National Cancer Institute

NCI Experimental Therapeutics Clinical Trials Network (ETCTN)

Clinical Trials Advisory Committee (CTAC) November 12th, 2014

Percy Ivy, MD

Associate Chief, Investigational Drug Branch
Cancer Therapy Evaluation Program

Program Director, Experimental Therapeutics Clinical Trials Network

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Goals and Objectives of The ETCTN

Research and Development for New Treatments

- Dose and schedule in early treatment trials
- Novel combination therapies

Tumor Characterization in Biomarker-driven studies

- Molecular characterization: expression, sequence and epigenetics
- Validated biomarker assays in qualified labs
- Functional imaging

Enhanced understanding of cancer biology

- Bedside to bench and back

Education and Training for young investigators

Challenges for the Experimental Therapeutics Clinical Trials Network

Accrual

- Smaller patient populations due to molecularly-defined diseases
- A scalable/flexible program that can rapidly adapt to accrual needs

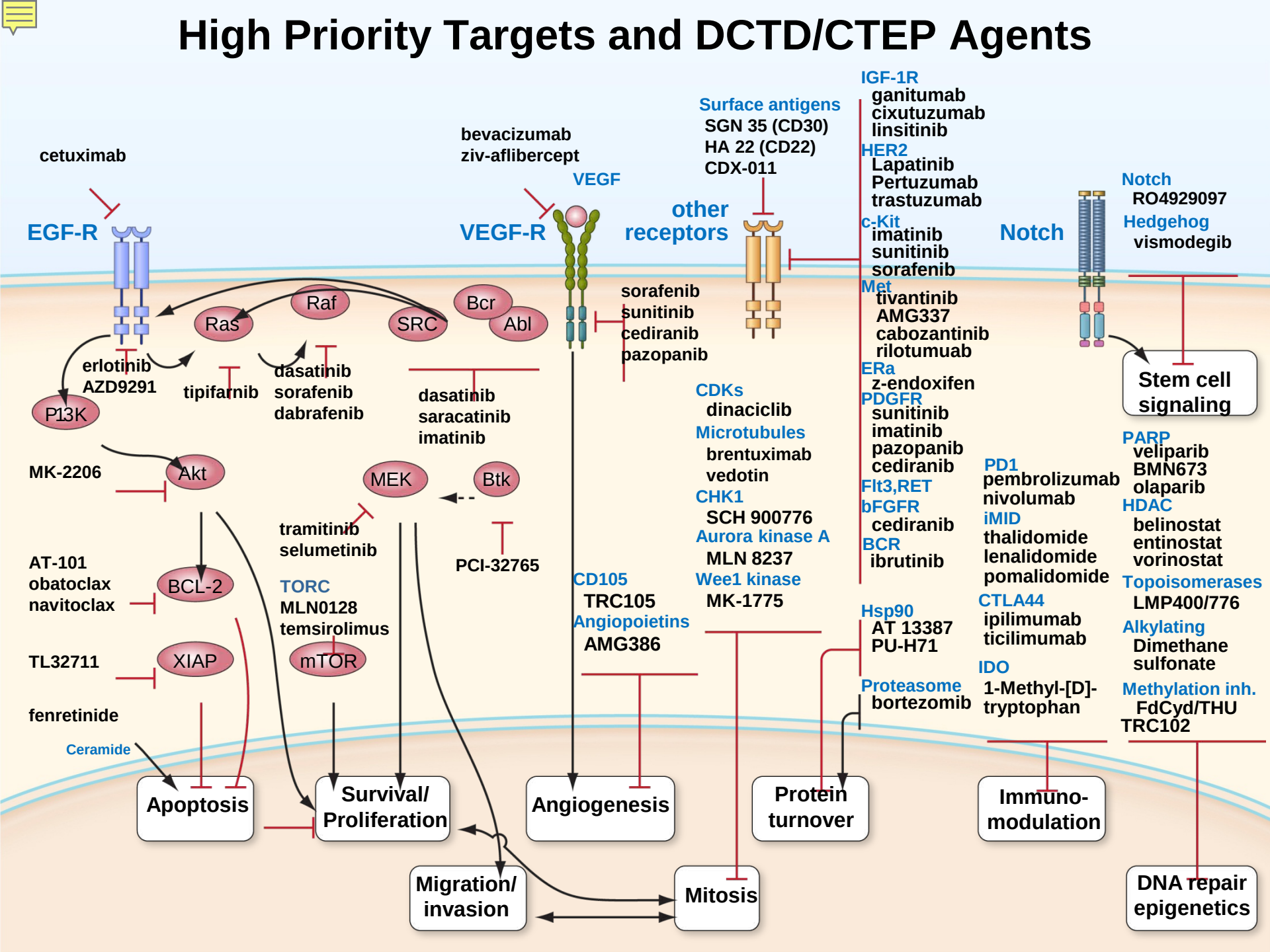
Biomarkers

- Often requires biopsies
- Fit for purpose, validated assays
- Functional imaging

More Facile Mechanisms for Translation

- To and From Bench to Bedside Collaborations
- More predictive animal models to evaluate tumor heterogeneity

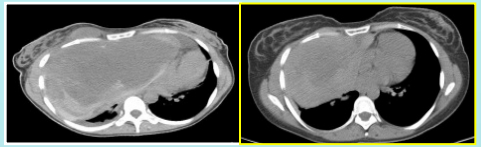
High Priority Targets and DCTD/CTEP Agents



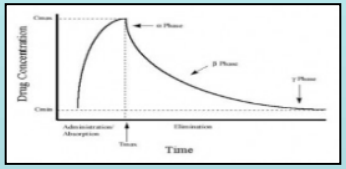
Clinical Translational Research and Cancer Biology: Bedside to Bench and Back

***Clinical observations:**

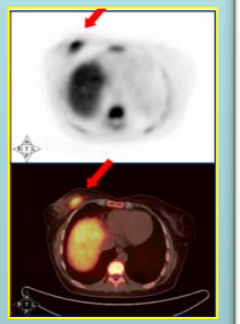
- Clinical response



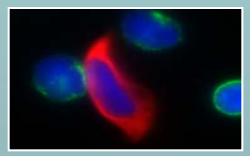
- PK



- Functional imaging



- Tumor and normal tissue PD markers
- CTCs, CECs



- Tumor-initiating cells

Patients eligible for early phase clinical trials

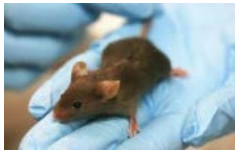
Analysis of tumor and Other tissues for pathway activation or biomarker *

Patient assigned to trial Based on molecular characterization of tumor

Patient monitoring *

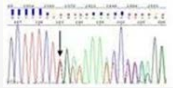
Patient monitoring: * **Post-treatment molecular re-analysis for response/ resistance**

Non-clinical models for targets

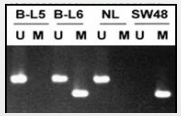


Translational research with clinical models

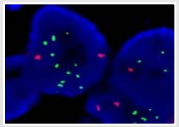
- Sequencing



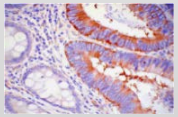
- Methylation



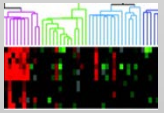
- FISH



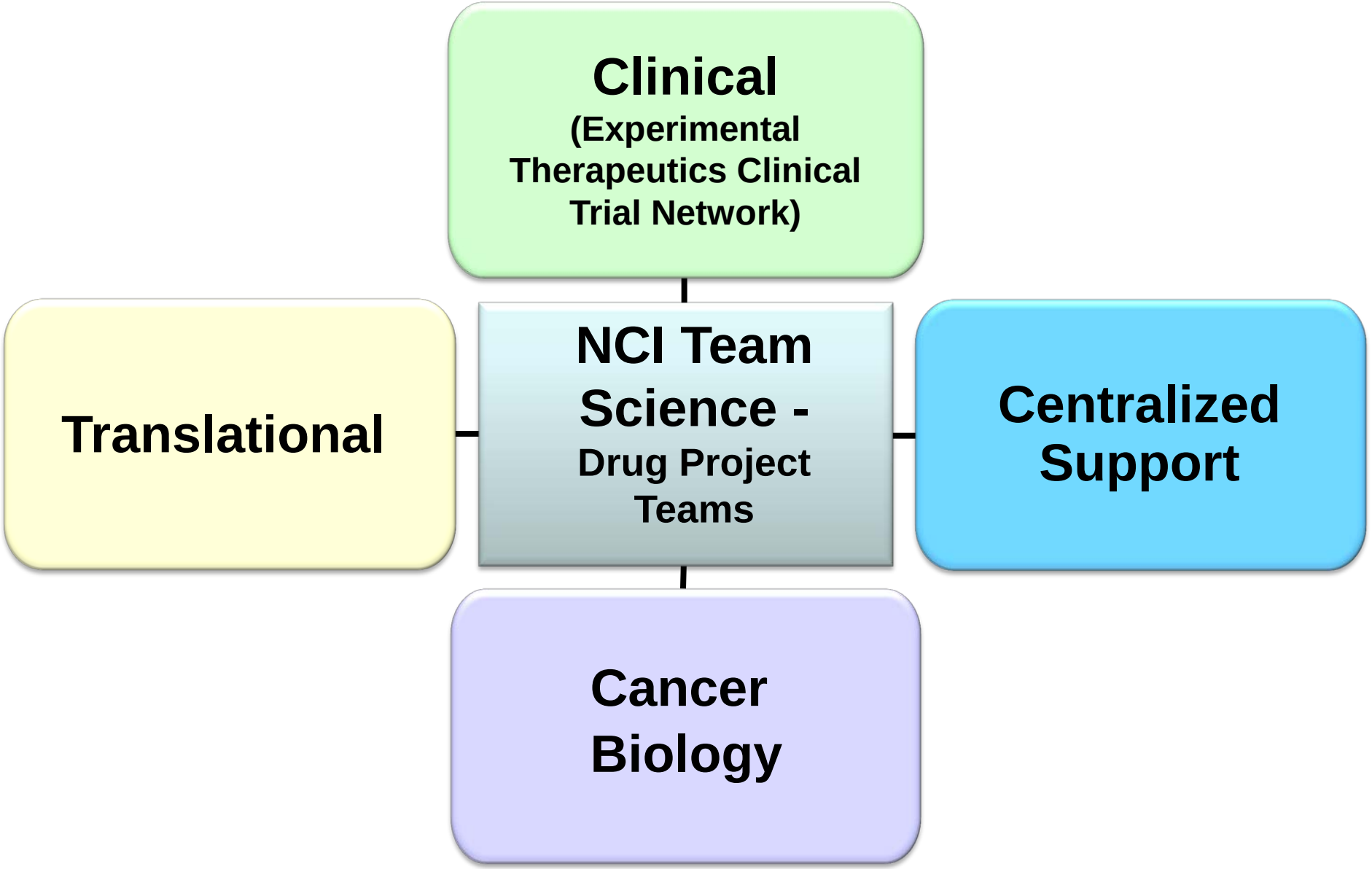
- IHC



- Expression array



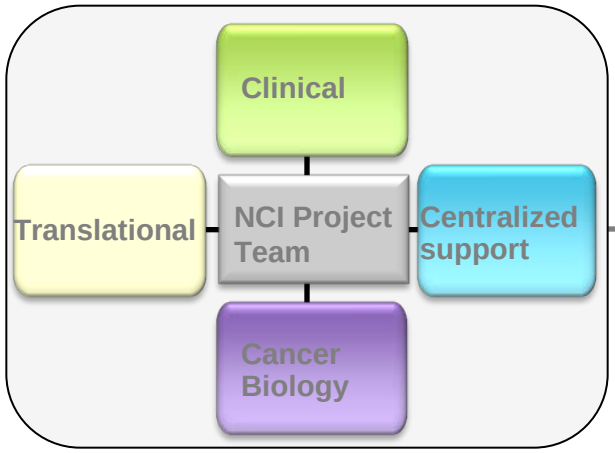
NCI Team Science-
Drug Development Project Teams



NCI Team Science-Project Development: Step 2 – NCI Division/Programs Project Team

NExT Program → NCI Project Team → Drug "X" Project Team → Protocol development

Step 2



- Request for Projects
- Important questions

Preliminary Drug Development Plan

Division of Cancer Treatment and Diagnosis/ Cancer Therapy Evaluation Program meeting

NExT Senior Advisory Committee I

Scientific

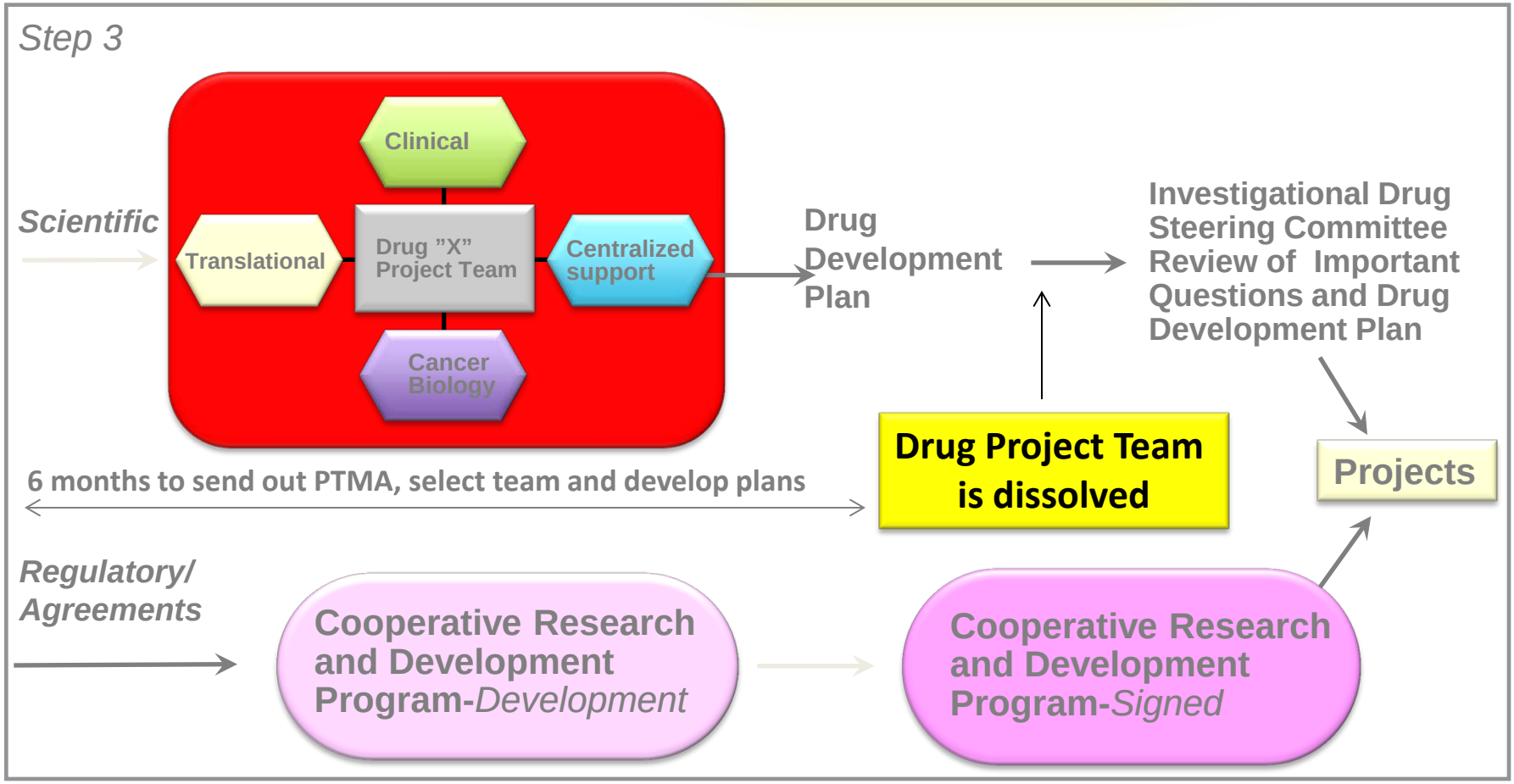
Regulatory/ Agreements

3

Drug Project Team Clock starts ticking

NCI Team Science-Project Development: Step 3- Extramural Project Team

NExT Program → NCI Project Team → **Drug "X" Project Team** → Protocol development



AZD9291 Project Team Timeline

- AZD9291 approved by NDeC on Jan 17, 2014
- AZD9291 drug project team formation approved by SAC1 on April 3, 2014
- AZD9291 PTMA issued May 20, 2014
- AZD9291 project team selected by PRC July 9, 2014
- AZD9291 team had 17 meetings over 10 weeks- required commitment
  - 7 meetings of full team
  - 10 meetings of subgroups of full team
- CRADA signed September, 2014
- IDSC presentation and unanimous (27-0) approval: October 22, 2014

From NExT approval to SAC2: 9.5 months

Goal was to decrease this interval from 21 months to 15 months

AZD9291 Project Team

Name	Branch	Role
External Members	Institution	
Clinicians		
Geoffrey Oxnard	Dana-Farber Cancer Institute	CRDL investigator
Pasi Janne	Dana-Farber Cancer Institute	Mentor/Team co-leader
Jonathan Riess	UC Davis	CRDL investigator
David Gandara	UC Davis	Mentor/Team co-leader
Penelope Bradbury	University Health Network-Princess Margaret Hospital	Clinician scientist
Translational scientists		
Jill Marie Kolesar	University of Wisconsin Hospital and Clinics	Pharmacology
Phil Mack	UC Davis	Genomics
Eric Haura	Moffitt Cancer Center	Kinome
Basic scientists		
Katerina Politi	Yale University	Preclinical mEGFR models
Jeffrey Engelman	Massachusetts General Hospital Cancer Center	Preclinical mEGFR models
Trever Grant Bivona	UCSF-Mount Zion	Preclinical mEGFR models
Internal members		
Jeff Moscow	IDB	Drug Monitor/Team co-leader
Helen Chen	IDB	Drug monitor
Shakun Malik	CIB	NSCLC expert from CIB
Udayan Guha	TOB	NSCLC expert from TOB/CC
Lokesh Agrawal	CDP	Biomarkers
Bhanu Ramineni	RAB	Regulatory
Ed Korn	BRB	Biostatistician

Biomarkers in ETCTN Trials

- Integral
  - Primary study endpoint
  - Used for patient selection
  - Used to determine patient treatment
  - Performed in a CLIA environment
  - May require an IDE

- Integrated
  - Used for patient description
  - Hypothesis generating
  - Provide evidence of pathway activation
  - CLIA ready
  - IDE not required

- Exploratory
  - Descriptive biomarkers
  - Not validated or fit for purpose

Prioritization

- Possibly phase dependent
  - Proof of mechanism
  - Proof of principal
  - Pharmacokinetics
  - Pharmacodynamics
- Propose innovative disease-based or biomarker-based clinical trials incorporating appropriate endpoints

Emphasis on fit for purpose, qualified assays

Biomarker Prioritization

Proof-of-Mechanism

- Tumor biomarkers
- Mechanism based studies to correlate with response or clinical benefit
  - Reduced expression of target proteins
  - Reduced mutant DNA expression
  - Plasma-based detection of mutated protein
  - Reduced expression driver mutations

Genomics

- WES assessments separating responders from non-responders
- RNA-seq/WES analysis of mechanisms of pathway adaptation and resistance

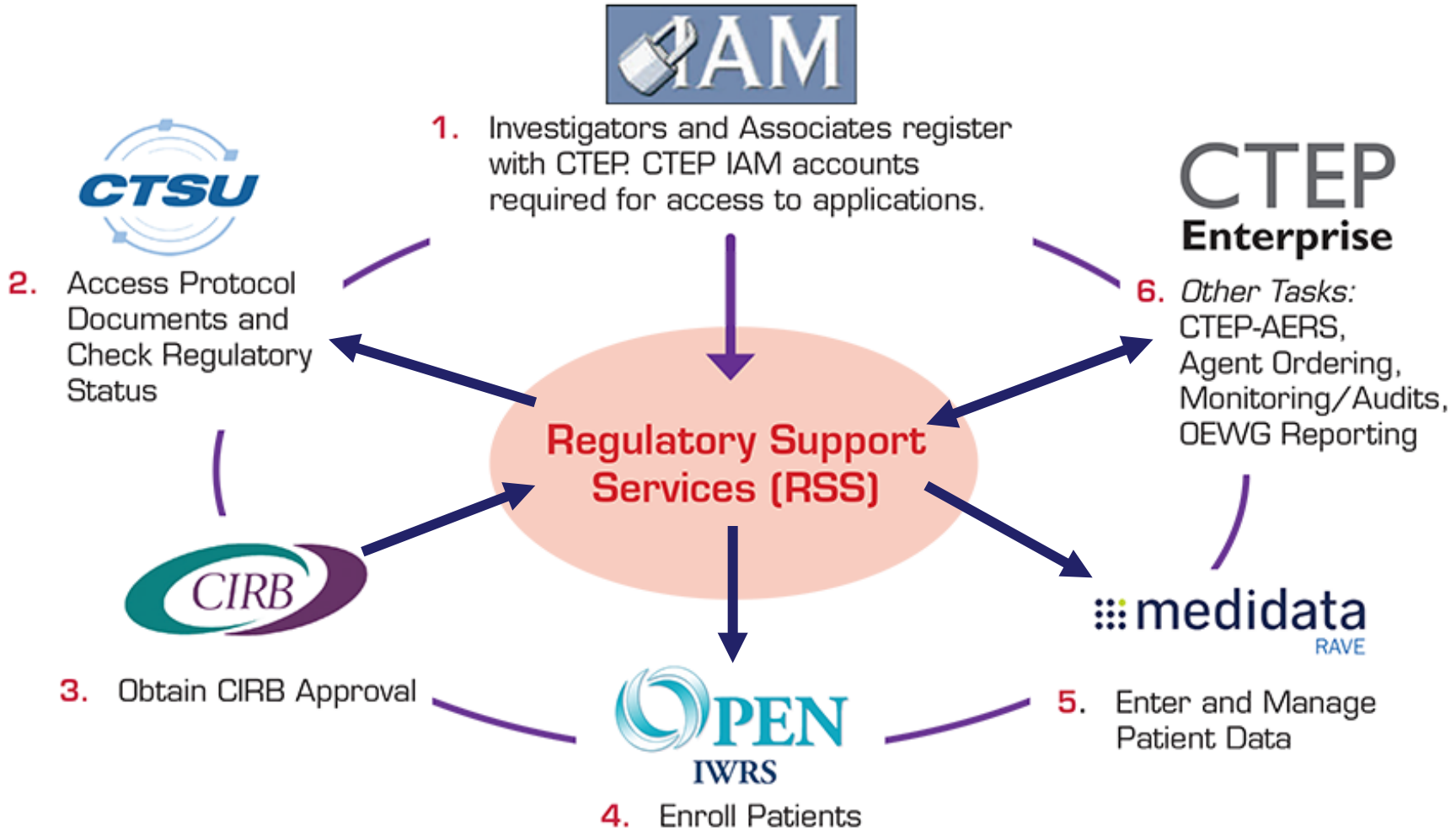
Non-invasive assessments

- MRI scans
- PET scans

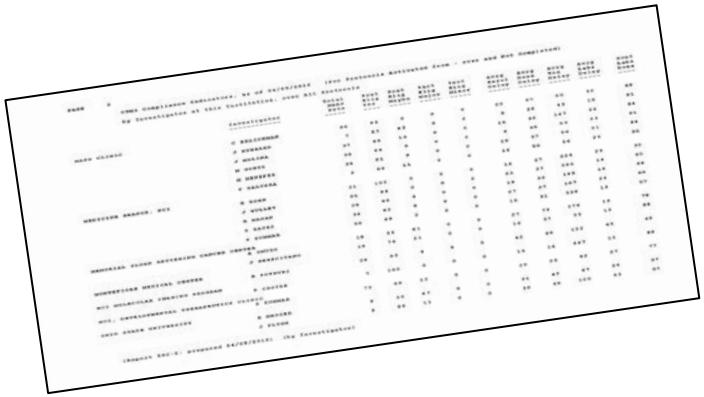
Agents currently on track for PTA/PTMA or solicitation

Agent	NSC/IND	MOA	CRADA/CDA *	PTA/PTMA
AT13387	749712/109876	Hsp90i	11/02/2009	To IDSC
BMN 673	771561/119558	Oral PARPi	06/21/2013	Mass Solicitation
AZD9291	781254/-------	EGFRi, 3rd Gen	04/03/2014	To IDSC
		ATRi	05/29/2014	In prep
		DNMTi	11/20/2011*	In prep
		cMeti	08/09/2013	In prep

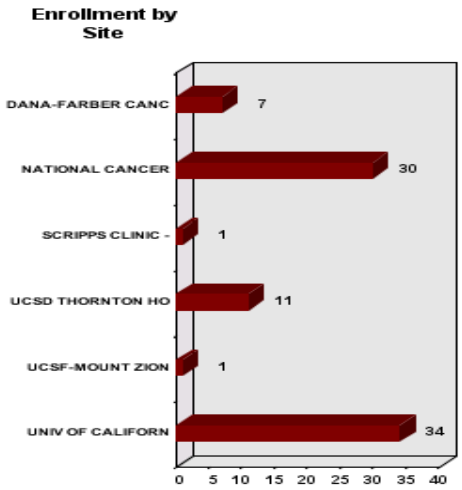
NCI-Sponsored Infrastructure for ETCN Trials

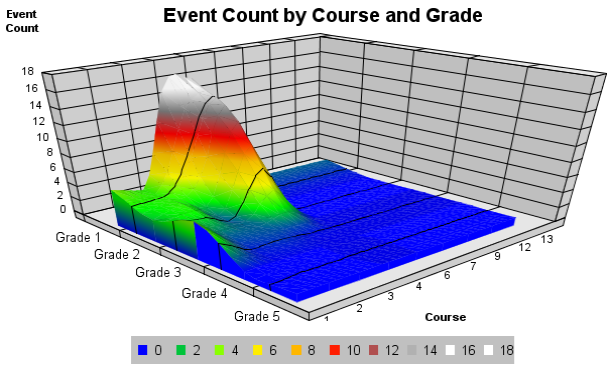


Theradex Instance of Medidata Rave: Web-based Reporting



August 1, 2014 NCI/CTEP
Moved from paper to web-based reporting for early clinical trials



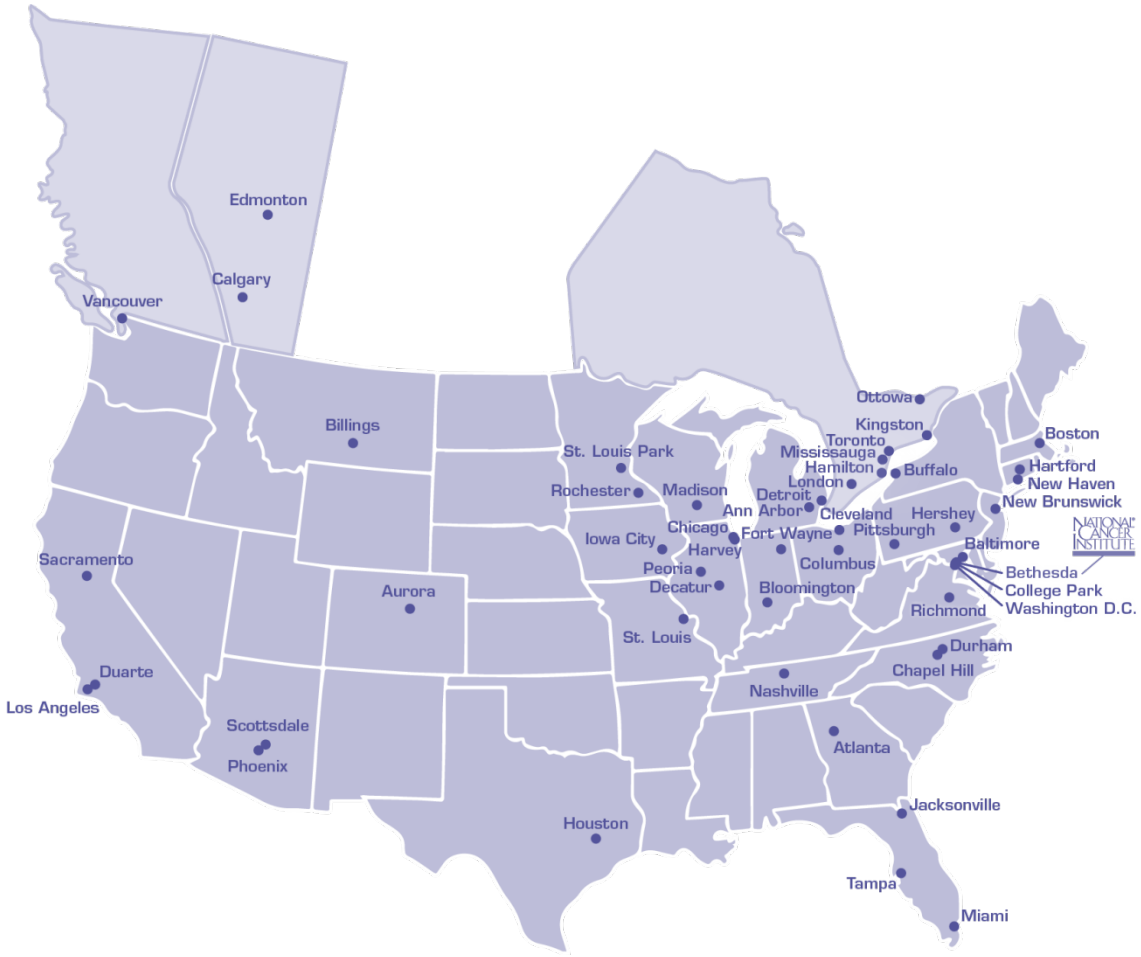


Compliance Overall for a Protocol
Protocol: 5582

	Value	Percent
Number of Patients	51	
Number of Courses	101	
Investigator Eligible Patients	50	98.0%
Investigator Ineligible Patients	1	2.0%
Monitor Eligible Patients	49	96.1%
Monitor Ineligible Patients	2	3.9%
Monitor Missing Info	0	0.0%
Courses Evaluable	96	95.0%
Courses Complete	85	84.2%
Courses with Dose Modifications	47	46.5%
Courses with Significant Toxicities	70	69.3%
Average Lab Delay (Days)	69	
Labs Completed per Protocol	9644	81.3%

* Real time, interactive, web-based, data summaries for monitoring and data mining/analysis

NCI Drug Development Programs: ETCTN Phase 1



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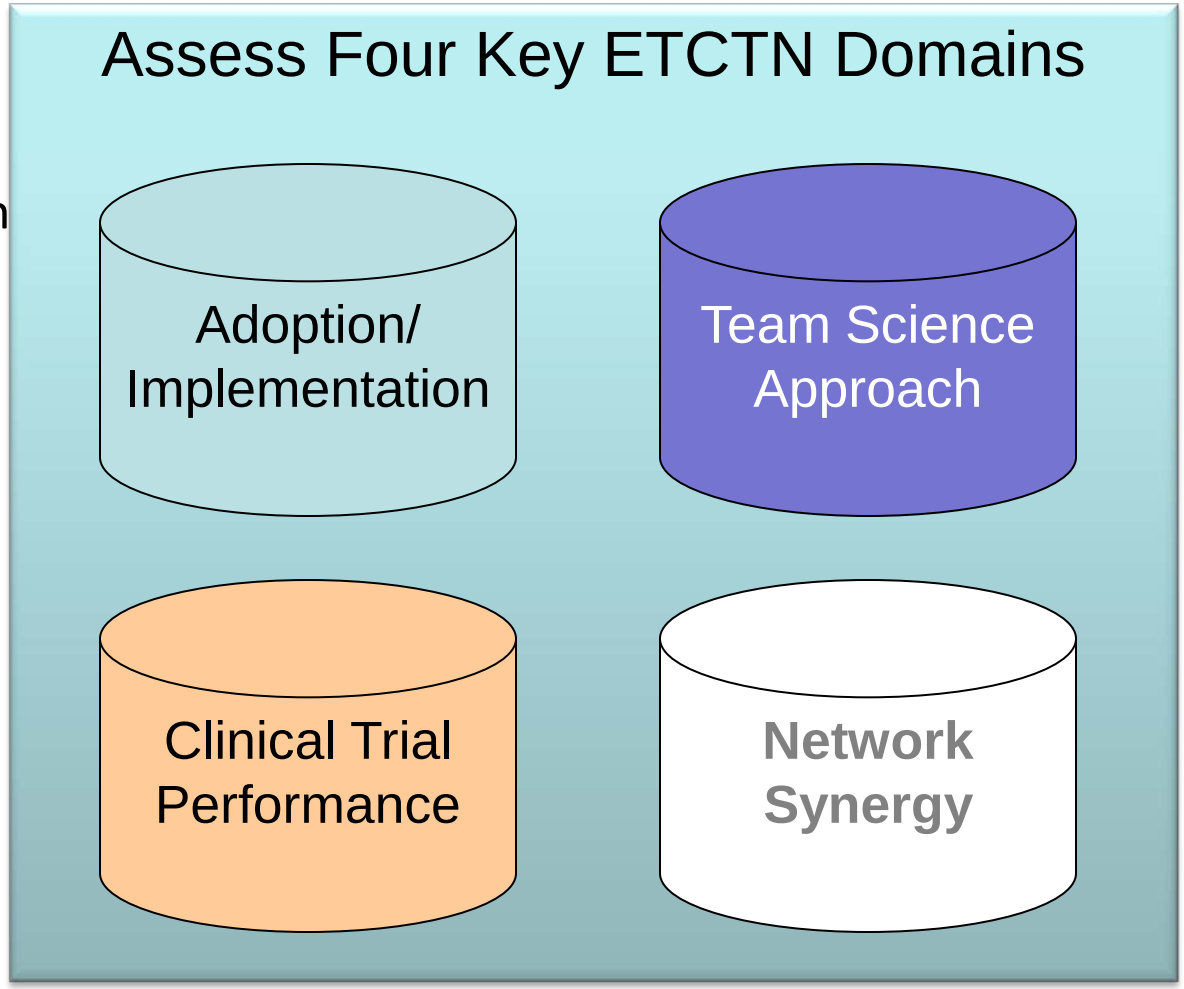
Evaluation of the ETCTN

Goals:

- Document ETCTN's implementation
- Identify course corrections if needed
- Provide data to guide decision making for program's subsequent funding cycle



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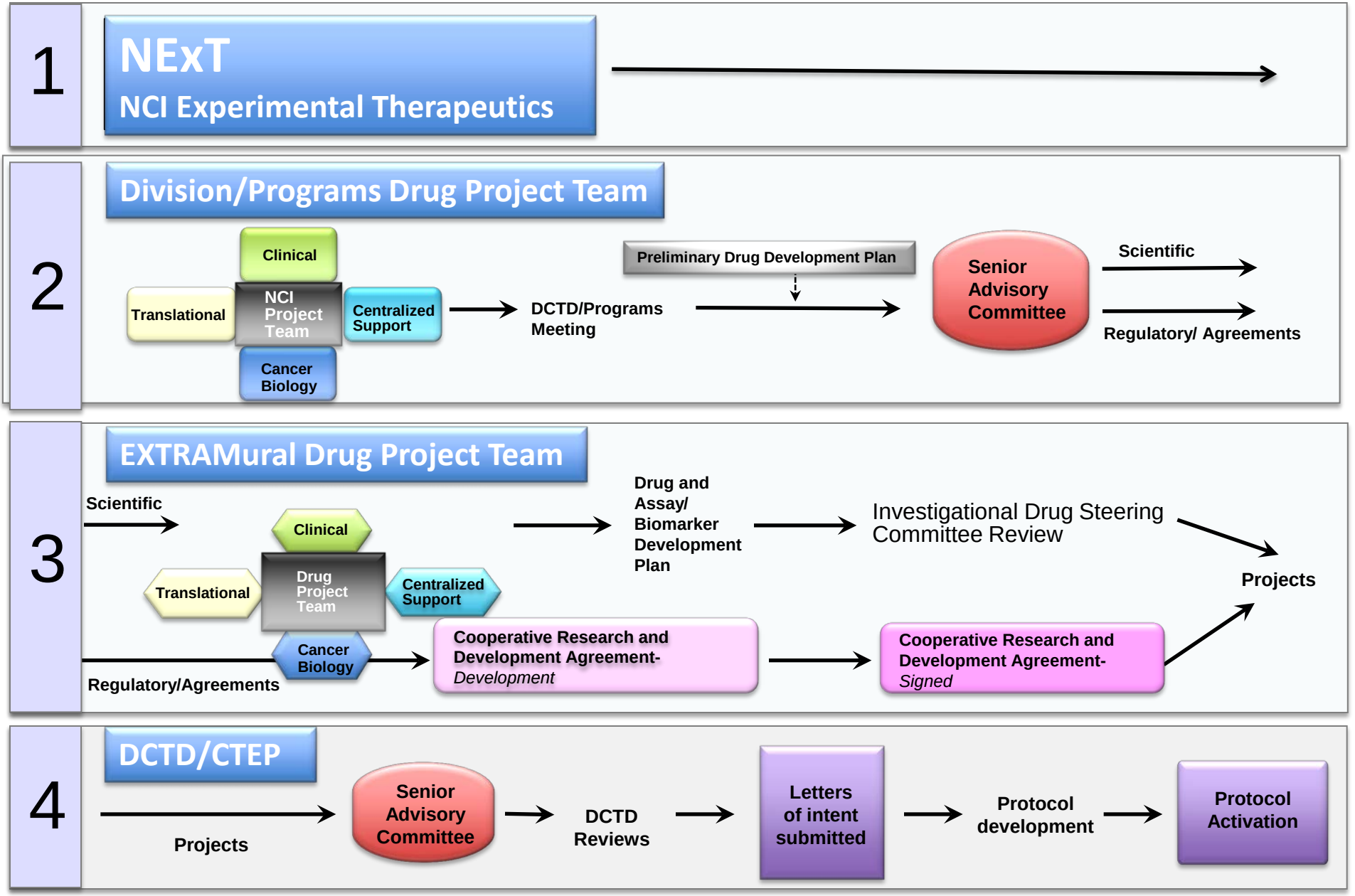
New Development Cycle for NCI Experimental Therapeutics



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Backup Slides

Division and Programs Project Team

Team members

- Clinical scientists- IDB and CIB
- Translational scientists with biomarker and imaging expertise- PADIS, MoCha, CDP, Others
- Cancer biologists- other NCI Divisions and Programs

Tasks

- Draft NCI development plan
- Review of company clinical projects/protocols
- Overview of other competitive agents and molecules
- Biomarkers appropriate for agent development
- Outline of preclinical studies- preliminary or concurrent

Presentation

- Initial NCI development plan to Division of Cancer Treatment and Diagnosis
- Input from Senior Advisory Committee (SAC I)

Extramural Project Team

Team members

- Clinical scientists
- Translational scientists with biomarker and imaging expertise
- Cancer biologists

Tasks

- Initial NCI agent drug development plan
- Description of clinical projects/protocols
- Biomarkers appropriate for agent development
- Outline of preclinical studies- preliminary or concurrent

Presentation

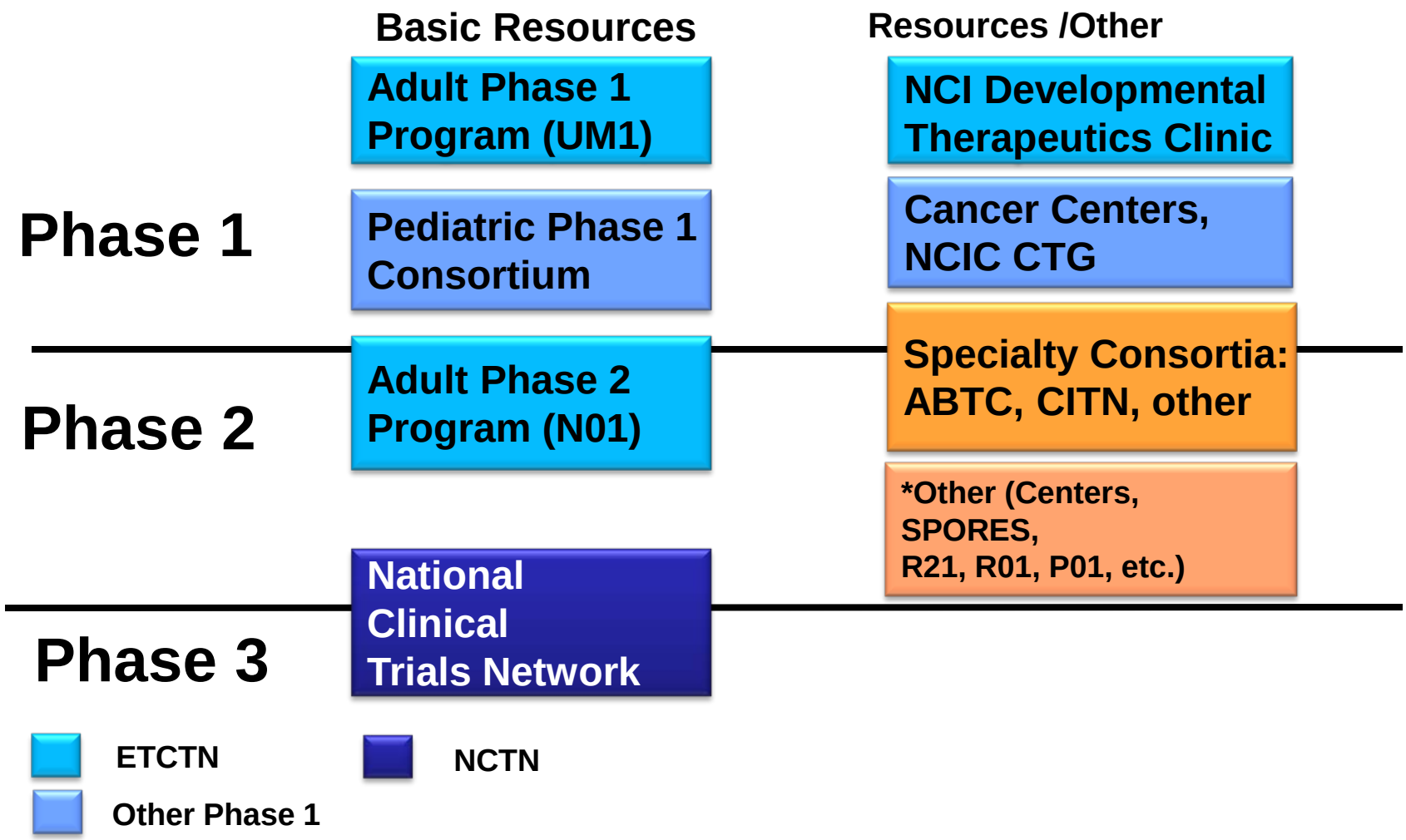
- Initial NCI agent drug development plan
- Input from the Investigational Drug Steering Committee

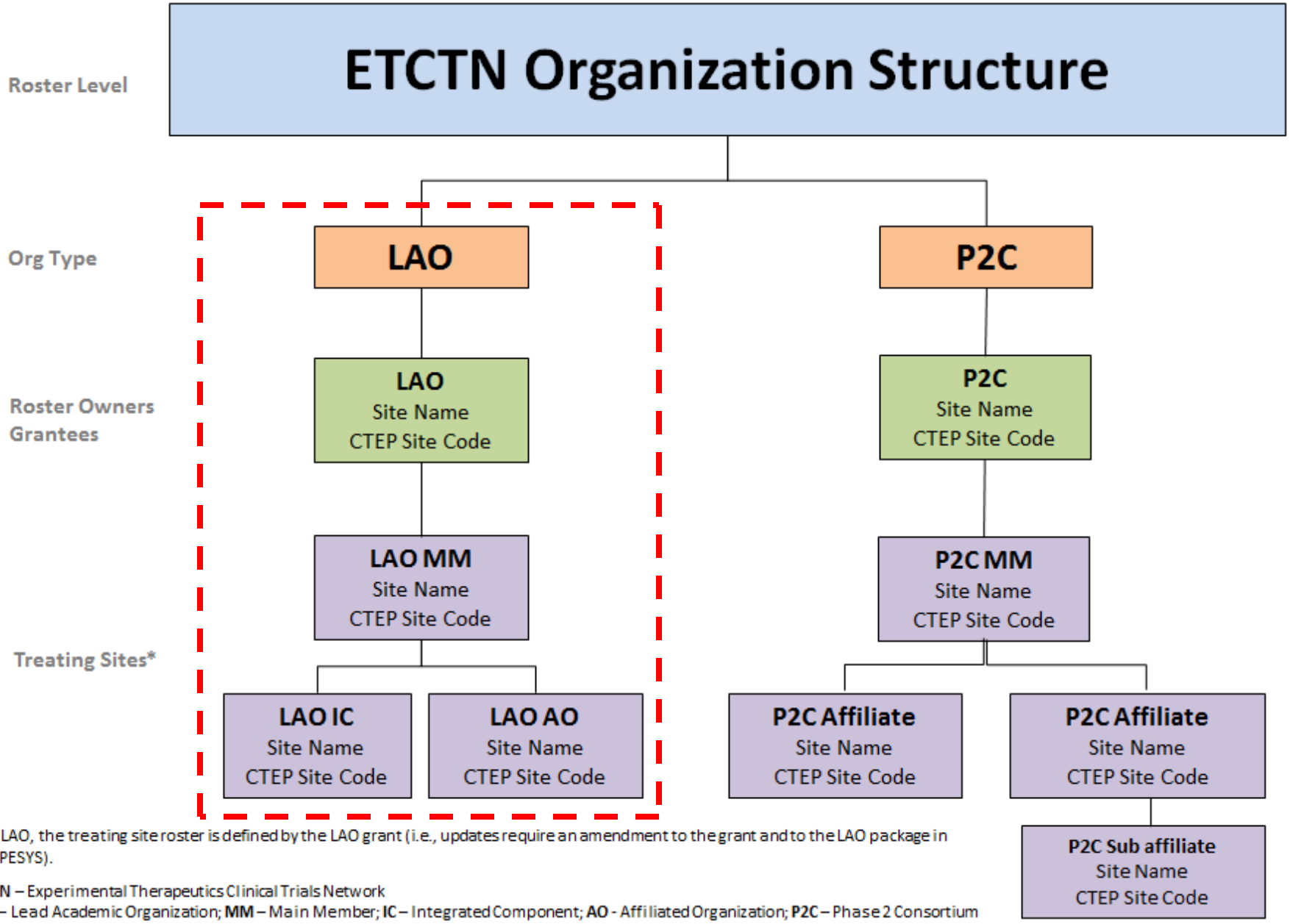
ETCTN Phase 1Principal Investigators

Institutions	PIs
City of Hope/Beckman Res. Inst.	Newman, Edward Lenz, Heinz-Joseph
Dana-Farber/Harvard Cancer Center	Kufe, Donald Flaherty, Keith Shapiro, Geoffrey
Duke U. North Carolina Wash. U.	Hurwitz, Herbert Dees, Elizabeth Lockhart, Albert
Johns Hopkins	Carducci, Michael Gocke, Christopher Gojo, Ivana Rudek, Michelle
Mayo - Rochester	Erlichman, Charles Huluska, Paul Sausville, Ed
NCI-DTC	Kummar, Shivaani

Institutions	PIs
Ohio State U.	Grever, Michael
Rutgers-Cancer Inst. NJ U. Wisconsin	DiPaola, Robert Liu, Glenn
U. Chicago	Ratain, Mark Maitland, Michael
U. Health Network	Siu, Lillian Sullivan, Dan
U. Pittsburgh	Chu, Edward Beumer, Jan
U. Texas – MDACC U. Colorado – Denver	Yao, James Eckhardt, Gail Meric-Bernstam, Funda
Yale University	Lorusso, Patricia Eder, Paul Berlin, Jordan

Transformed NCI Experimental Therapeutics Clinical Trials **Program**





*For LAO, the treating site roster is defined by the LAO grant (i.e., updates require an amendment to the grant and to the LAO package in CTEPESYS).

ETCTN – Experimental Therapeutics Clinical Trials Network
LAO – Lead Academic Organization; **MM** – Main Member; **IC** – Integrated Component; **AO** - Affiliated Organization; **P2C** – Phase 2 Consortium

Project Team Announcement and the Project Team Member Application

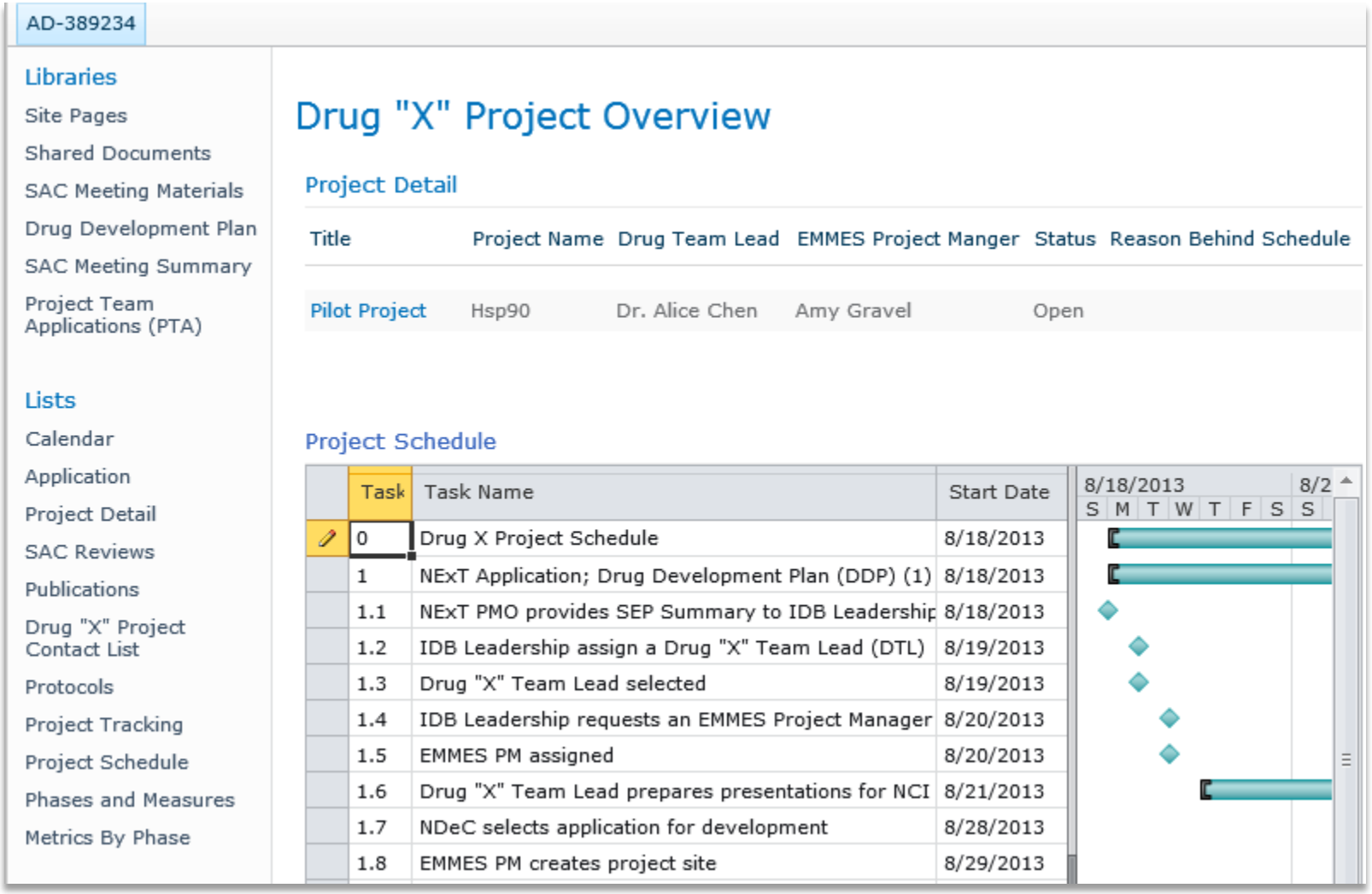
- Project Team Announcement (PTA)
  - Replaced the Mass Solicitation
- Project Team Member Application (PTMA):
  - Investigator applies as a clinical or translational project team member
  - NIH biosketch with statement indicating pertinent expertise
  - Specify affiliation (UM1, U01, NCTN, Consortium)
  - PRC review to select PT members
- Clinician Project Team (PT) members
  - Principal Investigators on the trials
  - Identified by the PT for the agent development plan

Drug Project Teams vs Mass Solicitation

Drug Project Teams (DPTs)	Mass Solicitation
Drug development plan designed by team of intramural and extramural scientists	Drug development ideas proposed by extra-mural investigators and selected by intramural staff
Limited number of LOI's generated as a result of DPT deliberations	Many LOI's generated that compete for placement
Application by individuals to be on DPTs	Application by teams to execute proposed studies
Nationally-recruited team members from multiple institutions work together	Institution-based teams compete with other institution-based teams
Drug development planning occurs during CRADA negotiations	Mass solicitation occurs after CRADA negotiations have been completed
Brief application for membership	LOI forms require extensive preparation

ETCTN Program Portfolio Management Portal

Provides the ability to manage and track experimental therapies from application submission through protocol accrual



Educational Materials

- Educational Materials on the ETCTN-CTSU website includes: links to the webinar recordings, checklists, and information sheets on 14 different topics :

  - Protocol Development
  - Protocol Amendments
  - Person Registration & CTEP-IAM
  - Rosters & Roles
  - The CTSU
  - Protocol Access & Communications
  - Regulatory Processing
  - The NCI CIRB
  - Patient Enrollment
  - Agent Ordering
  - Data Management
  - SAE Reporting
  - CDUS Reporting
  - Auditing and Monitoring

- All documents will be posted to the ETCTN pages on the CTEP website once development is complete

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ETCTN Education and Training

Since program launch, we have held a number of educational webinars for ETCTN members:

- For Leadership:
  - Kick-off and Overview
  - Rosters and Roles
  - Patient Enrollment
  - NCI CIRB
  - PIO Updates
  - Data Management
  - Biomarkers
  - Implementing Drug Project Teams
  - Web Reporting
- For Site Staff:
  - Introduction to the ETCTN, Centralized Services, and the CTSU Website
  - Patient Enrollment
  - Regulatory Processes
  - Data Management

Team Formation for Drug-Specific Project

- NCI-CTEP acquires an agent through NExT and announces a drug-specific project team will form (PTA)
- Investigators with documented expertise (e.g. basic, translational)

- ETCTN Investigators apply as basic, translational or clinical investigators (PTMA)
- Junior investigators along with senior mentors particularly encouraged (CRDL)

- Project Team is assembled
- Basic, Translational and Clinical Team Leaders are designated
- Members commit to a short-term, intense set of teleconference/web-based meetings with NCI-CTEP

Project Team Goals

- Arrive at pre-clinical/translational plan that addresses critical questions that will inform drug development
- Propose innovative disease-based or biomarker-based clinical trials incorporating appropriate safety, pharmacokinetic, pharmacodynamic and efficacy endpoints

Drug Development Plan presented to the Investigational Drug Steering Committee, after which full LOIs are written

Emphasis on Team Science and collaboration across ETCTN network

Project Team

Basic Science	Translational	Clinical	Other
Basic Scientist	*MD translational scientist*	Clinical Leader	Radiation Oncology
Basic Scientist	Translational researcher	**Career Development Investigator**	Cancer Imaging
	PhD translational scientist	**Career Development Investigator**	Biostatistics
		Mentor, Career Development Investigator	Biomarkers
IDB/IDSC Contacts		**Career Development Investigator**	
Senior Investigator, NCI-CTEP		Mentor, Career Development Investigator	
IDB Chief, NCI-CTEP		Investigator	
Administrative		NCI Intramural Investigator	
IDSC			
Bold denotes Career Development Investigator			
Italics denotes SPORE investigator			