FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

Conference on Clinical Cancer Research

Supported by:

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AACR Centennial 1907 – 2007 American Association for Cancer Research

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Design of a Disease-Specific Master Protocol

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Design of a Disease-Specific Master Protocol

Roy Herbst, MD/PhD
Yale Cancer Center

Modernizing Clinical Trial Process

- Some of the current challenges of drug development
  - Difficulties in recruiting cancer patients to clinical trials
  - Extensive bureaucratic processes required to initiate any clinical trial
  - Lengthy regulatory review
- Modernizing trial process with innovative approaches and new clinical trial designs is of high importance.
- Use novel design strategies combined with biomarker testing
  - to increase trial efficiency
  - improve future phase III clinical trial designs

Phase II Adaptive Screening Trials

- BATTLE (**B**iomarker-integrated **A**pproaches of **T**argeted **T**herapy for **L**ung Cancer **E**limination)
  - Heavily pretreated refractory non-small cell lung cancer (NSCLC)
  - Determined marker status of 11 biomarkers
  - Randomized patients to four different agents
  - Results were used to design two new BATTLE trials
- I-SPY 2 TRIAL (**I**nvestigation of **S**erial Studies to **P**redict **Y**our **T**herapeutic **R**esponse with **I**maging **A**nd mo**L**ecular Analysis **2**)
  - Investigates neoadjuvant treatment of new drugs added to traditional chemotherapy in women with locally advanced breast cancer
  - Designed to test multiple novel drugs and biomarkers over five-year timeframe
  - May test up to five drugs simultaneously
  - Add new drugs as existing drugs complete testing

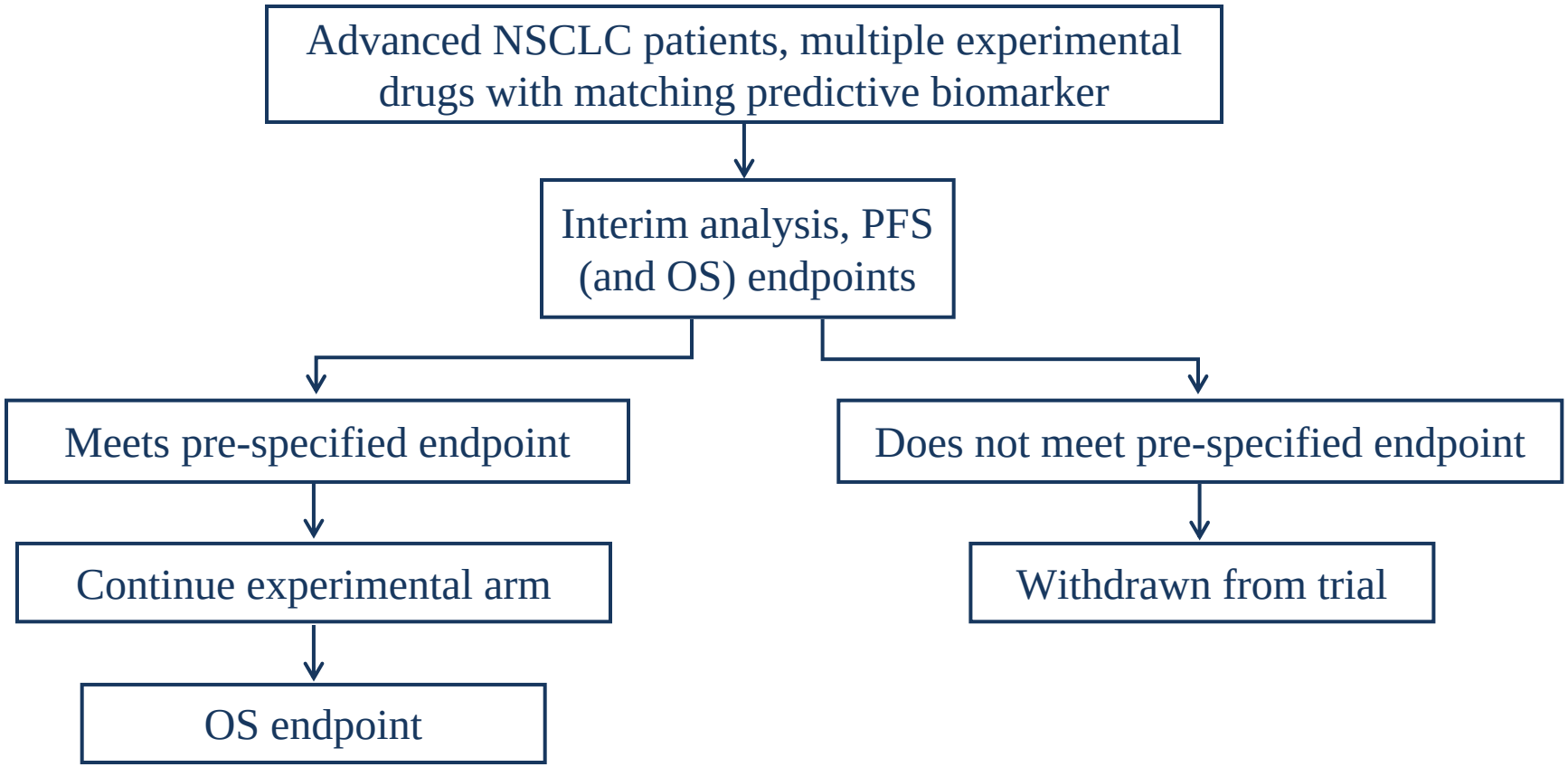
Moving to a Multi-arm Registration Trial

- We propose another alternative to traditional trial design
- Multi-arm, multi-marker/drug “master protocol” Phase III trial
  - Randomized, Controlled
  - No adaptive randomization
  - Multiple new therapies are tested simultaneously in a specific disease setting
  - Designed to allow FDA approval of new therapeutics
  - Assigns patients to experimental treatment vs standard-of-care control arm on the basis of specific biomarkers

Advantages of Master Protocol Multi-drug Registration Trial Design

- Grouping multiple studies reduces the overall screen failure rate
- Single master protocol will result in process and operational efficiency gains
  - Provides consistency
  - Trial infrastructure will be in place
  - Bring safe and effective drugs to patients faster

Master Protocol Multi-Drug Trial Design



Lung Cancer Example
Squamous Cell Carcinoma Mutation Incidence

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%
cMET	High copy-amplification	11%
ERBB2	Amplification	2%

Speakers

- **Roy Herbst**, MD/PhD, Yale Cancer Center
- **David Wholley**, M.Phil., FNIH
- **Eric Rubin**, MD, Merck
- **Lisa LaVange**, PhD, FDA
- **Jeff Abrams**, MD, NCI
- **Karen Arscott**, DO, Lung Cancer Alliance
- **Shakuntala Malik**, MD, OHOP, FDA

Acknowledgements

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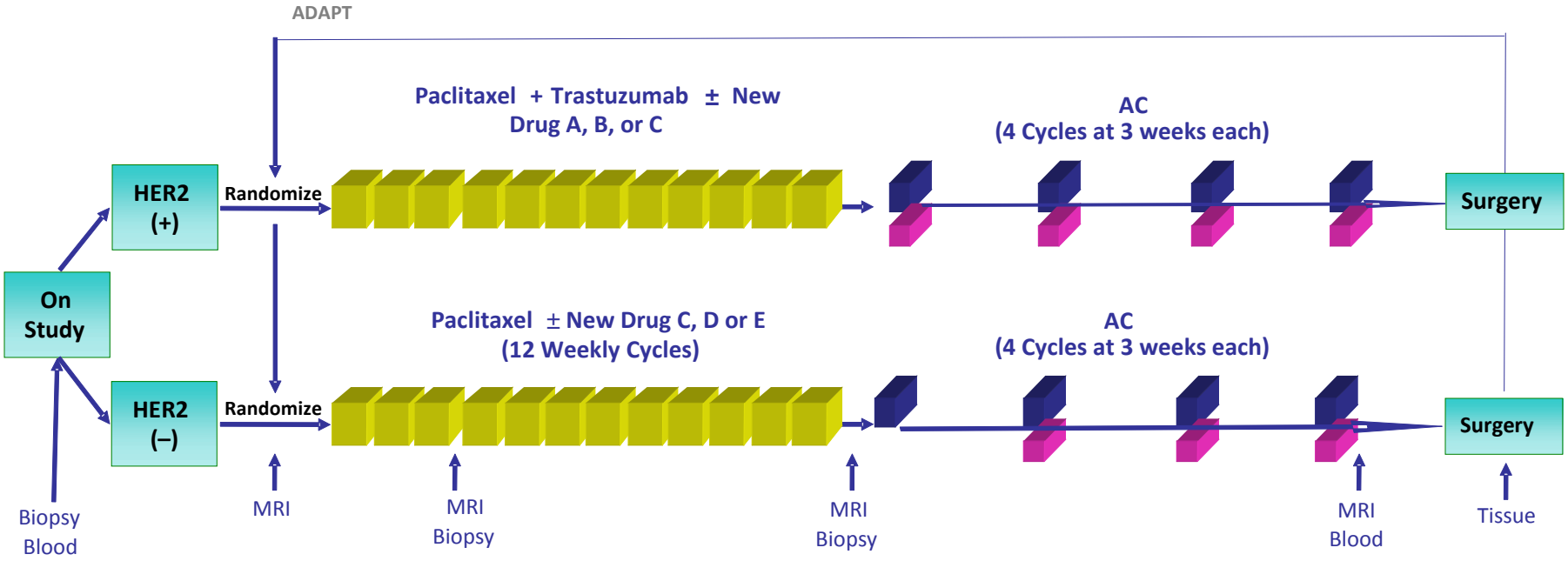
Organizational infrastructure for multi-drug trials

David Wholley

FNIH

The I-SPY 2 trial tests multiple new breast cancer agents using biomarkers and an adaptive trial design



Biopsy used for Biomarkers

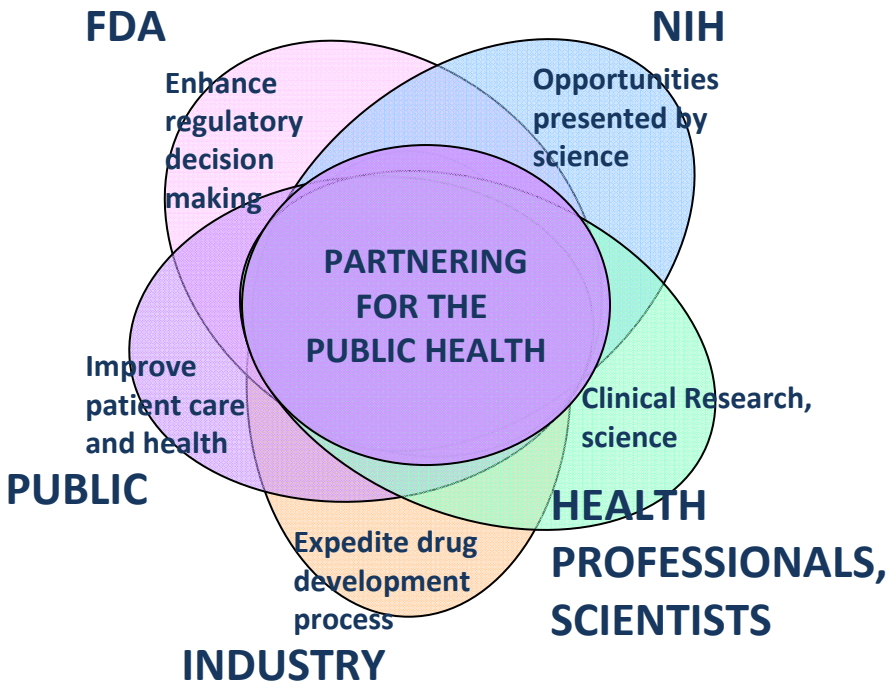
<u>Stratifying Biomarkers:</u>

Class I/II devices:	HER2 (IHC, FISH)
	MammaPrint
	ER, PR
IDE:	MammaPrint44K
	Her2 (RPMA, 44K-microarray)

I-SPY 2 is being conducted as a large-scale public-private partnership managed through the FNIH Biomarkers Consortium

Principal Investigators: Laura Esserman (UCSF) and Don Berry (MD Anderson)

- NCI
- FDA
- ~20 academic cancer centers
- Multiple pharmaceutical companies
  - Contributing agents
  - Funding
- Platform companies
- Laboratories
- Non-profit organizations
- Advocates
- Managed by FNIH and Quantum Leap Healthcare Collaborative



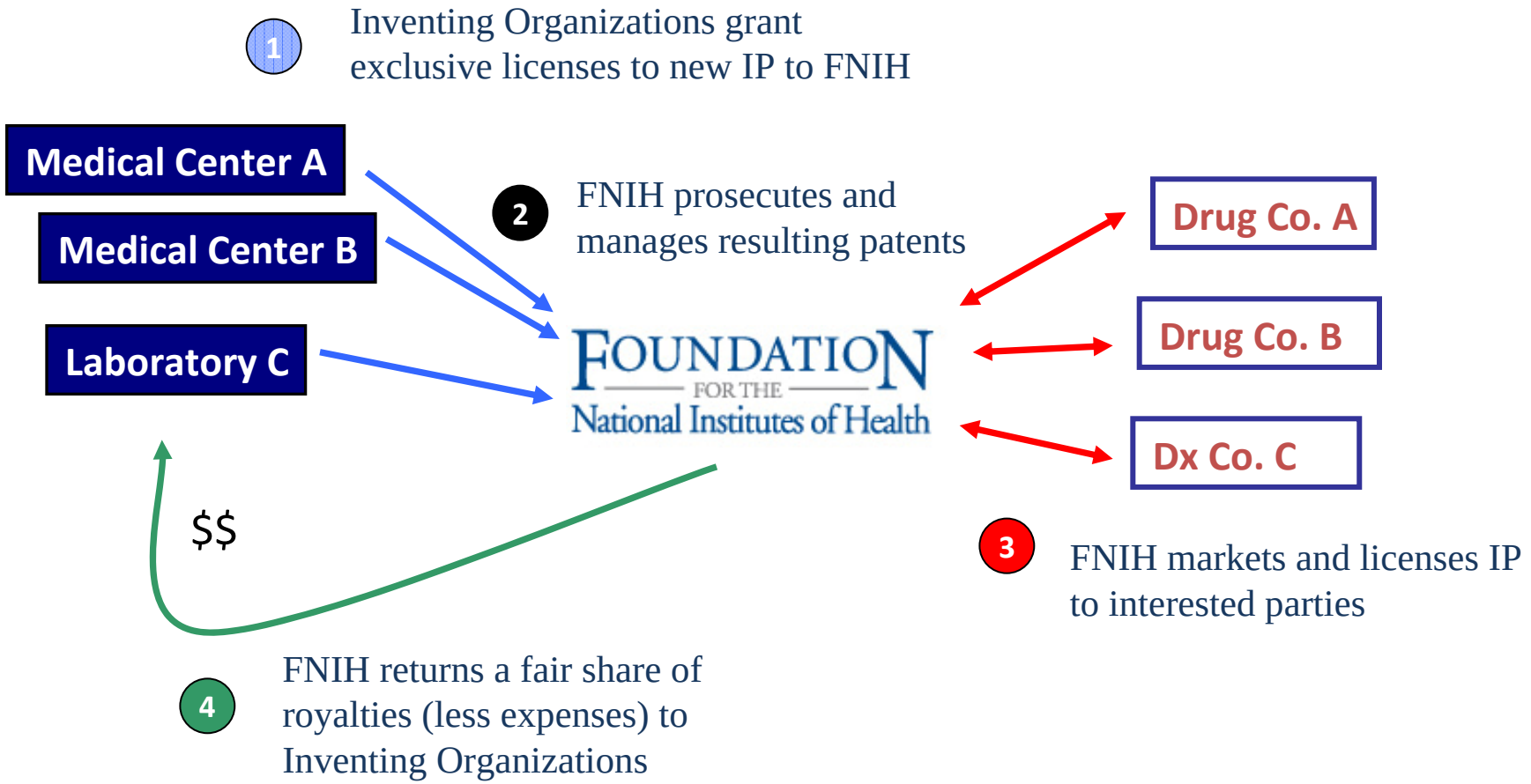
An Independent Agent Selection Committee chooses novel agents based on stringent criteria

- The IASC consists of 5-6 cancer drug development experts without current industry affiliations
  - Phase I testing on candidate agents must be completed
  - Agents must be compatible with standard paclitaxel therapy (no unacceptable additive toxicity)
    - For HER2/neu-directed agents, compatible with paclitaxel plus trastuzumab therapy
  - Known efficacy or rationale for efficacy in breast cancer
  - Targets key pathways/molecules in breast cancer, but only one novel agent per target pathway will be accepted in the trial
  - Fits strategic model for optimizing combinations of single/multiple molecular targeting drugs with or without standard chemotherapy
  - Willingness of company to contribute agent and sufficient availability

I-SPY 2 Organizational Principles, Efficiencies

- FNIH holds a Master IND (developed with FDA and NCI) that incorporates testing of multiple agents
- FNIH negotiates and holds all contracts with sites, pharma companies, biomarker companies, and other entities
- FNIH and QuantumLeap provide centralized co-administration and project management for the trial
- A centralized IT infrastructure (based on caBIG) ensures broad, timely dissemination of data and results
- Formal Data Access and Publication Guidelines ensure transparency and balance company and public health benefit
  - Data and samples are made broadly available to the research community for follow-on research
- FNIH also serves as a trusted 3rd party to manage data and intellectual property coming out of the trial, to maximize the public health benefit

FNIH acts as a trusted third party to ensure fair and appropriate licensing of new inventions arising from I–SPY 2



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Design of a Disease-Specific Master Protocol

Eric H. Rubin, MD
Merck

Proposed Master Protocol Multi-drug Registration Trial Design

- **Disease Model:** Relapsed, refractory non-small cell lung cancer (NSCLC)
- **Sponsor:** A **neutral third party**
  - e.g., CRO, academic coordinating center
  - Able to establish appropriate firewall procedures
- **Objective:** To compare overall survival (OS) of biomarker-selected patients treated with standard of care (SoC) vs. experimental targeted therapy
- **Standard of Care:** Will be determined prior to trial initiation by the steering committee

Trial Design – Drugs and Biomarkers

- The steering committee will evaluate each application to determine whether a drug/biomarker pair can enter the trial
- **Drugs**
  - Ready to enter a phase III confirmatory trial
  - **Each drug must have clinical data demonstrating activity in a responsive patient group**
  - Patient group can be identified by assessment of biomarker in patient tumor biopsies

Trial Design – Biomarkers and Screening

- **Each compound's biomarker is based on analytically validated test/platform** suitable for a pivotal trial
- This trial could use common screening platform that assays multiple biomarkers
  - If predictive biomarker is in a CLIA-approved platform, it could be considered adequate for patient selection and randomization
    - Would require Investigational Device Exemption (IDE) prior to trial start
    - If new drug shows clinical benefit in selected patient population the biomarker could be analyzed and given FDA clearance

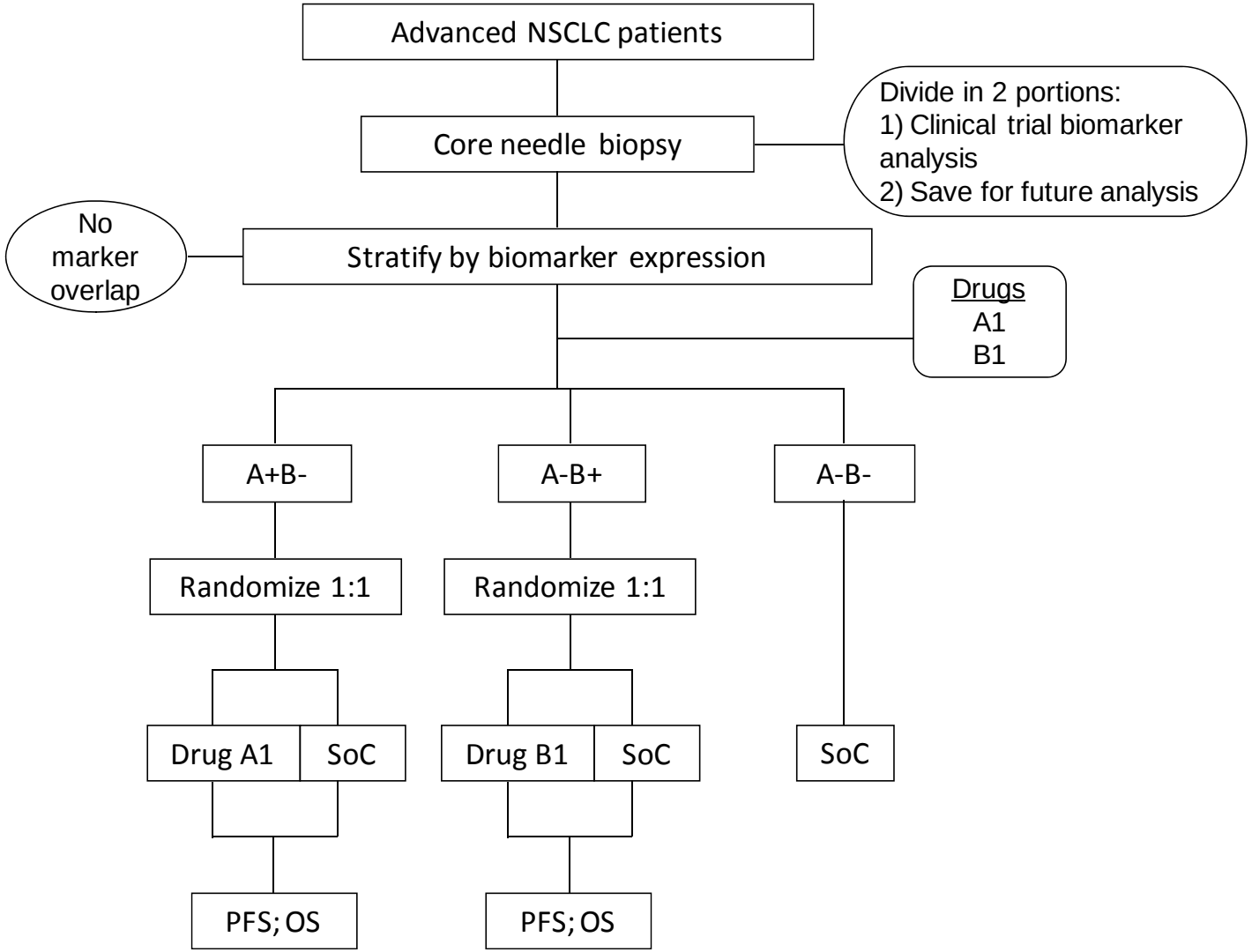
Use of a Multi-marker Platform

- Advantages
  - Conserves tumor samples
  - Testing protocols easier to standardize
  - Sponsors would not be responsible for designing their own diagnostic
- Considerations
  - Have not yet been used in registration trial
  - The process **would require close communication with the FDA** to determine its applicability

Potential Study Design

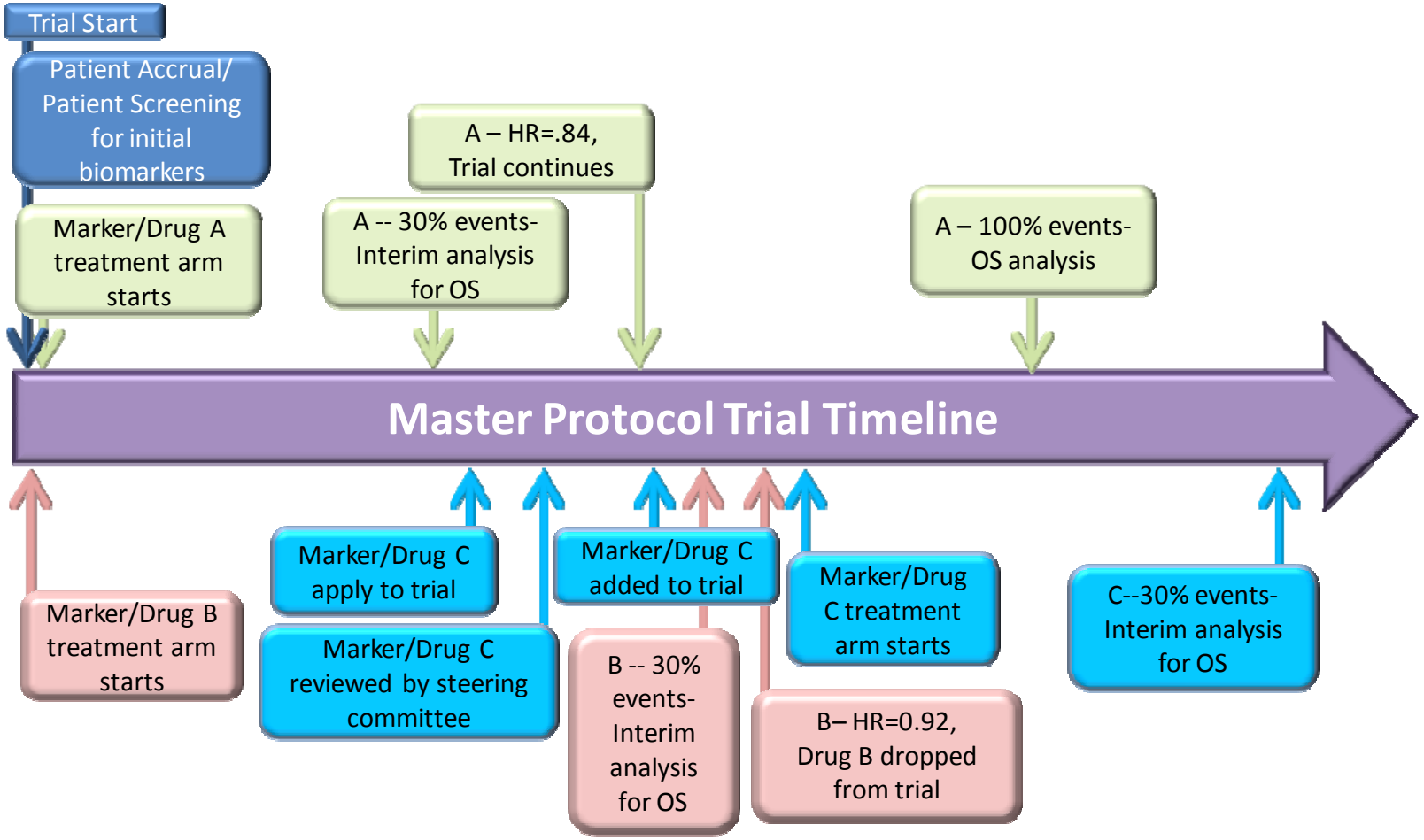
- At entry, patients will receive a fresh core needle biopsy, with the tissue analyzed with appropriate assay (s)
- Experimental treatment A targets Marker A-positive tumors; Drug B targets Marker B-positive tumors
  - Patients whose tumors are positive for marker A will be randomized to SoC vs drug A
  - Patients whose tumors are positive for marker B will be randomized to SoC vs drug B
- Primary endpoint: Overall Survival (OS)
  - Possible Interim Analysis when 30% of the OS events have occurred

Scenario: Two markers with no marker overlap; one drug per marker.



Master Protocol over Time

- Additional drug/biomarker combinations dropped and added to study



Case Study Example

- *PIK3CA* copy number increases or mutations identified in ~ one-third of squamous cell carcinomas
  - Target with PI3K inhibitor, e.g. BYL719

- *DDR2* tyrosine kinase mutations identified in 4% of squamous cell carcinomas
  - Shown to confer sensitivity to dasatinib

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Lisa LaVange, PhD
FDA

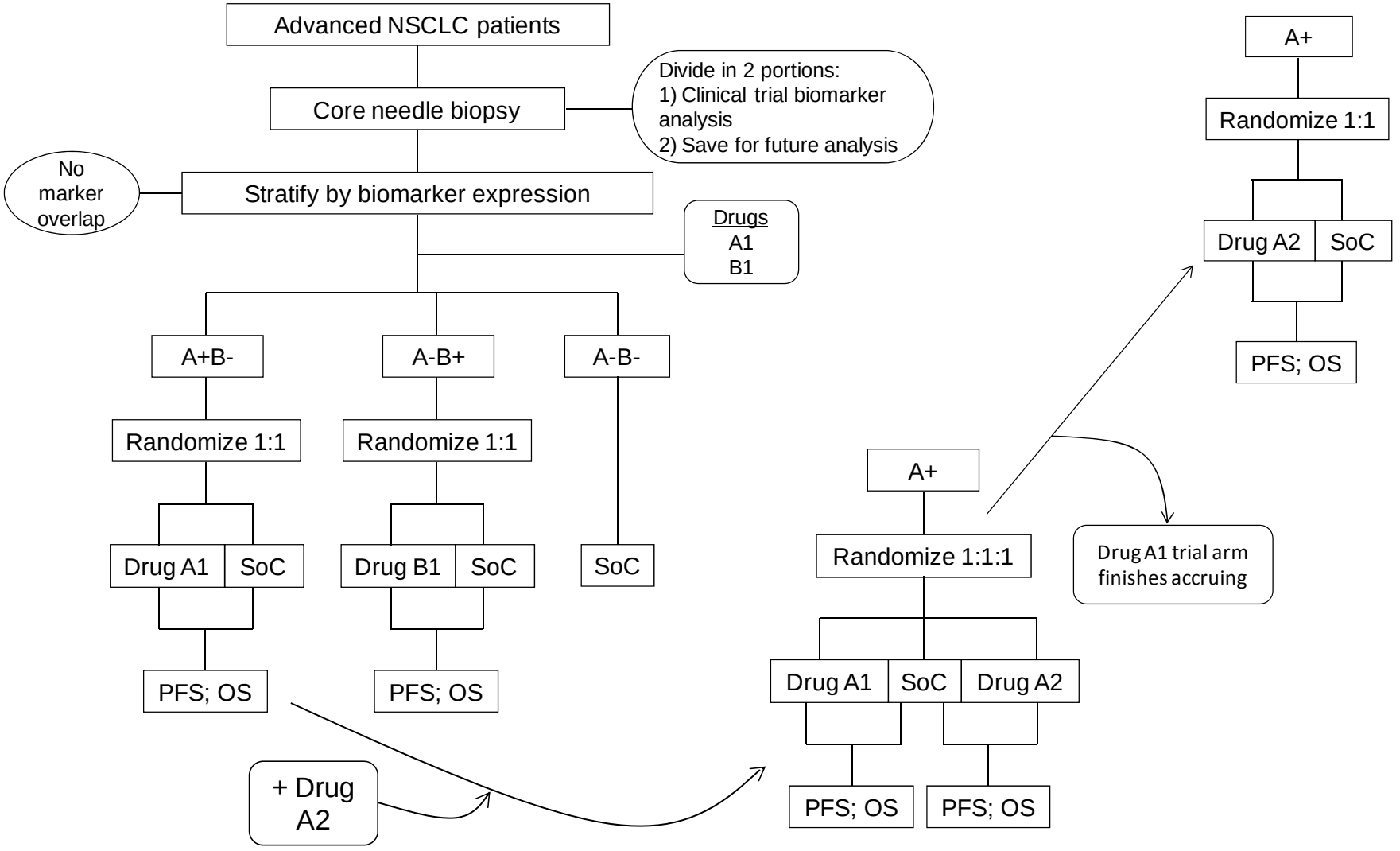
Potential Leveraging of Control Subjects

- Leveraging control patients across multiple trials is possible if a neutral 3rd party is running the trial
  - A CRO/Coordinating Center must establish appropriate firewall procedures
- Active drugs would not be compared to each other
  - Approval would be based on meeting pre-specified efficacy and safety criteria compared to SoC
- Which control patients are unique or shared may not need to be disclosed for analysis purposes
- Benefits to sharing control patients
  - Reduced recruitment time
  - Reduced trial costs

Example of Leveraging of Control Subjects

- Marker A/Drug A1 recruited/randomized 1:1 to Drug A1:SoC
- Marker A/Drug A2's protocol approved to begin recruitment
  - Randomization of Marker A patients changes to 1:1:1 Drug A1: Drug A2: SoC
  - Use of common protocol with standard procedures, visit schedules, and CRFs allows control patients to contribute data to both trials
- A1 trial completes enrollment while A2 trial is still ongoing
  - Randomization allocation reverts to 1:1 for Drug A2: SoC
  - Shared controls that have completed follow-up in Drug A1 trial
    - Data is unmasked for analysis of the Drug A1 protocol
    - Data remains masked to Drug A2 trial personnel
      - If necessary, data collection on A2 patients continues under the Drug A2 protocol

Scenario: Two markers with no marker overlap; two drugs target marker A.



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Jeff Abrams, MD
NCI

National Cancer Institute

ALCHEMIST

Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Cancer Institute

Drug Biomarkers in Lung Adenocarcinoma

TKI-sensitizing EGFR mutations:

10% in Western population

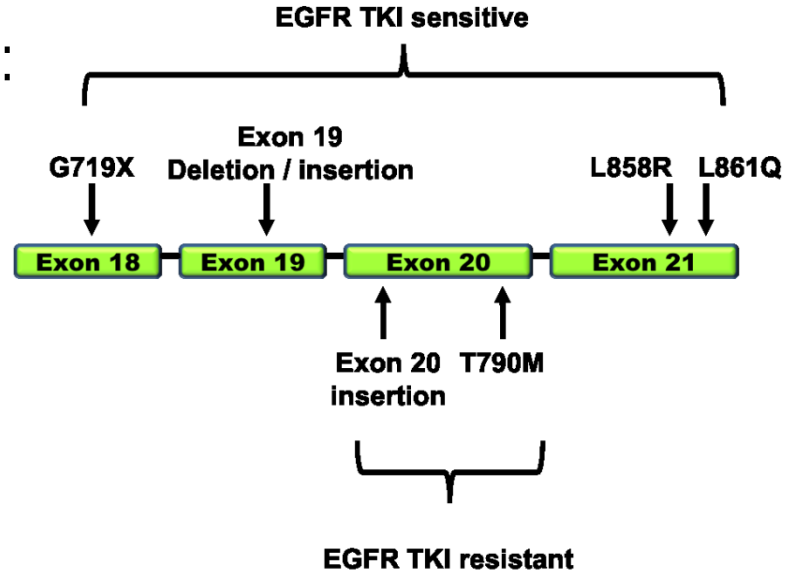
Up to 50% in Asian population

Enriched in:

- females
- non-smokers
- younger patients

Multiple tests in clinical use

No FDA-approved clinical assay

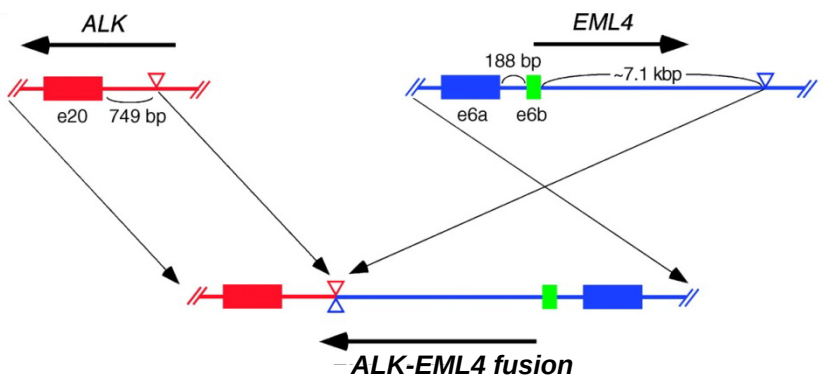


ALK Rearrangement

5-7% in Western population

FDA approved companion diagnostic:

Vysis Break Apart FISH probe



National Cancer Institute

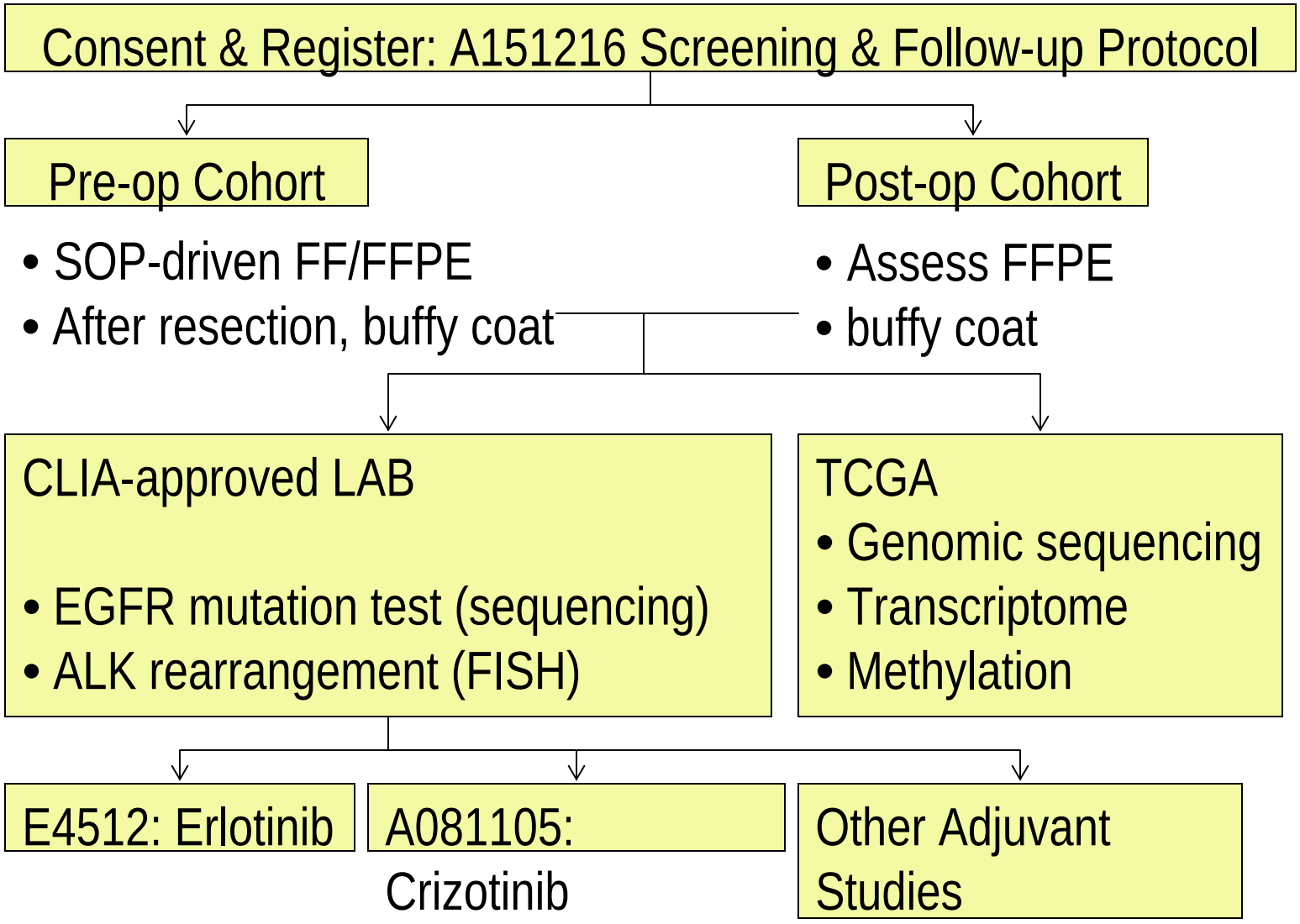
National Trial for Molecular Characterization of Early Stage Non-squamous NSCLC

Eligibility:

- Diagnosis of NSCLC (non-squamous)
- Clinical stage I, II, or III deemed resectable
- Pathologic stage I, II, or III that:
  - has been successfully resected
  - adequate tissue available
  - +/- local test for EGFR mutation or ALK rearrangement
- Patient Consent to allow
  - donation of de-identified cancer information for research
  - performance of central testing for adjuvant study referral
  - 5 year follow-up: treatment and outcome
  - contact regarding follow-up biopsy if cancer recurs
  - (optionally) re-contact if no recurrence at end of study

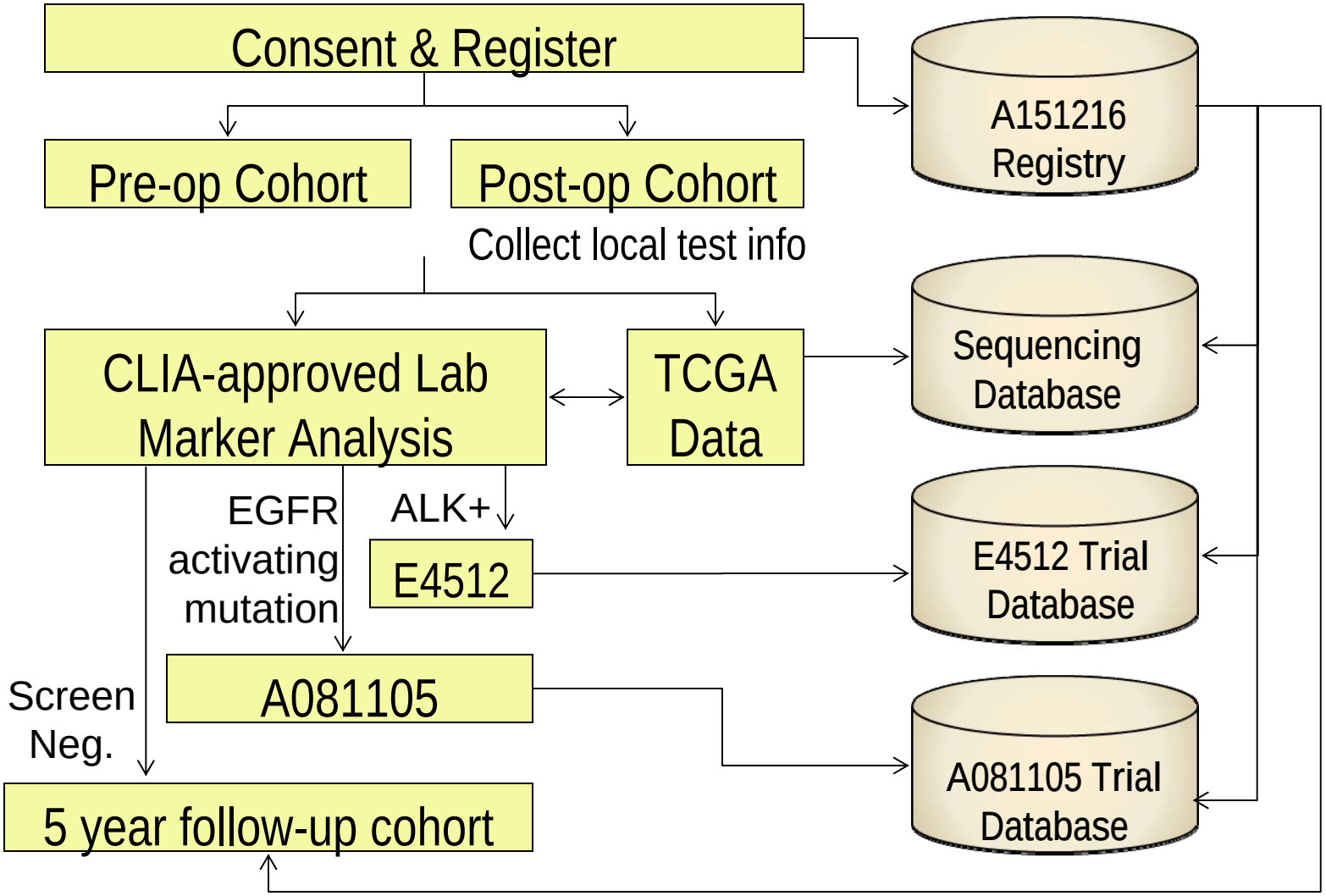
National Cancer Institute

Tissue Flow



National Cancer Institute

Data Flow



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Karen Arscott, DO
Lung Cancer Alliance

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Design of a Disease-Specific Master Protocol

Shakuntala Malik, MD
FDA/CDER/OHOP

Master Protocol Concept

Joint NCI Thoracic Malignancies Steering Committee & FDA Workshop Hyatt Regency Bethesda, Bethesda MD — February 2-3, 2012. “Strategies for Integrating Biomarkers into Clinical Development of New Therapies for Lung Cancer ”

Objective: To bring together leading academicians, clinicians, industry and government representatives to identify challenges and potential solutions in the clinical development of novel targeted therapies for lung cancer

Outcomes: Suggestion to develop Master protocols (by Dr Pazdur) for different stages of Lung Cancer

FDA Perspective

Targeted drug development presents unique opportunities for "personalized medicine"

Master protocols will

- Provide consistency of development approach regardless of intended target
- Better utilize limited resources (including patient resources)
- Bring safe and effective drugs to patients faster

Discussions of trial design and endpoints with FDA to occur once protocol and statistical analysis plan are well developed/near-final

FDA Perspective

FDA Drug approval will, however, depend on

- Integrity of data collected
- Results of the trials
  - Drug effect isolated (clear attribution to drug)
  - Results not only statistically significant but also clinically meaningful
  - Toxicity of the drug.
- Available therapies at the time of approval

Risk: Benefit Ratio

FDA-approved Therapy with Specific Targets in NSCLC

- Erlotinib (EGFR tyrosine kinase inhibitor)
- Bevacizumab (VEGF-A inhibition)
- Crizotinib (ALK inhibitor)

Demonstration of specific molecular abnormalities in patient's tumor not required in FDA-approved indication for erlotinib and bevacizumab but *is* required for crizotinib indication

FDA Perspective

Companion diagnostic assay/assay performance sufficient to reliably & reproducibly identify “marker-positive” population

Exploratory studies for “marker-negative” population will need to be conducted to:

- Differentiate between prognostic vs predictive markers
- Support device/test kit claims

CDRH should be involved at initial stages of assay development

FDA Perspective

New drugs/indications for lung cancer will continue to be approved by FDA based on a demonstrated effect on a surrogate endpoint that is **reasonably likely** to predict clinical benefit in a population where there is unmet clinical need.

Such approvals are likely to be based on relatively small trials; confirmatory trials **will** be required to confirm and characterize the actual clinical benefit.

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