Master Protocols in the USA: LungMAP/S1400 as a Unique Public-Private Approach to Drug-Biomarker Registration

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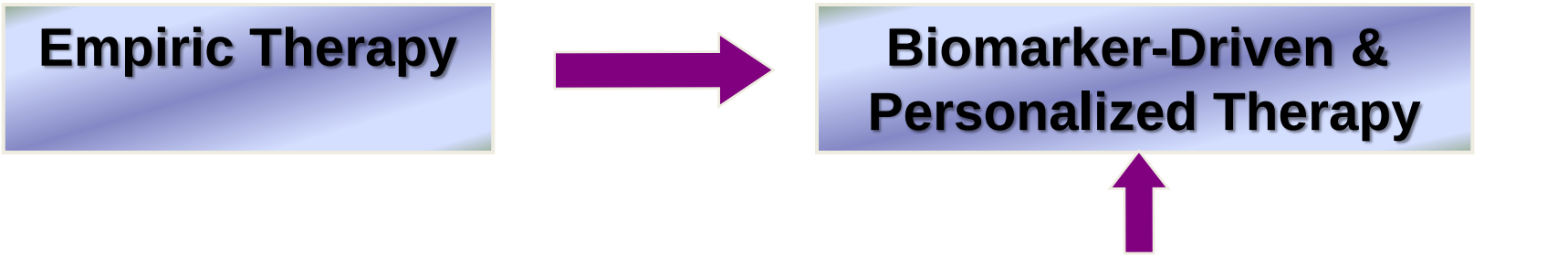
LUNG-MAP

Disclosures

- **Research Grants: AZ/Medi, BMS, Clovis, Genentech, JNJ, Lilly, Merck, Novartis**
- **Consultant: AstraZeneca, Boehringer-Ingelheim, Celgene, Clovis, Genentech, Guardant Health, Lilly, Merck, Novartis, Response Genetics, Synta**

Transition from Empiric to Personalized Cancer Therapy (Biomarker-Driven)



Tumor Molecular Profiling to identify drug targets (adequate tumor tissue)

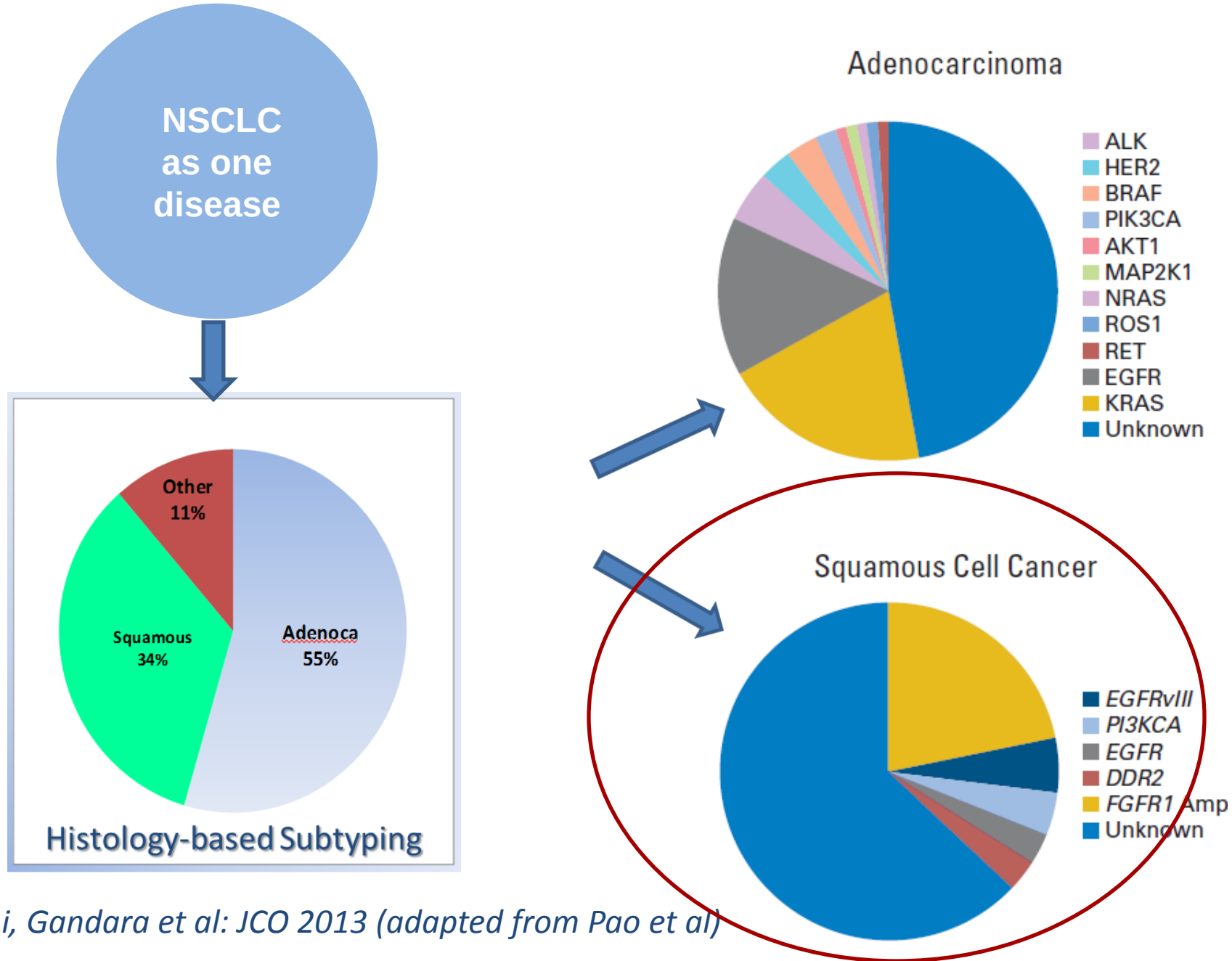
Drugs against the MolecularTargets

Predictive Biomarkers for the drugs

How do "Master Protocols" fit into this Paradigm Shift?
-Genomic Profiling
-Clinical Trial Design change

Gandara et al: Clin Lung Cancer, 2012

Evolution of NSCLC Subtyping from Histologic to Molecular-Based



Li, Gandara et al: JCO 2013 (adapted from Pao et al)

The Growing List of Guideline Recommendations for Molecular Testing

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2014
Non-Small Cell Lung Cancer

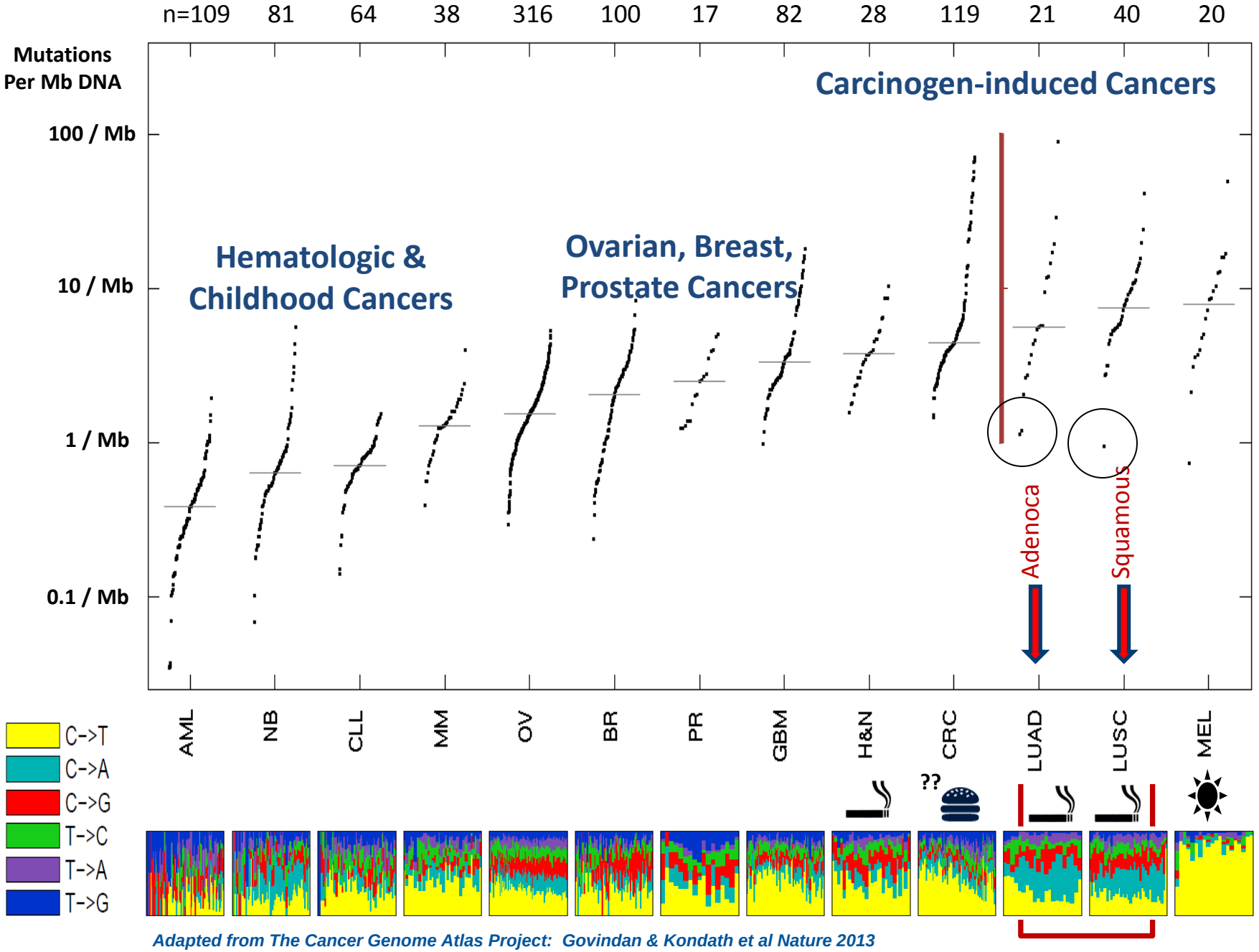
TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
EGFR mutations	erlotinib,[1] gefitinib,[2] afatinib[3]
ALK rearrangements	crizotinib[4], ceritinib[5]
HER2 mutations	trastuzumab,[6] afatinib[7]
BRAF mutations	vemurafenib,[8] dabrafenib[9]
MET amplification	crizotinib[10]
ROS1 rearrangements	crizotinib[11]
RET rearrangements	cabozantinib[12]

http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Note: EGFR mutations too rare (<3.6%) to be routinely tested in squamous cell carcinoma

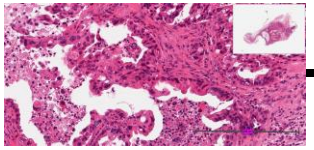
Magnitude of Genomic Derangement is greatest in Lung Cancer



Adapted from The Cancer Genome Atlas Project: Govindan & Kondath et al Nature 2013

Integration of Biomarkers into Clinical Practice: Past, Current & Future

1. Histomorphological Diagnosis:



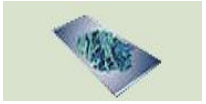
Empiric Approach (Past) (Compound-Based Therapy):
Clinical-histologic factors to select drugs for individual patients

2. Molecular Diagnosis:

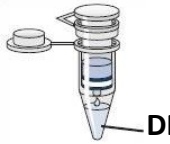
Archival FFPE tumor specimens

Archival cancer specimens

Macro- or Micro-dissection of Tumors



Extract tumor nucleic acids:



Current Approach (Target-Based Therapy V1.0):
Single gene molecular testing for decision-making in individual patients

Evolving Approach (Target-Based Therapy V2.0):
Multiplexed molecular tests with increased sensitivity & output for decision-making in individual patients

Near-Future Approach (Patient-Based Therapy):
Genomic profiling by high throughput next generation sequencing for decision-making in individual patients

Representative technologies:

Single Biomarker Tests:
- Sanger DNA Sequencing
- RT-PCR
- FISH
- IHC

Multiplex, Hot Spot Mutation Tests:
- PCR-based SNapShot
- PCR-based Mass Array SNP
- Sequenom

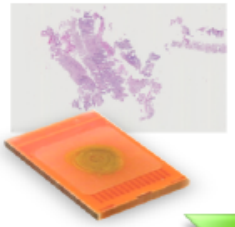
Initial High-Throughput Technologies:
- SNP/CNV DNA microarray
- RNA microarray

Next Generation Sequencing (NGS):
- Whole Genome or Exome capture Sequencing (DNA)
- Whole or Targeted Transcriptome Sequencing (RNA)
- Epigenetic profiling

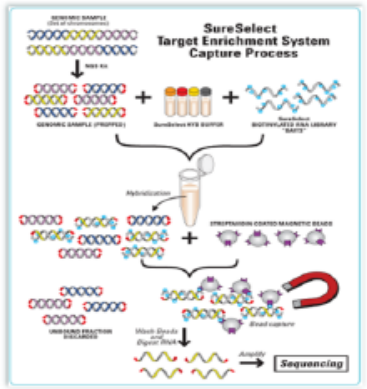
from Li, Gandara et al: JCO , 2013

Comprehensive Cancer Genomic Test: 200+ Genes

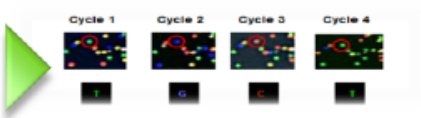
Foundation Medicine One



Fixed sample slides



DNA extraction, Library construction, Hybrid capture



Sequencing (Illumina HiSeq™ 2000)

ANALYSIS PIPELINE

- **Point Mutations**
  Bayesian algorithm
- **Short Insertions/deletions**
  Local assembly
- **Copy Number Alterations**
  Comparison with process-matched normal control
- **Rearrangements**
  Analysis of chimeric pairs

Annotation & Interpretation

dbSNP
COSMIC
Med. Literature

Clinical Report

<14 days

FOUNDATION MEDICINE

ResponseDX: Comprehensive Lung Profiling (Response Genetics, Inc)

FISH PANEL

Marker	Clinical Importance
ALK translocation	Sensitivity to crizotinib
ROS1 translocation	Sensitivity to crizotinib
RET translocation	Sensitivity to vandetanib
MET amplification	Sensitivity to crizotinib
FGFR1 amplification	Targets being tested in trials

RNA EXPRESSION PANEL

Marker	Clinical Importance
ERCC1	Insensitivity to platinum-based therapies
TS	Insensitivity to 5-FU and pemetrexed
RRM1	Sensitivity to gemcitibine
EGFR expression	Sensitivity to gefitinib
cMET	Sensitivity to TKI therapies

SEQUENCING PANEL

Marker						Clinical Importance
EGFR						Sensitivity to erlotinib
ERBB2 (HER2)						Sensitivity to lapatinib
BRAF						Sensitivity to vemurafenib, dabrafenib
DDR2						Potential sensitivity to dasatinib
KRAS						Unlikely to respond to erlotinib
ALK*	AKT1	HRAS	JAK2	KDR	MAP2K1	Targets being tested in ongoing trials
NOTCH1	NRAS	NTRK1	NTRK2	NTRK3	PIK3CA	
PIK3R1	PIK3R2	PTEN	PTPRD	CDKN2A	TP53	

*ALK point mutations only; translocations (e.g. EML4-ALK) require separate FISH test.

Guardant360 Panel 2015: Plasma NGS

Complete or Critical Exon Coverage in 68 Genes*

POINT MUTATIONS

AKT1	ALK	**APC**	**AR**
AFAR	**ARID1A**	ATM	**BRAF**
BRCA1	**BRCA2**	**CCDN1**	**CCND2**
CCNE1	CDH1	**CDK4**	**CDK6**
CDKN2A	**CDKN2B**	CTNNB1	**EGFR**
ERBB2	ESR1	EZH2	FBXW7
FGFR1	**FGFR2**	FGFR3	GATA3
GNA11	GNAQ	GNAS	HNF1A
HRAS	IDH1	IDH2	JAK2
JAK3	**KIT**	**KRAS**	MAP2K1
MAP2K2	**MET**	MLH1	MPL
MYC	**NF1**	NFE2L2	NOTCH1
NPM1	**NRAS**	NTRK1	**PDGFRA**
PIK3CA	**PTEN**	PTPN11	**RAF1**
RET	RHEB	RHOA	RIT1
ROS1	SMAD4	SMO	SRC
STK11	TERT**	**TP53**	VHL

AMPLIFICATIONS

- AR
- BRAF
- CCNE1
- CDK4
- CDK8
- EGFR
- ERBB2
- FGFR1
- FGFR2
- KIT
- KRAS
- MET
- MYC
- PDGFRA
- PIK3CA
- RAF1

FUSIONS

- ALK
- RET
- ROS1
- NTRK1

INDELS

- EGFR exon 19 deletions
- EGFR exon 20 insertions

*Complete exon coverage for genes in **bold**
**Includes TERT promoter region

Need for Paradigm Shift in Targeted Therapy Clinical Trial Design (Presumes Biomarker Potential)

"All Comer" Phase III Design adding Targeted Therapy to Chemotherapy

- When Marker not known or not validated (analytical)
- Marker (if known) can be retrospectively assessed
- Cautionary Tale: Most Phase III "All Comer" trials in NSCLC targeted therapy fail
- May be random differences in Marker+ and Marker- proportions per arm

Gandara et al: Clin Lung Cancer, 2014

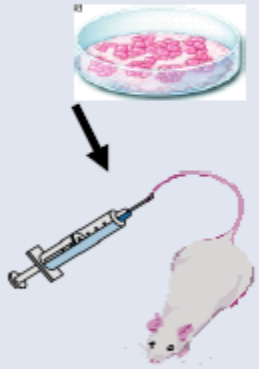
Classic RCT Design (Unselected): Phase III Trials of Chemotherapy +/- Targeted Agent* in 1st-line Therapy of Advanced Stage NSCLC

Target	Agent	Survival Benefit
MMPs	Prinomastat, Others	No
EGFR TKI	Gefitinib or Erlotinib	No
Farnesyl Transferase (RAS)	Lonafarnib	No
PKCα	ISIS 3521	No
RXR	Bexarotene	No
VEGFR (TKI)	Sorafenib	No
VEGF (Mab)	Bevacizumab	Yes
EGFR (Mab)	Panitumumab	No
TLR9 Agonist	PF-351	No
EGFR (Mab)	Cetuximab	Yes**
IGR1-R	Figitumumab	No
VDA	ASA-404	No

Need for a completely "New Way of Thinking" for development of Targeted Drug/Biomarker Combinations: "Master Protocol"

Integrated New Drug-New Biomarker Development Paradigm:

Phases of Development of a New Drug

Pre-clinical	Phase I	Phase II	Phase III	Drug Approval
	N=30	N=300	N=1600	Total Time ~90 mos (7.5 years)
~18 mo.	~18 mo.	~18 mo.	~36 mos	

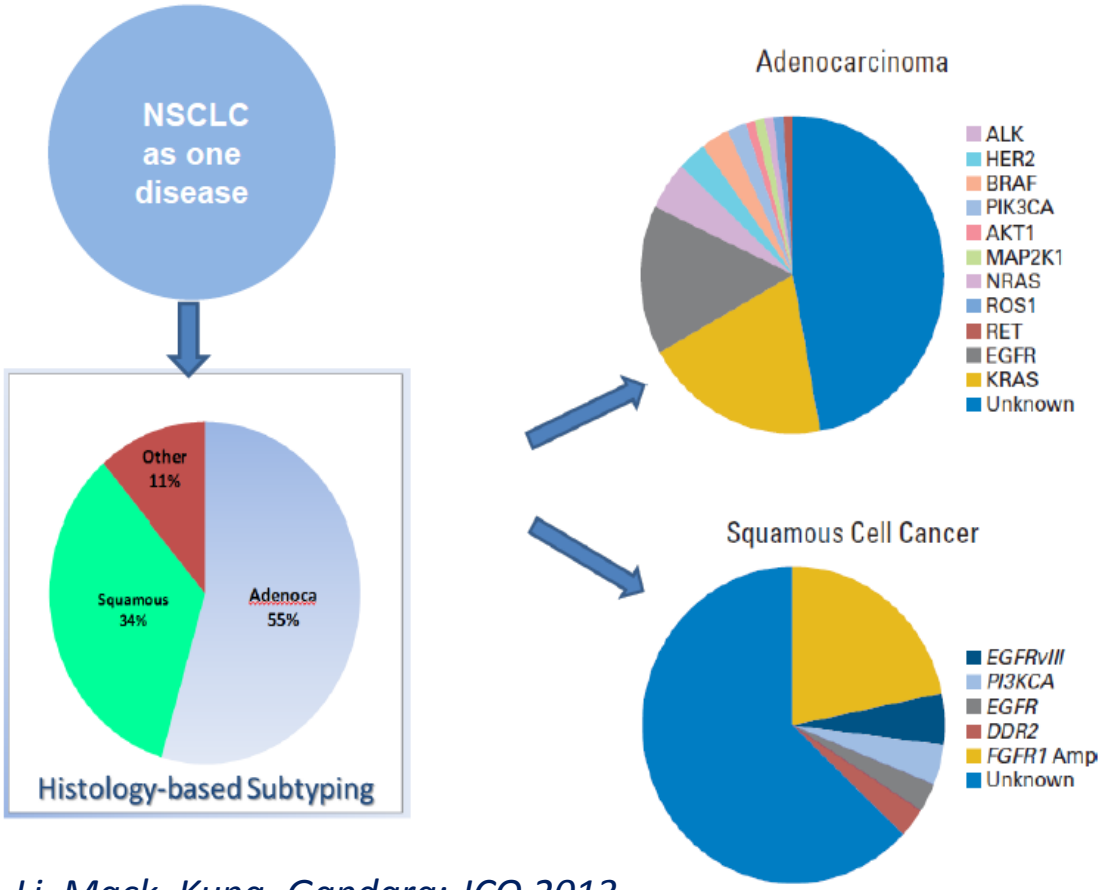
Phases of Development of New Biomarker linked to New Drug

Confirm Target	Integrate Biomarker	Biomarker Informative?	Clinical Validation	Clinical Application of Biomarker
Assay Development	Assay Performance	Assay Validation	Co-Primary Endpoint	

from Gandara et al: Clin Lung Cancer, 2012

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 Protocols:

- 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)

LUNG-MAP

"Strategies for Integrating Biomarkers into Clinical Development of New Therapies for Lung Cancer"

A Joint NCI Thoracic Malignancies Steering Committee-FDA Workshop

Bethesda MD – February 2-3, 2012

- Trial Design Challenges in the Era of Biomarker-driven Trials
  - Innovative Statistical Designs
  - Challenges for Community Oncology Practice participation
  - The Patient Perspective
- Drug & Biomarker Co-Development in Lung Cancer
  - Need for Early Co-Development
  - Need for Improved Pre-Clinical Models with clinical relevance
- Development of Future Lung Cancer Trials
  - TMSC Master Protocol Task Force in NSCLC
  - Biomarker-driven trial designs in both early stage adjuvant therapy & advanced stage NSCLC
  - Account for inter-patient tumor heterogeneity & genomic complexity of NSCLC

Master Protocol Subtypes

Umbrella Trials

Single Type of Cancer: Test multiple drug-biomarker combinations

- BATTLE
- I-SPY2
- SWOG Lung MAP (S1400): adv SCCA
- ALCHEMIST: early stage NSCLC
- ALK Master Protocol: ALK+ NSCLC

Basket Trials

Multiple Cancer Types: Test multiple drugs against single or multiple biomarkers

- Imatinib Basket
- BRAF+
- NCI MATCH

ALCHEMIST Trial Schema

Non-squamous NSCLC (n=6,000 to 8,000 pts)
Stage IB (≥ 4cm), II, IIIA

Complete resection + standard adjuvant therapy

→ Central EGFR & ALK genotyping

→ <u>EGFR-mutation</u>: Phase III trial of erlotinib vs placebo x 2 years (n=410) after any adj tx

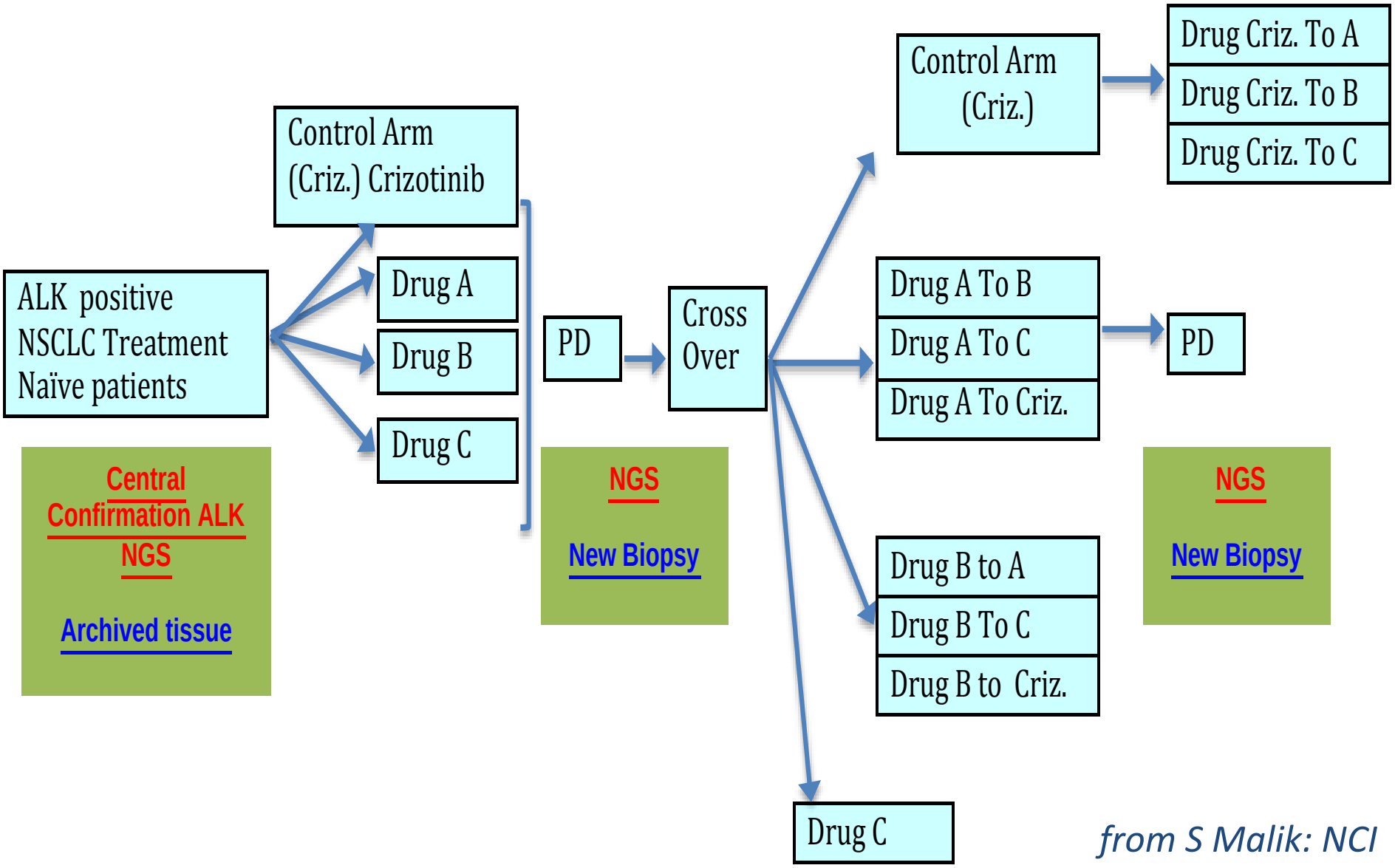
→ <u>ALK-rearranged</u>: Phase III trial of crizotinib vs placebo x 2 years (n=360) after any adj tx

→ <u>Non-Match</u>: Phase III trial of nivolumab vs placebo X 1 year after any adj tx

↓ FFPE tissue & blood specimen
(EGFR & ALK testing performed by RGI)

Advanced genomics at the NCI

ALK Master Protocol: Proposed Trial Design



from S Malik: NCI

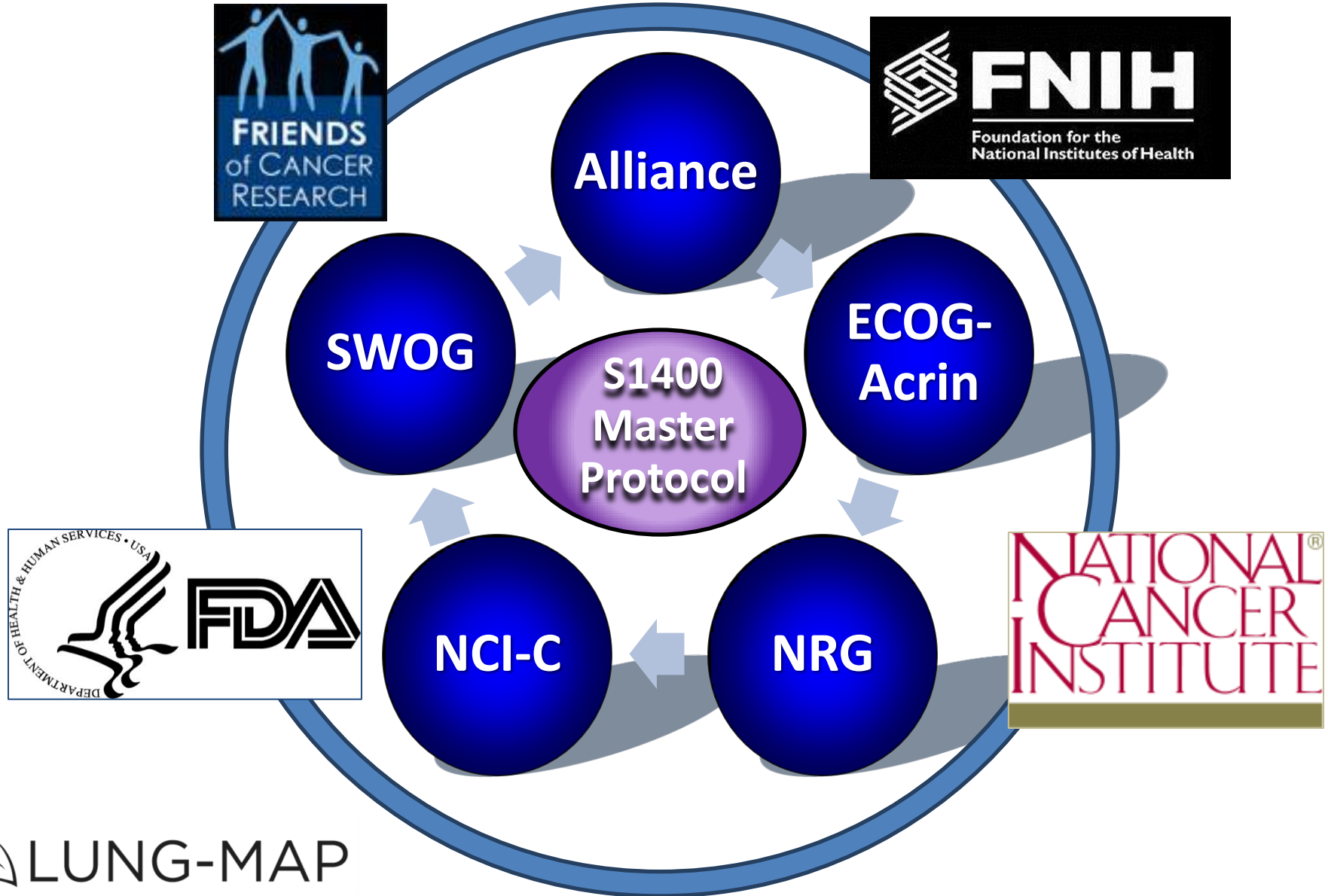
Rationale for "MASTER PROTOCOL" in SCCA

- **SCCA** represents an unmet need
- **Candidate molecular targets** are available from results of TCGA & other studies, identified by a **biomarker**
- **Drugs** (investigational) are now available for many of these targets
- Trials can be designed to **allow testing** & registration of **multiple new drug-biomarker combinations at the same time** ("MASTER PROTOCOL" concept)
- Result of this concept is **Lung-MAP (S1400)**, activated in June 2014

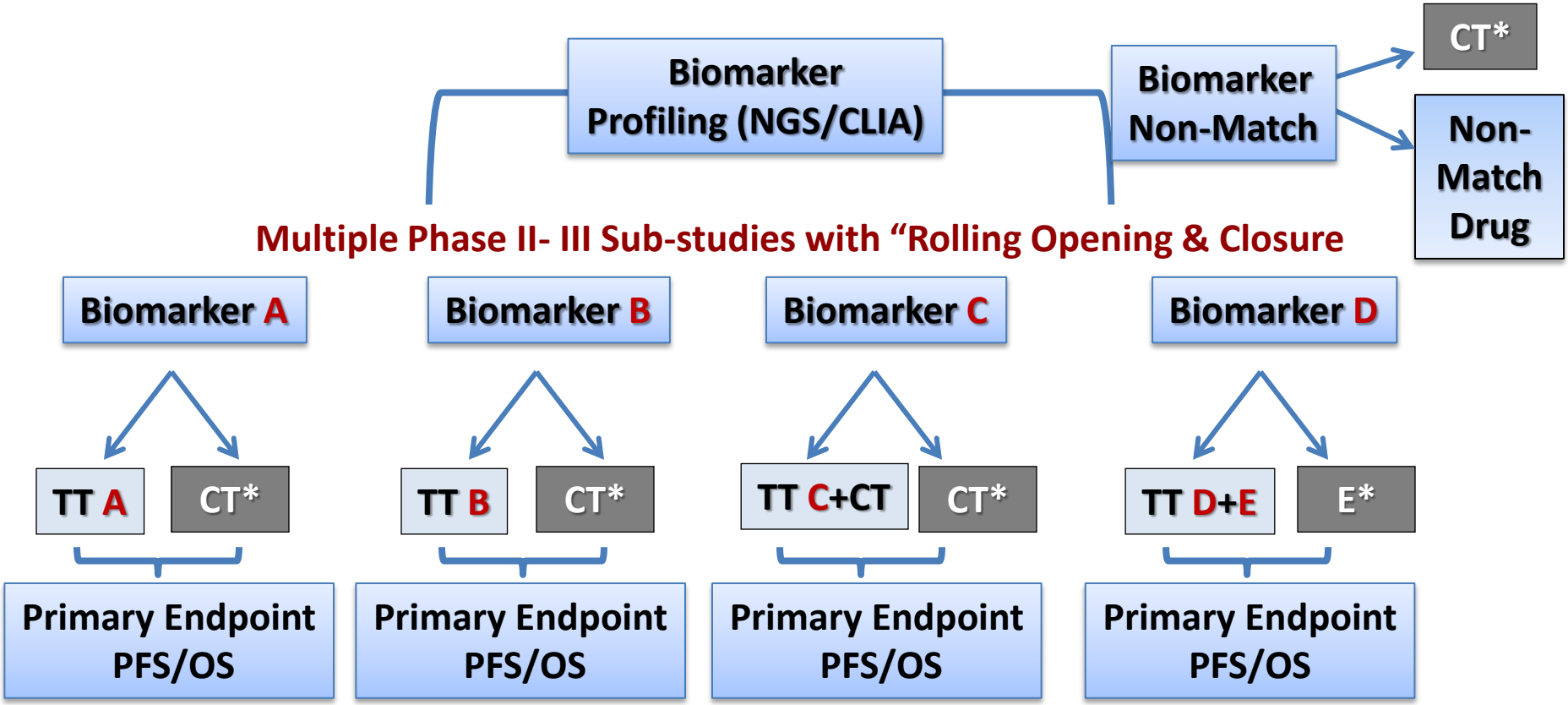
Therapeutic targets SCCA-TCGA 2012

Gene	Event Type	Frequency
CDKN2A	Deletion/Mutation/ Methylation	72%
PI3KCA	Mutation	16%
PTEN	Mutation/Deletion	15%
FGFR1	Amplification	15%
EGFR	Amplification	9%
PDGFRA	Amplification/Mutation	9%
CCND1	Amplification	8%
DDR2	Mutation	4%
BRAF	Mutation	4%
ERBB2	Amplification	4%
FGFR2	Mutation	3%

S1400 Lung-MAP Protocol: A Unique Private-Public Partnerships within the NCTN



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

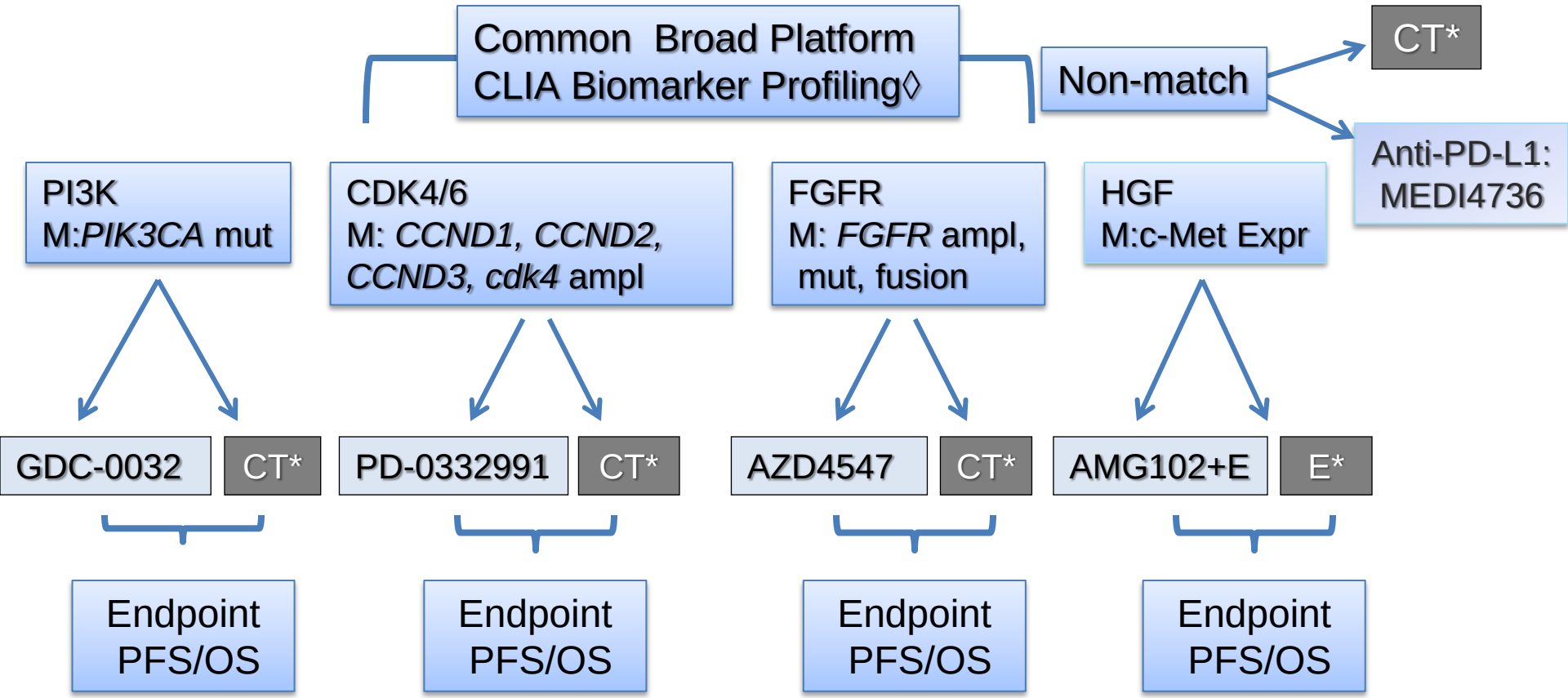


TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

Project Chair: V. Papadimitrakopoulou
Steering Committee Chair: R. Herbst
SWOG Lung Chair: D. Gandara

LUNG-MAP

LUNG-MAP (S1400): Squamous Lung Cancer- 2nd Line Therapy

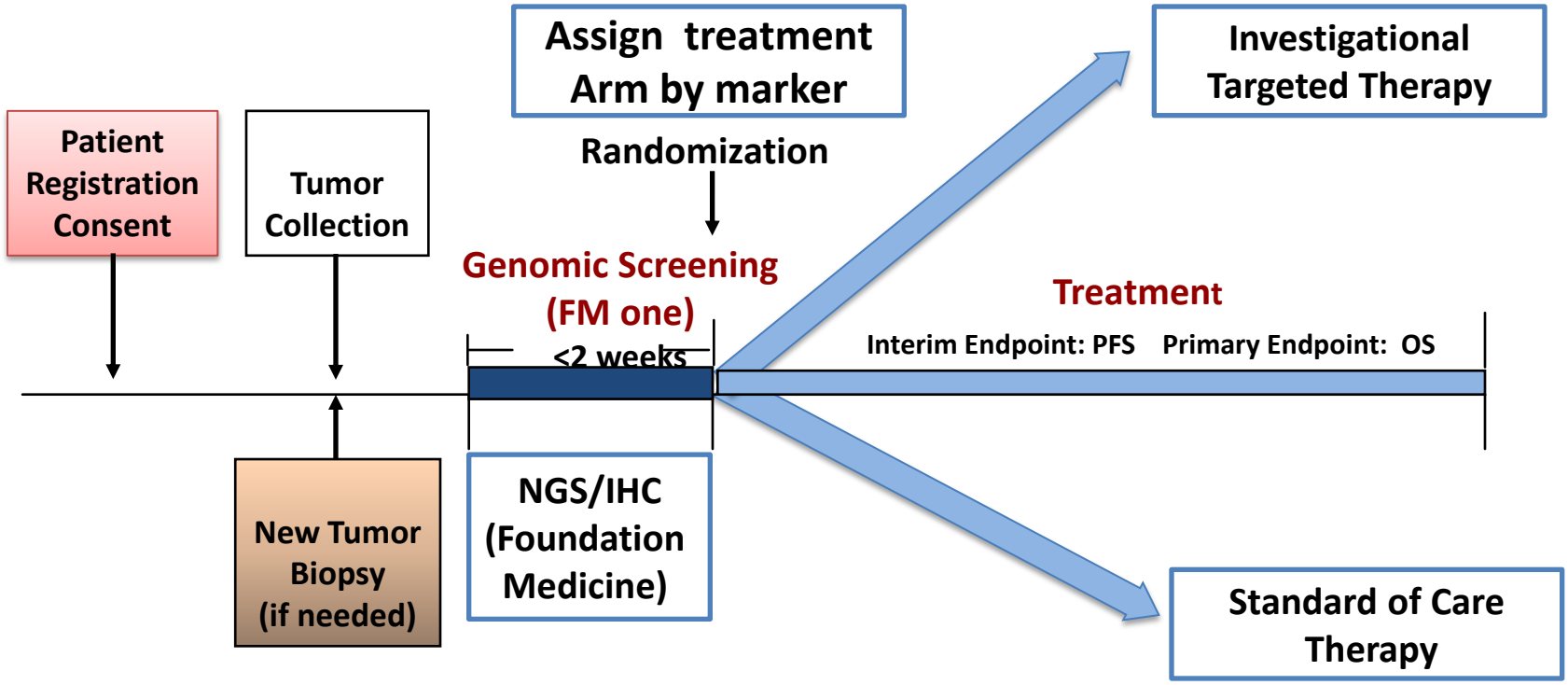


TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib
◊ Archival FFPE tumor, fresh CNB if needed

LUNG-MAP

Project Chair: V. Papadimitrakopoulou
Steering Committee Chair: R. Herbst
SWOG Lung Chair: D. Gandara

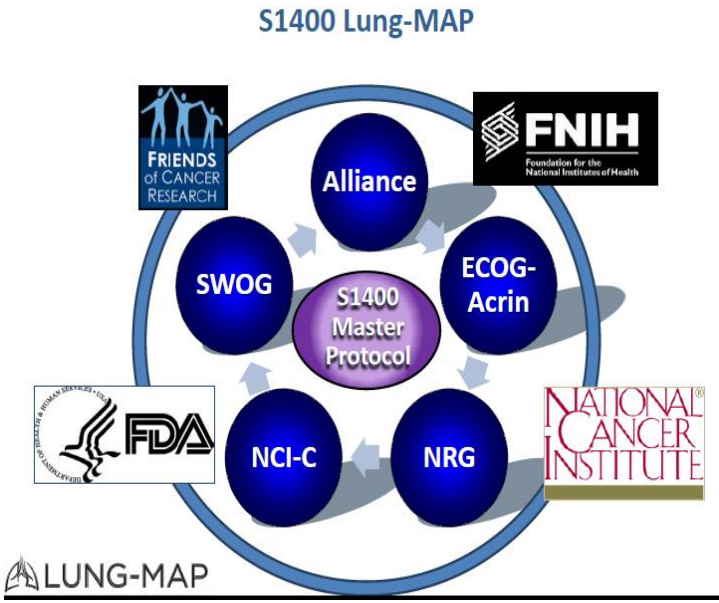
LUNG-MAP (S1400): Squamous Lung Cancer- 2nd Line Therapy

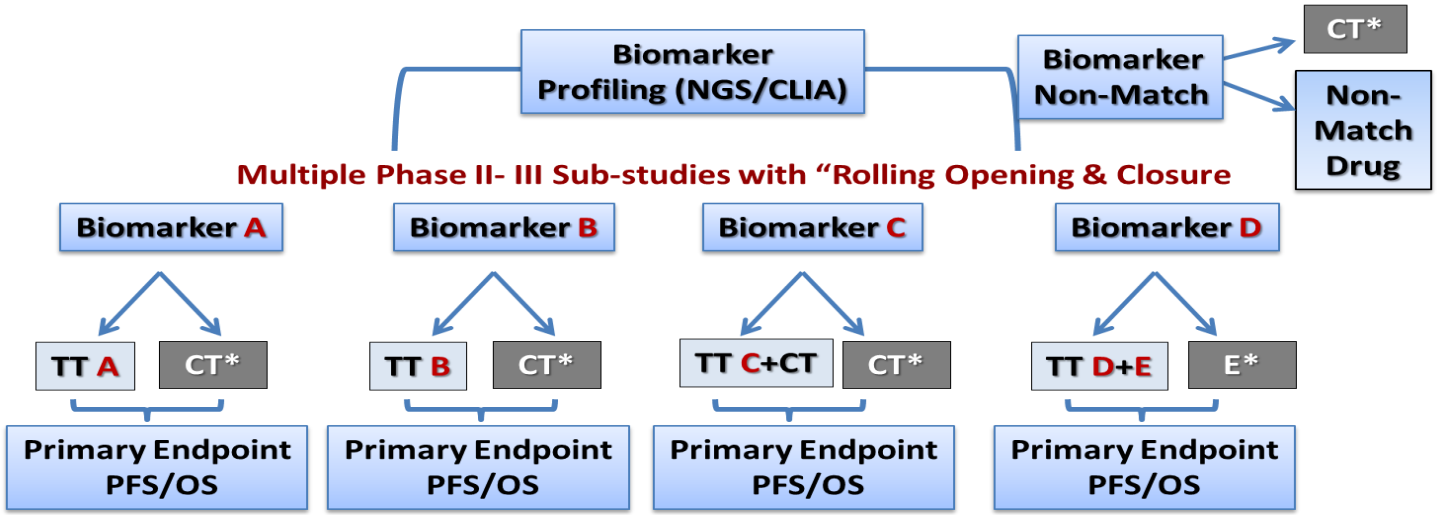


- Organizers: NCI-TMSC, FDA, FNIH, FOCR
- **Participants:** Entire North American Lung Intergroup (SWOG, Alliance, ECOG-Acrin, NRG, NCI-Canada)
- Screening: **up to 1,000 patients/year**
- With 4-6 arms open simultaneously, anticipate a "hit rate ~65% in matching a patient with a drug/biomarker arm

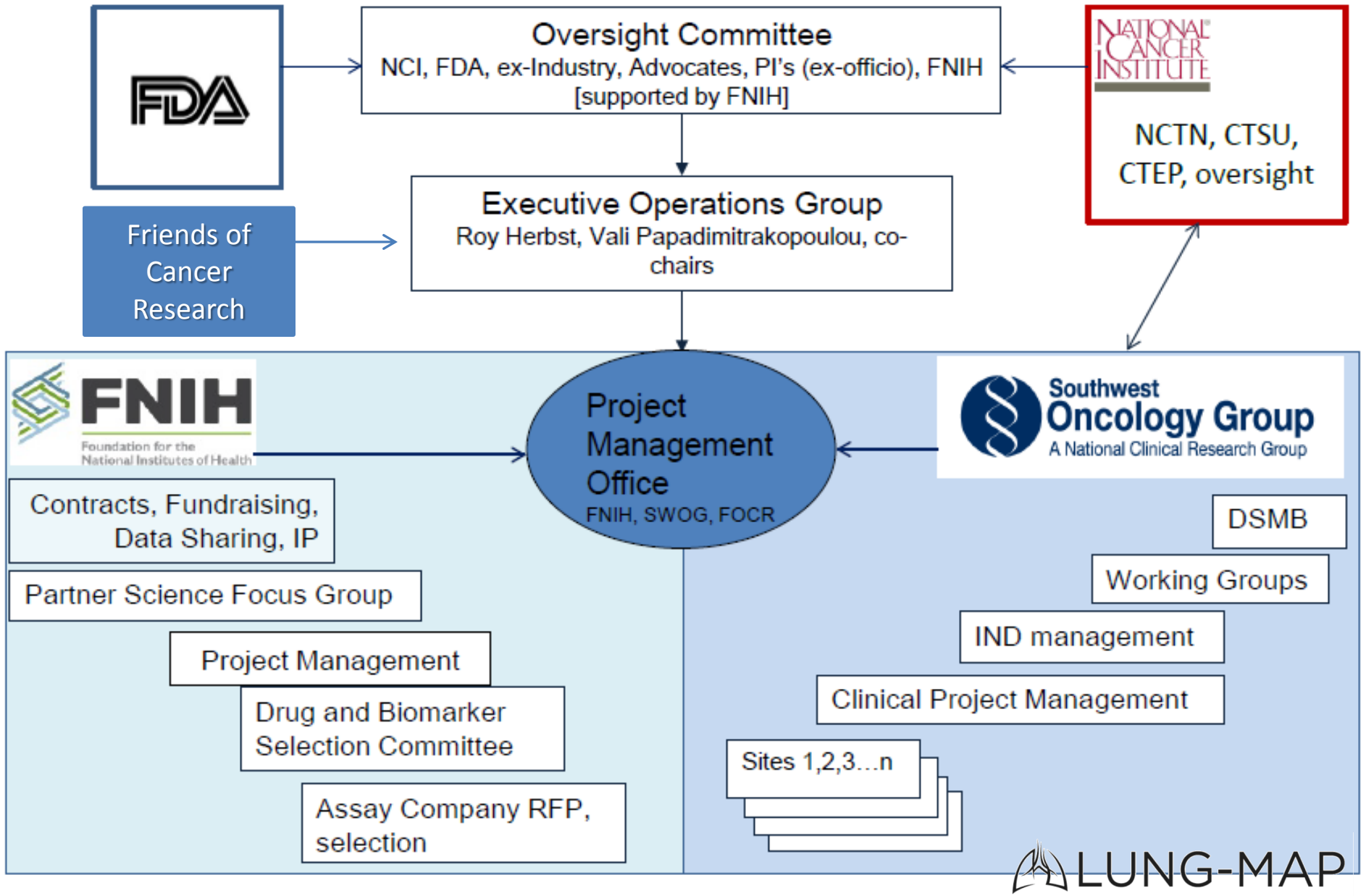
Key Aspects of Lung MAP

- What is the governance and oversight structure for Lung-MAP?
- How was the NGS assay selected?
- What is the process for drug-biomarker selection?
- What are the statistical assumptions to facilitate drug-biomarker registration?
- Is Lung-MAP "self-sustaining"?





Lung MAP Governance Structure



How was the NGS Assay selected? (RFP)

- Foundation Medicine One: One comprehensive genomic profile to simultaneously detect all clinically relevant classes of genomic alterations in a single assay
- Focused on 236 known clinically & biologically relevant cancer genes (all coding exons and selected introns)
- Validated high accuracy achieved by high, uniform coverage: >99.5% of exons covered >100X
- Able to use small amounts of tissue routine FFPE samples including needle biopsies (≥50ng of DNA)
- Customized computational biology algorithms validated for high accuracy in clinical samples with high stromal contamination

Frampton, et. al.,
Nature Biotechnology Oct. 20th 2013
doi:10.1038/nbt.2696

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

Foundation Medicine NGS test platform (CLIA/CAP)

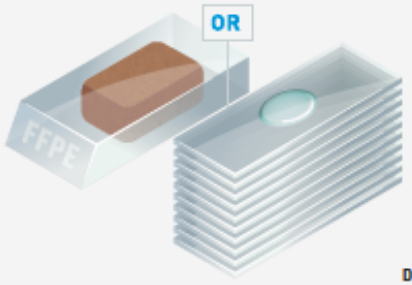
Classification rules

1) DNA extraction

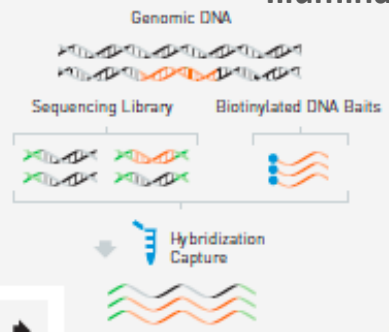
2) Library construction: selected cancer genes

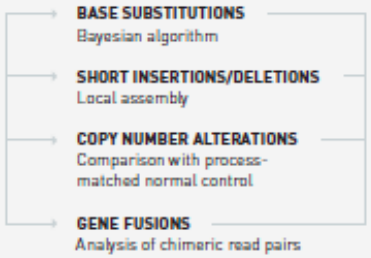
3) Analysis pipeline

4) Master protocol CTA



Illumina HiSeq 2500





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

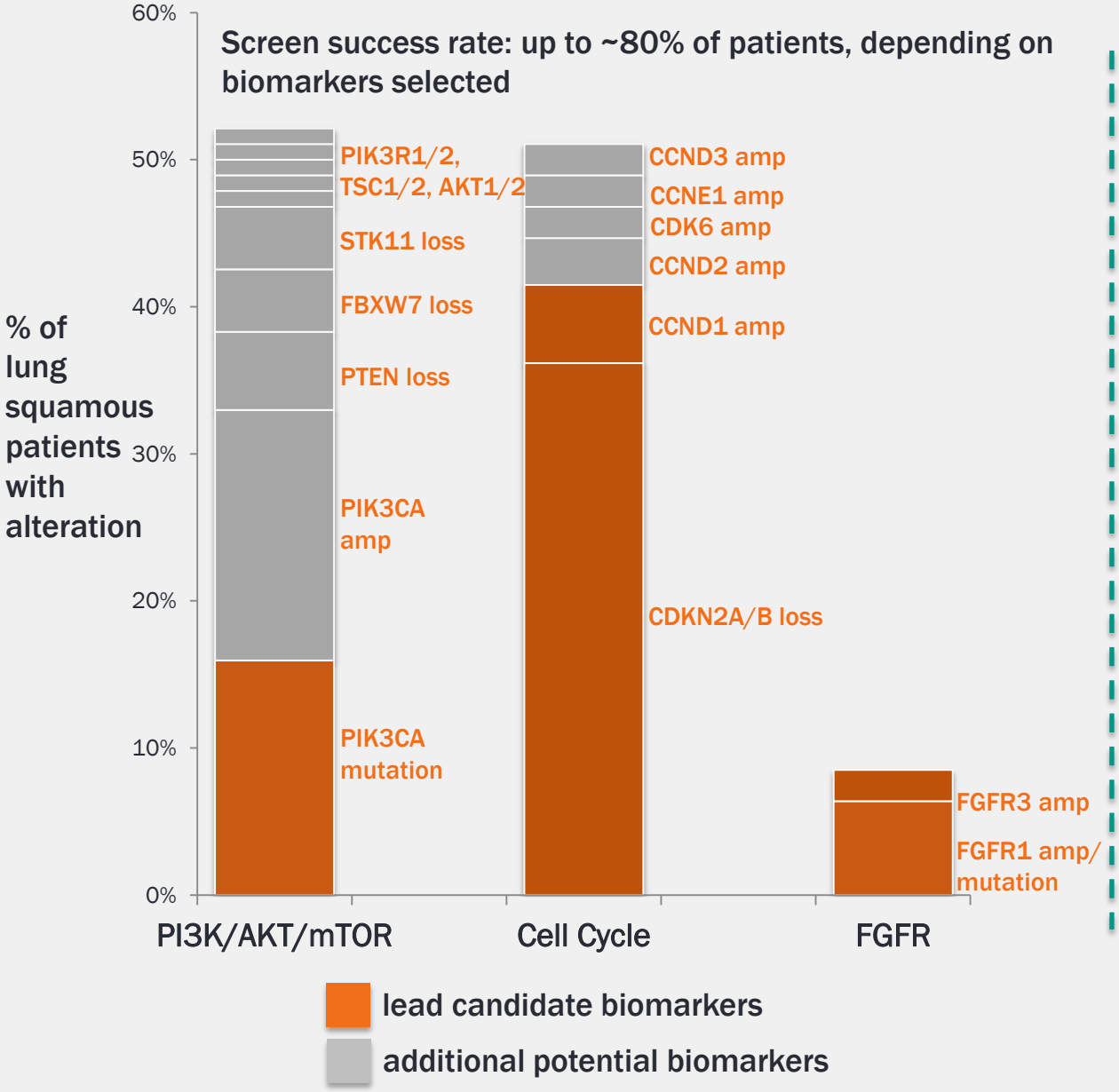
Non-NGS biomarkers:

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

Classification rules (preliminary)

PIK3CA mutation	CCND1 amplification or CDKN2A/B deletion, and RB1 wild-type	FGFR1/2/3/4 amplification, mutation or fusion
↓	↓	↓
PI3K inhibitor	CDK4/6 inhibitor	FGFR inhibitor

Biomarker trial design based on comprehensive genomic profiling



How are the Drug/Biomarker combinations selected?
Drug Selection Committee for Lung MAP

Sources of new drugs/biomarkers:

- **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**

List of potential targets and drugs

Target	Drug	Biomarker	Prevalence
IGFR	LDK378	IGFR expression	60%
PI3K	BKM120 (PI3Ka) MLN1117 (AKT)GSK2110183	PI3K expr/ amplif, *PIK3CA* mut PTEN loss AKT , PIK3CA fus.	25%. 16% 15%
FGFR	LY2874455 JNJ42756493 FGF Trap-GSK3052230	FRGFR expr FGFR1, 2 amplif, *FGFR 1, 2* mut	 15%. 10%
p53	MK-1775 (+gem)	*TP53* mut	81%
MET	AMG337 LY2801653 JNJ38877605 Foretinib (GSK1363089)	MET expression	50%
HGF	AMG102	HGF expression	
PD-1	MEDI4736 (PD-L1)	PDL-1 expression	50%

List of potential targets and drugs

Target	Drug	Biomarker	Prevalence
HDM2	Anti-HDM2	HDM2 amplif	
RANKL	Denosumab	RANK/RANKL expr	
Notch	LY2835219	*Notch1* mut	8%
EGFR	CO1686	L858R, Del(19), T790M	1-3%
RAS	MEKi+panPI3K	*RAS*	
CKN2A	LY2835219 (CDK4/6)	*CDKN2A* mut, deletion, methylation CCND1 amplif	15%, 30% 21% 13%
HER3	HER3mAb	HER3 expression	
mTOR1/TORC2	MLN0128	*STK11,TSC1, TSC2* mut	2%, 3%, 3%
Raf	MLN2480	TBD	

What are the statistical assumptions? Lung-MAP Sub-studies

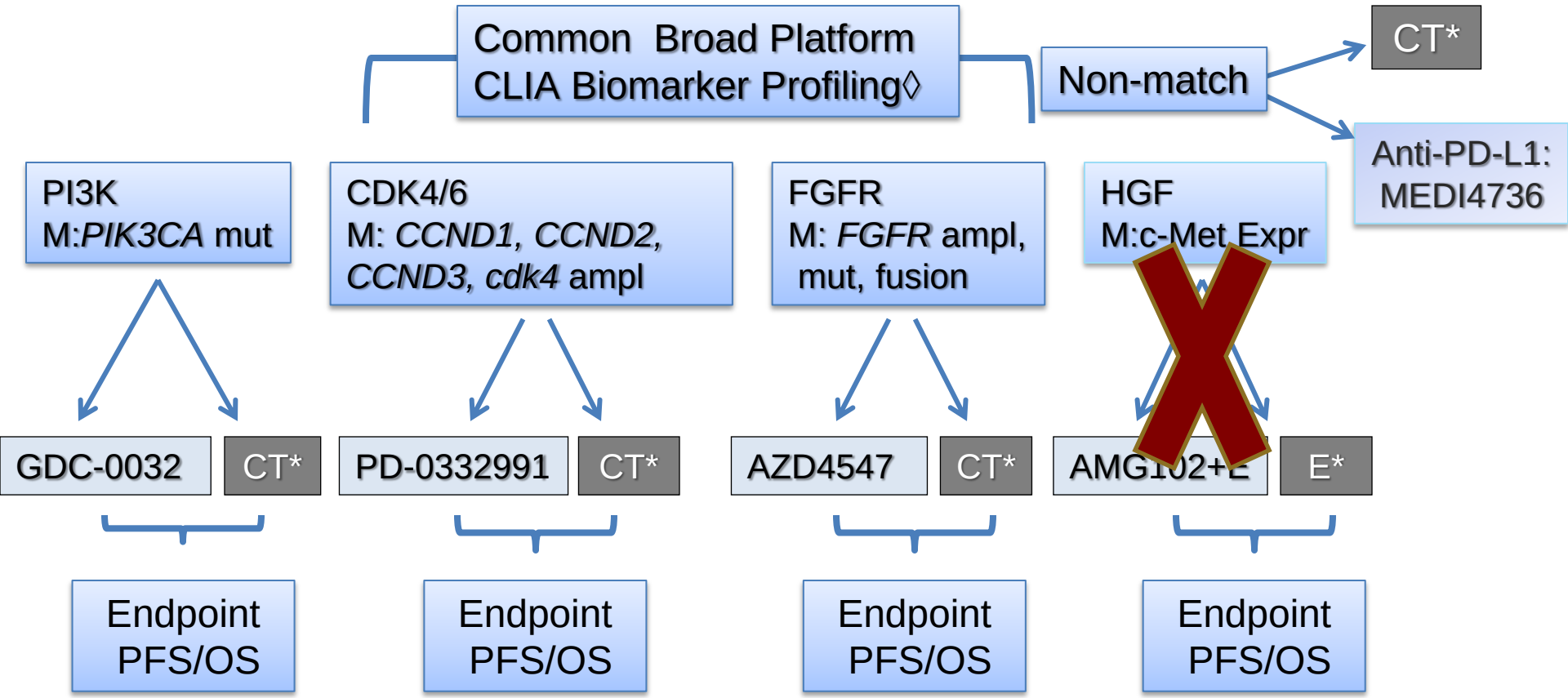
		Phase 2		Phase 3	
Sub-study ID	Prevalence Estimate	Approximate Sample Size	Approximate time of analysis	Sample Size	Approximate time of analysis
S1400A	56.0%	170	8	380	21
S1400B					
GNE+	5.6%	78		288	
FMI+	8.0%	152	19	400	72
S1400C	11.7%	124	11	312	45
S1400D	9.0%	112	11	302	53
S1400E	16.0%	144	9	326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

Is Lung-MAP self-sustaining?

Activation of Lung-MAP within 1st month (July 2014)

LUNG-MAP

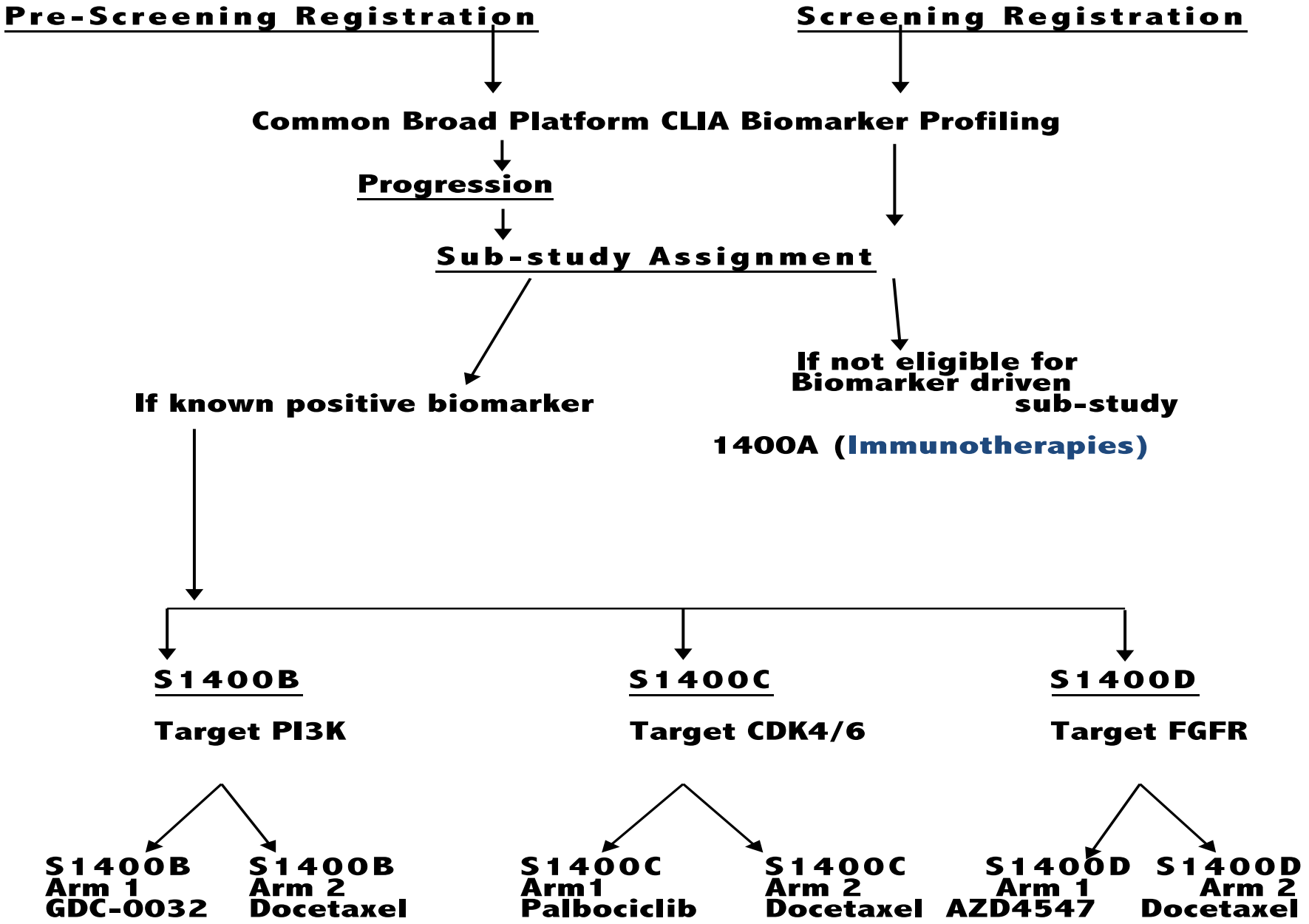
LUNG-MAP (S1400): Squamous Lung Cancer- 2nd Line Therapy



TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib
◊ Archival FFPE tumor, fresh CNB if needed

Project Chair: V. Papadimitrakopoulou
Steering Committee Chair: R. Herbst
SWOG Lung Chair: D. Gandara

LUNG-MAP


Pre-Screening Registration
Screening Registration
Common Broad Platform CLIA Biomarker Profiling
Progression
Sub-study Assignment
If known positive biomarker
If not eligible for Biomarker driven sub-study
1400A (Immunotherapies)
S1400B
Target PI3K
S1400C
Target CDK4/6
S1400D
Target FGFR
S1400B Arm 1 GDC-0032
S1400B Arm 2 Docetaxel
S1400C Arm1 Palbociclib
S1400C Arm 2 Docetaxel
S1400D Arm 1 AZD4547
S1400D Arm 2 Docetaxel

Is Lung-MAP "self-sustaining"?

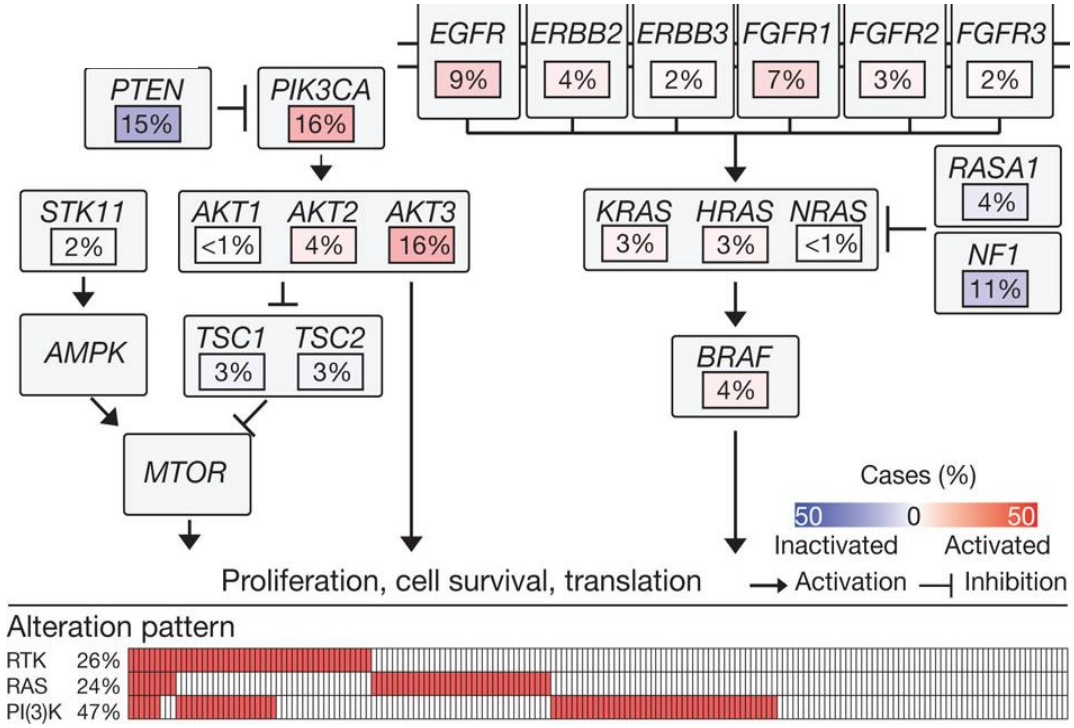
Lung MAP designed to be adaptable with changes in the therapeutic landscape

- **Example: recent approval of Nivolumab in 2nd line therapy of Squamous Lung Cancer**
  - **Lung MAP modified to be 2nd line and beyond (i.e some substudies are now 2nd-3rd line, others 2nd line)**
  - **One planned immunotherapy combination substudy is 2nd line with Nivolumab control arm**
  - **Another planned substudy is 3rd line after Nivolumab PD**

Is Lung-MAP "self-sustaining"?

New Targets-New Opportunities

- PARP
- mTORC1/mTORC2 (RICTOR)
- PI3K/PTEN
- Wee-1 kinase
- ATR
- VEGFR2
- TRK
- Drug combinations (Immunotherapies)



Hammerman et al: Nature 2012

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

NCT #TBD

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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

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LUNG-MAP