FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2013 Conference on Clinical Cancer Research

Supported by:

ASCO® American Society of Clinical Oncology

Susan G. Komen FOR THE CURE®

November 7, 2013 • Washington, DC

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2013 Conference on Clinical Cancer Research

Lung Cancer Master Protocol Activation Announcement

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2013 Conference on Clinical Cancer Research

Jeff Allen, PhD
Friends of Cancer Research

Panelists

- **Jeff Allen, PhD**, Friends of Cancer Research
- **Roy Herbst, MD, PhD,** Yale Cancer Center
- **David Gandara, MD,** UC Davis Cancer Center
- **Vali Papadimitrakopoulou, MD**, MD Anderson Cancer Center
- **Ann Ashby, MBA,** Foundation for the NIH
- **Vince Miller, MD,** Foundation Medicine
- **Jeff Abrams, MD,** Clinical Investigations Branch, NCI
- **Janet Woodcock, MD,** CDER, FDA
- **Mary Redman, PhD,** Fred Hutchinson Cancer Center

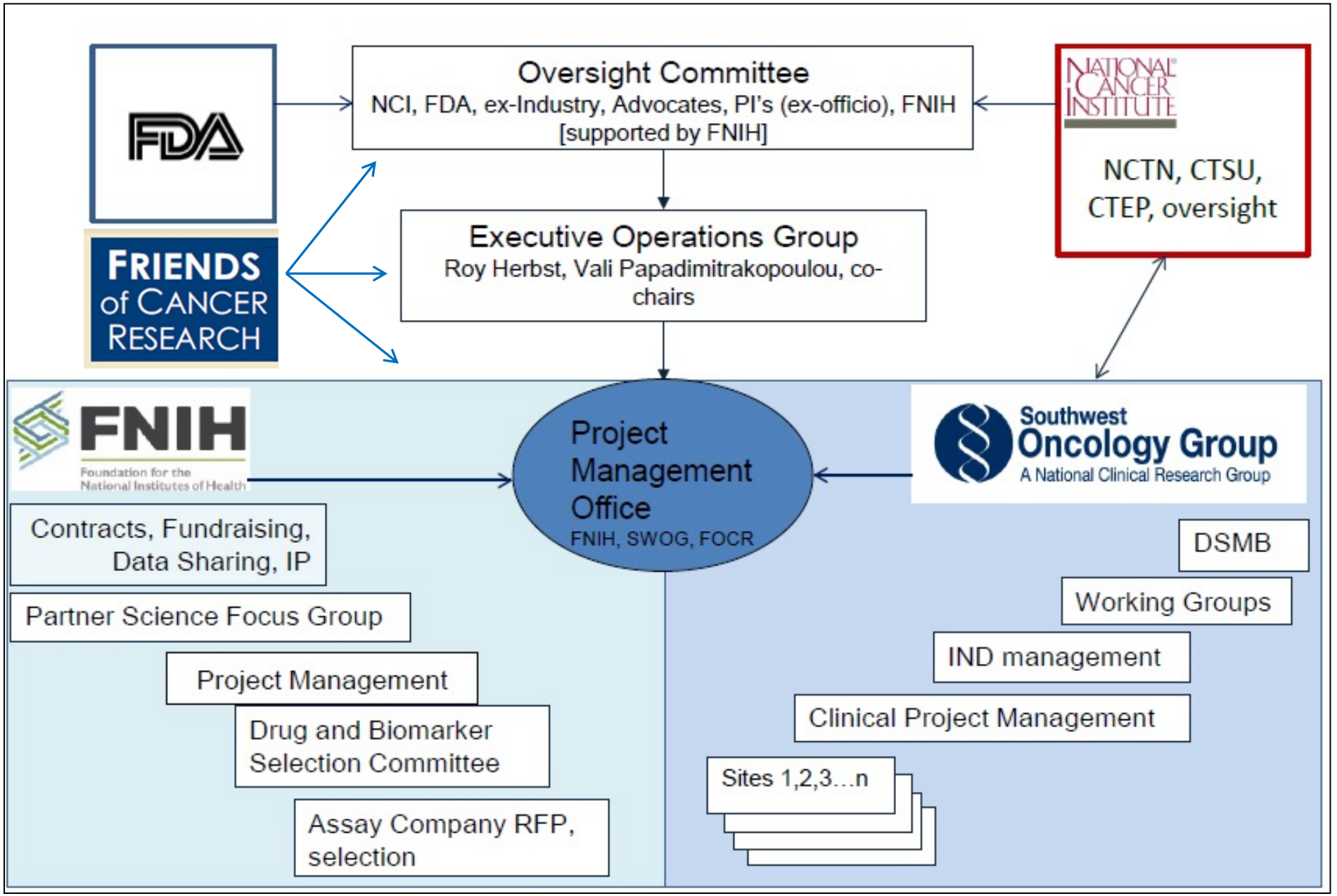
FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2013 Conference on Clinical Cancer Research

Roy Herbst, MD, PhD
Yale Cancer Center

Governance Structure: S1400 Master Lung-1 Project



Multi-Sector Oversight Committee

Name	Affiliation
Roy Herbst (co-chair)	Yale Cancer Center
Ellen Sigal (co-chair)	Friends of Cancer Research
Jeff Abrams	NCI
Jeff Allen	Friends of Cancer Research
David Chang	Amgen
Andrea Ferris	LUNGevity
David Gandara	UC Davis Cancer Center
Rich Gaynor	Eli Lilly
Fred Hirsch	University of Colorado Cancer Center
Pasi Janne	Dana Farber Cancer Institute
Vali Papadimitrakopoulou	MD Anderson Cancer Center
Eric Rubin	Merck
Regina Vidaver	National Lung Cancer Partnership
Jack Welch	NCI
Janet Woodcock	CDER, FDA
Steven Young	Addario Lung Cancer Medical Institute (ALCMI)

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

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2013 Conference on Clinical Cancer Research

David Gandara, MD
University of California Davis Comprehensive Cancer Center

"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**
  - Failure of "All Comer" designs for drug development in NSCLC
  - Need for Early Co-Development of drugs & associated biomarkers
- **Development of Future Lung Cancer Clinical 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

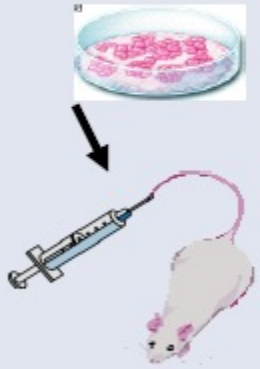
Classic RCT Design ("All Comer"): Phase III Trials of Chemotherapy +/- Targeted Agent* in 1st-line Therapy of Advanced Stage NSCLC

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**
IGFR-1	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	

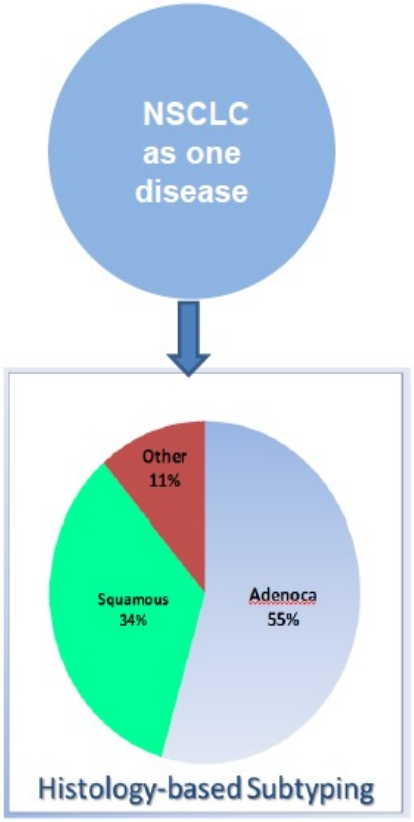
Phases of Development of New Biomarker linked to New Drug

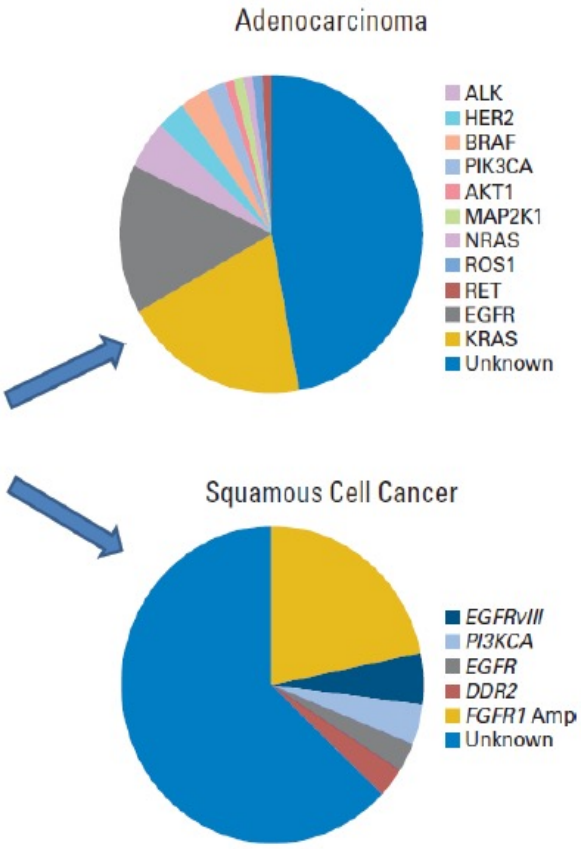
Confirm Target	Integrate Biomarker	Biomarker Informative?	Clinical Validation	Clinical Application of Biomarker
Assay Development	Assay Performance	Assay Validation	Co-Primary Endpoint	

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





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)

Li, Mack, Kung, Gandara: JCO 2013

Parallel Efforts in "Master Protocol" Design for NSCLC

NCI Thoracic Malignancy Steering Committee (TMSC) Task Force

- Early Stage NSCLC (ALCHEMIST)
- Advanced Stage NSCLC
  - Non-Squamous

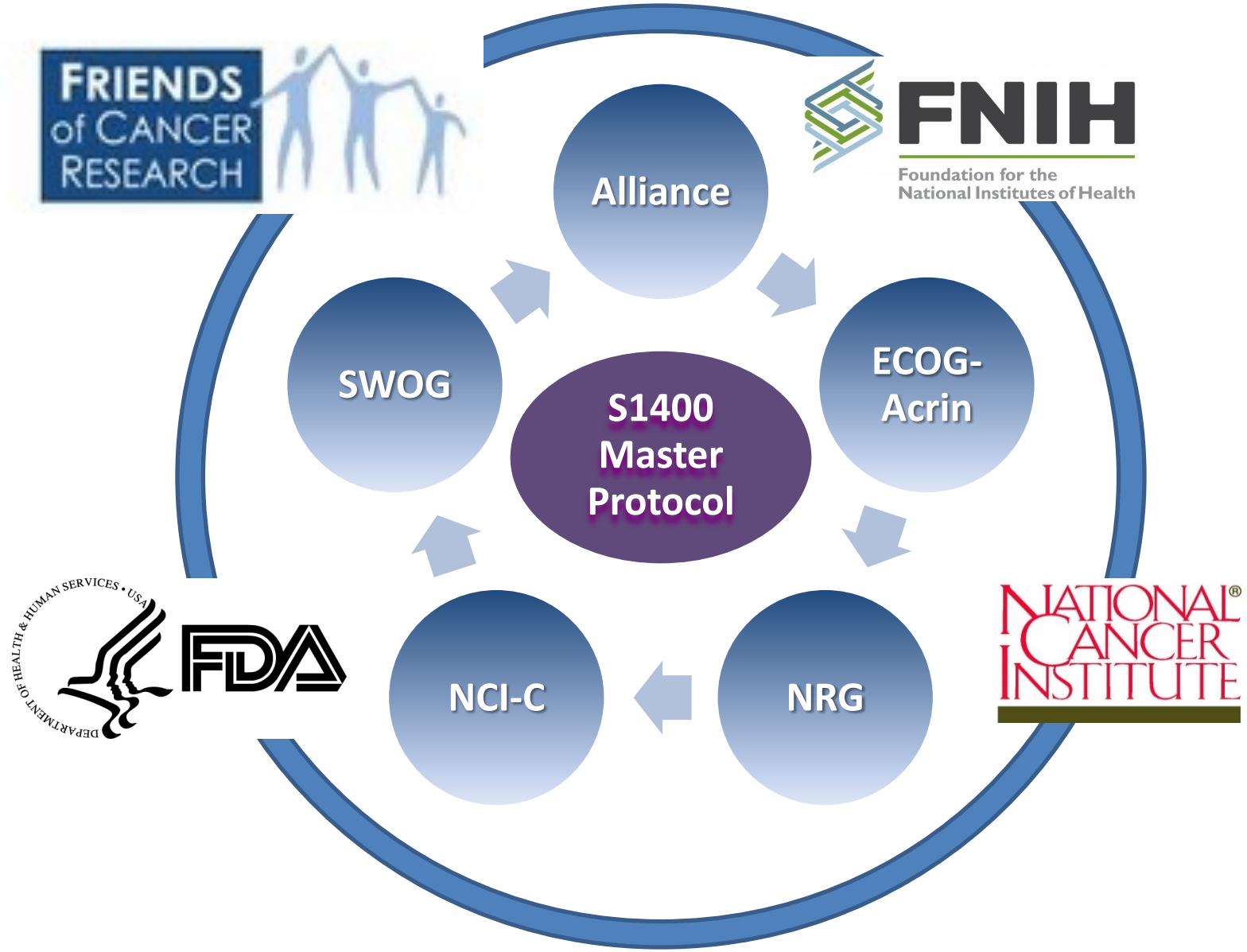
Friends of Cancer Research (FOCR) Task Force

- Advanced Stage NSCLC
  - Squamous (SCCA):

SCCA represents an Unmet Need

- All recent new targeted therapies have been in Adenoca (EGFR/ALK)
- Many new molecular targets have been found in lung SCCA
- Drugs for each of these targets

S1400 Master Protocol
Unique Private-Public Partnerships with the NCTN



FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2013 Conference on Clinical Cancer Research

Vali Papadimitrakopoulou, MD
MD Anderson Cancer Center

Phase II/III Biomarker-Driven Master Protocol for Second Line Therapy of Squamous Cell Lung Cancer (SCCA)

Study Chair: Vali Papadimitrakopoulou, MD
UT/MDACC, Dept of Thoracic/Head & Neck Med Oncology
Cooperative Groups Co-chairs: Alliance: Everett Vokes, MD
ECOG: Suresh Ramalingam, MD
NCI Co-Chair: Jack Welch, MD
NCIC: Glenwood Goss, MD
NRG: Jeff Bradley, MD
SWOG: David R. Gandara, MD

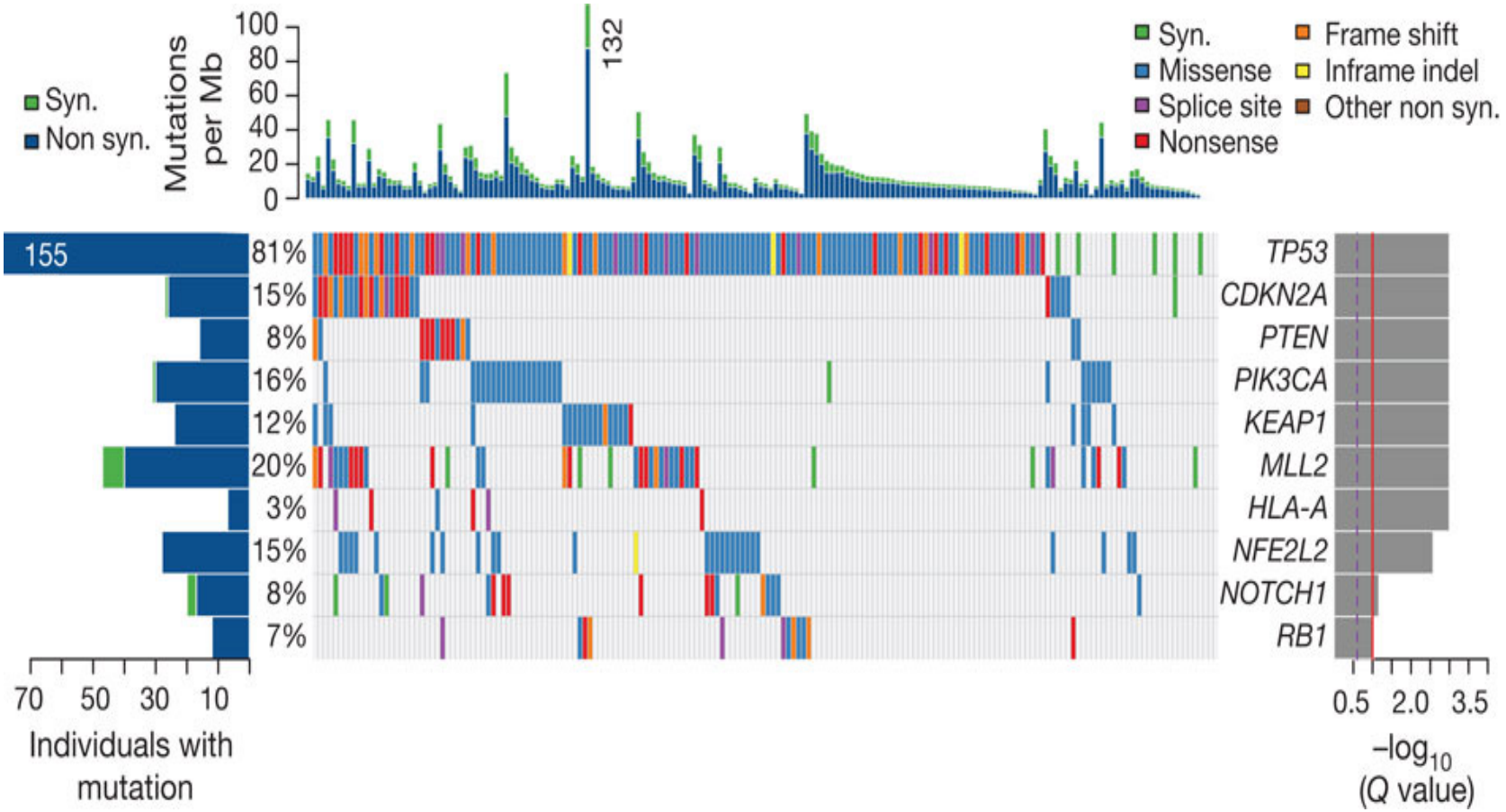
Steering Committee Co-Chair: Roy S. Herbst, MD, PhD
Statistical Co-chair: Mary W. Redman, Ph.D.
Molecular Pathology co-Chair: Ignacio Wistuba, MD
Correlative Science co-Chair: F Hirsch MD, PhD, P Mack PhD

Rationale for Master Protocol Designs

- **NSCLC: multiple and often independent mutations and potential therapeutic targets.**
- **Lung SCCA "orphan" group- substantial developments in therapeutics have yet to be seen.**
- **Subgroup selection (genotype or phenotype-driven) refined strategy in a Multi-arm Master Protocol with 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"
- **Grouping multiple studies: reduces overall screen failure rate , multi-target screening by NGS platform: sufficient "hit rate" uninterrupted accrual.**
- **Bring 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 SQCC.



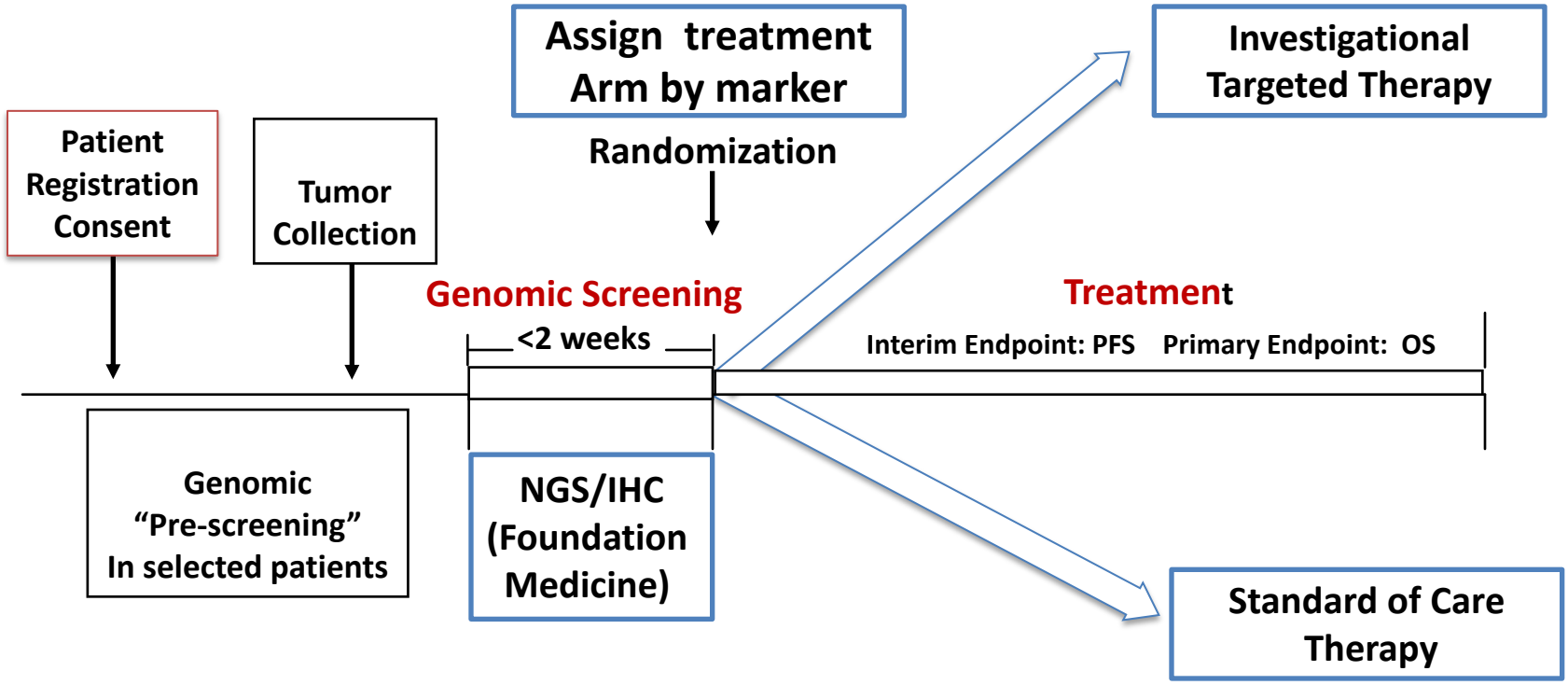
PS Hammerman *et al. Nature* **000**, 1-7 (2012) doi:10.1038/nature11404

nature

Assumptions, Major Elements and Objectives

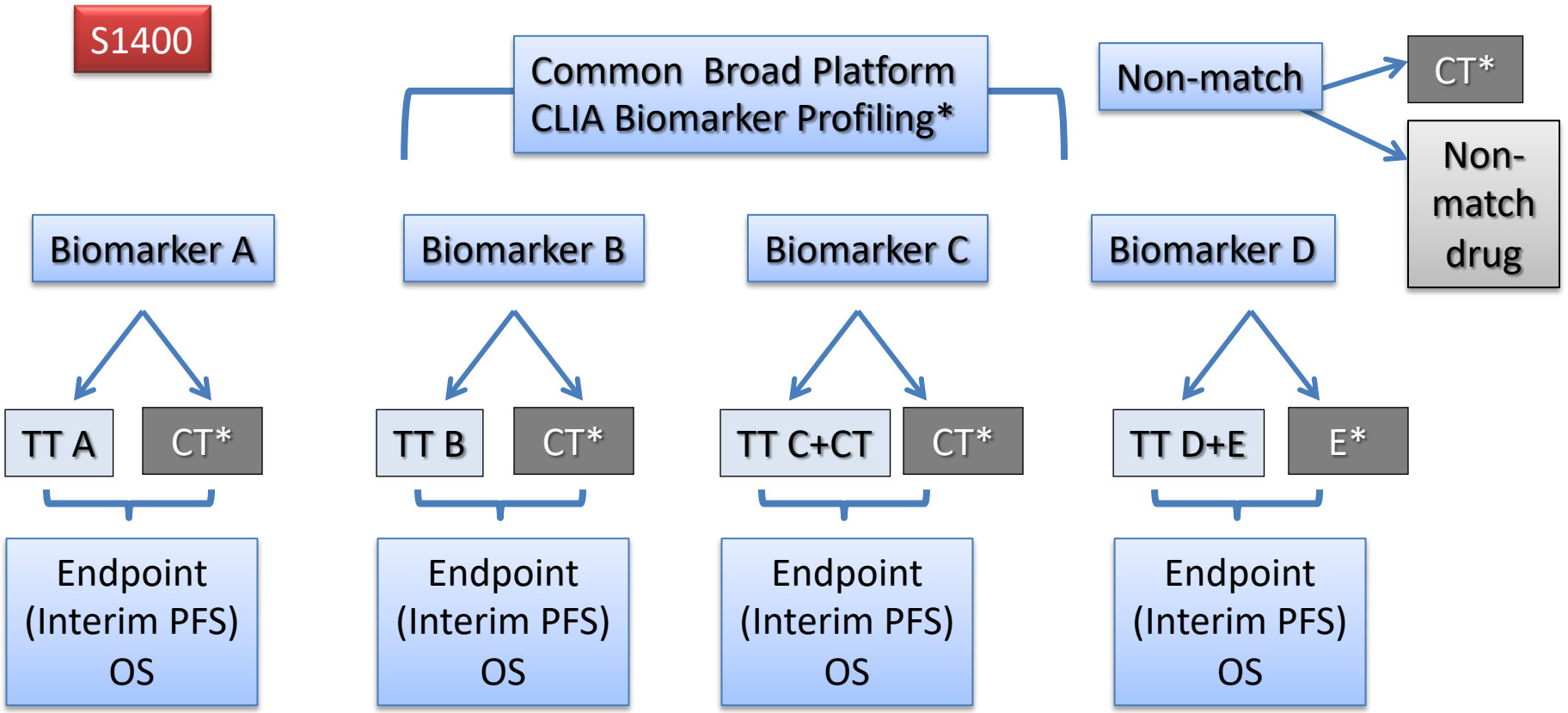
- **Each drug clinical data demonstrating biologic activity in a responsive patient group against a measurable target, using predictive biomarker assay that has been analytically validated and is suitable for a pivotal trial.**
- **Squamous cell carcinoma (SCCA), advanced stage, 2nd line therapy**
- **Multi-arm randomized, controlled phase II/III registration protocol. Each arm opens/closes independent of other arms, independently powered for OS. Positive results at "rolling" interim analysis determine if a protocol arm proceeds to phase III portion.**

- **Primary Objectives:**
  - **A) Phase II Component:** PFS targeted therapy (TT) vs SOC
  - **B) Phase III Component**: OS for TT vs SOC within each biomarker-defined subgroup.
- **Secondary Objectives:**
  - **A) Phase II:** Toxicities associated with TT versus SoC.
  - **B) Phase III:** a)PFS b) RR and c) toxicities associated with TT versus SoC.
- **Exploratory Objectives:** A)Additional predictive tumor/blood biomarkers , B) resistance biomarkers at progression C) tissue/ blood repository from patients with refractory SCCA.



- Organizers: FOCR,NCI-TMSC, FDA, FNIH
- Participants: Entire North American Lung Intergroup (SWOG, Alliance, ECOG-Acrin, NRG, NCI-Canada)
- Screening: 500-1,000 patients/year
- With 4-6 arms open simultaneously, "hit" rate ~70% in matching a patient with a drug/biomarker arm.

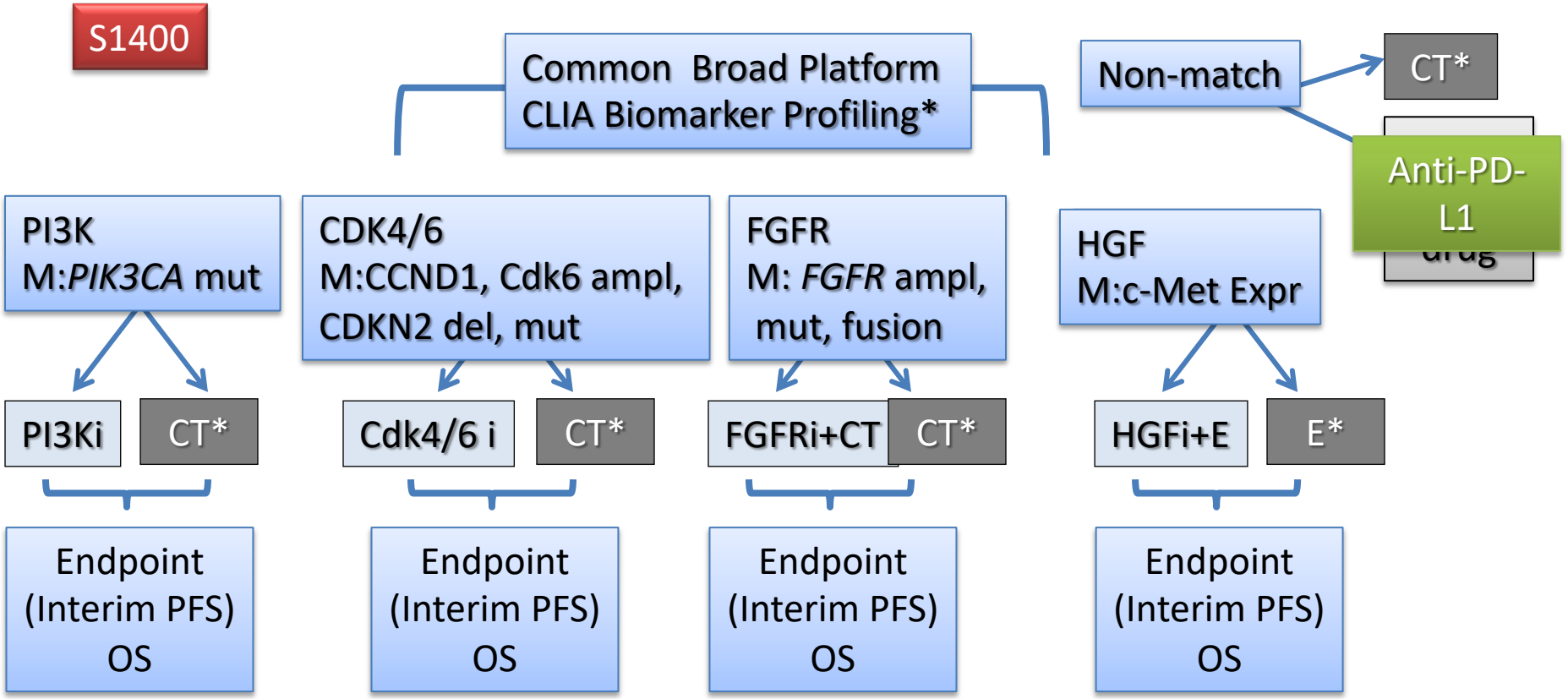
MASTER PROTOCOL



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

*Archival FFPE tumor, fresh CNB if needed

MASTER PROTOCOL



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

*Archival FFPE tumor, fresh CNB if needed

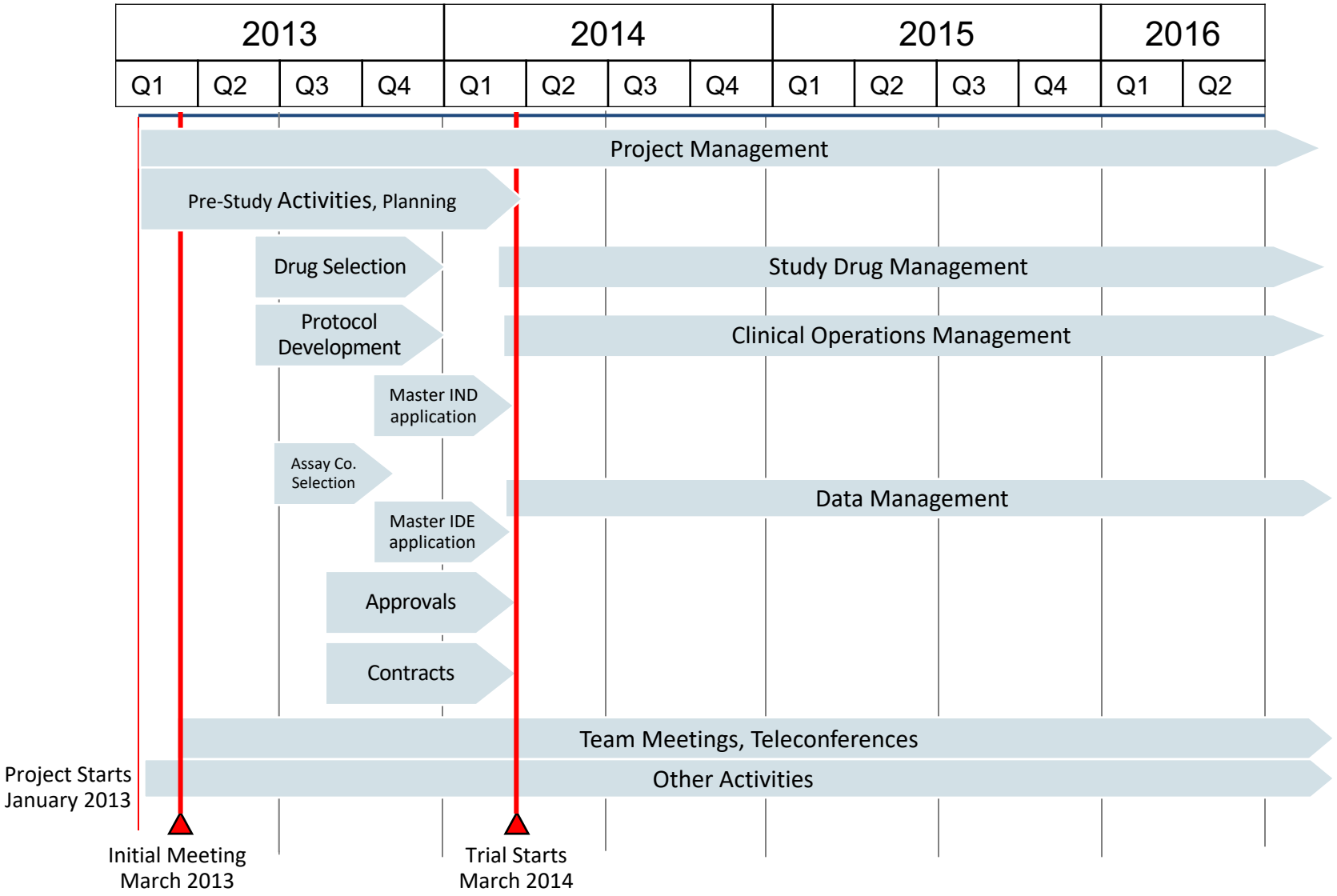
Statistics

- Phase II component
  - Primary outcome: PFS
  - median null PFS = 3 months
  - HR^{pfs} = 0.5 (two-fold increase), Power = 90%, 1-sided type I error = 10%
  - Analysis at 55 progression events
  - Threshold to continue to phase III: ~ 41% improvement in PFS
  - RR compared between arms to evaluate if evidence to stop study for early signs of efficacy
- Phase III Design
  - Primary outcome: OS
  - median null OS= 8 months
  - HR^{os} = 0.67 (50% increase), Power = 90%, 1-sided type I error = 2.5%
  - Interim analyses at 50% and 75% of expected 256 deaths
- Sample size justification: approximate patient pool in the US 35,800 -- approx 4% clinical trial participation rate → 625-1250 screened/yr → 500-1,000 enrolled/yr

Phase II and III sample size and analysis times

Marker Prevalence		Phase II Component		Phase III Design	
@1,000 accrued/ year	@500 accrued/ year	N	Analysis Time (Months)	Total N	Analysis Time (Months)
2.5%	5%	68	34	272	145
5%	10%	80	20	284	81
7.5%	15%	90	15	296	60
10%	20%	100	12	306	49
12.5%	25%	104	11	314	43
15%	30%	110	10	324	38
17.5%	35%	116	9	330	35
20%	40%	124	8	334	33
22.5%	45%	124	8	340	31
25%	50%	136	7	348	29
27.5%	55%	136	7	350	28
30%	60%	150	6	354	27

LMP: First Patient In (FPI) -- Q1 2014



FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2013 Conference on Clinical Cancer Research

Ann Ashby, MBA
Foundation for the NIH

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2013 Conference on Clinical Cancer Research

Vince Miller, MD
Foundation Medicine

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2013 Conference on Clinical Cancer Research

Jeff Abrams, MD

Clinical Investigations Branch, NCI

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2013 Conference on Clinical Cancer Research

Janet Woodcock, MD
CDER, FDA

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2013 Conference on Clinical Cancer Research

Mary Redman, PhD
Fred Hutchinson Cancer Center

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2013 Conference on Clinical Cancer Research

Supported by:

ASCO® American Society of Clinical Oncology

Susan G. Komen FOR THE CURE®

November 7, 2013 • Washington, DC