ETCTN

Experimental Therapeutics Clinical Trials Network

Team Driven. Cancer Therapy Focused.

Phase 2 Clinical Trials Component of the ETCTN

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DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

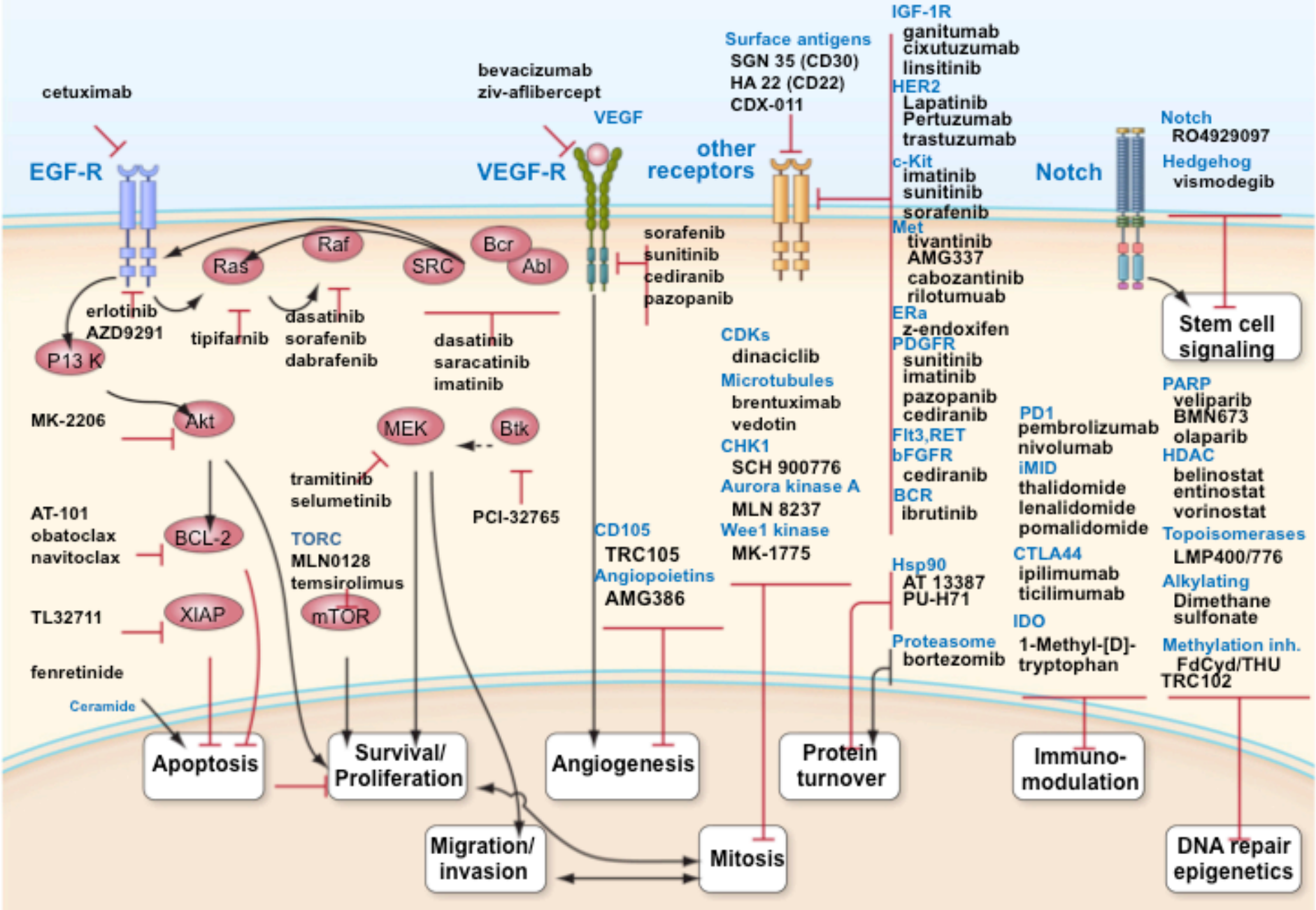
NIH

NATIONAL CANCER INSTITUTE

Role of NCI/DCTD in Early Clinical Development of New Cancer Therapies

- NCI/DCTD forms collaborations with Pharma and academic medical centers to develop new anticancer agents and new combinations of agents
- Underlying concept is that important public health needs are not met by Pharma activities alone – role of NCI/DCTD is to expand indications of novel agents as well as the understanding of their biology

High Priority Targets and DCTD/CTEP Agents



Recently developed NCI IND agents

Agents that have achieved FDA approval based *in part* on early development in CTEP collaborative early phase programs

Agent	Indication
Azacytidine	Myelodysplastic syndrome (secondary)
Bortezomib	Mantle Cell Lymphoma (secondary)
Ipilumumab	Melanoma (primary)
Lenalidomide and bortezomib	Multiple Myeloma (secondary)
Oxaliplatin	Colorectal Cancer (primary)
Romidepsin	Peripheral T Cell Lymphoma (secondary)
Sorafinib	Thyroid Cancer (secondary)
Ziv-aflibercept	Colorectal Cancer (secondary)

Pending FDA approval

Dinutuximab (ch14.18)	Neuroblastoma (primary)

In pivotal trials based on development in CTEP program

Cediranib and Oliparib	Ovarian Cancer
Selumetinib	Uveal Melanoma (secondary)

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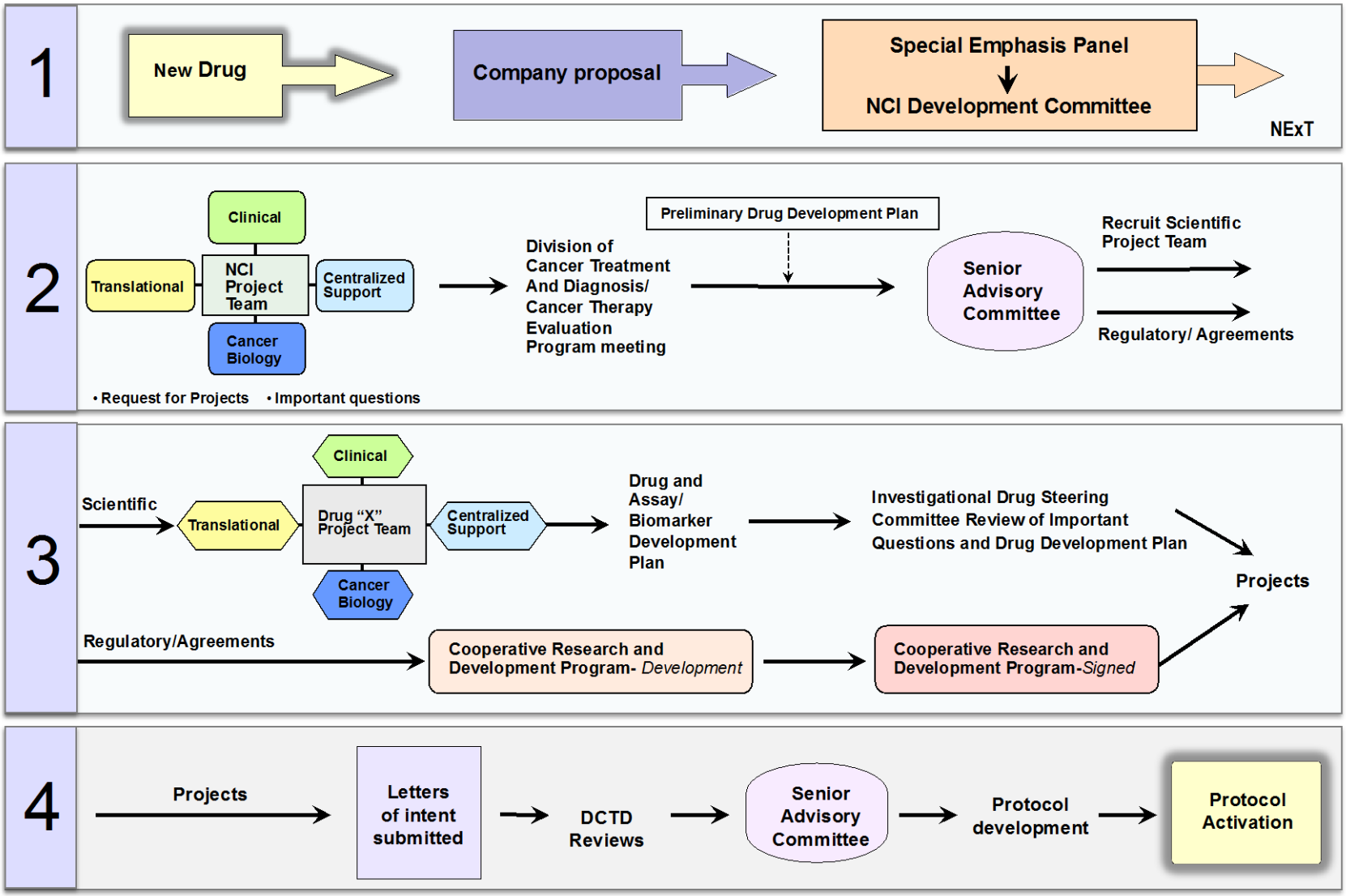
- Underlying concept is that important public health needs are not met by Pharma activities alone – role of NCI/DCTD is to expand indications of novel agents as well as the understanding of their biology
- Many interrelated NCI programs are devoted to this effort, from initial evaluation of proposed collaborations and preclinical development through initial clinical evaluation.

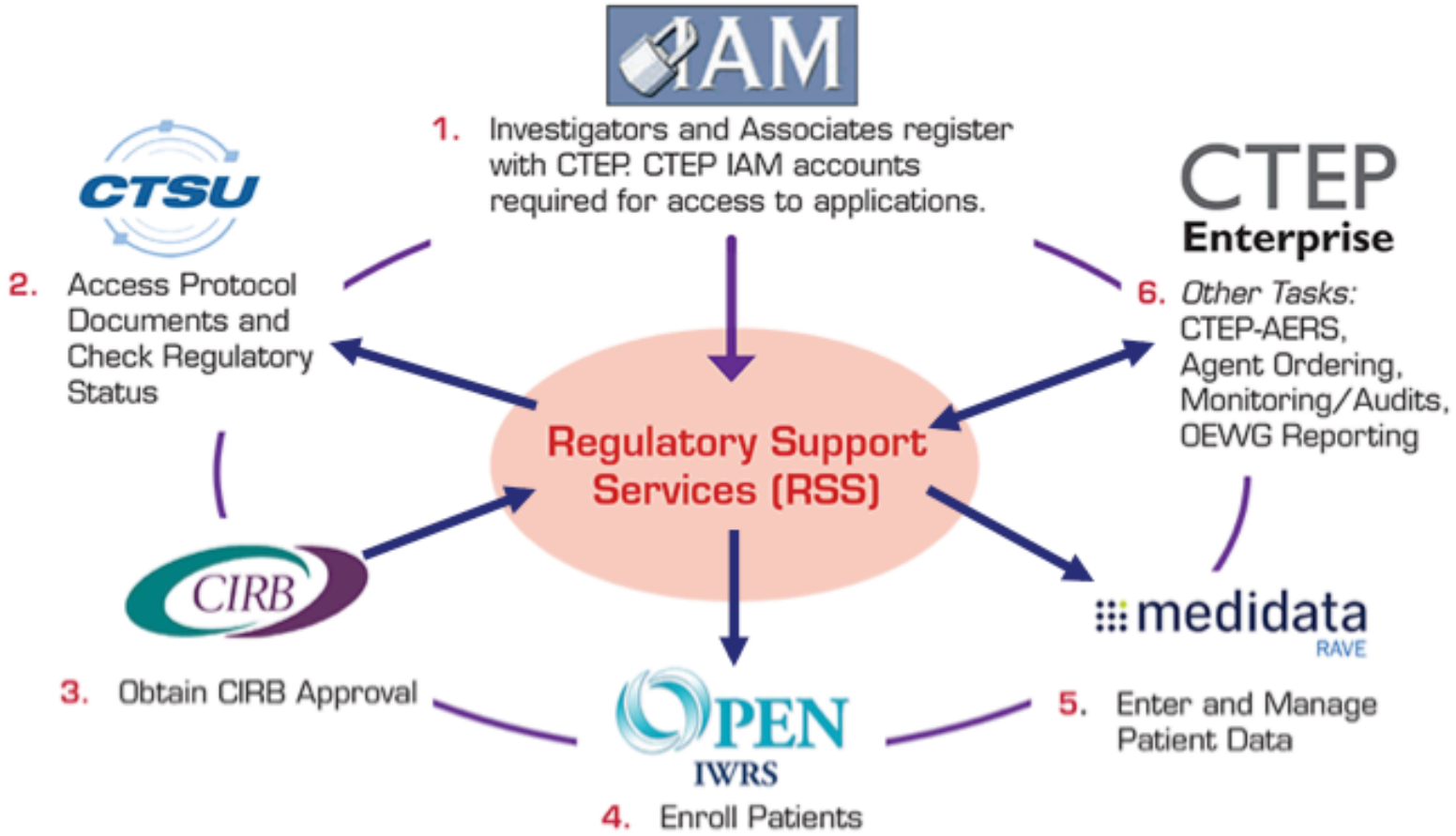
New Development Cycle for Early Experimental Therapeutics



Role of ETCTN in NCI Drug Development

- The Experimental Therapeutics Clinical Trials Network (ETCTN) is the network of clinical trial sites and infrastructure that is solely devoted to the conduct of the earliest clinical studies of Investigational New Drugs (INDs) sponsored by NCI.
- Assures the development of NCI IND agents up to the point of hand-off to NCTN and/or back to Pharma: defining dose, schedule, target engagement, biomarkers of response, and demonstration of clinical activity
- Involves a community of extramural experts in the CTEP drug development strategy for NCI IND agents
- Maintains an experienced network of investigators focused on mechanism-based early phase studies that require intensive monitoring for safety and intensive intervention for correlative studies

Centralized clinical trial support services to support ETCTN



Consolidating the NCI ETCTN initiative

- The ETCTN is currently composed of two distinct clinical components: Phase 1 UM1 grant program and Phase 2 N01 contract program
- Both the phase 1 and phase 2 programs consist of lead organizations, either the grant or contract holders, and multiple affiliated centers that contribute to accrual and scientific goals
- The Phase 1 program was recently re-competed as part of the formation of ETCTN
- The expiration of contracts for the phase 2 program is an opportunity to develop ETCTN into a unified grant program to adapt to the era of targeted therapies
- As clinical science has evolved, current programmatic separation of phase 1 and 2 activities is not desirable.

Evolution of the science of early phase trials

Requirements for early phase trials have evolved:

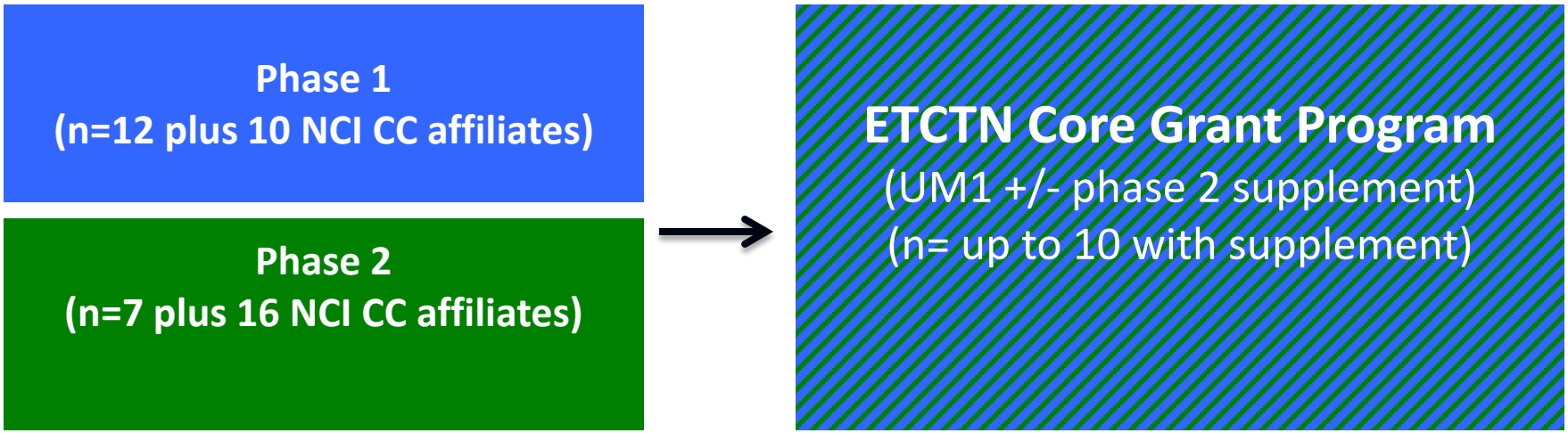
- Disease-focused context traditionally associated with phase 2 trials now frequently required in phase 1 studies
- Disease-specific biomarker incorporation into trials, both for eligibility and proof of target engagement, are now almost always required for early stage drug development
- Pharma has already adopted flexible early phase study design, quickly building phase 2 endpoints into phase 1 studies when signal of activity is detected

Phase 2 Program goals: How do we make the program fit the science?

Program goals reflecting new realities:

- Shorter duration from phase 1 initiation through proof-of-activity by placing pharmacology-focused investigators (phase 1) with disease-focused investigators (phase 2) in the same program to quickly explore signals of activity.
- Enhance biomarker incorporation into phase 2 study design
- Maintain experienced phase 2 investigators in ETCTN and on ETCTN project teams that develop early phase studies
- Expand pool of eligible patients for rare tumor subtypes
- Further leverage ETCTN centralized clinical trial support resources

Separate vs unified ETCTN structure



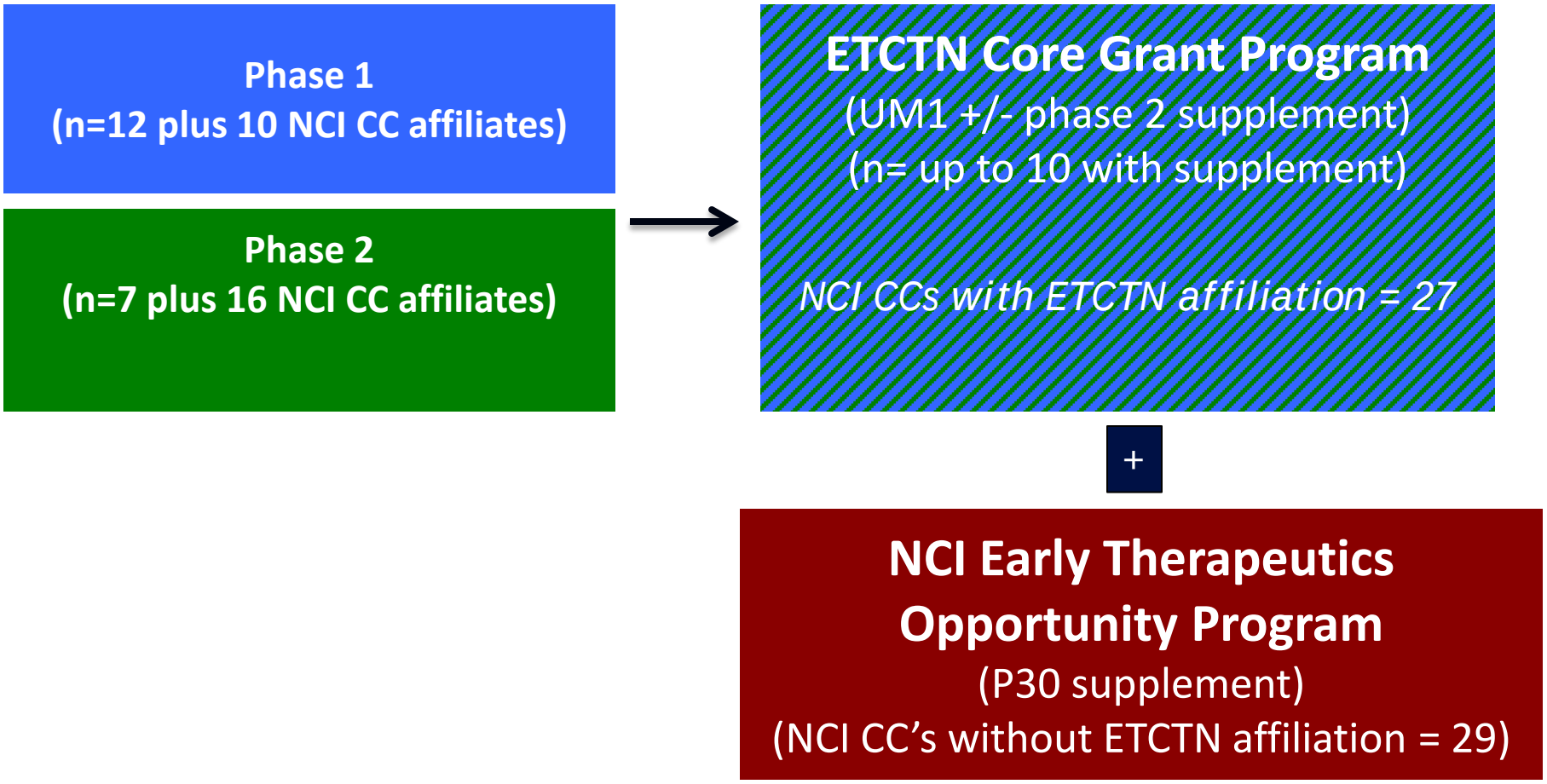
Current

Proposed

ETCTN Core Grant Program

- Current phase 1 grantees will compete for supplements to expand phase 2 expertise
  - May include current NCI phase 2 programs or qualified experimental therapeutics programs at other NCI CC's
  - Opportunity to redistribute the 23 NCI CCs currently affiliated with the phase 2 contract program into more streamlined alignments
    - 7 NCI CC's affiliated with different UM1 and N01 LAO's
  - Flexibility in number of supplements requested to optimize network
- A limited-competition RFA is soon to be published for UM1 supplements; focus will be on scientific leadership/expertise for ETCTN phase 2 studies

ETCTN Pilot Collaboration with NCI CC Program



NCI Early Therapeutics Opportunity Program – Pilot collaboration with NCI cancer centers program

- Proposal designed to greatly expand participation in early drug development studies for both physician-scientists and patients
  - Study leadership proposal
  - Phase 2 study participation proposal

NCI Cancer Centers and ETCTN Phase 2 study leadership

- In the NCI Early Therapeutics Opportunity Program, an investigator from any clinical NCI-designated cancer center could submit an Letter of Intent (LOI) to CTEP and, if approved by the Protocol Review Committee (PRC), the PI could receive:
  - Full ETCTN clinical trial support for the study – including CIRB, registration and data management support, and accrual from ETCTN sites
  - Funds for salary reimbursement (% effort)
  - Funds for accrual to the study at the PI's home institution
- LOIs must be approved and submitted by cancer center
- Administered as a P30 administrative supplement after LOI approved by PRC

NCI Cancer Centers and ETCTN Phase 2 study accrual

- NCI Cancer Centers would be able to open selected ETCTN phase 2 studies that require screening for rare tumor subsets.
- Reimbursement via P30 supplement with some restricted funding.
- Approximately 30 of the non-ETCTN NCI CC's after the revised UM1 grants are awarded can compete for approximately 15 phase 2 accrual supplements
- Supplements intended to offset per-patient research study costs, not screening costs.

NCI Cancer Centers and ETCTN Phase 2 study accrual

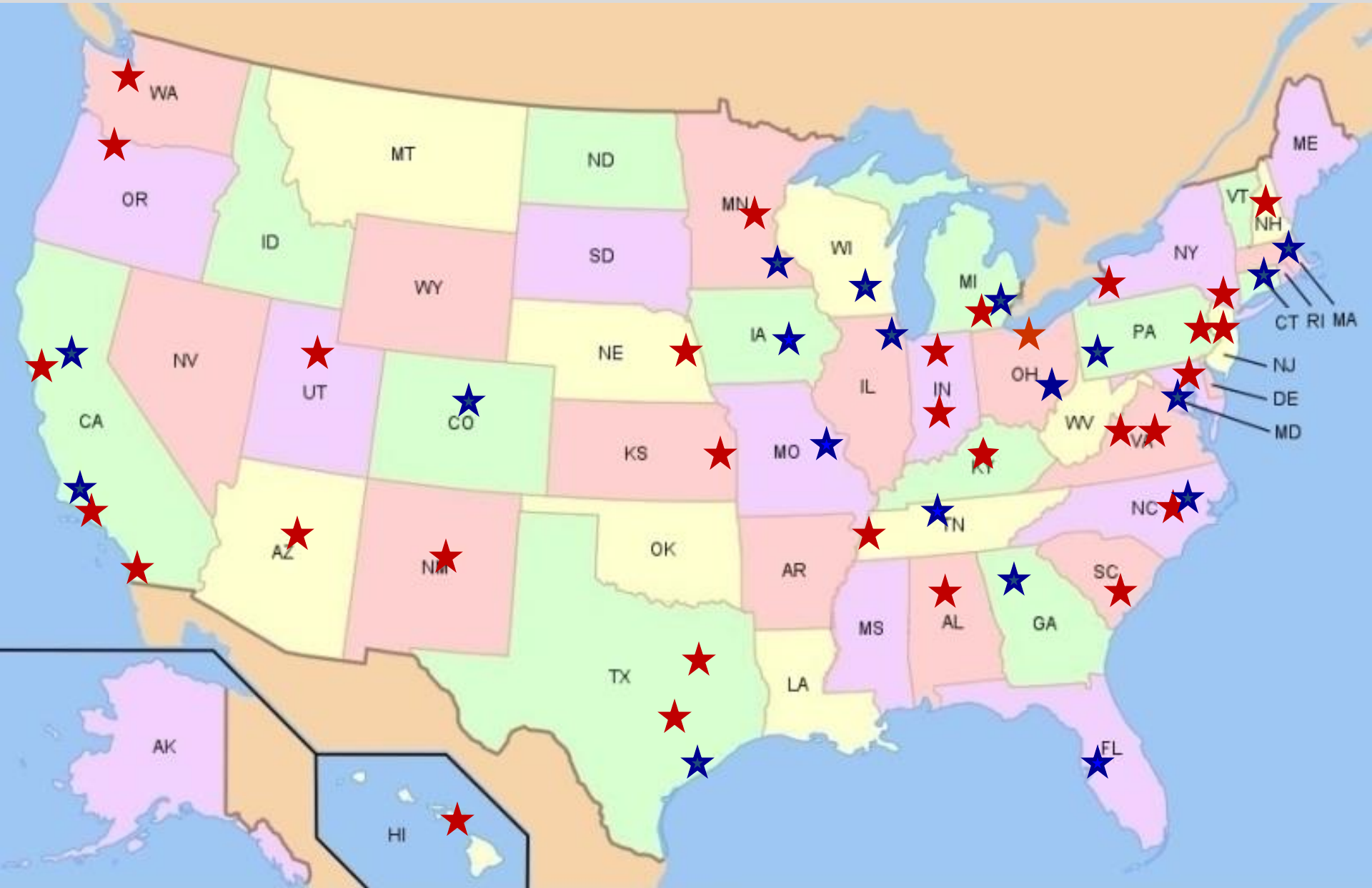
- Review criteria will include: Relevant patient accrual history, molecular screening practices, investigator qualifications, access to special populations
- Annual renewal of supplements will depend on demonstration of minimum accrual during previous year.
- New supplements may be awarded to additional cancer centers after the first year using funds not spent on renewals.

ETCTN – NCI CC Pilot Programs Timelines

- Study Leadership: Announcement soon after UM1 revisions announced (Jan, 2016)
  - Will accept LOI's anytime after that date
- Phase 2 accrual: Announcement soon after UM1 revisions announced
  - Dates for acceptance of supplement applications TBD
- Overall additional accrual to ETCTN trials with both proposals is up to 91 patients per year
  - Study leadership n=16
  - Rare population accrual n=75

NCI-Designated Cancer Centers (clinical)

(Red= cities gaining ETCTN opportunity under proposal)



Metrics for Pilot NCI CC collaboration

- Number of accepted LOI's
- Accrual to studies opened through leadership supplement
- Number of NCI CC's participating in both programs
- Accrual to studies for rare tumors

Renewal would depend on performance of pilot program

Total budget request

Total Proposed Annual Allocation of Funds $10,000,000 per year

Proposed Annual Allocation of Funds for UM1 supplements: $9,000,000 per year

UM1 Phase 2 Supplements	**$9,000,000**	
Unrestricted Funding	$7,200,000	80%
Salary support and travel	$1,000,000	8%
Per-case patient accrual and biopsy acquisition	$6,200,000	72%
Restricted funding – For Biomarker Studies	$1,800,000	20%
NCI Cancer Centers Pilot Collaboration with ETCTN	**$1,000,000**	
Study leadership supplements (n=4 @ $62,500/supplement)	$250,000	
Supplements for study accrual (n=15 @ $50,000/supplement)	$750,000	

Open for discussion
Questions for CTAC:

How can we increase participation in ETCTN clinical trials?

How can we generate more phase 2 trial concepts (with supporting data) for testing NCI-IND agents?

What other initiatives could be undertaken to develop NCI-IND agents?