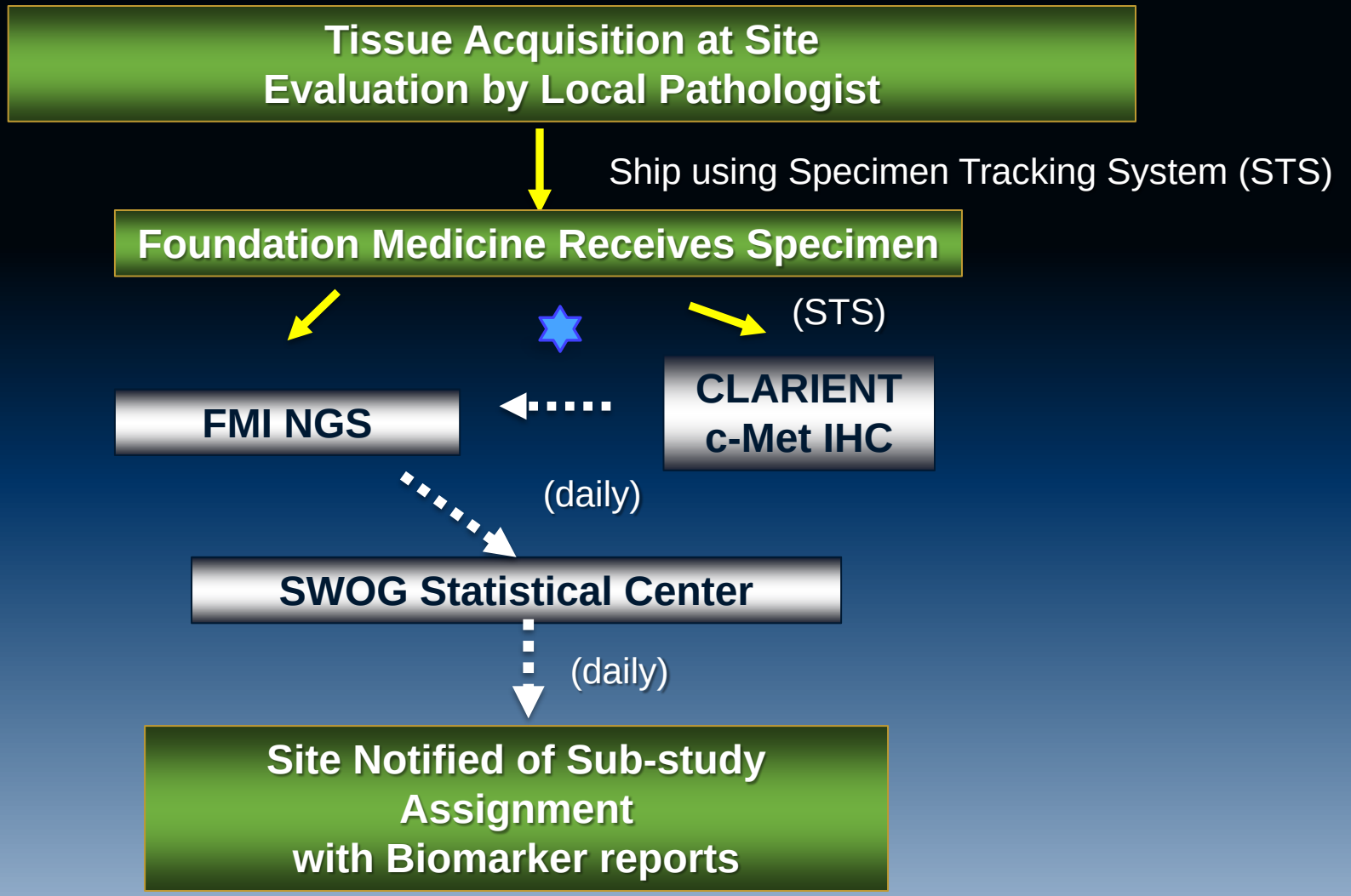
Supplementary assays	Non-match arm
MET IHC (+)	All assays (-)
MET pathway inhibitor	Anti-PD-L1 Ab

Classification rules (preliminary)

PIK3CA mutation	CCND1, D2, D3 amplification , CDK4 amplif	FGFR1/2/3/4 amplification, mutation or fusion
PI3K inhibitor	CDK4/6 inhibitor	FGFR inhibitor

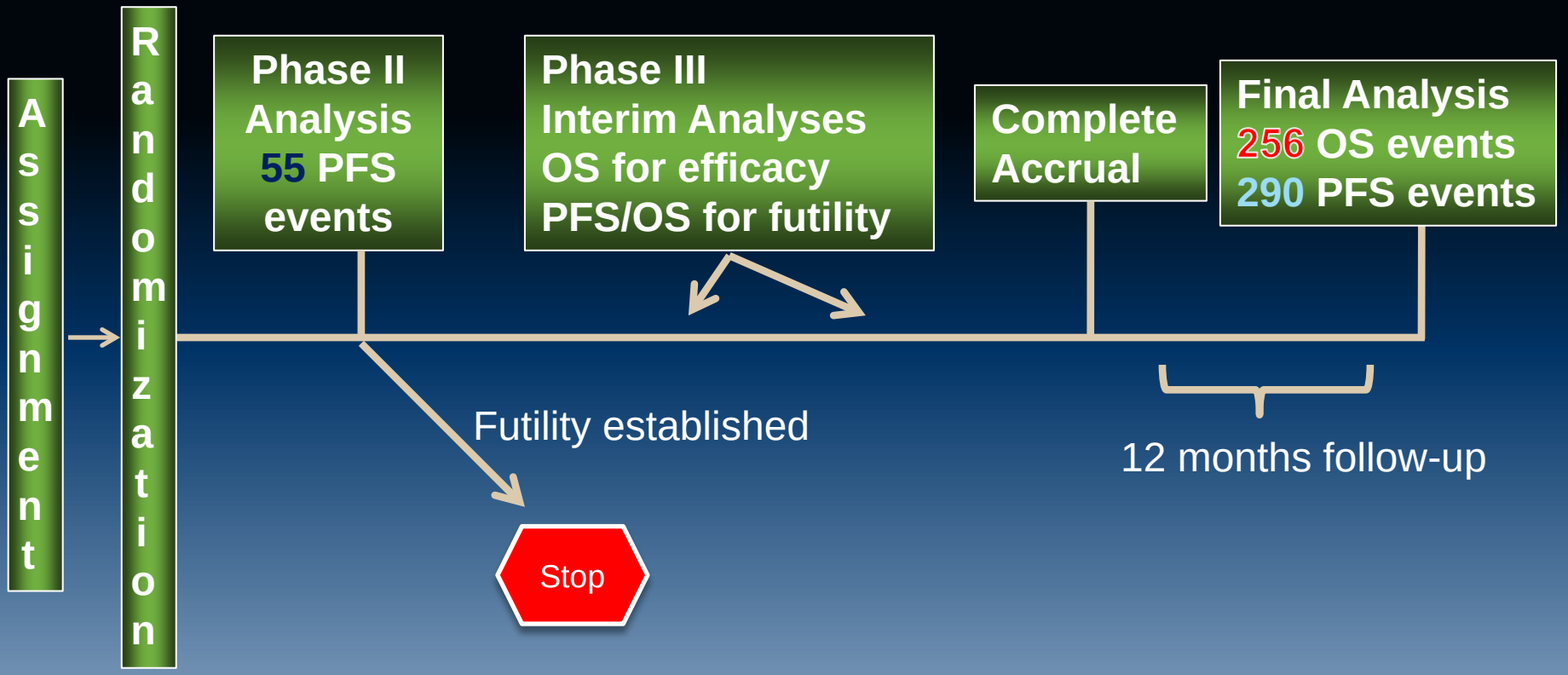
LUNG-MAP

Tissue Flow / Reporting Flow



LUNG-MAP

Study Design Within Each Sub-study



LUNG-MAP

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

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

LUNG-MAP

Sample Size for Active Sub-studies

		Phase 2		Phase 3	
Sub-study ID	Prevalence Estimate	Sample Size Estimate	Decision Time Estimate	Sample Size	Study Duration
S1400A	56.0%	170	8	400	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

Where are we now?

- Study Activated June 16, 2014
- As of October 27, 2014
- IRB Approvals:
  - 353 sites
  - 29 sites with at least 1 patient accrual
- Accruals:
  - 59 patients registered to S1400 (23 in last month)
  - 44 patients notified of their sub-study assignment
  - 19 patients registered to a sub-study

S1400A: 8
S1400B: 0
S1400C: 3
S1400D: 2
S1400E: 6

Key Aspects of Drug Selection

Sources:

- Investigator/Drug Selection Committee initiated,
- Pharmaceutical company initiated
- Solicited by RFA

Initial Qualification:

- Investigational drug/biomarker combination with preclinical & clinical data supporting safety & potential efficacy as a targeted therapy or “non-match” therapy in lung SCC
- Ready or near ready to enter the Lung-MAP phase 2 clinical protocol

Key Aspects of Drug Selection

- **Candidates are evaluated by the Lung-MAP Drug Selection Committee (DSC), comprised of:**
  - Key investigators & clinical researchers
  - Biomarker & molecular target experts from academia, NCI and FDA
  - Non-conflicted industry-based drug developers

- **Candidates are scored based on:**
  - Target appropriateness for Lung-MAP
  - Drug/Biomarker preclinical & clinical data
  - PK/PD data

Project Evolution

- Total Sample Size Projected over 5 years=5,000

(625-1250 screened/yr to accrue 500-1000/yr)

- New studies roll in in real-time (2 new in planning)

-PARP inhibitor for *BRCA-1, -2 mut*

-Combination immunotherapy for non-match Arm (anti-PD-L1+anti-CTLA4).

- Correlative science projects based on tissue/blood repository at SWOG.

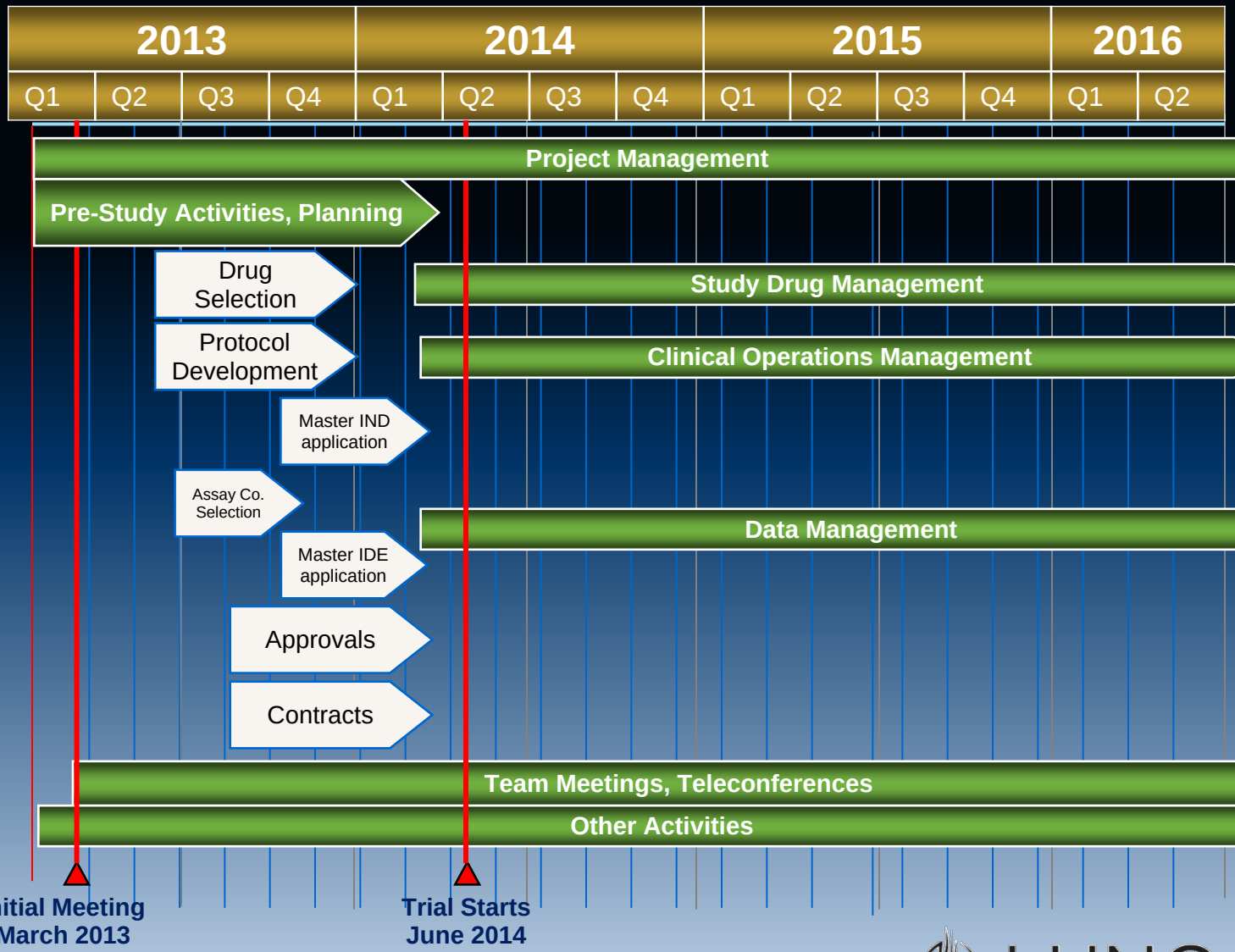
Novel Clinical Trial Designs for NSCLC

Improving the drug development process

- **Biomarker-driven clinical trials require rigorous biomarker testing and validation.**
- **Selecting genomic sub-sets with clear driver mutation designation is the right path but may prove to be challenging as clear drivers yet to be identified may be exceedingly rare.**
- **Complex genomic landscapes may require combination targeted therapy but preclinical models do not always directly translate in the clinical setting.**
- **Emergence of immunotherapy and potential immunotherapy combinations mandates definition of subsets that may benefit, biopsy-driven clinical trials to capture dynamic nature of immune checkpoint expression.**
- **Lessons learned from well designed clinical trials based on robust teams serve as the building blocks for future cures.**

Thank you

- **Hossein Borghaei, D.O. ECOG-ACRIN, Fox Chase Cancer Center (Sub-study A).**
- **Jeffrey A. Engelman, MD, Ph.D., ALLIANCE, Massachusetts General Hospital Cancer Center (Sub-study B).**
- **Corey J. Langer, M.D. NRG, University of Pennsylvania, Hematology Oncology Division, Abramson Cancer Center (Sub-study B).**
- **Martin J. Edelman, M.D. , NRG,The University of New Mexico (Sub-study C)**
- **Kathy S. Albain, M.D.SWOG,Loyola University Medical Center (Sub-study C)**
- **Charu Aggarwal, M.D., M.P.H. ECOG-ACRIN, Abramson Cancer Center (Sub-study D)**
- **Primo N. Lara, Jr., M.D. SWOG,UC Davis Comprehensive Cancer Center (Sub-study D)**
- **Mark A. Socinski, M.D., ALLIANCE, Pittsburgh School of Medicine (Sub-study E.)**
- **David R. Spigel, M.D., SWOG, Sarah Cannon Research Institute Sub-study E)**


2013
2014
2015
2016
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
Q1
Q2
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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

S1400 Registration and Sub-study Assignment

Screen for eligibility, consent patient and confirm that required amount of tissue is available for submission
(pathologist to complete the *Local Pathology Review Form*)

↓

Register to S1400 in OPEN

↓

Submit tissue specimen within 1 day after registration
(Ship to FMI and and log shipment using the Specimen Tracking System)

↓

Within 16 days after S1400 registration

↓

Site staff receives email from SWOG with sub-study assignment
(Assignment will also display in the *Sub-study Assignment* form in Rave®)

Post Sub-study Assignment

Evaluate common eligibility and sub-study specific eligibility criteria

↓

If patient IS eligible for assigned sub-study

↓

Register to sub-study in OPEN within 42days of receiving sub-study assignment email to receive randomized sub-study treatment assignment

↓

Administer protocol treatment within 7 working days of sub-study registration, conduct follow-up, obtain and submit specimens and forms per sub-study protocol

Funding Highlights

- Sites will receive up to $5,869 ($1,079 screening/$4,790 registration) for each patient on trial
- If biopsies are needed, sites will receive $3,000/$6,000 for the biopsies performed at screening and/or progression after initial response on Arm 1
- Sites will be reimbursed for additional research based procedures
- Sites will be reimbursed $1,333 for extra audit visits outside regular schedule

Funding Changes

FDA has requested tests/procedures to be performed on the investigational and standard of care arms. Sites will be reimbursed for the following additional procedures on both arms.

Sub-study	Additional Funding for Procedure/Test
S1400A	TSH T3/T4*
S1400B	HbA1c, Lipase, Amylase
S1400C	EKG, HbA1c*
S1400D	OCT Scan, Ophthalmological Assessment, MUGA, Phosphate, Urinalysis, Troponin
S1400E	No changes

*This is an added test requested by the Company as part of the amendment