National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

NCI's Evolving Late Phase Clinical Trials System

NCI National Clinical Trials Network (NCTN) Overview

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on behalf of the

Division of Cancer Treatment & Diagnosis:

Biometric Research Branch, Cancer Diagnosis Program, Cancer Imaging Program, Cancer Therapy Evaluation Program, Radiation Research Program

Division of Cancer Prevention:

NCI Community Oncology Research Program (NCORP)

CTAC Meeting – November 12, 2014

NCTN Milestones

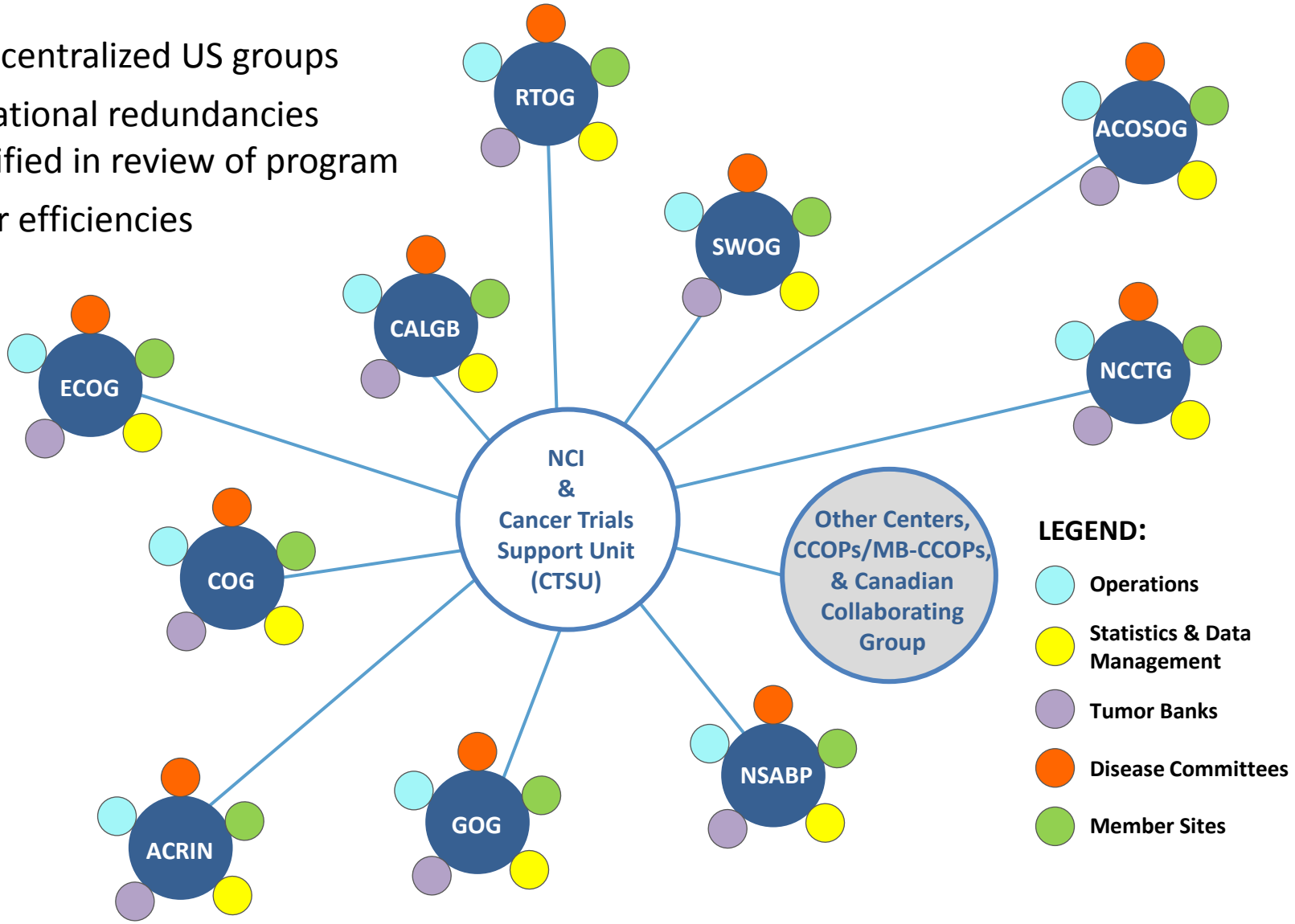
May 2010	NCI conducts an extensive review of its late-phase Cooperative Group clinical trials program with widespread stakeholder input on revising the program
November 2011	NCI Board of Scientific Advisors approves plan to transform former Cooperative Group Program with a Request for Application (RFA) for an integrated National Clinical Trials Network (NCTN) - plan includes a consolidated organizational structure with funding for 1 pediatric group and up to 4 adult groups
July 2012	NCI releases NCTN Funding Opportunity Announcements
January 2013	NCTN applications due January 15, 2013
July 2013	Peer-Review of NCTN applications
March 1, 2014	NCI launches the National Clinical Trials Network (NCTN)

Vision for Transformation of System for NCI Late-Phase Tx/Imaging Trials - 2014 and Beyond

- **Launch trials rapidly & complete accrual per defined guidelines through integrated national network sites**
- **Promote user-friendly, harmonized processes to extramural community (investigators, patients, advocates, & industry) & facilitate collaborations with partners**
- **Provide common infrastructure to perform large scale testing of increasingly smaller subsets of molecularly-defined cancers (Examples: LUNG-Map, ALCHEMIST, MATCH)**
- **Focus on research questions not well supported in a commercial environment**

Structure of Late-Phase Clinical Trials Program Prior to NCTN

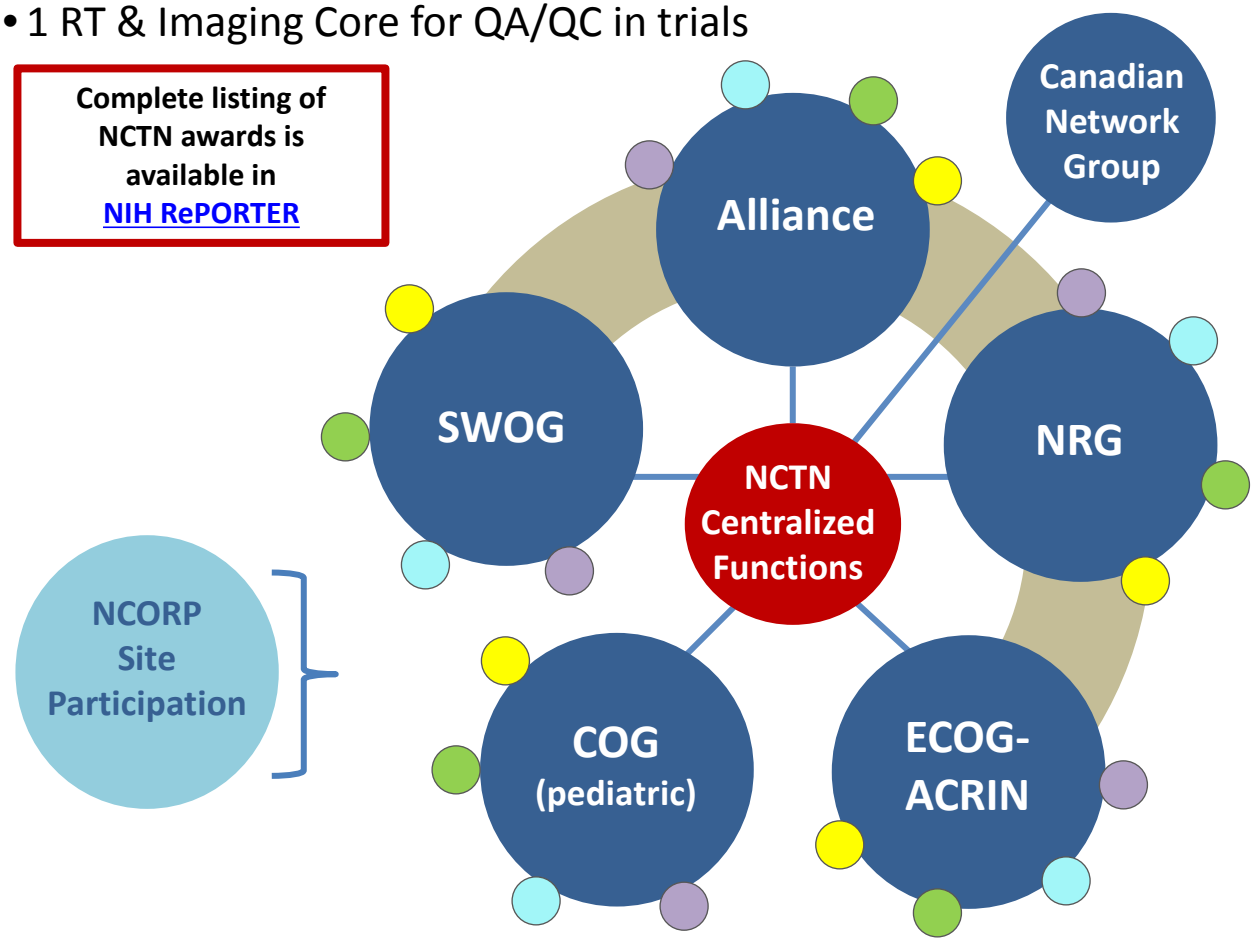
- 10 decentralized US groups
- Operational redundancies identified in review of program
- Fewer efficiencies



NCTN Structure - Optimize Scientific Opportunities

- 5 US Network Groups (4 adult & 1 pediatric) with Operations & Statistics/Data Mgt Ctrs and 1 Canadian Collaborating Network Group
- 30 Lead Academic Participating Sites (LAPS) to provide leadership in development, accrual & conduct of clinical trials in association with the adult US trial Groups
- 7 Integrated Translational Science awards to help incorporate translational science into trials
- 1 RT & Imaging Core for QA/QC in trials

Complete listing of NCTN awards is available in NIH RePORTER



LEGEND:

- Centralized Functions for operational efficiencies:
  - Centralized Institutional Review Board
  - Cancer Trials Support Unit
  - Radiotherapy/Imaging Cores
  - Common Data Management System Central Hosting
- 30 Lead Academic Participating Sites (LAPS)
- Operations
- Statistics & Data Management
- Tumor Banks
- Member Sites

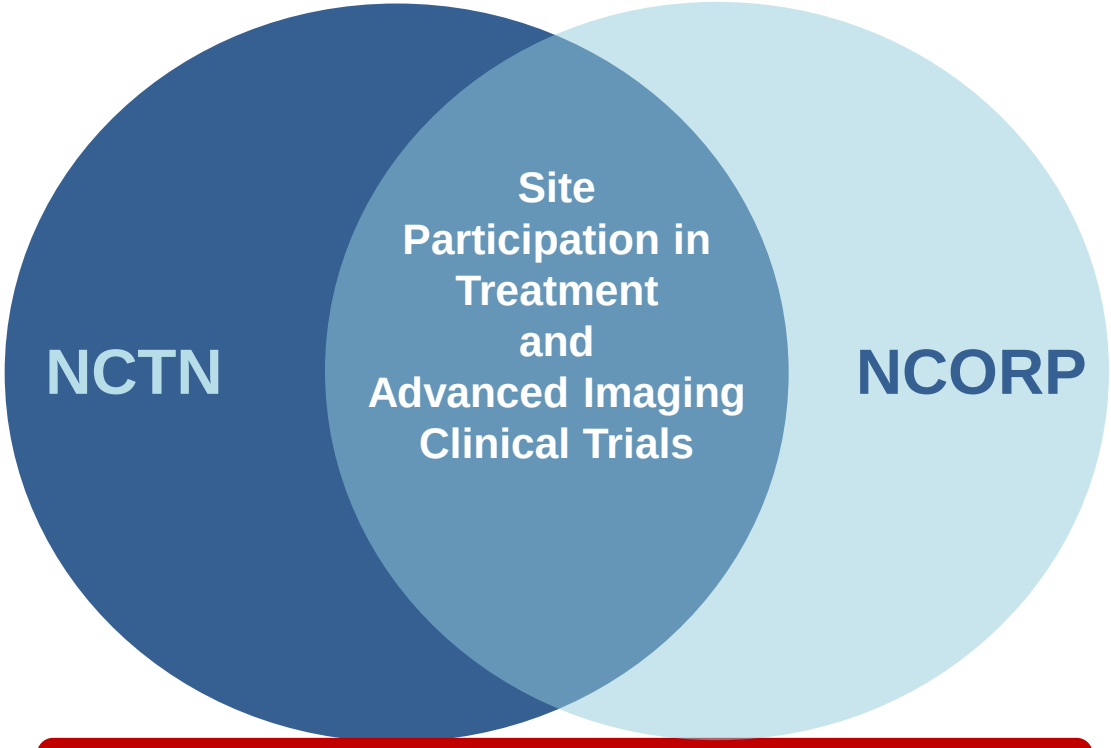
Relationship of NCTN and NCORP

NCTN Focus:

- Late-Phase Treatment Trials
- Advanced Imaging Trials

NCORP Focus:

- Cancer Prevention & Control Trials
- Cancer Care Delivery
- Comparative Effectiveness Research



NCTN/NCORP CENTRALIZED FUNCTIONS

Major Components of NCTN Program

5 US Network Operations Centers (4 adult & 1 pediatric)

- Provide scientific leadership for developing & implementing multi-disciplinary, multi-site trials in a range of diseases and special populations with specific scientific strategies and goals

With 5 Associated US Network Statistics and Data Management Centers

- Provide statistical expertise to ensure effective scientific design & conduct of trials as well as innovation in statistical methodology in addition to data mgt and analysis of all NCTN studies

1 Canadian Collaborating Network Group

- Partners with the US Network Groups in the conduct of selected, late-phase, multi-site clinical trials, helping to reduce regulatory barriers & expanding the geographic extent of patient accrual

30 Lead Academic Participating Sites (LAPS)

- Provide scientific leadership in the development & conduct of trials in association ≥ 1 adult US Network Groups as well as substantial accrual to trials conducted across the entire NCTN

7 Integrated Translational Science Awards

- Provide support for leadership and expertise to facilitate incorporating translational science into Network Group clinical trials

1 Radiotherapy & Imaging Core Services Center

- Provides scientific and technical expertise for incorporating quality assurance and image data management for applicable clinical trials conducted by the NCTN that require specialized QA/QC

Operations and Statistics/Data Mgt Centers

Network Group	Operations Center Principal Investigator (*contact PI)	Statistics/Data Mgt Ctr Principal Investigator (*contact PI)
Alliance for Clinical Trials in Oncology (Alliance)	Brigham & Women's Hospital, Inc. Monica Bertagnolli (*)	Mayo Clinic Dan Sargent
Children's Oncology Group (COG)	Children's Hospital of Philadelphia Peter Adamson	University of Florida Meenaski Devidas
ECOG-ACRIN Cancer Research Group (ECOG-ACRIN)	ECOG-ACRIN Medical Research Foundation Robert Comis (*)	Dana-Farber Cancer Institute Robert Gray
NCIC Clinical Trials Group (NCIC-CTG)	Queen's University (Kingston, Ontario) Elizabeth Eisenhauer	N/A
NRG Oncology (NRG)	NRG Oncology Foundation, Inc. Norman Wolmark (*)	University of Pittsburgh Joseph Costantino (*)
SWOG	Oregon Health & Sci University Charles Blanke (*)	Fred Hutchinson Can Research Ctr Michael LeBlanc

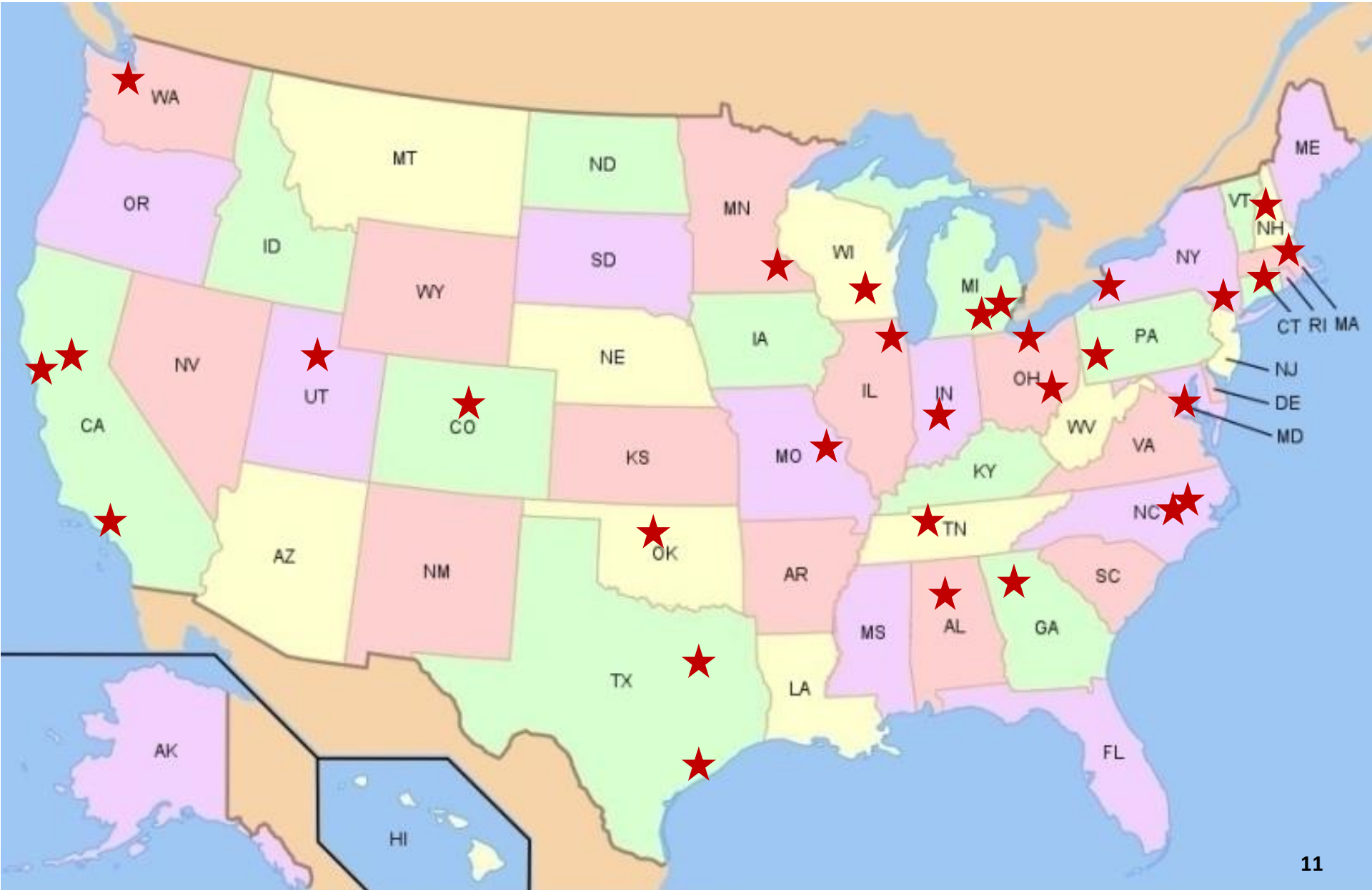
30 Lead Academic Participating Site (LAPS) Awardees

Institution	PI
CASE WESTERN RESERVE UNIVERSITY	MACHTAY, MITCHELL (contact)
DANA-FARBER CANCER INST	BURSTEIN, HAROLD JOHN (contact)
DARTMOUTH COLLEGE	DRAGNEV, KONSTANTIN H.
DUKE UNIVERSITY	CRAWFORD, JEFFREY (contact)
EMORY UNIVERSITY	RAMALINGAM, SURESH S. (contact)
FRED HUTCHINSON CAN RES CTR	APPELBAUM, FREDERICK
JOHNS HOPKINS UNIVERSITY	BRAHMER, JULIE RENEE (contact)
INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS	MILLER, KATHY D
MAYO CLINIC ROCHESTER	ALBERTS, STEVEN R (contact)
OHIO STATE UNIVERSITY	GOLDBERG, Richard (contact)
ROSWELL PARK CANCER INSTITUTE CORP	LEVINE, ELLIS G (contact)
SLOAN-KETTERING INST CAN RES	AGHAJANIAN, CAROL (contact)
STANFORD UNIVERSITY	WAKELEE, Heather (contact)
UNIVERSITY OF ALABAMA AT BIRMINGHAM	ALVAREZ, RONALD DAVID (contact)
UNIVERSITY OF CALIFORNIA DAVIS	GANDARA, DAVID R (contact)
UNIVERSITY OF CHICAGO	KINDLER, HEDY L (contact)
UNIVERSITY OF COLORADO DENVER	ELIAS, ANTHONY D

30 Lead Academic Participating Site (LAPS) Awardees

Institution	PI
UNIVERSITY OF MICHIGAN	ZALUPSKI, MARK M
UNIV OF NORTH CAROLINA CHAPEL HILL	CAREY, LISA A
UNIVERSITY OF OKLAHOMA HLTH SCIENCES CTR	MANNEL, ROBERT S (contact)
UNIVERSITY OF PITTSBURGH AT PITTSBURGH	BRUFSKY, ADAM M (contact)
UNIVERSITY OF SOUTHERN CALIFORNIA	LENZ, HEINZ JOSEF (contract)
UNIVERSITY OF TX MD ANDERSON CANCER CTR	ENG, CATHY (contact)
UNIVERSITY OF TX SOUTHWESTERN MEDICAL CENTER	SCHILLER, JOAN H.
UNIVERSITY OF UTAH	GAFFNEY, DAVID K
UNIVERSITY OF WISCONSIN-MADISON	KAHL, BRAD (contact)
VANDERBILT UNIVERSITY MED CTR	BERLIN, JORDAN D
WASHINGTON UNIVERSITY	BARTLETT, NANCY L (contact)
WAYNE STATE UNIVERSITY	FLAHERTY, LAWRENCE E
YALE UNIVERSITY	HOCHSTER, HOWARD S (contact)

Geographic Locations of the Main Academic Centers for the 30 NCTN Lead Academic Participating Site (LAPS)



1 Radiation Therapy/Imaging Core Services Center

Institution	Title of Award Application	PI
AMERICAN COLLEGE OF RADIOLOGY	IROC (IMAGING AND RADIATION ONCOLOGY CORE)	FOLLOWILL, D (contact)

7 Integrated Translational Science Awards (ITSAs)

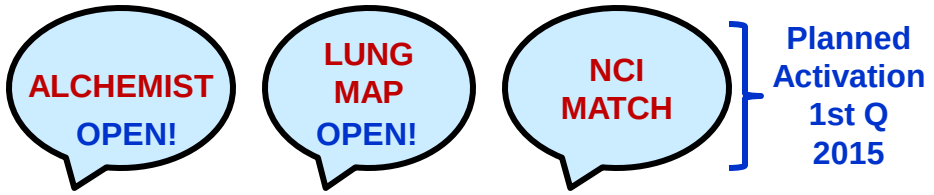
Institution	Title of Award Application	PI
CHILDREN'S HOSPITAL OF PHILADELPHIA	COG SOLID TUMOR MALIGNANCIES	ADAMSON, P (contact)
COLD SPRING HARBOR LABORATORY	SWOG TRANSLATIONAL (XENOGRAFT-DRUG DISCOVERY)	TUVESON, D (contact)
EMORY UNIVERSITY	ECOG-ACRIN THORACIC MALIGNANCIES RESEARCH	RAMALINGHAM, S
MONTEFIORE MEDICAL CENTER (BRONX, NY)	ECOG-ACRIN LEUKEMIA TRANSLATIONAL RESEARCH	PAIETTA, E (contact)
OHIO STATE UNIVERSITY	ALLIANCE -SWOG LEUKEMIA RESEARCH	MARCUCCI, G (contact)
UNIV OF NORTH CAROLINA CHAPEL HILL	ALLIANCE-NRG ONCOLOGY RNA/DNA SEQUENCING	HAYES, D (contact)
WASHINGTON UNIVERSITY	NRG ONCOLOGY GENOPROTEOMICS CENTER	Mutch, D (contact)

Research Agenda for Late-Phase Clinical Trials System

- Emphasis on phase 3, practice-changing, treatment and advanced imaging trials, especially in research areas that are not well supported in a commercial environment
- Combinations of novel & molecularly targeted agents developed by different sponsors
- Integration of new agents & imaging approaches into standard of care
- Evaluation of multi-modality regimens (e.g., Surgery, Radiotherapy, IP therapy)
- Therapies for pediatric cancers, rare cancers, and uncommon presentations of more common cancers
- Different treatment and imaging approaches already approved for clinical care

NCI: Developing National Strategy for Precision Medicine - NCTN Opportunities

- **Help advance molecular profiling from research use into the clinic**
- **Genotype to Phenotype:**



  - Develop portfolio of trials across spectrum from early stage to advanced disease
  - Screen for molecular features that may predict response to a drug with a given mechanism of action
  - Analyze tumor specimens at relapse to define mechanisms of resistance
  - Develop public database that links clinical outcomes with molecular tumor **characteristics for continued research**
- **Phenotype to Genotype:**

  - Molecular mutations or changes in gene expression may explain why patients responded to a treatment that did not work for others

ALCHEMIST Background

- **ALCHEMIST will evaluate molecularly targeted therapy in early stage NSCLC with non-squamous histologies (i.e., adenocarcinoma, large cell ca, etc.) that has been completely surgically resected**
- **Molecularly targeted therapy has improved outcomes within these histologies in advanced NSCLC**
  - erlotinib (target: EGFR activating mutation)
  - crizotinib (target: EML4-ALK)
- **This has lead to routine testing of EGFR mutations and ALK rearrangement in advanced disease**
- **Not known if these agents are beneficial in the adjuvant clinical setting**

ALCHEMIST Structure

ALCHEMIST is an integrated research effort with 3 component trials:

1. **Screening Trial - A151216:** Eligible patients will have their tumor tissue tested for genetic changes in ALK or EGFR. If tissue testing is positive, they will be referred to one of the treatment trials. If negative, they will be followed for 5 years. All patients contribute information to the national public resource for research.

2. **Erlotinib Treatment Trial - A081105:** Erlotinib vs. placebo will be evaluated in patients with activating EGFR mutations following standard of care adjuvant therapy

3. **Crizotinib Treatment Trial - E4512:** *Crizotinib vs.* placebo will be evaluated in patients harboring the Anaplastic Lymphoma Kinase (ALK) fusion protein following standard of care adjuvant therapy

ALCHEMIST-Screening & Tx Trial Schema

Trials conducted at sites in the NCI Clinical Trials Networks: NCTN & NCORP

Stage IB (≥ 4cm)-IIIA non-squamous NSCLC (n=6000-8000)

Pre-op cohort

Post-op cohort

Complete resection + standard adj therapy per treating physician

Central EGFR & ALK genotyping

FFPE tissue & blood specimen

<u>EGFR-mutation</u>: A05 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

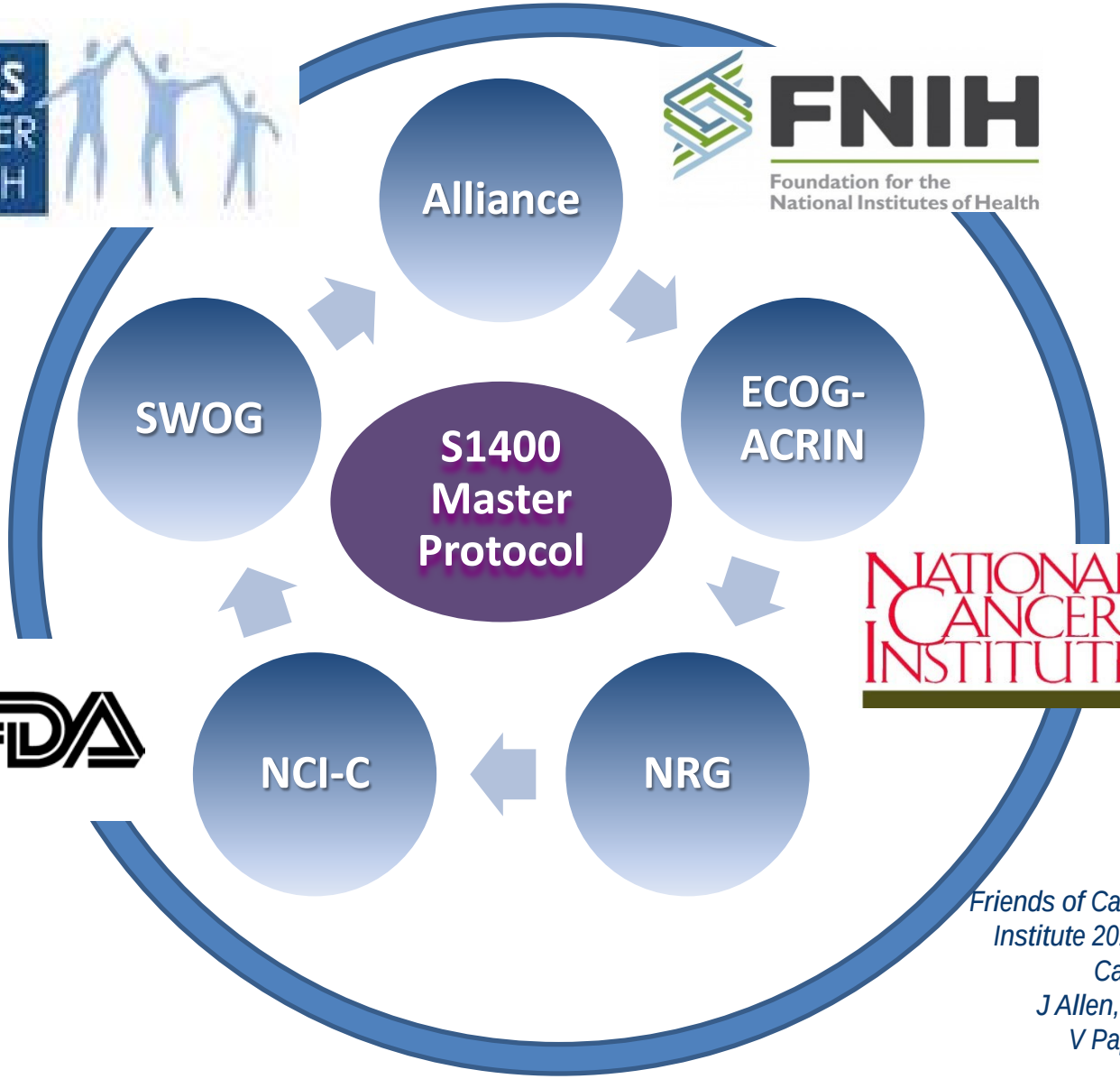
<u>Without Molecular Alterations</u>: Followed q6 months x 5 years after any adj tx

FFPE tissue from biopsy done at recurrence

Epidemiologic Questionnaire & Advanced genomics analysis at the NCI Center for Cancer Genomics for all screened patients

S1400 Master Protocol

Unique Private-Public Partnerships with the NCTN



FRIENDS of CANCER RESEARCH

FNIH Foundation for the National Institutes of Health

NATIONAL CANCER INSTITUTE

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA FDA

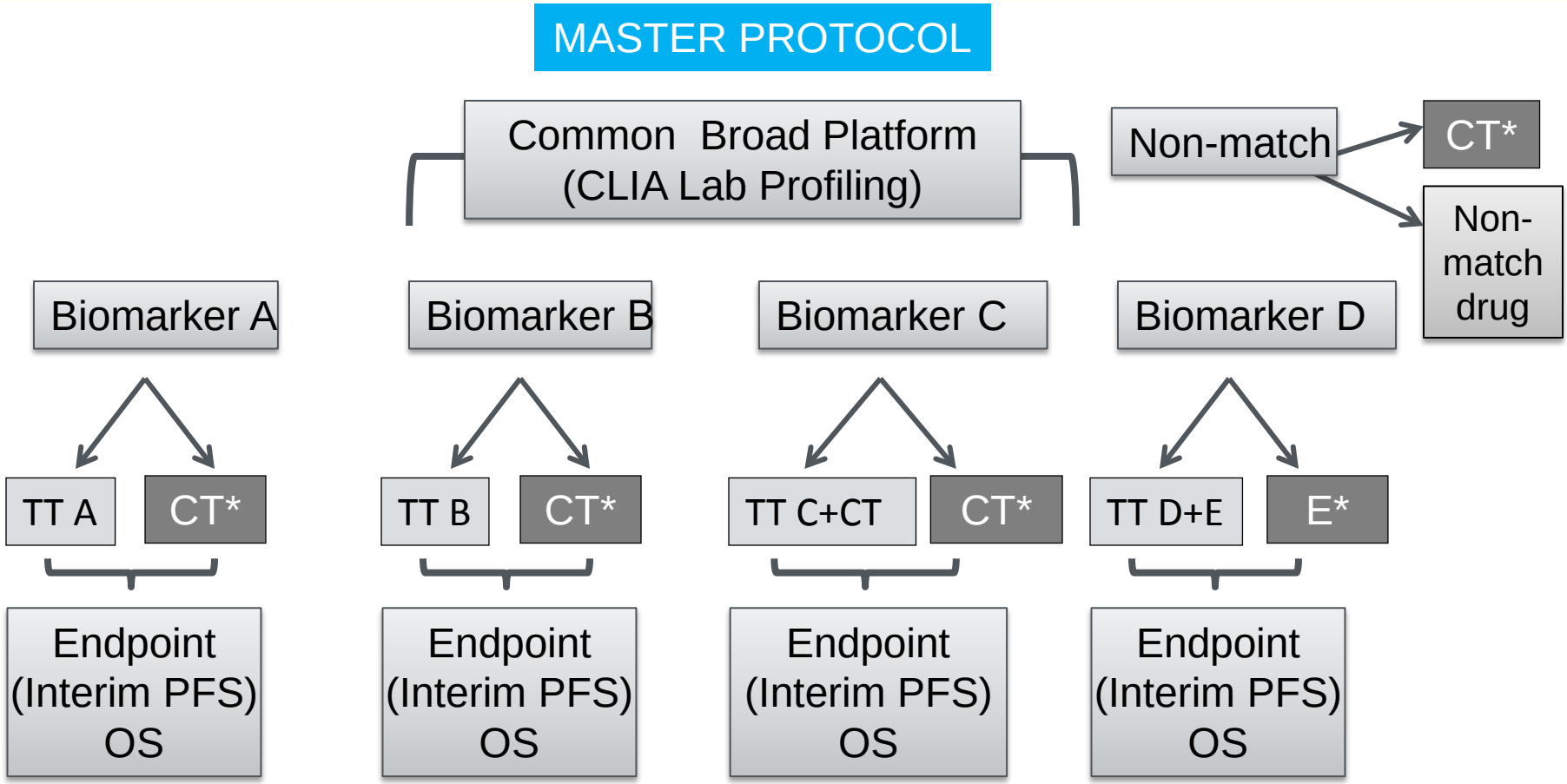
Friends of Cancer Research & Brookings Institute 2013 Conference on Clinical Cancer Research – J Allen, R Herbst, D Gandara, V Papadimitrakopoulou

LUNG – MAP (Master Protocol – S1400)

Biomarker Study for 2nd-Line Tx of Squamous Cell Lung Ca

- Special Private-Public Partnership
- Multi-arm randomized, controlled phase 2/3 registration protocol
- Each arm opens/closes independent of others, independently powered for Overall Survival (OS). Positive results at “rolling” interim analysis determine if a arm proceeds to phase 3 portion
- Each drug with clinical data demonstrating biologic activity in responsive patient group against measurable target, using predictive biomarker assay analytically validated & suitable for a pivotal trial
- Led by SWOG with participation by all Groups in the NCTN and by all sites in the NCORP and NCTN

LUNG – MAP (Master Protocol – S1400)



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

Friends of Cancer Research & Brookings Institute 2013 Conference on Clinical Cancer Research – J Allen, R. Herbst, D. Gandara, V Papadimitrakopoulou

NCI-MATCH

- **Umbrella protocol for multiple, "signal-seeking" single-arm phase II trials across various histologies**
  - Identify mutations/amplifications/translocations in patient tumor sample & match patients to targeted agent
  - Tumor biopsies & sequencing at progression to illuminate resistance mechanisms
    - De-identified samples submitted to central labs
    - Whole-exome sequencing (research purposes) to detect non-ambiguous germline variants
- **IND for protocol template**
  - Arms could be added or deleted without affecting other arms
- **Initially focused on single-agents (commercial or experimental)**
  - Combinations will be considered for targets that have validated combination targeted therapy
  - Need minimum dose/safety established in phase 1 trials
- **Study will be reviewed by the CIRB**
- **Will be led by ECOG-ACRIN & open to entire NCTN and NCORP Networks - anticipate opening in 1st Quarter 2015**

Additional Precision Medicine Trials Planned for NCTN

- **PEDIATRIC MATCH**
  - Umbrella protocol for multiple, “signal-seeking” single-arm phase II trials across various histologies in early stages of planning for pediatric patient population similar to the Adult NCI MATCH study

- **ALK Master Protocol**
  - Evaluation of 2nd generation ALK inhibitors compared to crizotinib in advanced lung cancer (1st-line)

NCTN Meeting on Accrual Challenges

Objective:

Explore how to best work across the NCTN to identify opportunities and strategies to collectively address accrual to challenging and genomic-driven trials

Participants:

Representatives from all 30 LAPS, the 5 US NCTN Groups & the NCTN Canadian Collaborating Network, Patient Advocates, and NCI (DCTD, DCP, OD)

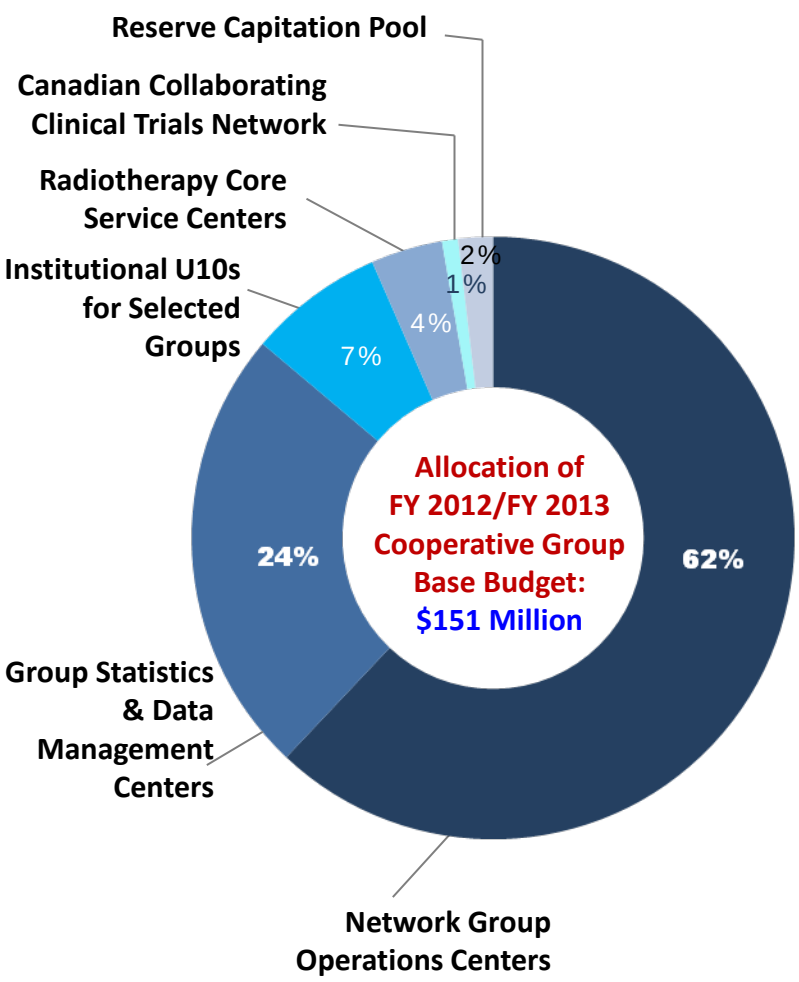
When:

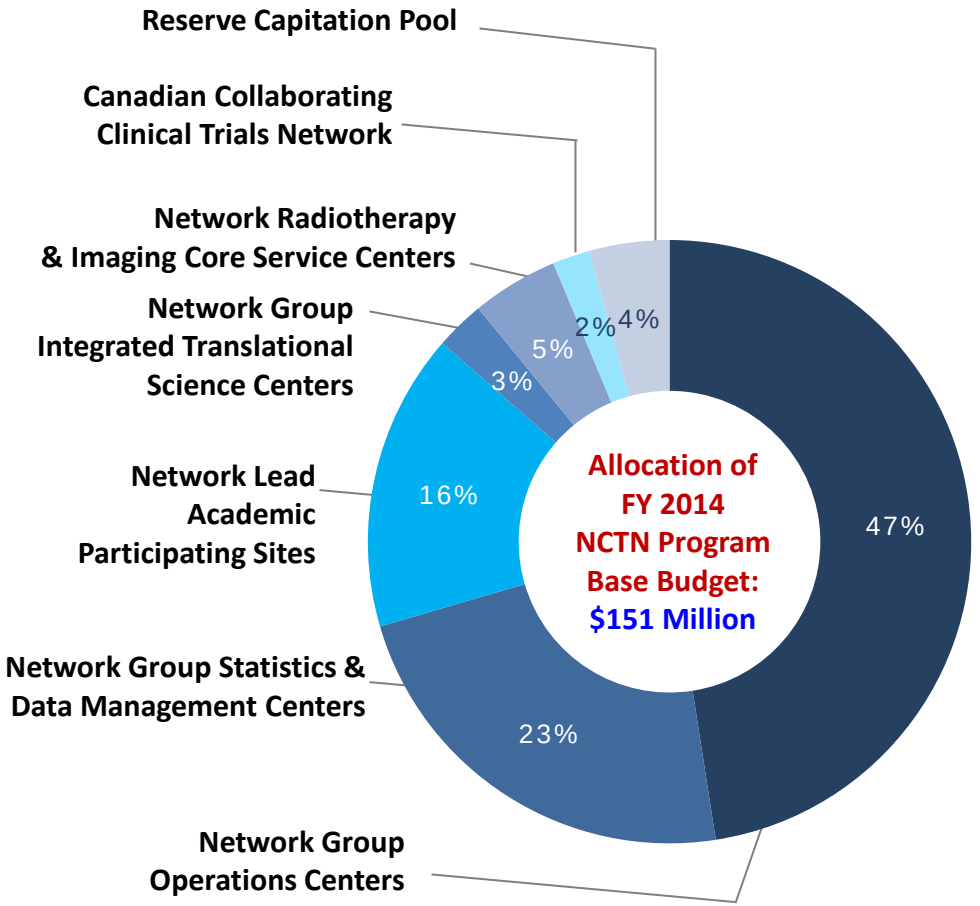
December 4-5, 2014 (NCI Shady Grove)

Sponsor:

Foundation for the NIH

Comparison of Cooperative Group Program Funding and NCTN Program Funding





NCI provided approximately $24 million to consolidate infrastructures & more than $40 million to transition to a common data management system (Medidata Rave®), develop an integrated IT system for the tumor banks, and implement specific precision medicine clinical trials.

NCTN-Related Annual Funding

Additional Estimated Annual NCI Support

(This is an approximation and is dependent on annual NCI appropriations)

NCI Central IRBs (Adult & Pediatrics)	$4.5 Million
Cancer Trials Support Unit	$14.0 Million
Tumor Banks	$8.6 Million
BIQSFP	$10.0 Million
NCORP Treatment Trials (estimated)	$33.1 Million
TOTAL:	$70.2 Million

Other NCI support includes but is not limited to:

- Common Data Management System (Medidata Rave®)
- Clinical Trials Monitoring
- Drug Storage and Distribution
- Regulatory Oversight & Monitoring (CTEP IND Studies)

NCTN Accrual Projections

Average Annual Total Accrual (Intervention & Screening)

FY 2007 – FY 2013 (7 Yr Avg): ≈ 23,670

FY 2010 – FY 2013 (3 Yr Avg): ≈ 20,900

Projection for Year 1 of NCTN: ≈ 19,000 to 20,500

With new Network, accrual reporting can now be done in real-time across a variety of accrual categories to help with collaborative planning & development of new trials