National Cancer Institute

NCI Experimental Therapeutics Clinical Trials Network(ETCTN)

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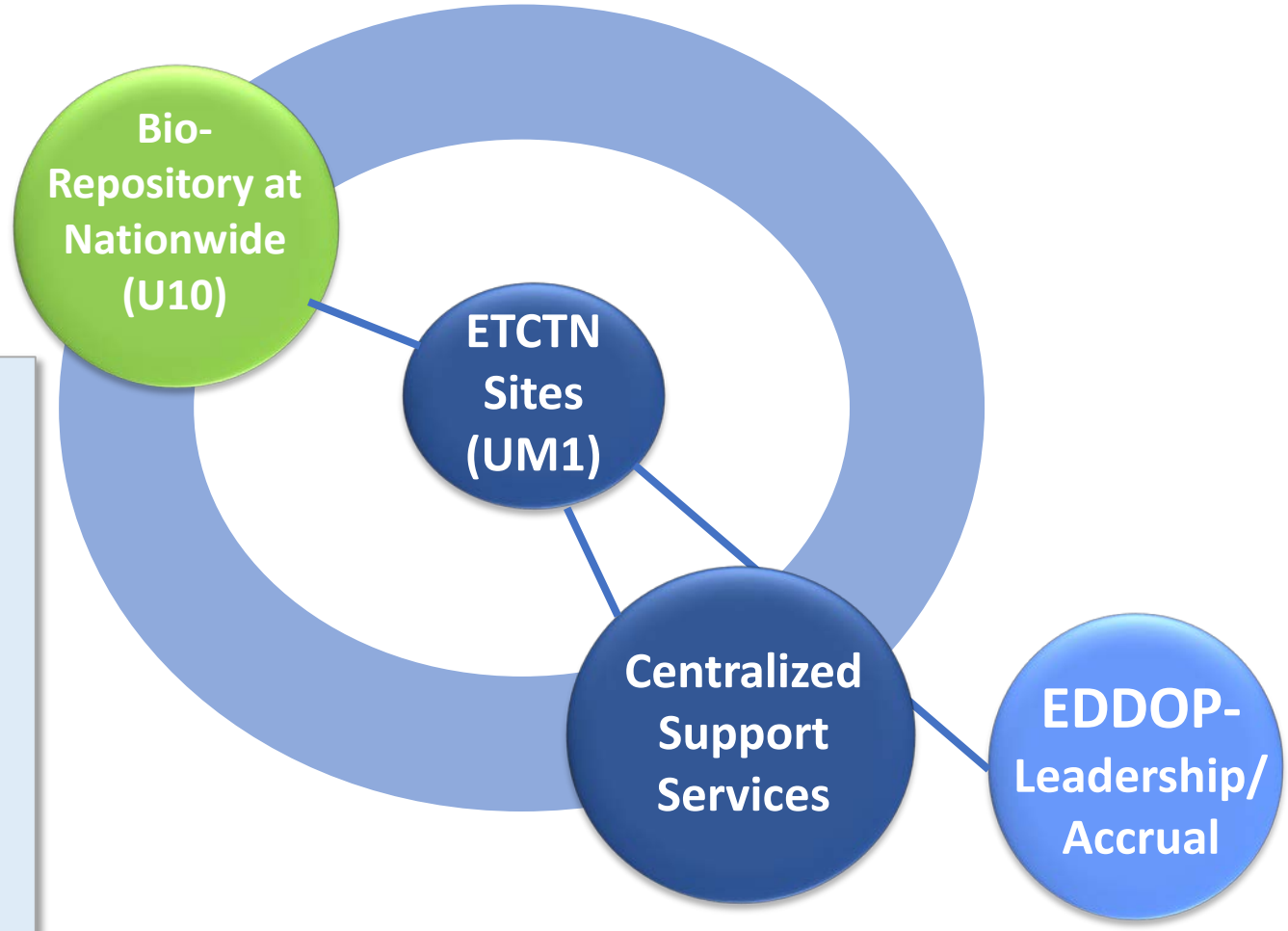
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Experimental Therapeutics Clinical Trials Network (ETCTN)

≈ 41 enrolling North American sites



UM1 network first renewal RFA/FOA

- **12** Lead Academic Organization (LAO) sites (includes NCI-Clinical Center)
- **29** Affiliated Organizations (AO) sites
- **2120** patients enrolled through Q4 2017

Clinical trials

- Activated studies: **82**
- Ongoing studies: **132**
- Closed studies: **37**
- Completed/Admin Completed studies:**11**

Goals and Objectives of Experimental Therapeutics Clinical Trials Network

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

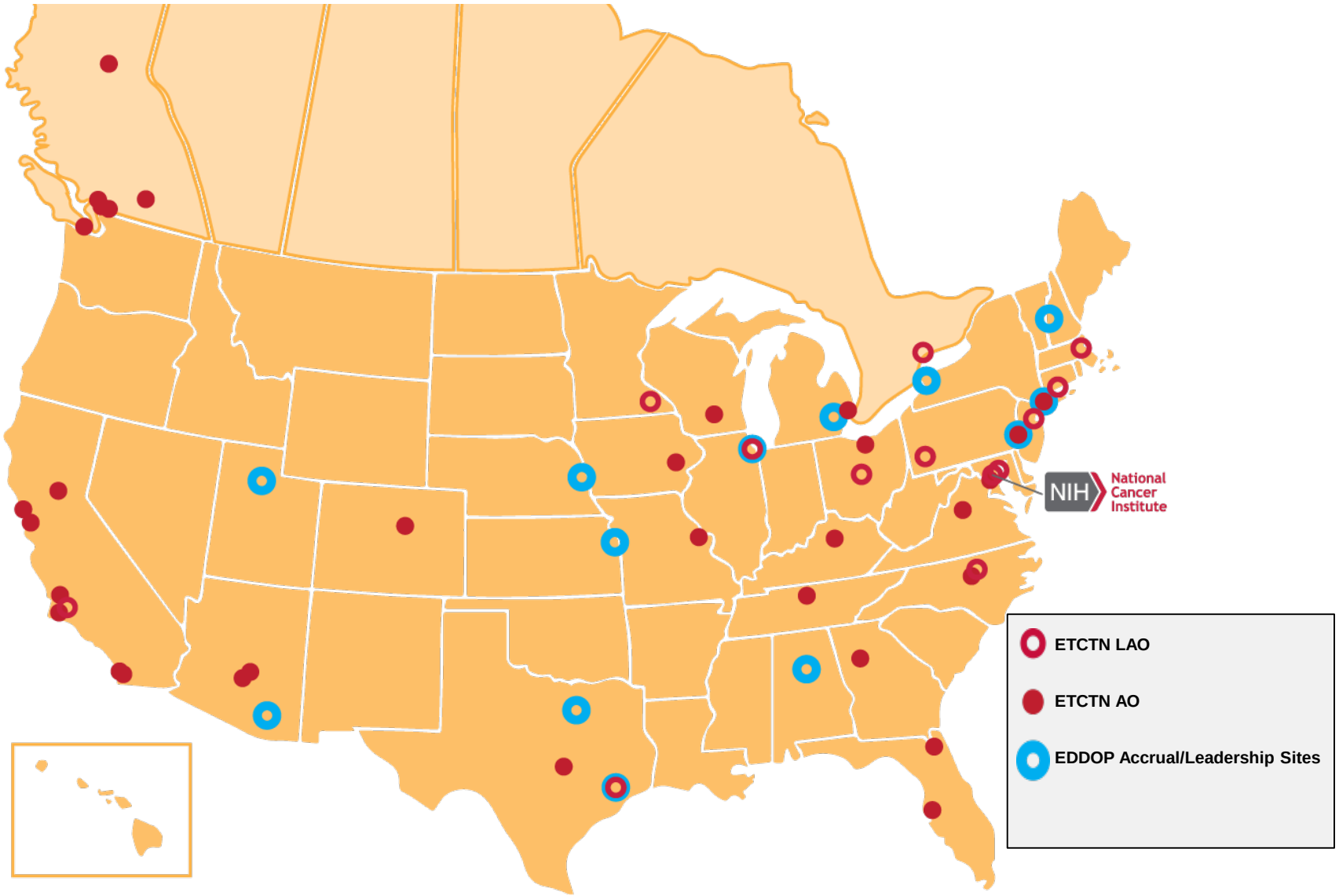
ETCTN – Transformation to a Network Structure

- **Collaborative approach to clinical trial development and implementation**
  - Moved from mass solicitations to **extramural project teams** early in clinical development planning
  - Involve **disease-specific clinical** expertise from all sites
  - Enhance **study participation** across the network

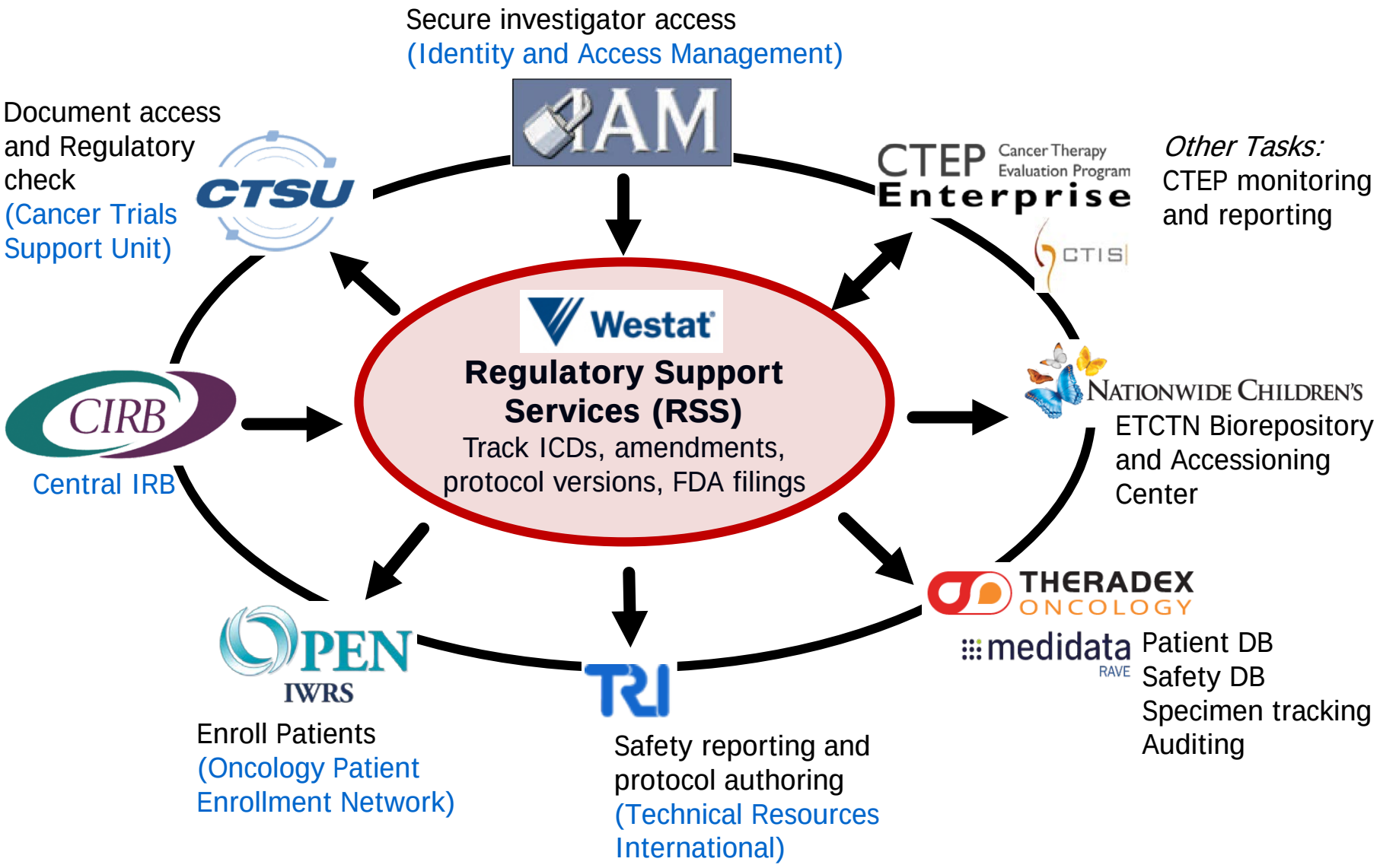
- **Assuring Reproducible Translational Science**
  - Transformed the approach to **biomarkers** from laboratory developed tests (**LDTs**) to analytically **validated, fit for purpose bioassays**

- **Site Re-Organization and Infrastructure Support**
  - Moved from siloed sites to a **unified trials network** with centralized infrastructure support
  - Further enhanced **GCP principles** in all aspects of ETCTN trials

Experimental Therapeutics Clinical Trials Network: Lead Academic (12) and Affiliated Organizations (41); Experimental Drug Development Opportunities Program (15)



ETCTN central infrastructure support



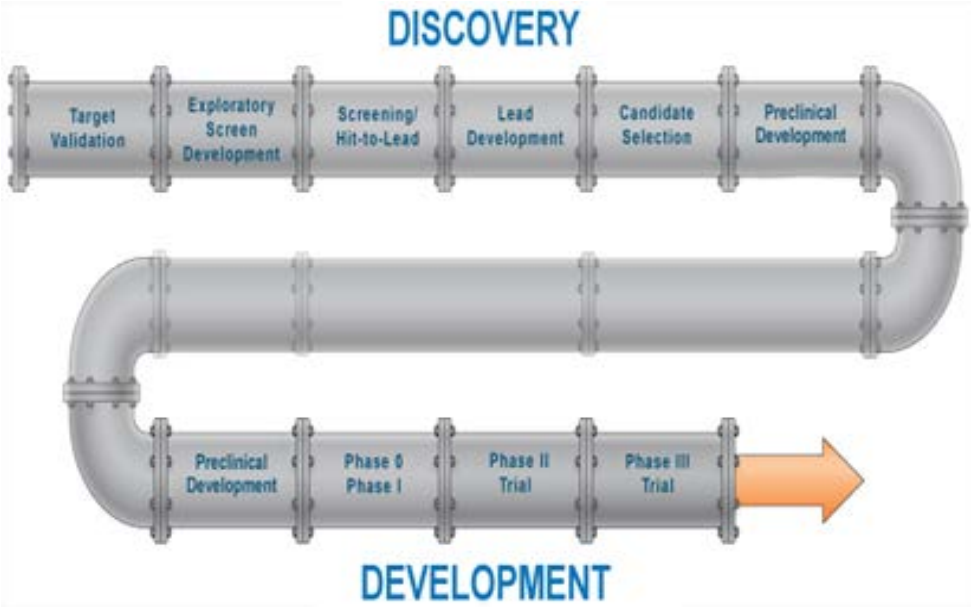
External review of Agents and Trials in the ETCTN

- **All agents come from the NExT (NCI Experimental Therapeutics) Pipeline**

  Review of applications

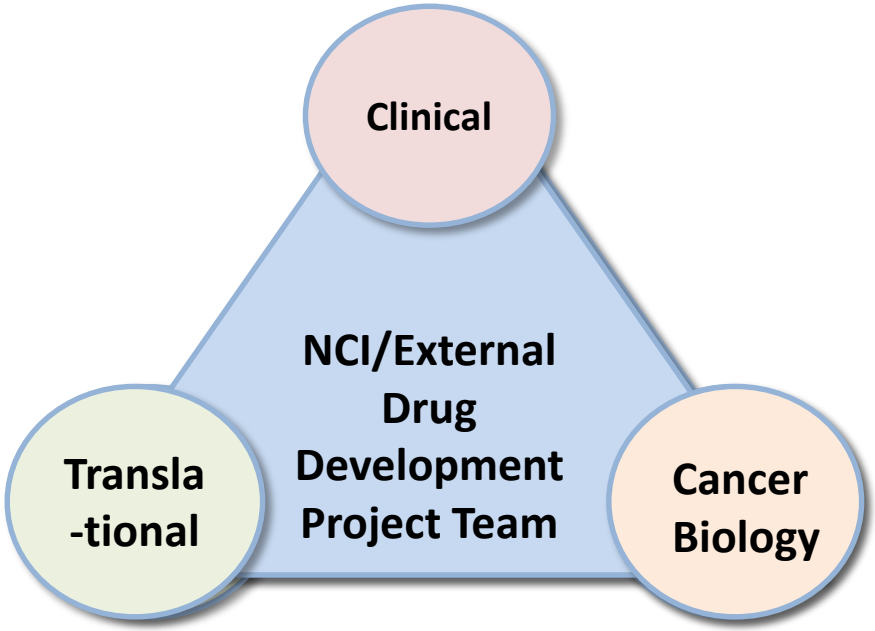
  by external experts

  (https://next.cancer.gov/)



- **All trials proposed by drug development project teams are reviewed by Investigational Drug Steering Committee**
  - IDSC is composed of ETCTN PIs, external experts and NCTN members

ETCTN drug development project teams

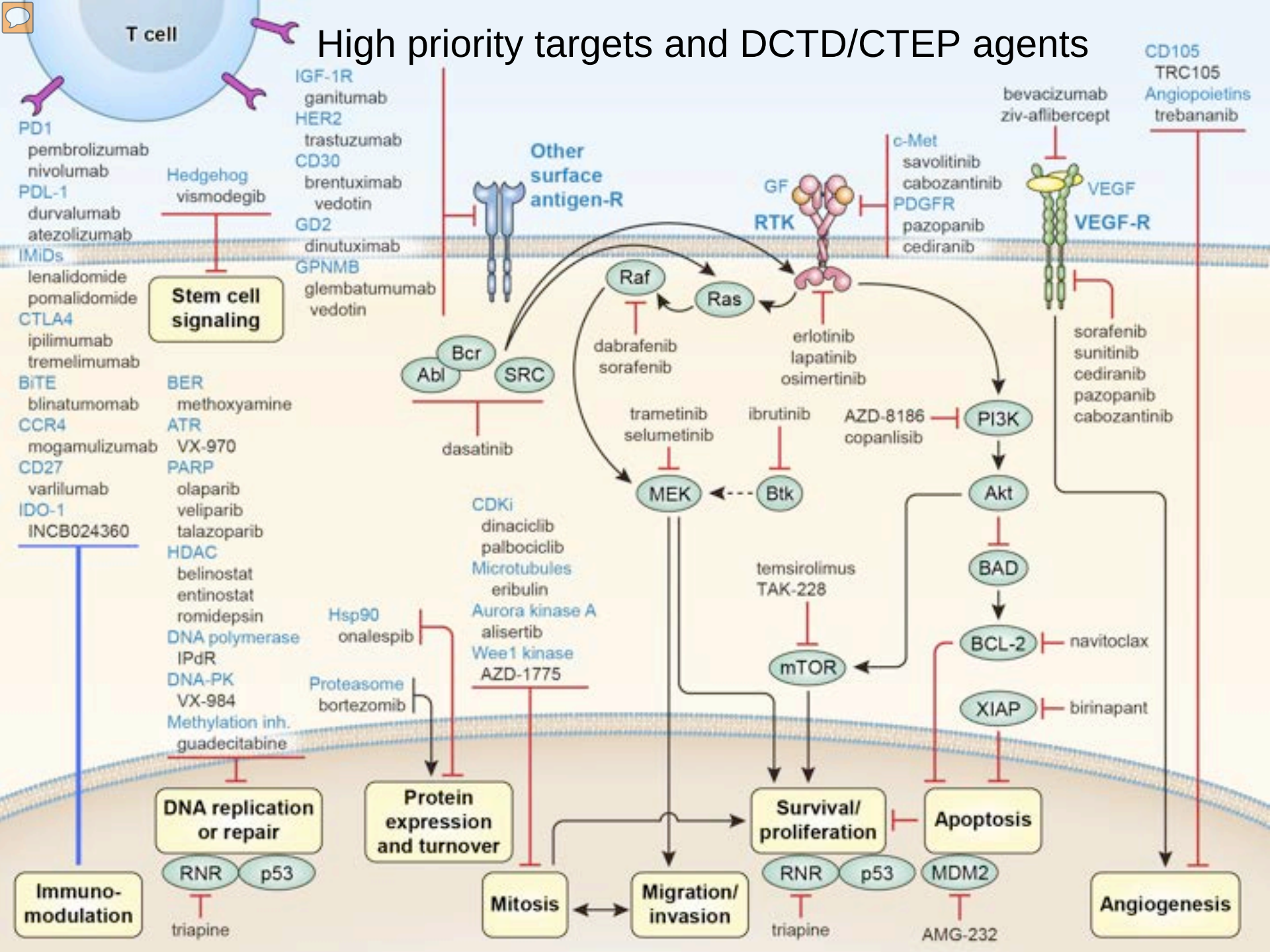


- Extensive extramural involvement
- Reflects heavy emphasis on early career development
- Drug development and CRADA negotiations occur in parallel
- Unsolicited LOIs accepted after Project Team deliberations

Drug development project teams (14):

- AT13387 (onalespib) (HSP90i)
- Osimertinib (AZD9291, T790M EGFRi)
- M3814 (DNA-PKcs i)
- 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 i)
- Ixazomib (proteasome i)
- Pevonedistat (NEDD8i)
- M3814 (DNA-PKi)
- 3 others starting

High priority targets and DCTD/CTEP agents

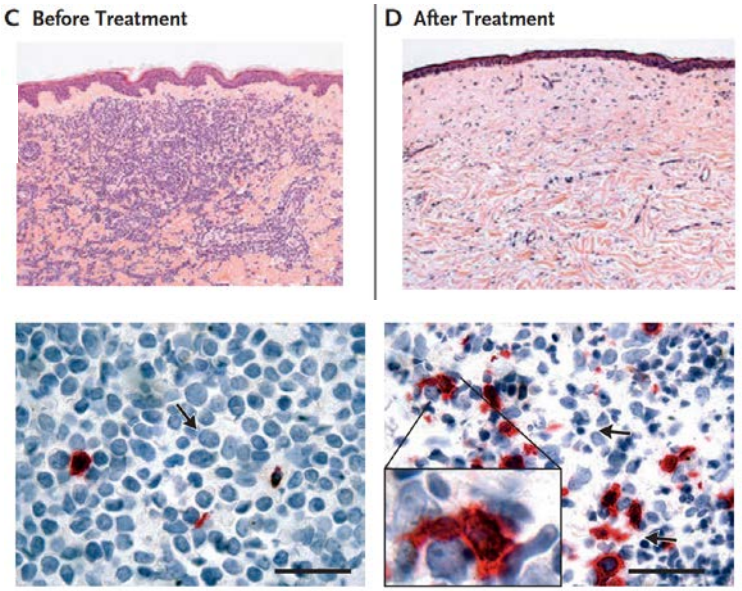


High impact NCI/CTEP IND agent clinical trials

- **FDA approval**
  - Dinutuximab (ch14.18)- Neuroblastoma
- **Orphan Drug and Breakthrough Designation application**
  - Triapine- Advanced uterine cervical cancer (11.08.2017)
  - Selumetinib- NF1 (02.14.2018)

Ipilimumab in Relapsed Hematologic Malignancies post-Allogeneic HSCT (9204)

- 28 patients enrolled to 3 or 10 mg/kg
- Among 22 receiving 10 mg/kg:
  - **5 CR (4 extramedullary AML and 1 AML evolving from MDS)**
  - **2 PR**
  - **6 with reduced tumor burden**
  - **4 patients with durable response > 1 year**
- Responses associated with:
  - *In situ* infiltration of cytotoxic CD8+ T cells
  - Decreased activation of regulatory T cells
  - Expansion of subpopulations of effector cells in peripheral blood

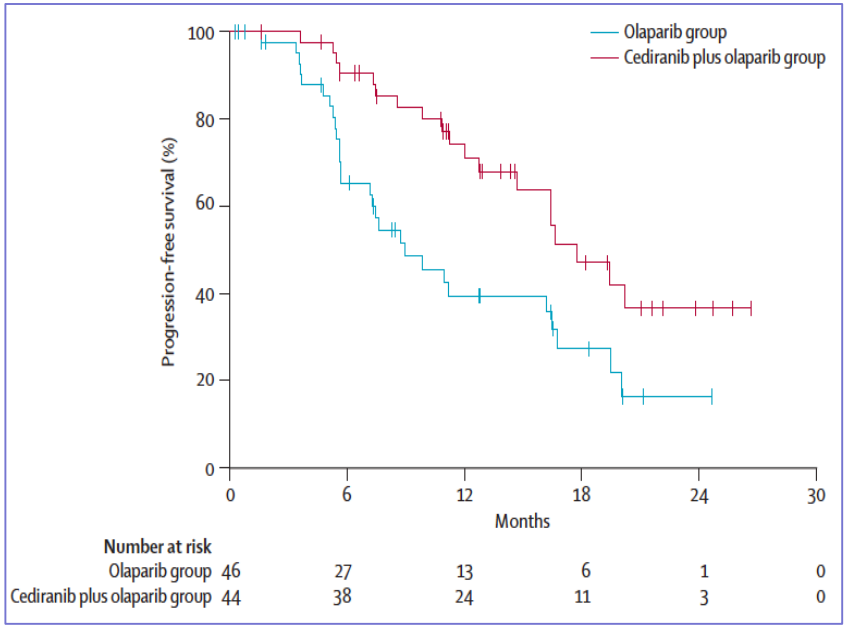


Follow-up studies: evaluation of nivolumab and ipilimumab/decitabine in the same population (CTEP 10026)

Davids et al., NEJM, 2016 (Career Development Award; Mentor R. Soiffer)

Olaparib and Cediranib in Platinum-Sensitive High-Grade Serous Ovarian Cancer (8348)

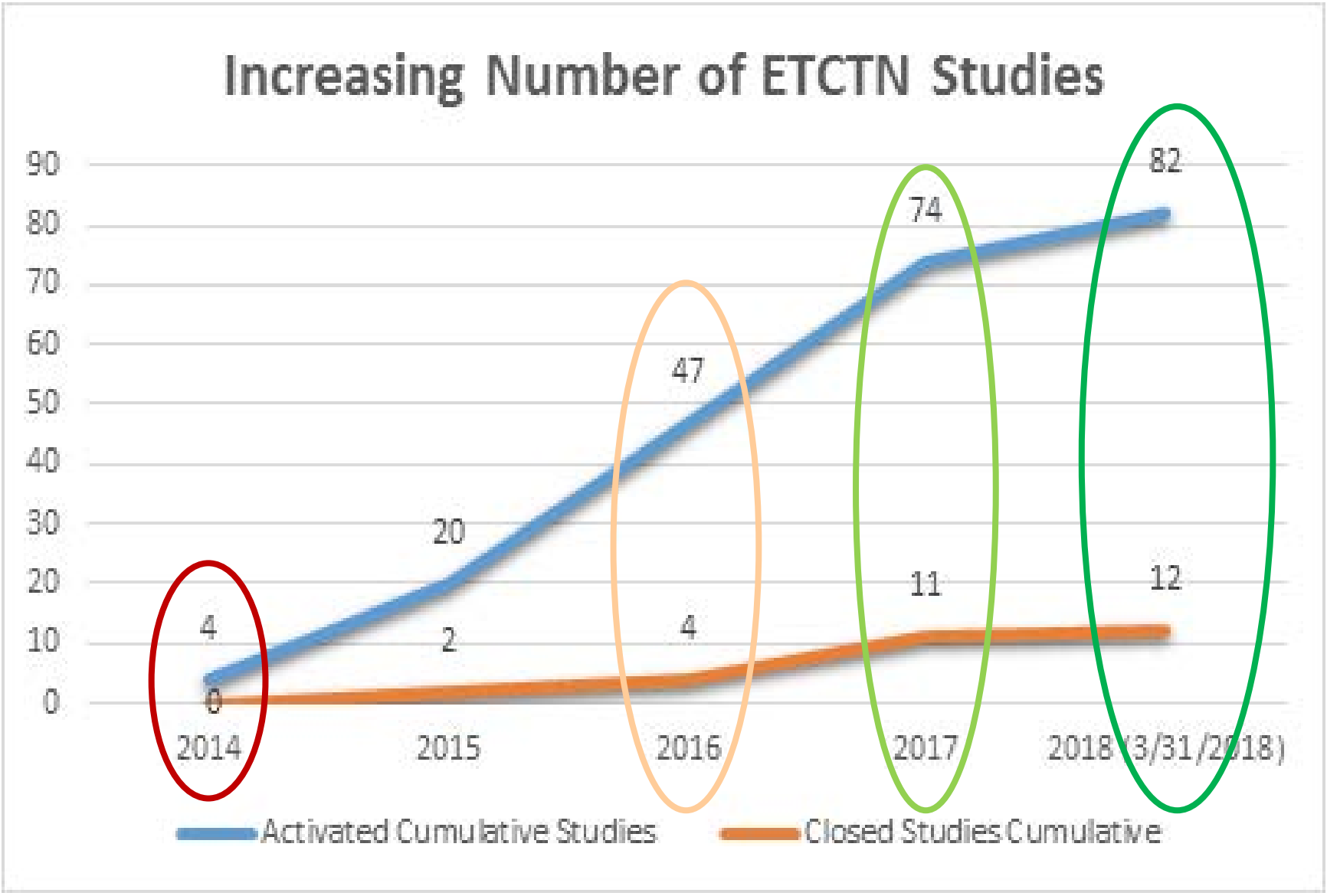
- Based on pre-clinical data indicating that **VEGFR inhibition can establish a PARP-dependent microenvironment**
- 46 patients randomized to olaparib alone and 44 randomized to cediranib + olaparib
- Improvement noted in ***BRCA* carriers as well as non-carriers** (effect size greater in non-carriers)
- Has led to an extensive follow-up program and phase 3 and 2/ 3 pivotal trials in platinum sensitive & resistant patients



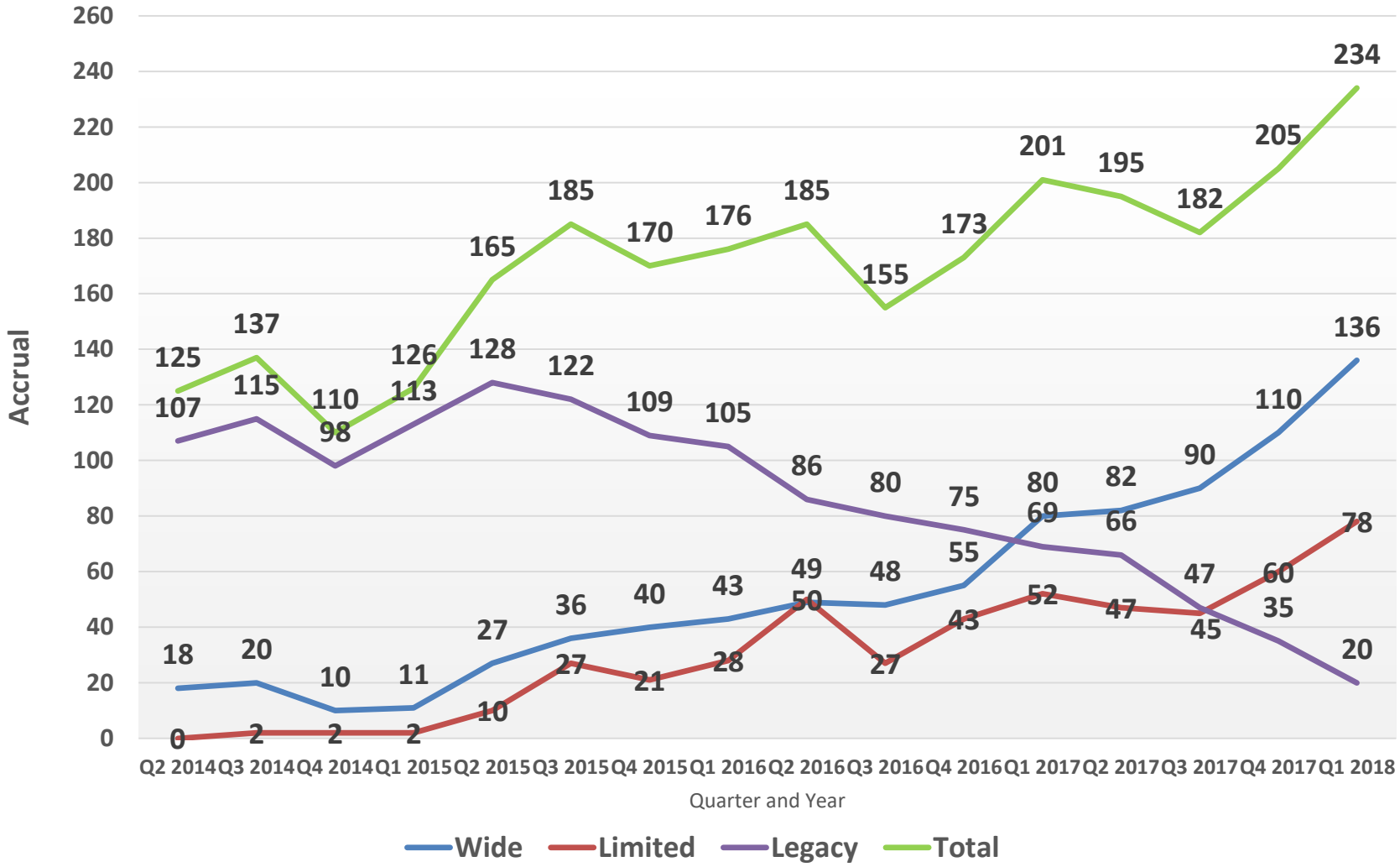
Cediranib Aims for a Comeback
J Natl Cancer Inst, 2015, Vol. 107, No. 3

Liu et al., Lancet Oncol, 2014
(Career Development Award; Mentor U. Matulonis)
2014 Award from the Research Foundation of the Columbia Hospital

	Olaparib	Ced/Olap
PFS events	28	19
Median PFS	9.0 mo	17.7 mo
p=0.005		
HR 0.42 (95% CI: 0.23-0.76)		


Increasing Number of ETCTN Studies
90
80
70
60
50
40
30
20
10
0
4
20
47
74
82
0
2
4
11
12
2014
2015
2016
2017
2018 (3/31/2018)
Activated Cumulative Studies
Closed Studies Cumulative

Quarterly ETCTN Accrual (Limited, Wide, Legacy and Total) Q2 2014 – Q1 2018



Career Enhancement and Development for Early Career Investigators (03.2014-01.2018)

Activity	Number of LOIs (% of total)
LOIs from Project Teams with early career PI's	45 (90)
Unsolicited/pre-solicitation LOIs with early career PI	60 (31)
Activated or transitioned ETCTN protocol with early career PI	44 (60)

ETCTN External Program Review

- **Reviewers were recruited from government and pharma, both nationally and internationally in January 2018**

  Greg Reaman, FDA, USA
  Eric Rubin, Merck & Co., USA
  Janet Dancey, NCIC & ORI, Canada
  Ian Walker, CRUK, UK

- **Review questions included:**
  - Have **phase 1 /2 trials opened** at an adequate rate?
  - Are trials answering **important questions and optimally designed**?
  - Were steps taken to adapt to cancer **precision medicine** challenges?
  - Does the program conform to **GCP standards**?
  - Is **team science** promoted? Is this a collaborative, interactive research network?
  - Are adequate clinical research opportunities provided for **early career investigators**?

- Reviewers **responded positively to all questions**, thought the program **achieved its goals and objectives,** and provided additional **input for future endeavors.**

ETCTN transformation during the 2020-2025 award period:
Leveraging NCI resources to enhance drug development & productivity

1. Address the need to find rare or uncommon, molecularly defined subsets of patients – a challenge for phase 2 studies

2. Enhance requirements for **high quality biopsy material** for correlative studies

3. Improve ability to perform **validated biomarker assays** to characterize and monitor **molecularly defined subsets** of common or uncommon tumors (validation of integral/integrated biomarkers)

1. Recruit rare or uncommon, molecularly defined subsets of patients

- **Lead and Affiliate Organizations will apply as teams**
  - **Encourage multiple PI applications**
  - Leads to have a minimum of **one Phase 1 investigator**
  - Leads and Affiliates to have a minimum number of **identified key investigators** responsible for **disease-specific** accrual
    - **4** distinct disease-specific investigators **for each Lead**
    - **2** distinct disease-specific investigators **for each Affiliate**
  - Award will provide **partial salary support** for each team member- NCI can provide academic credit through grant salary support
  - Funded co-investigators will have **performance criteria outlined in Terms of Award** for performance opening studies and accrual

2. Improve the quality of biopsy specimens

- **Organize ETCTN-wide initiatives with ETCTN-funded investigators to improve biopsy quality**
  - **Partial salary support** for these team members will be provided
  - Funded investigators will have **performance criteria in the Terms of Award**
- **Lead academic organization teams to include**:
  - An **Interventional Radiologist and Research Pathologist** for acquisition of high quality specimens
- **Each Affiliate team to include**
  - An **Interventional Radiologist** for acquisition of high quality specimens; **Research Pathologist** optional

3. Enhance use of biomarker assays to achieve Precision Medicine goals

- **Increase use of biomarker assay resources developed through NCI resources**
  - Pharmacodynamic Assay Development and Implementation Section (**PADIS**) lab and network
  - Cancer Immune Monitoring and Analysis Centers (**CIMACs**) for Immuno-Oncology (IO) studies
  - Molecular Characterization (**MoCha**) lab for genomic and transcriptomic evaluation
  - ETCTN **biorepository and accessioning** center
- **Scale back UM1 Biomarker Assay Development supplements**
- **Consolidate ETCTN PK activities**
  - Two **U24-funded PK consortia**
  - **Remove funding** for PK assays from core ETCTN UM1 awards

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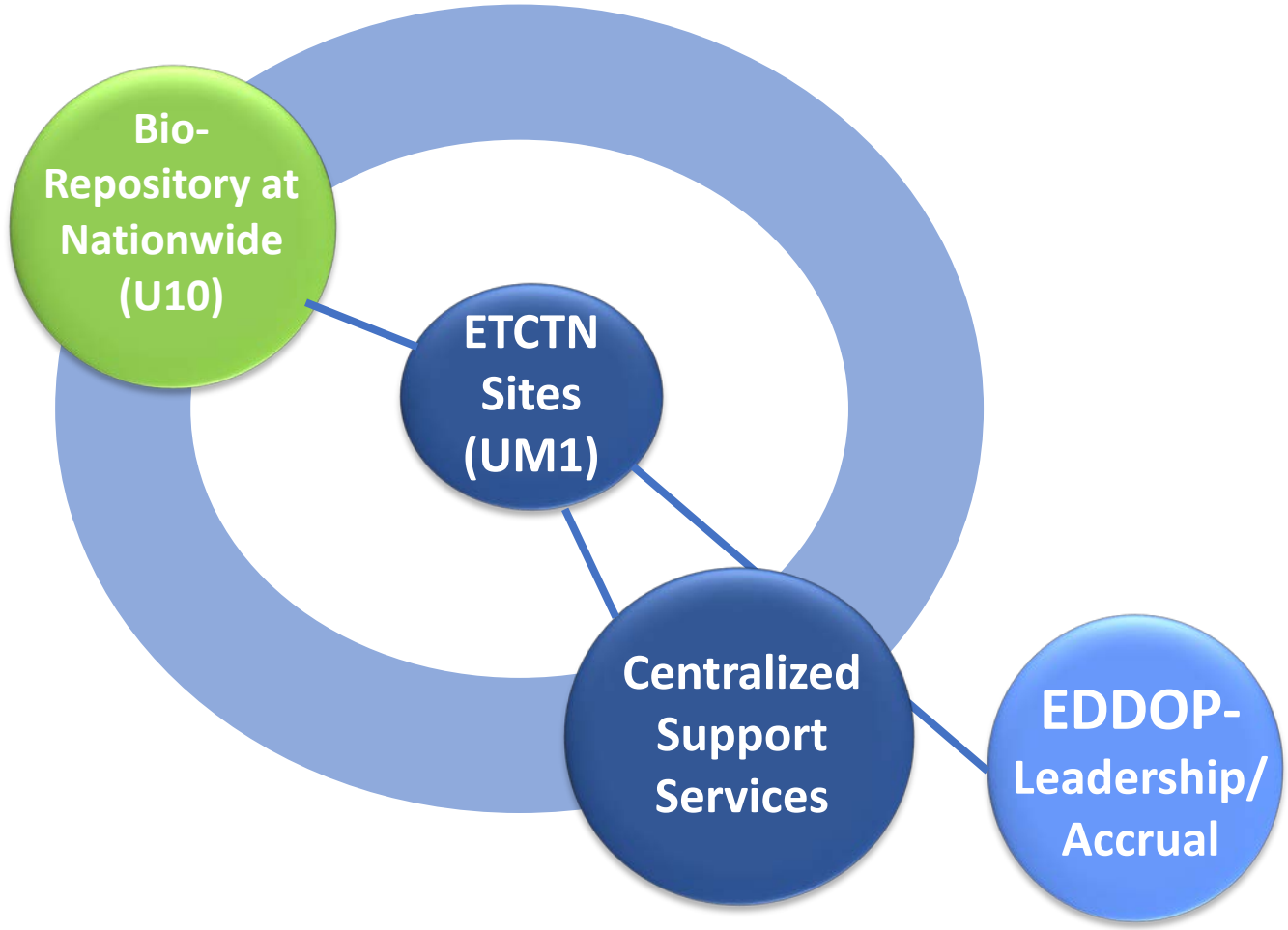
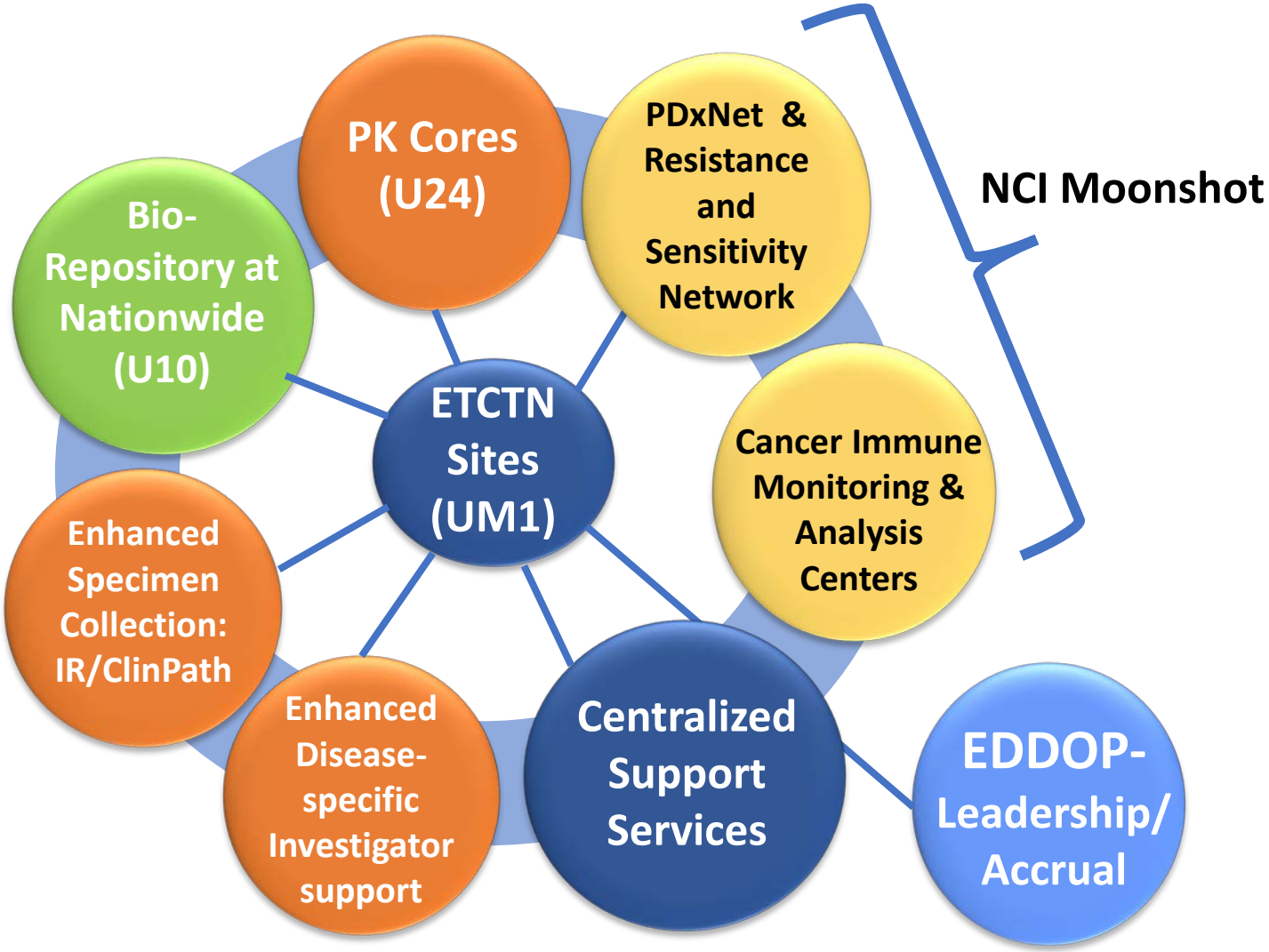


Proposed updates/changes to ETCTN Network

- Affiliated organizations
- New ETCTN initiatives
- ETCTN biorepository (U10)
- Early drug development opportunities programs in NCI CCs (EDDOP) for accrual and leadership



Additional goals for the ETCTN 2020-2025

- **Use of Moonshot networks/centers** for preclinical work in support of clinical trials (e.g., PDxNet, DRSN)
- **Broaden classes of agents** under NCI development (e.g., radiopharmaceuticals, cellular therapies)
- Include **ePRO**'s in early phase ETCTN studies for safety and tolerability determinations
- Further development of **risk-based monitoring approaches**

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