Board of Scientific Advisors

NCI Experimental Therapeutics Clinical Trials Network (ETCTN) Project Period 3

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Investigational Drug Branch

Cancer Therapy Evaluation Program

Division of Cancer Treatment and Diagnosis

NIH NATIONAL CANCER INSTITUTE

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ETCTN Timeline

2013 - 2015
- Central Support Services/Infrastructure
- CrDL
- Early Career Investigators (**ECIs**)
- Drug Development **Project Teams**
- **Biomarker Review Committee**
- ETCTN Monthly Disease Diagrams
- EET Biobank
- Investigational Drug Steering Committee (Start 2005, **Integrated PTs** 2014)

2019
- Interventional Radiology WG Alda Tam, MDACC
- NCLN

2020
- Disease-Focused Clinical Investigators
- ECIs
- U24 PK/Ref Labs
- CATCH-UP

2024: E-FCIT

2026
- ECIs
- E-FCIT

Project Periods

2014-2020 | **2020-2026** | **2026-2032**

2014 UM1 award

2017 CIMACs **PDX**Net

2018 Drug Resistance & Sensitivity Network

2020 UM1 award

2023 ARTNet – Acquired Resistance To Therapy Network

2023: PDXNet CIMACs

Blip! 2024

UM1 award - PND

Jan 2020 — **COVID-19 Pandemic** — **May 2023**

Challenge: Accrual & Network Connectivity

What are the challenges or problems ETCTN faces?

- Need to establish the recommended phase 2 doses and schedules of investigational agents; and that they are accurate, safe, tolerable and pharmacodynamically optimal for single agents or combination therapy
- Lagging accrual in biomarker-driven or rare patient populations for early phase trials; how will team science help?
  - Lack of network wide operations offices with a statistical office to further facilitate the design, conduct, monitoring and analysis of clinical trials and coordination with central DSMB **for the ETCTN.**
- Underserved and underrepresented constituencies often do not have access to investigational and cutting-edge therapies

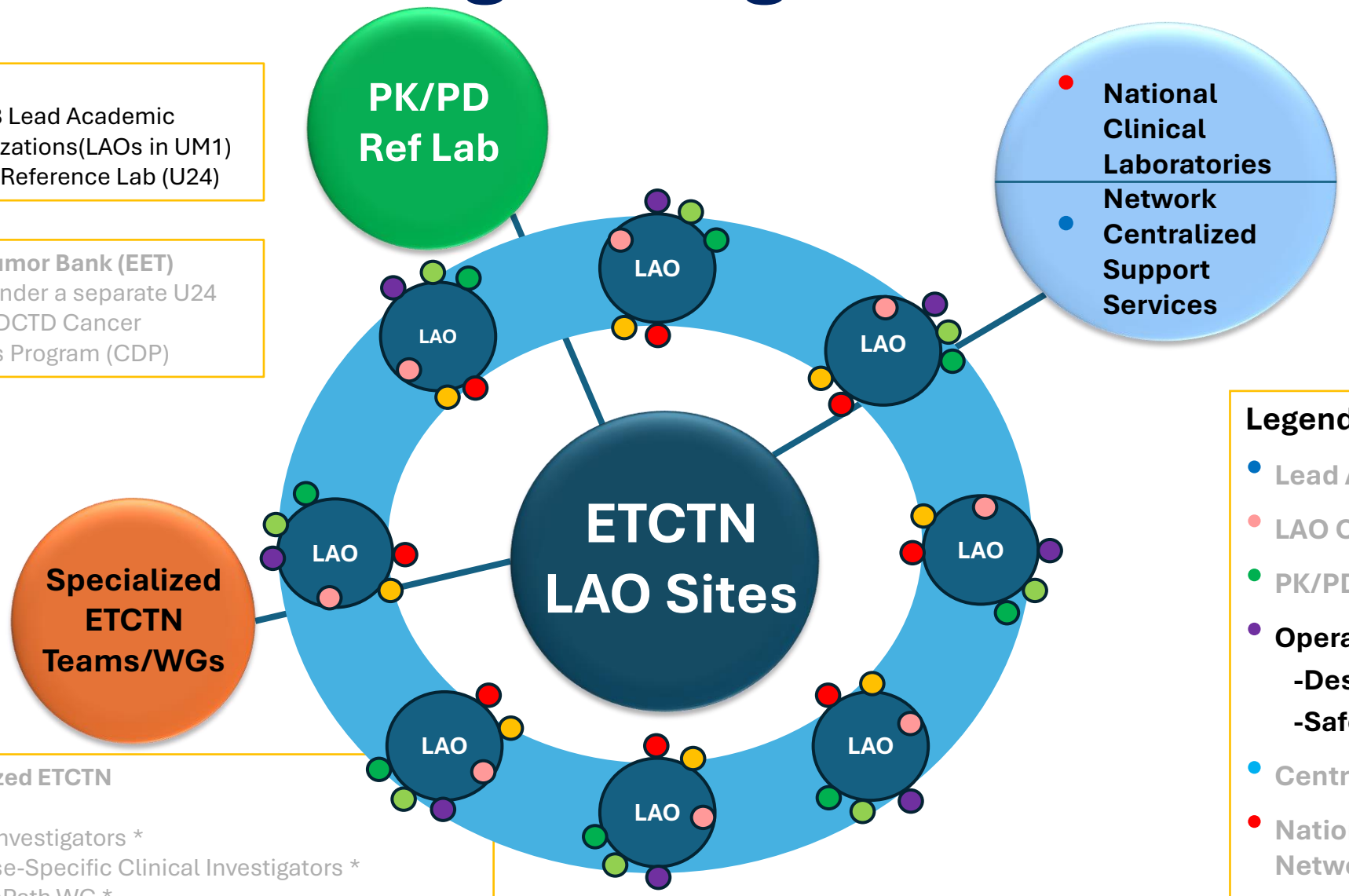
Goals of the Experimental Therapeutics Clinical Trials Network: Project Period 3 (2026-2031)

- Science of clinical trial design, dose optimization and drug development of new cancer treatments
- Expand team science approaches in drug development including operations and statistical support
- Enhance accrual science applied to underserved/ underrepresented communities in clinical trials

ETCTN Program Organizational Structure

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

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



National Clinical Laboratory Network (NCLN)
-Molecular Characterization (MoCha)(WES, RNAseq, ctDNA)
-PADIS (Assays-m IHC, Luminex)
-CIMACs
-Others

Specialized ETCTN Teams:
- CrDL investigators *
- Disease-Specific Clinical Investigators *
- IR/ClinPath WG *
- E-FCIT (Equity-Focused Clinical Investigator Teams

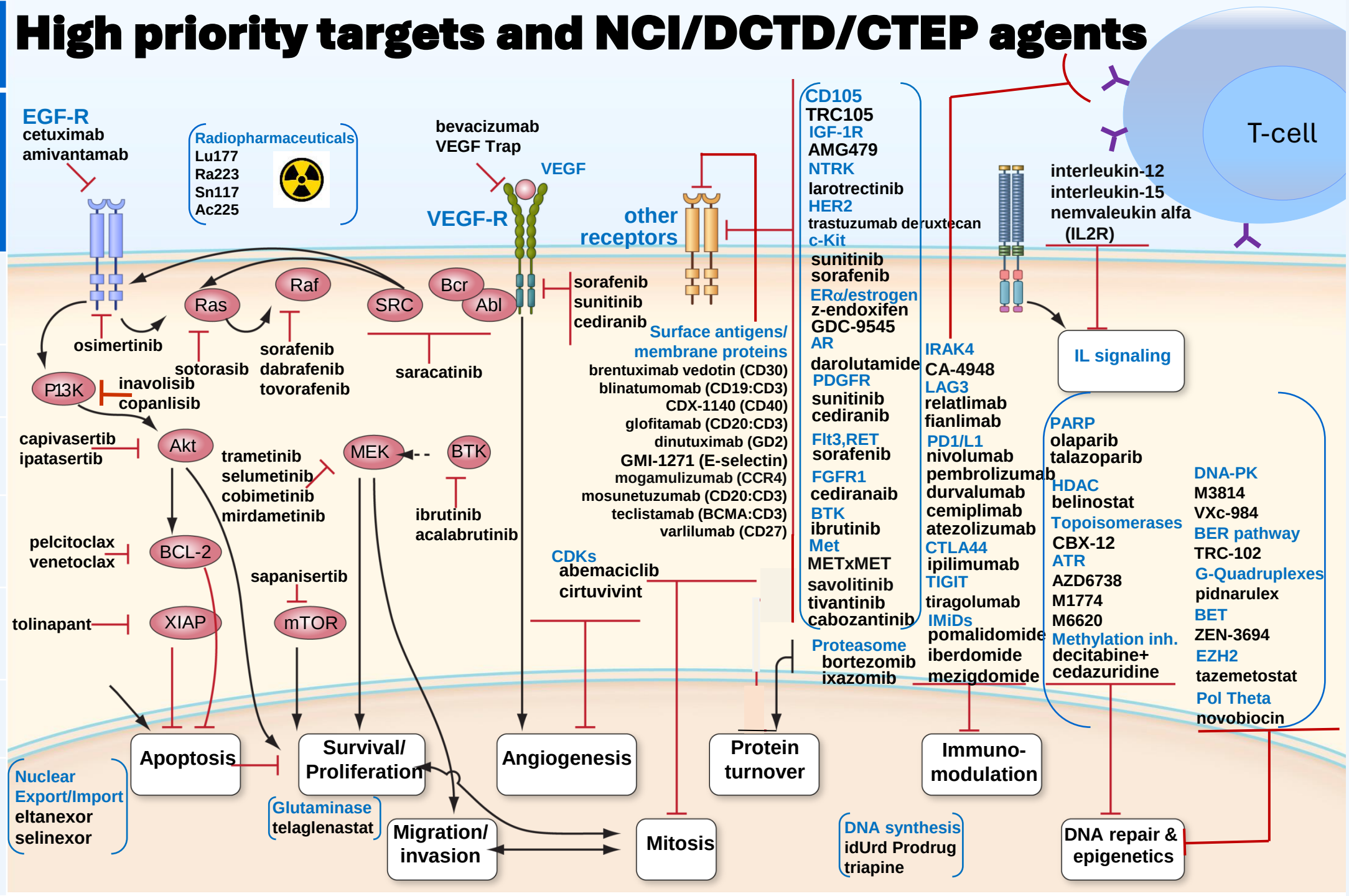
Legend:
- Lead Academic Organizations (LAOs)
- LAO Consortium Membership (AO)
- PK/PD Reference Laboratory
- Operational/Statistical
  - -Design, monitoring, analysis
  - -Safety monitoring/DSMB
- Centralized support services
- National Clinical Laboratory Network
- ETCTN Tumor Bank (EET)

High priority targets and NCI/DCTD/CTEP agents

CTEP AGENTS

Broad range of agents addressing:

- Signal Transduction
- Cell cycle
- DNA Repair
- Apoptosis Modulation
- Epigenetic Targets
- Angiogenesis
- Immuno-modulation



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 ⭐

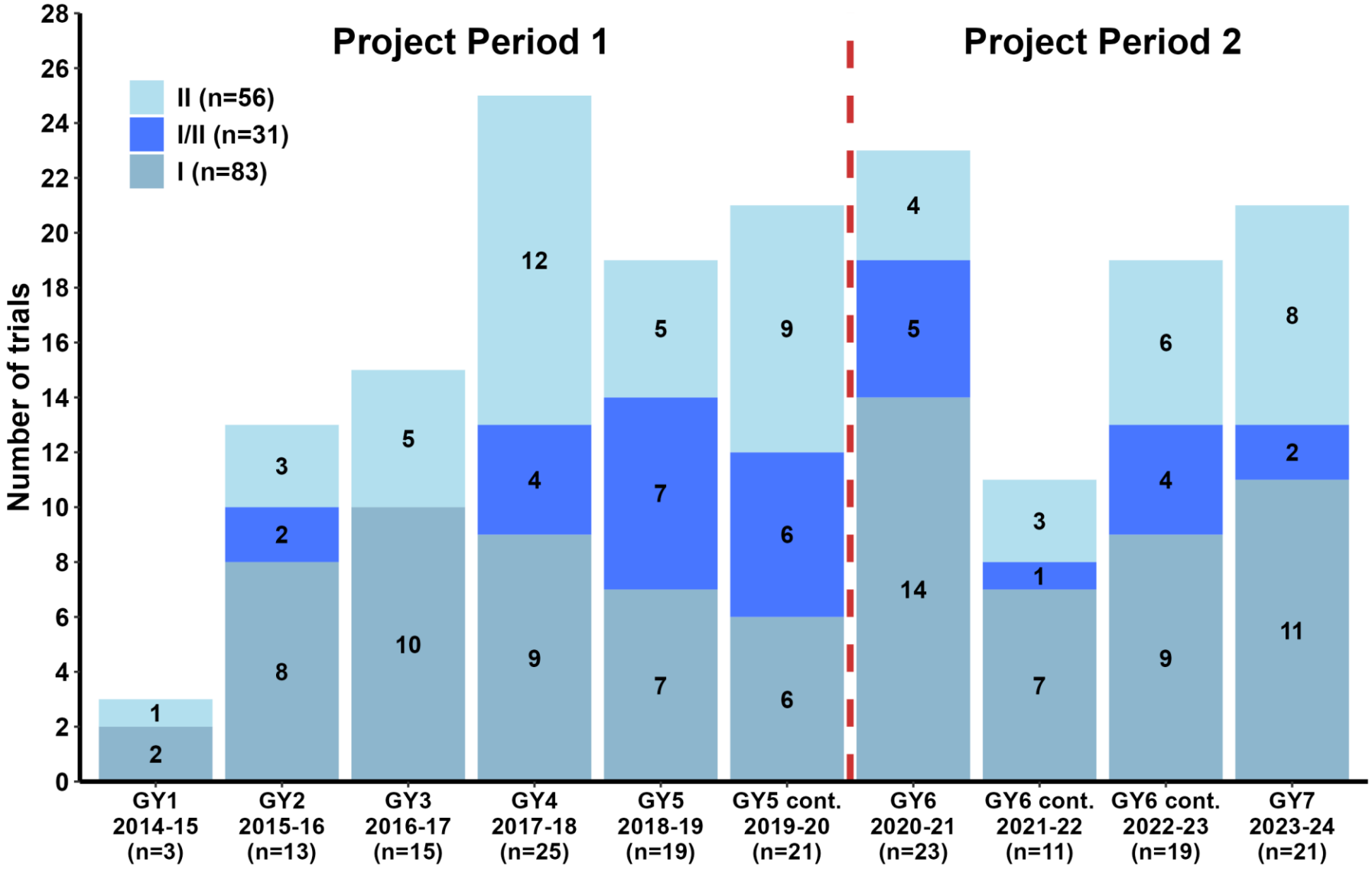
- **Use of NCI resources: National Clinical Laboratory Network (MoCha, PADIS, CIMACs)** and Biorepository and accessioning center
- Scale back laboratory developed assays
- Develop PK/PD reference laboratories

I am going to review three major accomplishments

- Novel phase 1 and 1/2 combination studies
- Establishment and performance criteria for the use of biopsies and biomarkers
- One year budget supplement, CATCH-UP.2020 for patient populations with limited access to cutting edge and investigational therapies

- All remaining accomplishments are provided in the backup slides

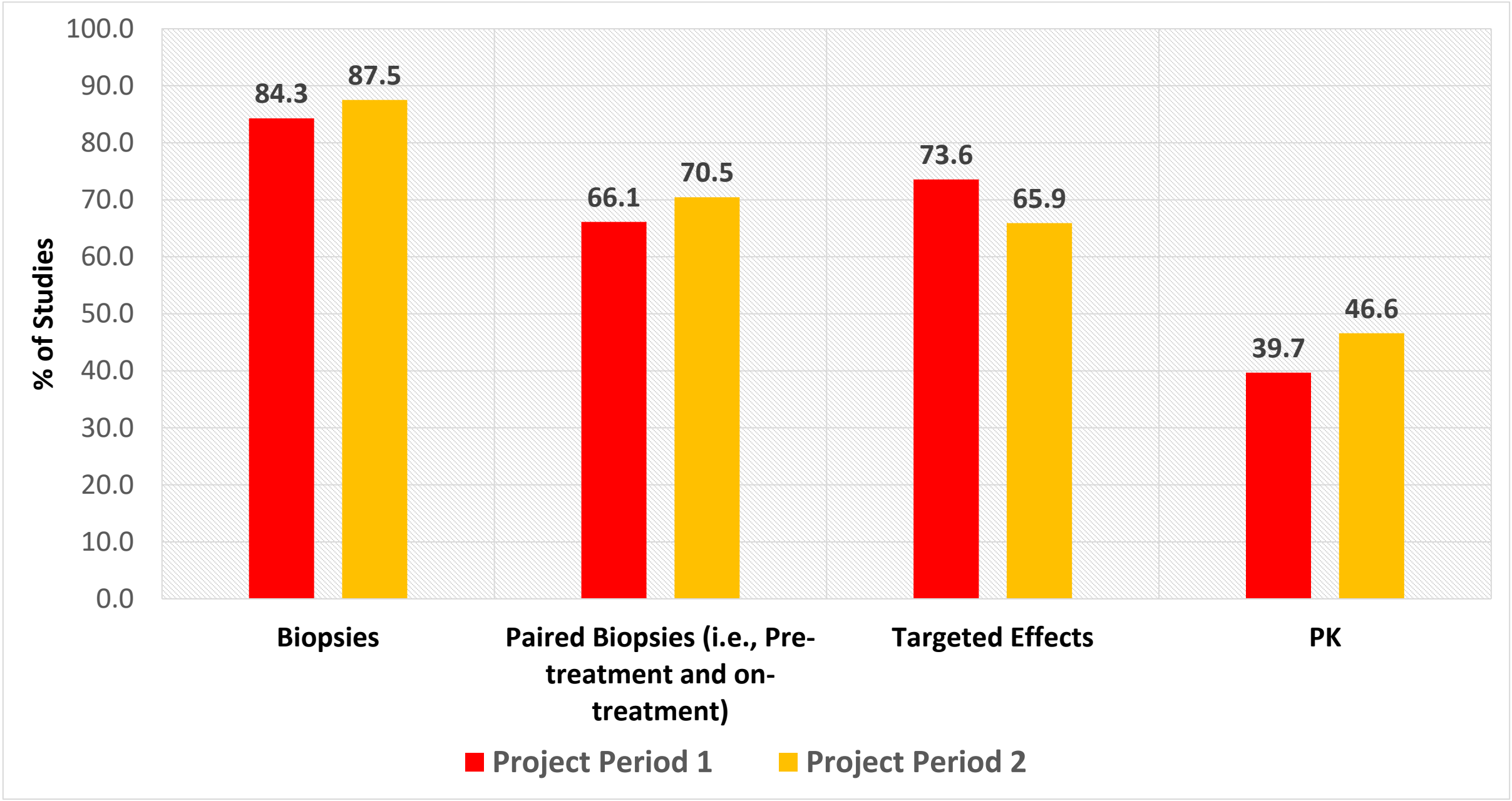
ETCTN Phase 1 and 1 / 2 novel combination studies (170)



ETCTN Accomplishments-Project Period 2

- **New agent development**
  - Evaluate new molecular entity
  - First in human, combinations and studies demonstrating activity
  - Immuno-oncology agents
- **Early Career Investigators 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
  - **Defined** when optional vs. mandatory biopsies are performed based on biomarker type
  - **General metrics improved**

Biomarkers and Biopsies in ETCTN Studies (109 trials)



CATCH-UP.2020 :

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

- Congressional budget line item-mandated supplement in 2020 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.*

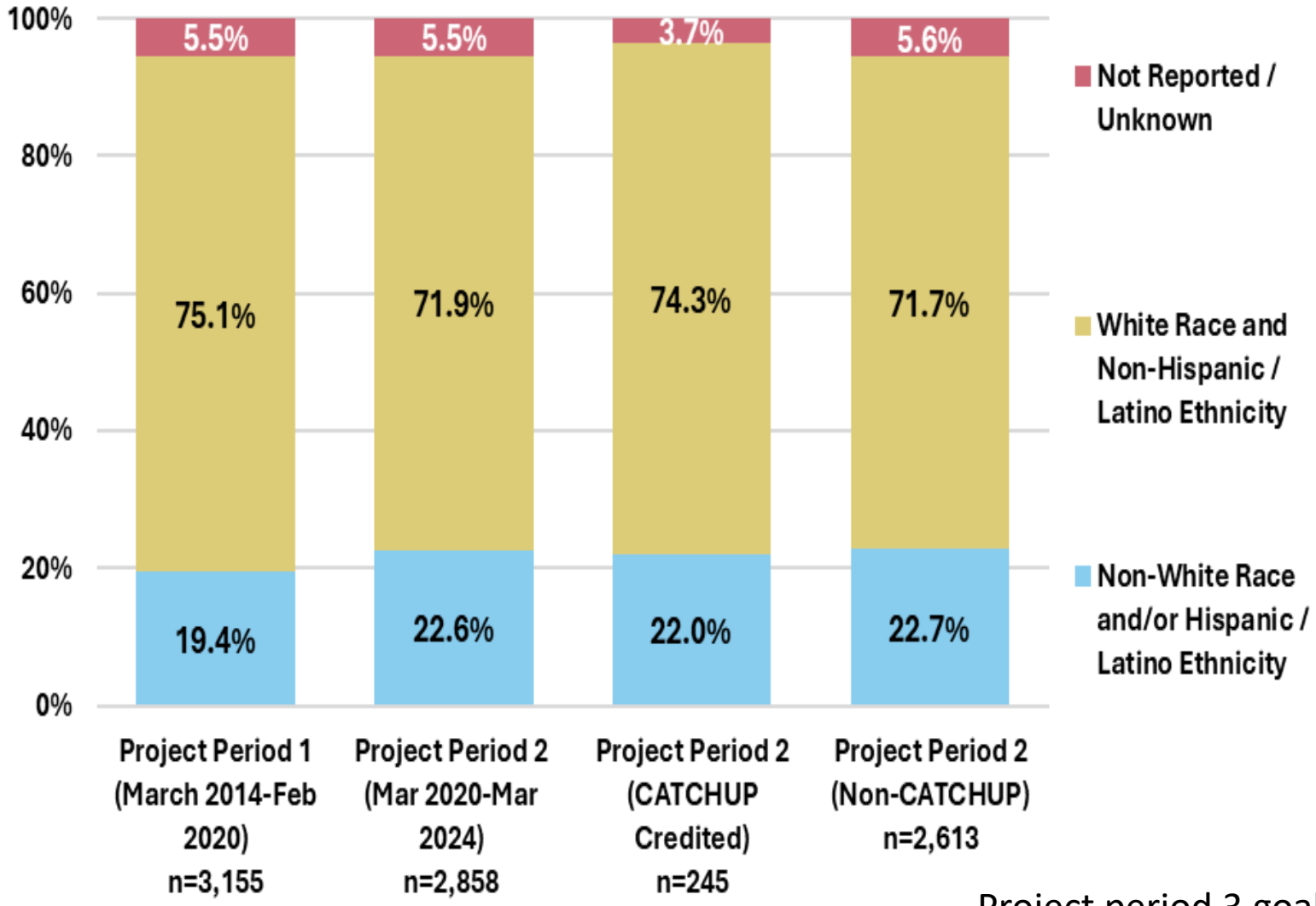
Equity-Focused Clinical Investigator Teams

- 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 accrual by race and ethnicity- current Inclusion /Enrollment



Project period 3 goal is to increase to 25-30%

ETCTN External Program Review Overall Assessment

-Melding of innovative, novel therapeutics through NExT with the NCI's broad clinical/translational infrastructure is a winning combination; curating the NCI CRADA-based portfolio is a critical success factor

- Reviewers **responded positively to all questions**, thought the program **achieved its goals,** and provided additional **input for future endeavors.**
- Vibrant and healthy ETCTN program with a **rich historical legacy training generations of oncology drug developers**

-Program needs to continue and evolve for the **benefit of future generations**

-Thoughtful , **high impact clinical and translational trials** advancing the field of drug development

Recommendations/Concerns from External ETCTN Review

Clinical trial design

- **Conduct trials focused on dose optimization and tolerability**
- **Biomarker enriched clinical trials** that are hypothesis driven, labor and resource intensive (70-80% obtained paired biopsies, analysis ongoing)
- **Use of adaptive trial designs ((i. e., non-3+3) phase 1 dose escalation designs, possible basket studies** and use of PROs**)**
- Extensive resources invested by NCI and organizational structure **leveraged for impactful clinical trials will require increased funding for ongoing high performance**
- Enrollment of **underserved/underrepresented patient populations**
- **Accrual productivity, mentorship** for enthusiastic/motivated **early career investigators (ECIs)**
- Succession planning for ECIs for all UM1 grants

Proposed Budget for ETCTN Project Period (FY2026-2031)

ETCTN Program Component	Clinical Trials	Awards	Years	Proposed Annual Budget Total Cost (in millions)	% Change from Prior Project Period
ETCTN Lead Academic Organizations (LAOs) –with Ops & Stats **UM1:** Up to 8 awards	**YES**	**≤8**	**6**	**$15.2**	**Increase of 10%**
ETCTN PK/PD Core Research Laboratories – U24: 1 award	**NO**	**1**	**6**	**$1.068**	**No change**
ETCTN Administrative Supplements	**YES**	**~**	**6**	**$0.60**	**Reduction of 60%**
Contract Funding: Centralized support services from multiple NCI contracts	**NO**	**Multiple**	**Multi-year**	**$4.24**	**Increase of 112%**
Overall ETCTN Program: Flat budget, incr. from ~$18.4M currently				**$21.108**	**Increase of 15%**

Justification:

-**UM1s/LAOs: Inflationary increases, reimbursement for biopsies, increased infrastructure/FTEs,** workload and **reporting requirements** to CT.gov; **Outreach to UUPPs, accessibility/ availability; support for 2+ senior co-PIs (UUPPs, Stats, Ops); NCI 11% incr. salary cap; accrual up to 700-800 patients annually.**

-**Contracts:** ETCTN receives regulatory, safety & monitoring support for drug development, contracting **costs rise at ~4%/yr. inflation**(7-8% during the pandemic) ,maintain **level of support**; and **new services (**assisted protocol writing, early phase central IRB, **Gov-sponsored DSMB**, **data management**, auditing, RAVE protocol build, **IROC budgets**, etc.) CTSU may be able to support **infrastructure and Ops & Coordination Center + Statistical Office need,** coordination UM1 LAO and DSMB is a **new task**

-**Overall**, A **flat budget** is requested for the 6 years of the funding cycle (2026-2031). **No COLA**. a **15% increase in annual funding** compared to the previous cycle is justified & requested.

Thank You

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