

Clinical Trials Advisory Committee Program Overview and update:

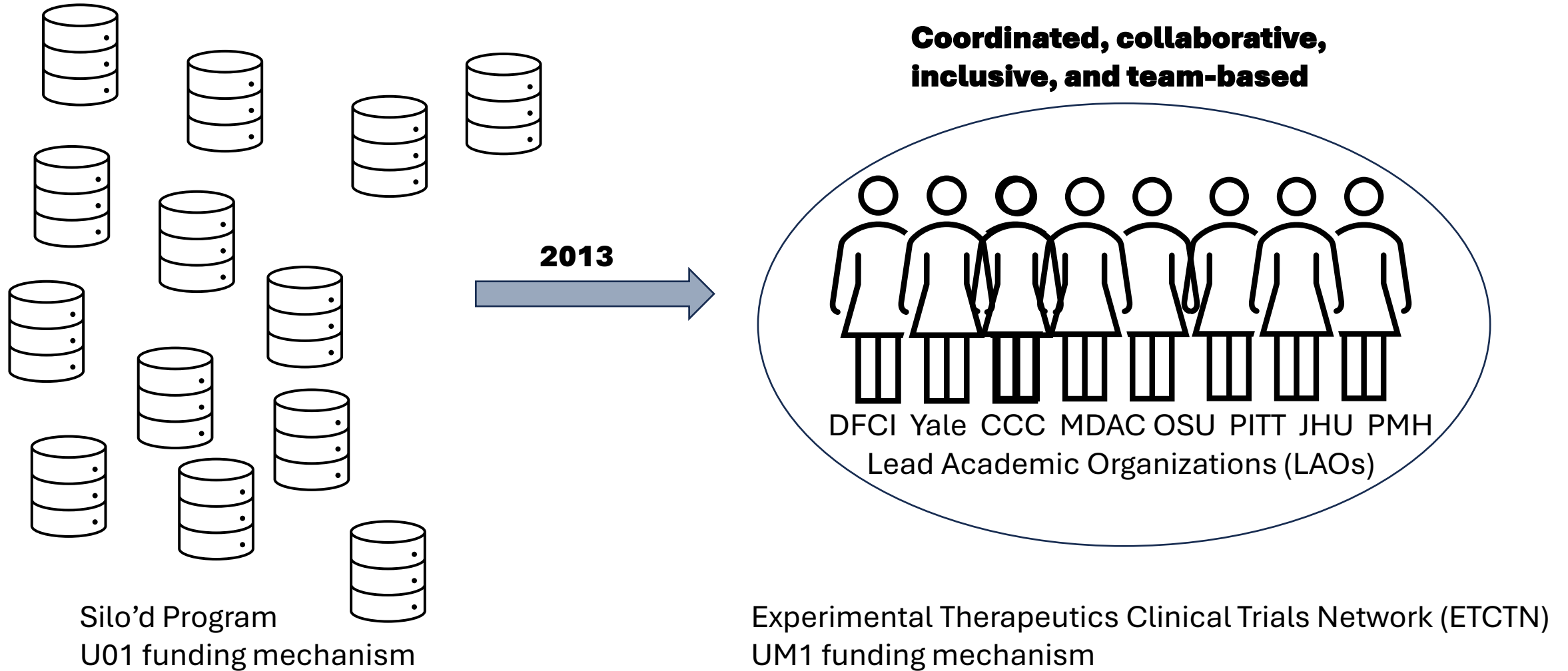
NCI Experimental Therapeutics Clinical Trials Network(ETCTN)

**Presenter, Percy Ivy, MD
Program Director
Investigational Drug Branch
Cancer Therapy Evaluation Program**

**Steve Reeves, PhD
Program Director
CCCT**

November 6, 2024

ETCTN Formation 2013-2024



Transformation to ETCTN

- Transforming the NCI Experimental Therapeutics Development (ETD) Program into the ETCTN **required a complete redesign of NCI's clinical research program**
- Release of the Funding Opportunity Announcement (FOA) (March 1, 2014).
 - Strengthen **GCP standards** further in the clinical trial operations in the ETCTN
 - Develop and implement a **new, centralized infrastructure**
 - Incorporate **team science** into the drug development process
 - Develop a **collaborative** process involving the **extramural community**
 - Add **scientific rigor to biomarker incorporation into clinical trials**; biomarker assay review process (BRC) was developed and implemented

ETCTN Program Organizational Structure

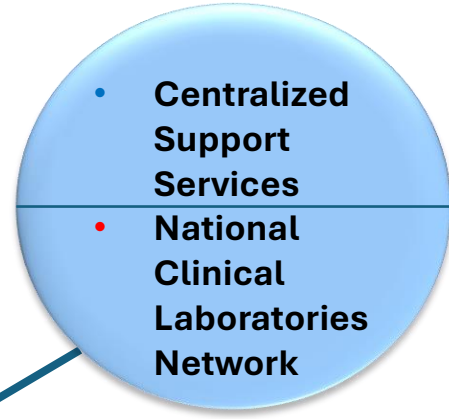
2 RFAs

- Up to 8 Lead Academic Organizations (LAOs in UM1)
- PK/PD Reference Labs (U24)

ETCTN Tumor Bank (EET)
 Funded under a separate U24 Grant by DCTD Cancer Diagnosis Program (CDP)

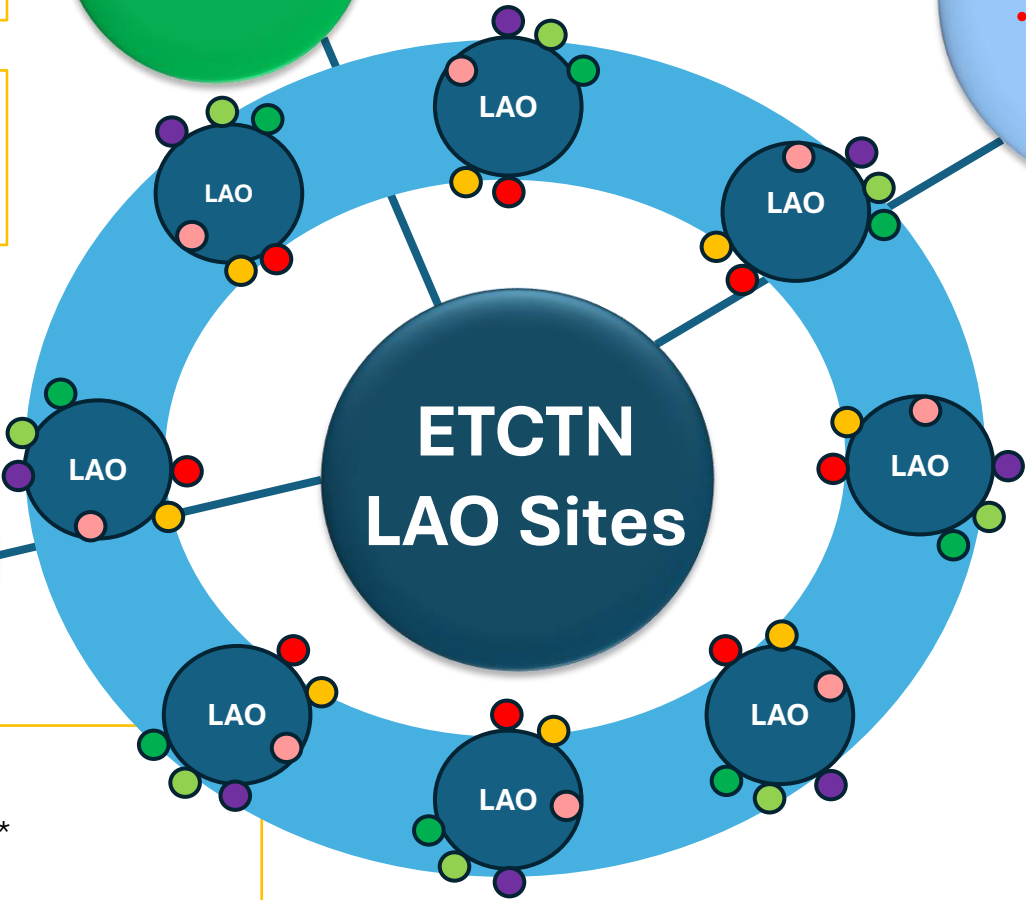
Specialized ETCTN Teams:

- Disease specific investigators *
- IR/ClinPath WG *
- CrDL investigators *



National Clinical Laboratory Network (NCLN)

- Molecular Characterization (MoCha)(WES, RNAseq, ctDNA)
- PADIS (Assays-m IHC, Luminex)
- CIMACs
- Others



Legend:

- Lead Academic Organizations (LAOs)
- LAO Consortium Membership (AO)
- PK/PD Reference Laboratory
- Support Services/Statistical
 - Design, monitoring, analysis
 - Safety monitoring/DSMB
- Centralized support services
- National Clinical Laboratory Network
- ETCTN Tumor Bank (EET)

ETCTN Timeline

2013 - 2015

- Central Support Services
- CrDL
- Early Career Investigators (ECIs)
- Drug Development Project Teams
- ETCTN Monthly Disease Diagrams
- EET Biobank
- Investigational Drug Steering Committee

(Start 2005, Integrated PTs 2014)

2020

- Disease-Focused Clinical Investigators
- ECIs
- U24 PK/Ref Labs
- CATCH-UP

2026

- ECIs
- E-FCIT

2019

- Interventional Radiology WG Alda Tam, MDACC
- NCLN

Project Periods

2014-2020

2020-2026

2026-2032

2014
UM1 award

2020
UM1 award

UM1 award - PND

2017
CIMACs
PDXNet

2018
Drug
Resistance &
Sensitivity
Network



2023
ARTNet – Acquired
Resistance
To Therapy Network

2023: PDXNet



Jan 2020

May 2023



COVID-19 Pandemic



Challenge: Accrual & Network Connectivity

Goals for ETCTN – Period 1 (2014 – 2020)

Research, development and improvement of cancer treatments

- Advance the **clinical development of NCI-IND agents** with early phase studies
(*Complementary collaboration with pharma partners*)
- Determine **dose, schedule and sequence for NCI-IND agents and combination regimens**
- Perform **disease-specific activity** studies of NCI-IND-agents and combinations (*Prioritize cancers and cancer subsets where industry is not investing*)

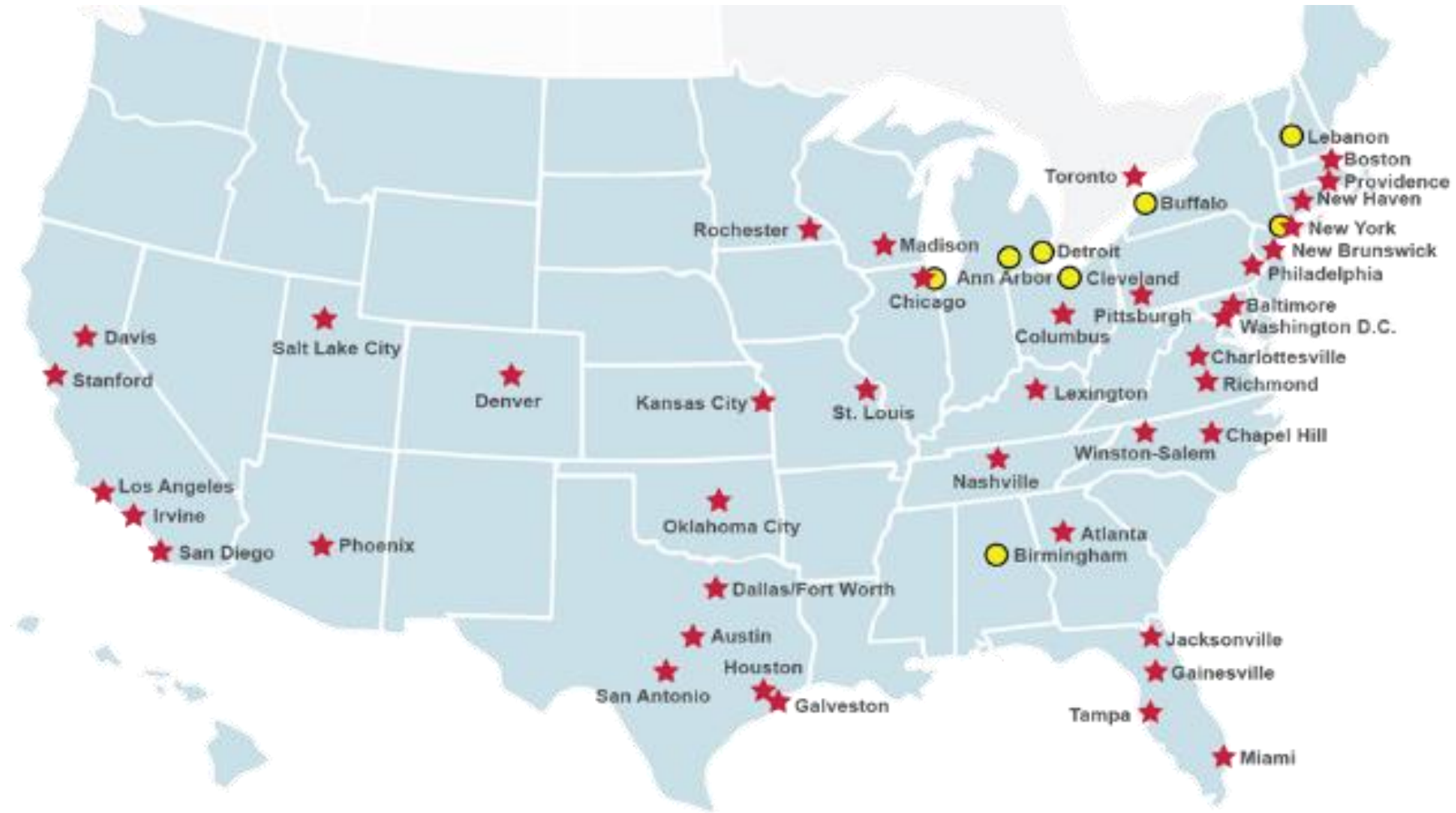
Biomarker and cancer biology-driven studies using patient derived specimens

- Acquire **high quality patient tumor specimens** for correlative studies
- Incorporate **fit-for-purpose PD/biomarker assays** into ETCTN trials

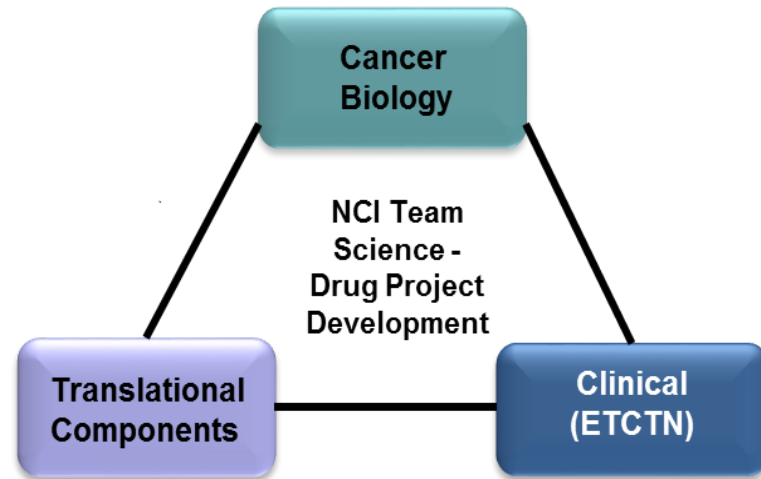
Career enhancement for early career investigators

- Experience **leading clinical trials in the ETCTN**
- Play a significant role on the drug development Project Teams

ETCTN Participating Sites



ETCTN drug development project teams

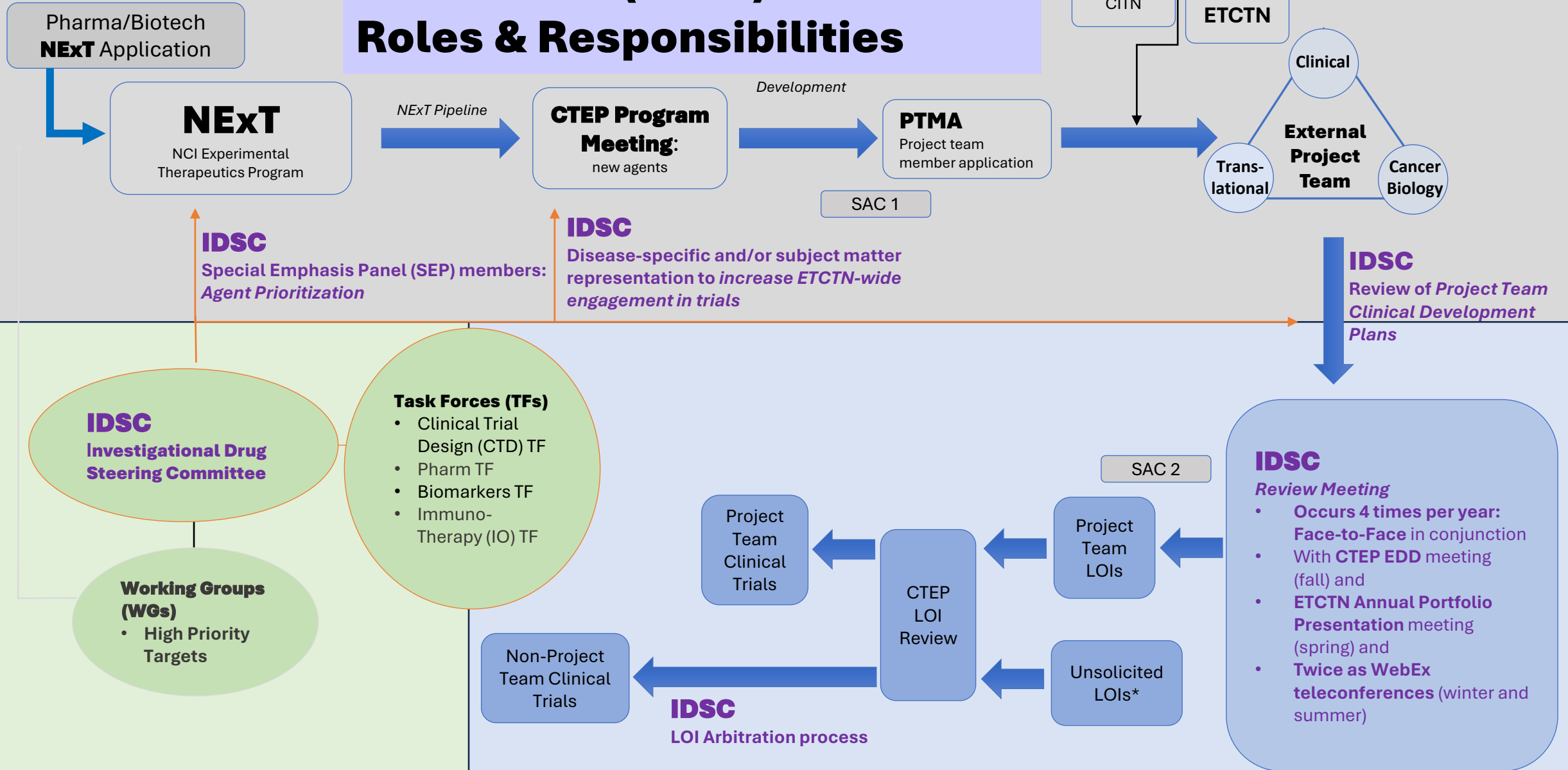


- **Extensive extramural involvement**
- **Reflects heavy emphasis on career development**
- **Drug development and CRADA negotiations occur in parallel**
- **Unsolicited LOIs accepted after Project Team deliberations**

DDP teams (26): (Agents thru NExT)

- AT13387 (onalespib) (HSP90i)
- Osimertinib (AZD9291, T790M EGFRi)
- Rociletinib (CO-1686; EGFR)
- VX970 (ATRI)
- Durvalumab (PD-L1i)
- Atezolizumab (PD-L1i)
- T-VEC (Talimogene laherparepvec, oncolytic virus)
- AMG-232 (mdm2i)
- Anetumab ravtansine (BAY 94-9343, anti-mesothelin)
- Copanlisib (BAY 80-6946, PI3Ki)
- CB839 (glutaminase)
- Rad-223 (radiopharmaceutical)
- Ixazomib (proteasome i)
- Pevonedistat (NEDD8i)
- M3814 (DNA-PKi)
- Rogaratinib (FGFR; preclinical and clinical teams)
- DS8201a (HER2)
- Hu5F9-G4 (anti-CD47)
- GMI-1271 (preclinical; Eselectin)
- Elimusertib (BAY 1895344) (ATR)
- Abemaciclib (CDK4/6i)
- Ipatasertib (ATR)
- Selinexor (XPO1)
- CBX-12 (TOPO1)
- Pidnarulex (G4 Stabilizer)

Investigational Drug Steering Committee (IDSC): Roles & Responsibilities

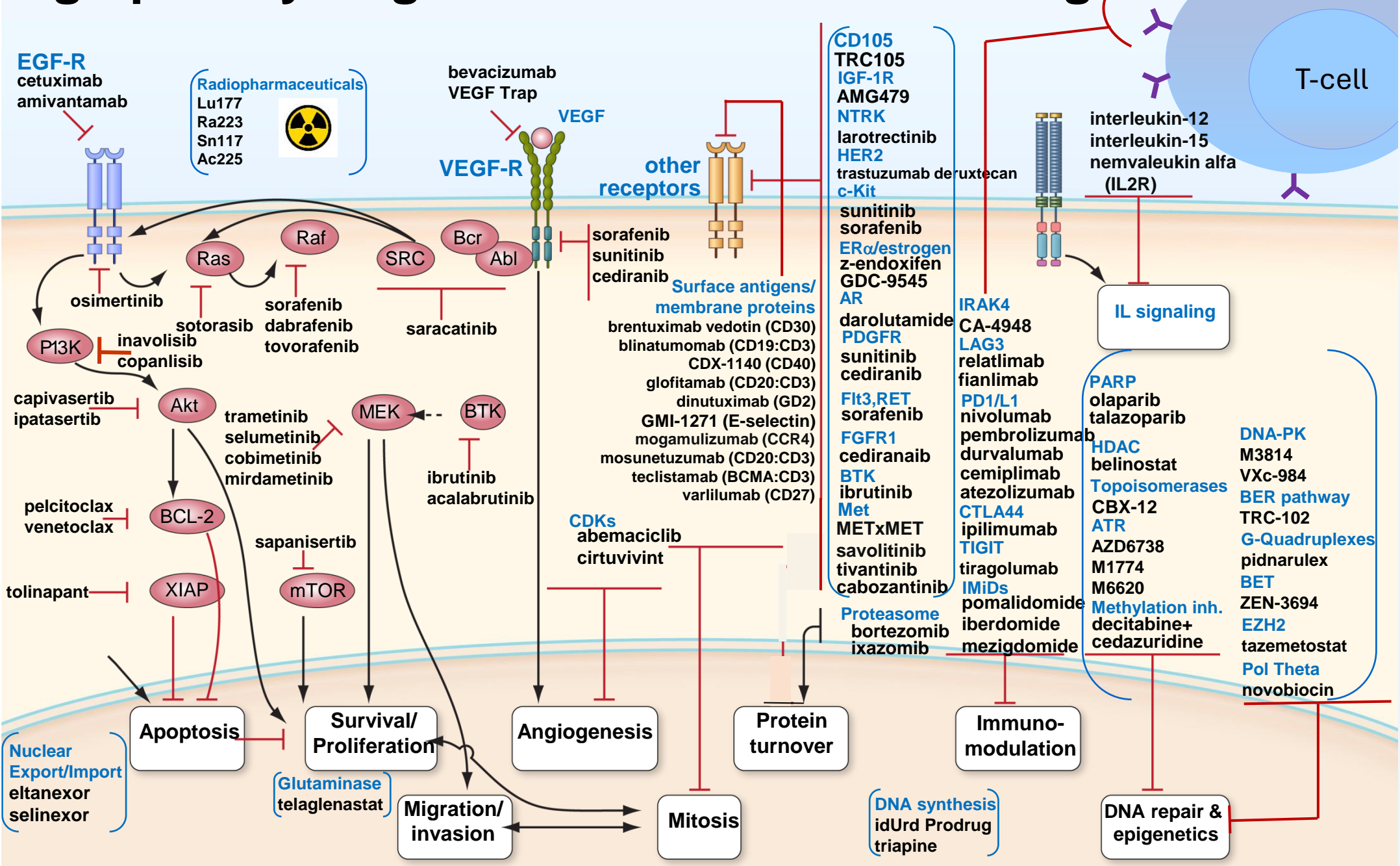


*Proposals outside the initial DDP for this agent(s)

CTEP AGENTS

High priority targets and NCI/DCTD/CTEP agents

- Broad range of agents addressing:
- Signal Transduction
 - Cell cycle
 - DNA Repair
 - Apoptosis Modulation
 - Epigenetic Targets
 - Angiogenesis
 - Immuno-modulation



Disease Focused Clinical Investigators (D-FCI)

- D-FCI webinars are intended to **enhance investigator collaborations** for the **conduct of ETCTN sponsored cancer clinical research studies.**
- Since November 2020; **Webinars held every 3 – 4 months**
- **Disease focused groups (11):**
 - Women malignancies
 - Brain
 - Lymphoma/Myeloma
 - Leukemia
 - GU
 - GI
 - Sarcoma
 - Skin and other melanoma
 - Thoracic
 - Head and Neck
 - Solid tumor/Phase I
- **Pairing mentors and early career investigators** to chair the disease focused group webinars

Goals for the current Project Period 2 (2020-2026)

1. Compete more effectively for patients

- Encourage multiple PI applications
- At least one PI should be a Phase 1 investigator
- Identified key investigators responsible for **disease-specific** accrual; 4 for LAO and 2 for AO
- Partial salary support for each team member
- Performance criteria outlined in Terms of Award

2. Improve quality of biopsy specimens

- **Interventional Radiologist and Research Pathologist** for acquisition of high-quality specimens with partial salary support and performance criteria

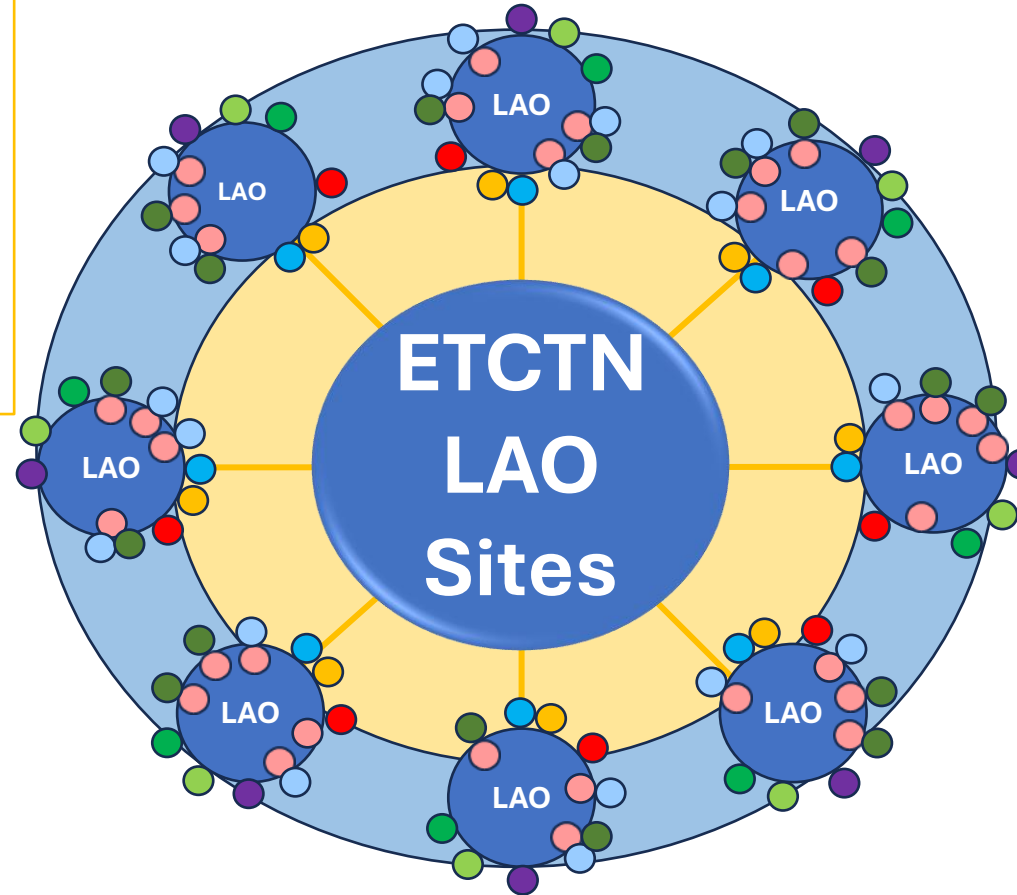
3. Enhance use of validated biomarker assays

- **Use of NCI resources: National Clinical Laboratory Network (MoCha, PADIS, CIMACs)** and Biorepository and accessioning center
- Scale back laboratory developed assays
- Develop PK/PD reference laboratories

ETCTN Program Proposed Organizational Structure: Specialized Teams

ETCTN Goals

- Trial design, dose optimization & development- CrDL, LAOs, IRs, DSCIs



Specialized Teams Legend:

- Career Development LOI PIs (CrDL)
- Disease-Specific Clinical Investigators (DSCIs)
- Interventional Radiology WG (Intra-LAO, ETCTN IR Network)-developed standards, SOPs & CRFs
- **Accrual of Underserved/Underrepresented Communities/Patient Populations**
- **Statistical Office/Support Services**
- **Safety monitoring/DSMB**
- Lead Academic Organizations (LAOs)
- LAO Consortium Membership (Affiliated Organizations (AOs))
- PK/PD Reference Laboratory; **pharmacogenomics**
- National Clinical Laboratory Network (NCLN)
- ETCTN Tumor Bank (EET)

CATCH-UP.2020 :

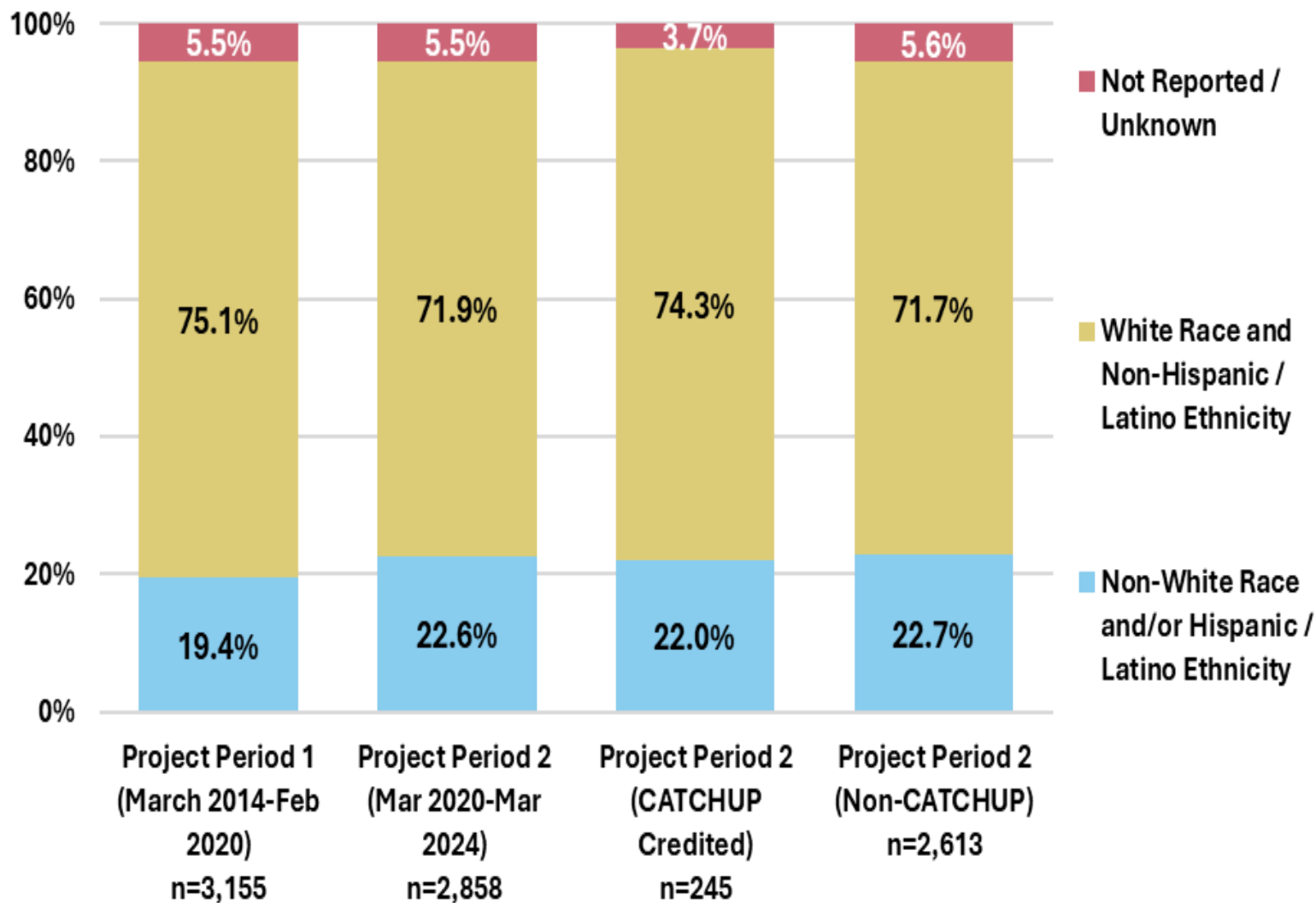
Preliminary work to enhance accrual of underserved/ underrepresented patient populations (UUPPs) to ETCTN clinical trials

- Congressional budget line item-mandated supplement to NCI Cancer Center Support Grants to accrue underserved populations to ETCTN trials
- 24 accruals/site; **at least 50% must be underserved patients** (access, barriers & familiarity with health care delivery system)
- One year of funding; *VERY SHORT TIMELINE*

Centers	Trials activated (in 1-2 months)	Screened patients	Enrolled patients	% underserved / underrepresented
8	111	571	373	51%

- **Best practices established:** *1) motivated investigators, 2) work with Community Outreach Offices, 3) patient navigators/ community immersion, 4) telemedicine & 5) genomic data screening.*

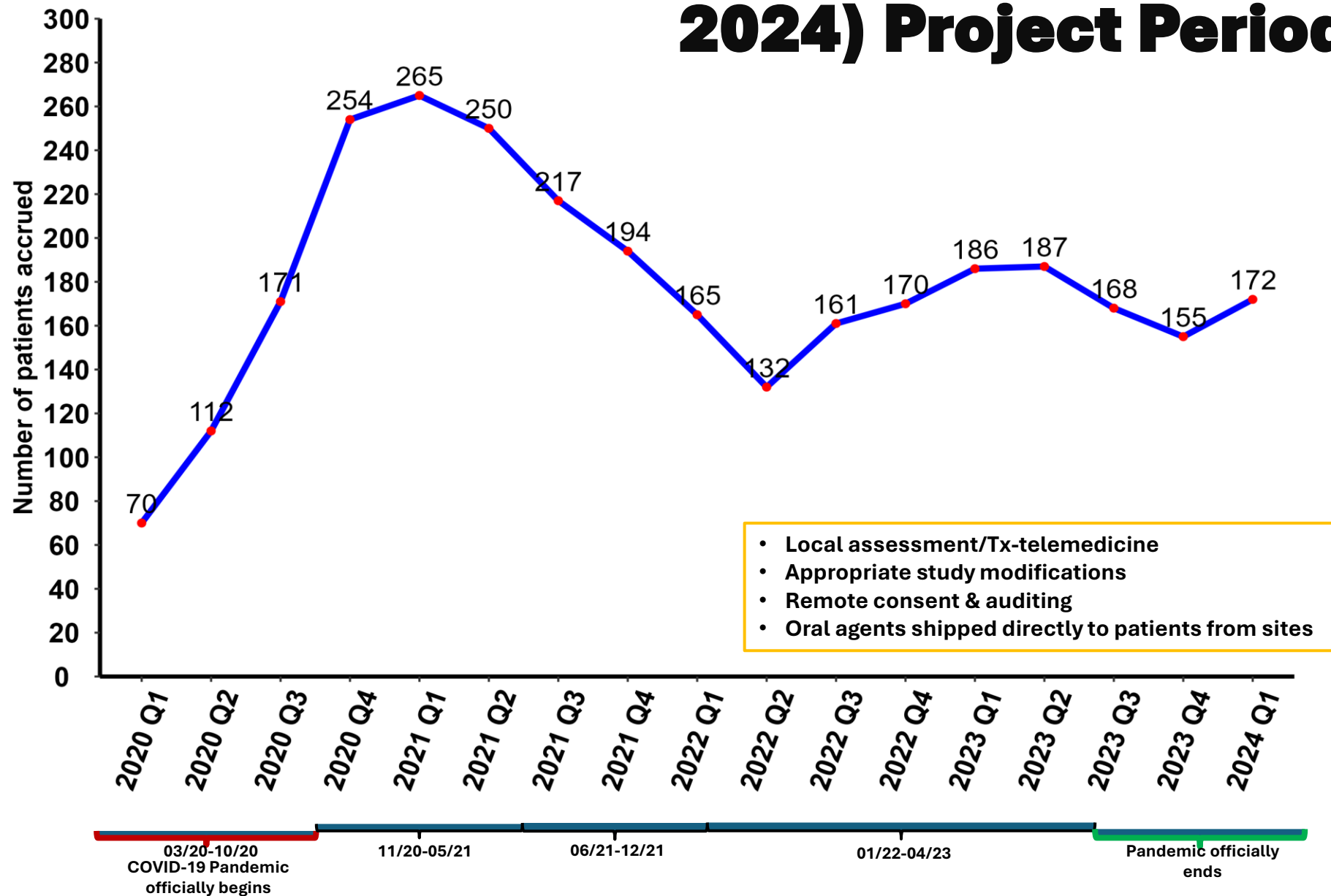
ETCTN accrual by race and ethnicity- current Inclusion /Enrollment



Equity-Focused Clinical Investigator Teams

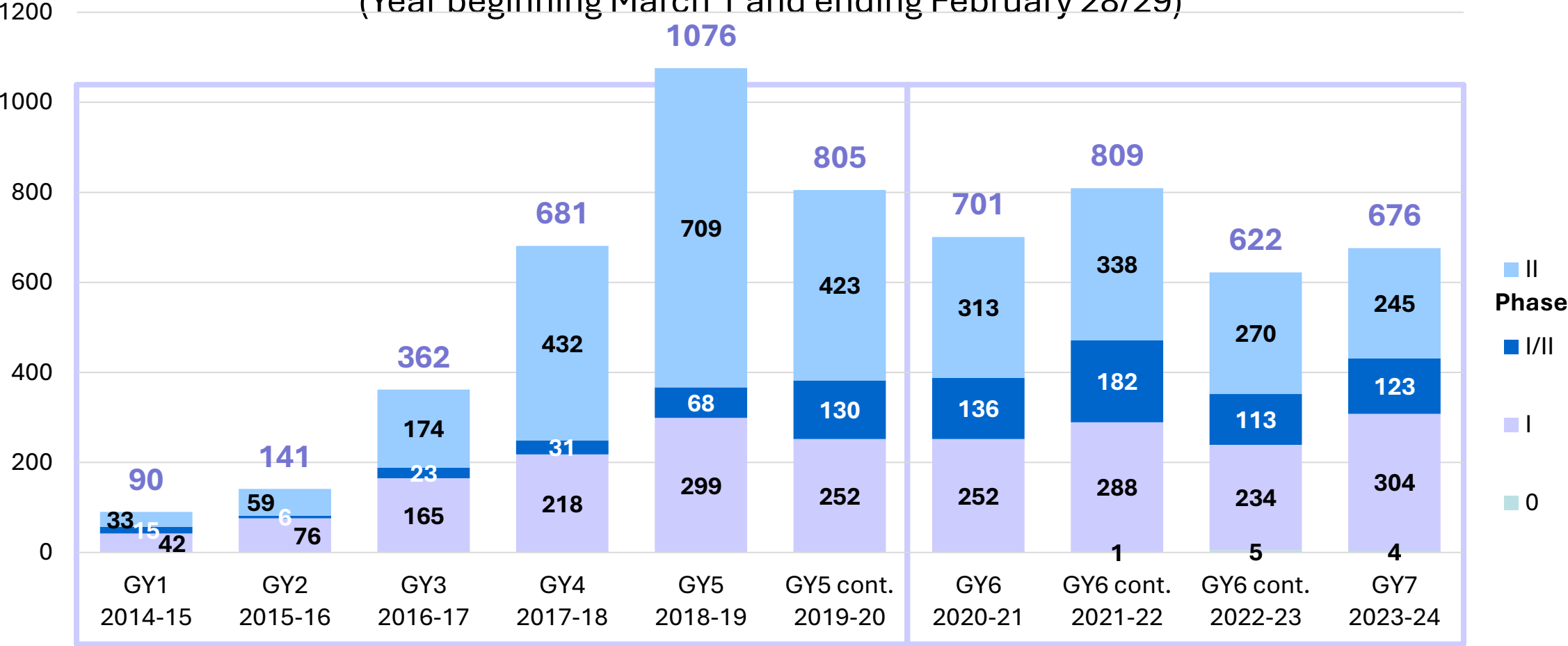
- Building on CATCH-UP success and **using best practices** and lessons learned
- ETCTN UM1 supplements:
 - **Absorb highest performing CATCH-UP centers into LAOs**
 - Yale- U. Kansas
 - JHMI- Wake Forest
 - Princess Margaret: U Miami
 - UPMC: UC Irvine
 - Enable these sites to **develop additional teams** under CATCH-UP “parent”
- Establish **E-FCIs in LAOs** which did not absorb CATCH-UP sites
 - DFCI

ETCTN Interventional Accrual (Q1 2020 – Q1 2024) Project Period 2



ETCTN Intervention Accrual by Year and Trial Phase

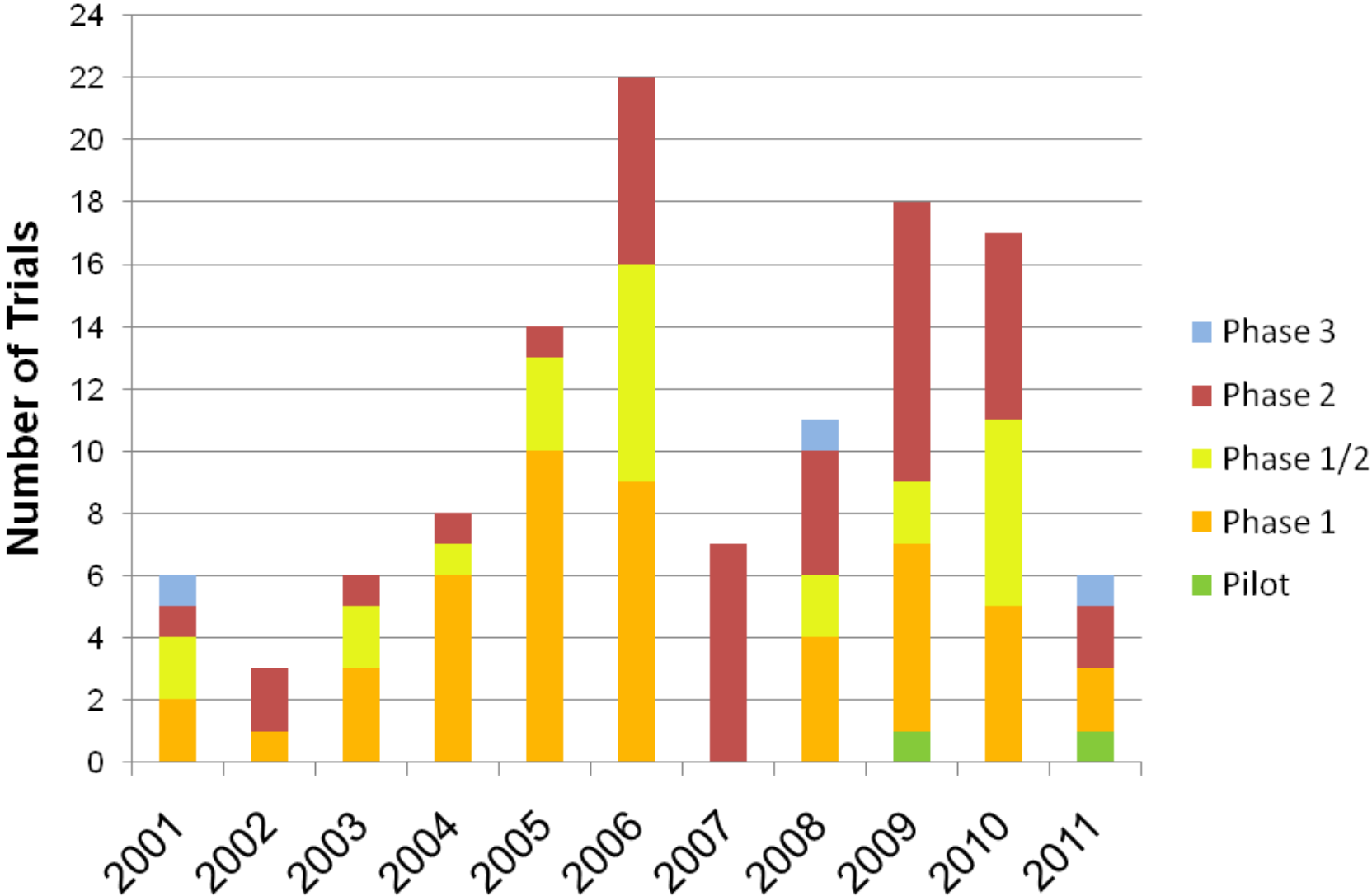
(Year beginning March 1 and ending February 28/29)



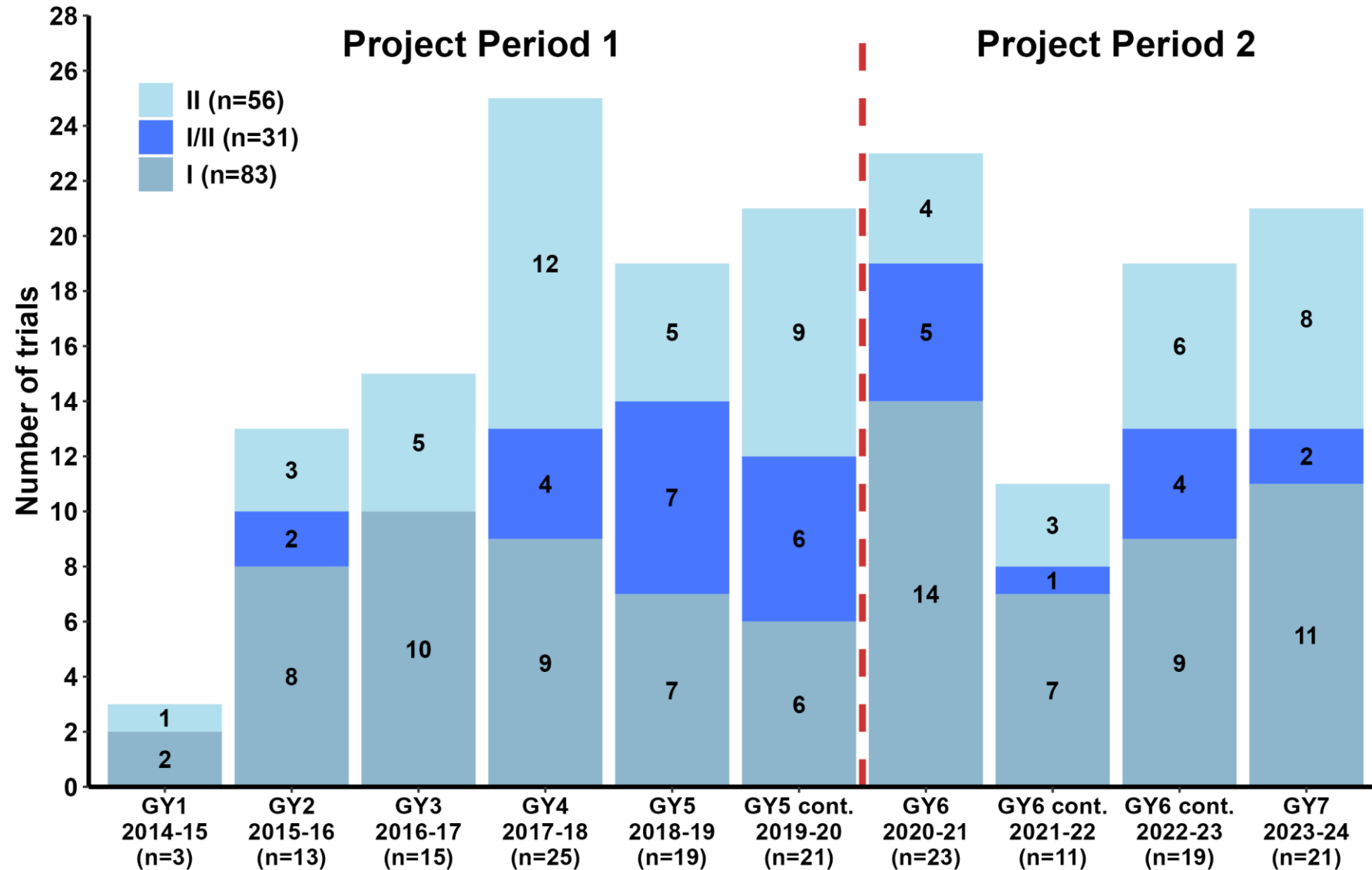
Project Period 1

Project Period 2

Investigational Agent Combination Trials (118)



ETCTN Phase 1 and 1 / 2 novel combination studies (170)

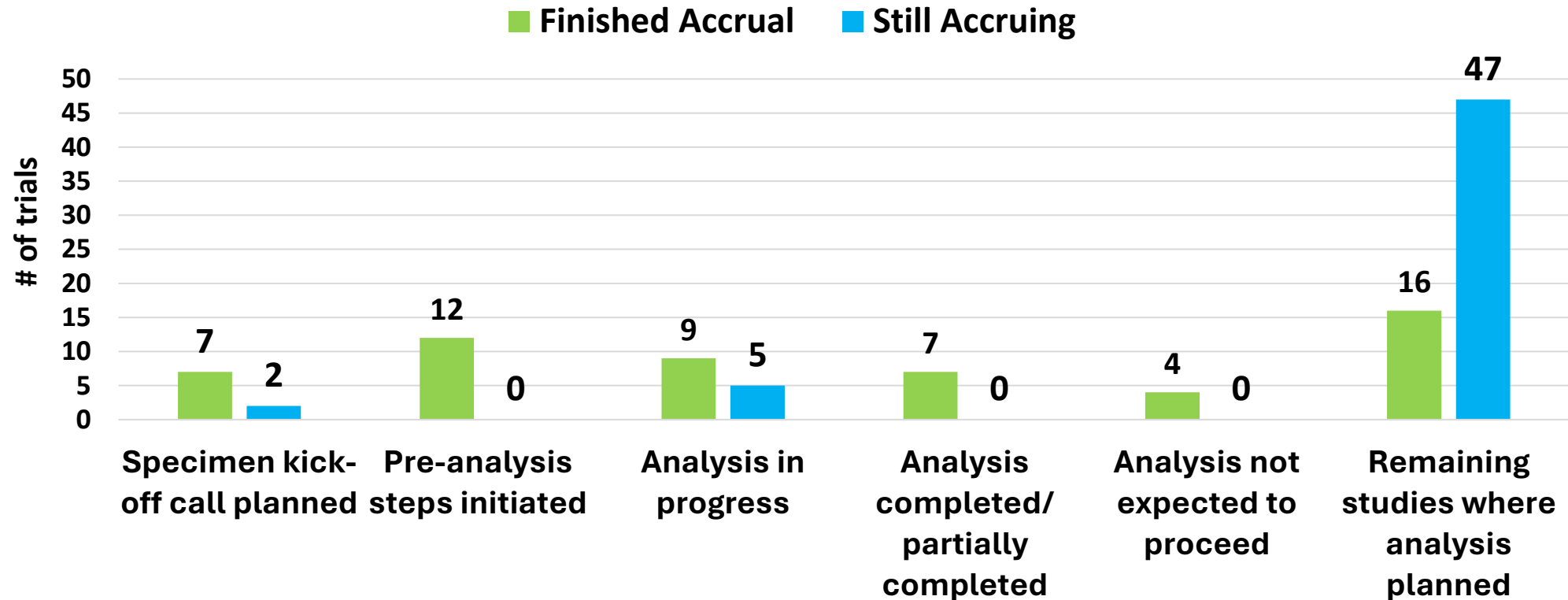


ETCTN Accomplishments

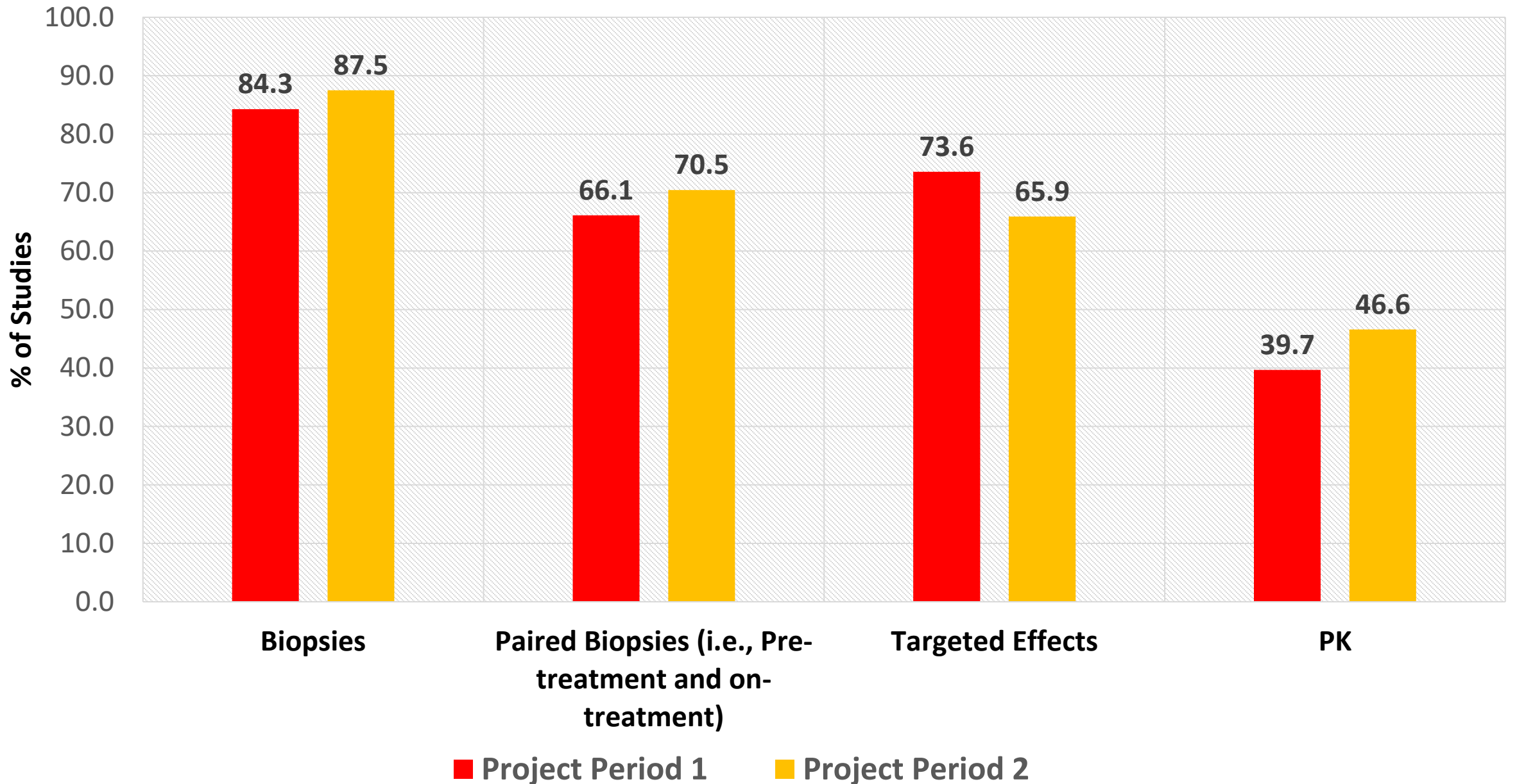
- **New agent development**
 - Evaluate new molecular entity
 - First in human, combinations and studies demonstrating activity
 - Immuno-oncology agents
- **ECIs increased from 27 (26% of all protocols) to 40 (45 % of all protocols)**
- **Biomarkers and biopsies**
 - **Codified** the use of biomarker assays- technically & clinically validated; fit-for-purpose; NCLN
 - Uniformly **categorized** the types of biomarkers used in early clinical trials- integral, integrated, exploratory
 - **Determined** when optional vs. mandatory biopsies are performed based on biomarker type
 - **General metrics improved**

Status of Biomarker Analysis for the 109 ETCTN Trials Using the EET Biobank

Glimpse of Specimen Analysis Status for ETCTN Trials Using the EET Biobank



Biomarkers and Biopsies in ETCTN Studies (109 trials)



Thank you