Pediatric Early Phase Clinical Trials Network (PEP-CTN) RFA Concept

Malcolm A. Smith, MD, PhD

NIH NATIONAL CANCER INSTITUTE

Board of Scientific Advisors Meeting
June 15, 2023

Pediatric Early Phase Clinical Trials Network (PEP-CTN)

- Built upon prior experience of COG Phase 1/Pilot Consortium
- PEP-CTN Funded in 2018 after open competition
- Leadership
  - Chair: Brenda Weigel, MD; U of Minnesota
  - Vice-Chair: Elizabeth Fox, MD; SJCRH
  - Statistician: Charles Minard, PhD; Baylor College of medicine
- Utilizes COG clinical trials infrastructure
  - COG Operations Center for protocol development
  - COG Statistics and Data Management center for Medidata Rave study builds and data management

PEP-CTN Member Institutions

- 21 premier COG pediatric core member sites in the U.S.
- 21 non-core member sites in the U.S., Canada and Australia
- Non-core member sites join for phase 2 components of studies and for pilot studies
- Geographic distribution achieved

Clinical Trial Accomplishments

- Completion of **ADVL1412** that defined activity of **nivolumab ± ipilimumab** for selected pediatric solid tumors
- **ADVL1414** defined RP2D of selinexor that is being used in ACNS1821 study of **selinexor** + XRT for children with diffuse intrinsic pontine gliomas (DIPG) or other high-grade gliomas
- **PEPN1924** evaluated **trastuzumab deruxtecan (DS8201a)** in patients with recurrent HER2+ osteosarcoma
- Phase 1 clinical trials of **pevonedistat** with standard of care agents for AML (**ADVL1712**) and for solid tumors (**ADVL1615**)
- Determination of PK behavior for multiple agents

PEP-CTN Clinical trials

Protocol	Phase
PEPN1812 Flotetuzumab in AML	1
PEPN1924 DS8201a in OS	2
PEPN2011 Tegavivint in solid tumor incl CNS	1/2
PEPN21EHR-PBTCN15 EHR Data Transfer Pilot	feasibility
PEPN2111 CBL0137 in solid tumor incl CNS and lymphoma	1/2
PEPN2112 Elimusertib in solid tumors	1/2
PEPN2113 Uproleselan in AML	1
PEPN2121 Tiragolumab + Atezolizumab in SMARCB1/A4 deficient tumors	2
PEPN22P1 PK of VCR using BSA banded infant dosing tables	Pilot

PEP-CTN and Pediatric CITN (PED-CITN) Clinical Trials

- Support for the CITN will end later in 2023
- Two PED-CITN clinical trials are ongoing in 2023
  - PED-CITN-02: GD2-Targeted Modified T-cells (GD2CART) for Patients with Relapsed/Refractory Osteosarcoma and Neuroblastoma
  - PED-CITN-03: Magrolimab (anti-CD47 MAB) and Dinutuximab in Patients With Relapsed or Refractory Neuroblastoma or Relapsed Osteosarcoma
- The PEP-CTN will assume responsibility for completing PED-CITN-02 and PED-CITN-03

PEP-CTN Clinical Trial Infrastructure Enhancements

- Selected 21 “non-Core” member sites to increase accrual potential for phase 2 trials
- Incorporated central review process for all PEP-CTN clinical trials using the CTSU Source Document Portal
- Adopted DTLs for all PEP-CTN clinical trials and participating in CTEP protocol deviation integration pilot with plans to implement in all future trials

PEP-CTN / PBTC Pilot Study for Electronic Laboratory Data Transfer from Participating Institutions to MediData RAVE

- Develop databases in Medidata Rave on the PEP-CTN and PBTC URLs for sites to directly load lab data from select completed studies from local EHRs
- Map the data extraction process locally and implement tools to enable direct electronic lab data transfer to Rave EDC
- Demonstrate ability to upload lab data to Rave EDC
- Compare lab data received through this process with data entered in Rave EDC during the original conduct of the study
- Assess impact of this process on participating sites and the operations centers of PBTC and PEP-CTN to assess feasibility of utilizing for future studies & expanding implementation consortium-wide

PEP-CTN Accrual and Challenges during Funding Period

	2018	2019	2020	2021	2022	Grand Total
Grand Total (Intervention)	95	34	49	44	75	306
Grand Total	95	34	49	95	75	357

- Year 1 required transitioning procedures and clinical trials from the previous Phase 1/Pilot Consortium to the PEP-CTN and required setting up the Agent Prioritization Committee
- The COVID-19 pandemic during 2020-2022 had impacts both on patient enrollment and on new protocol development
- Enhanced complexity of interactions with pharmaceutical companies resulting from changes in regulatory landscape
- Agents being dropped from clinical development and delays in agents proceeding to clinical development

External Reviewer Feedback (1)

- PEP-CTN identified as an important resource that plays a pivotal role in pediatric drug development
- Streamlining of process for agent prioritization while maintaining high standards for moving agents into pediatric testing
- Need for enhanced communication strategies with pharmaceutical companies
  - More proactive outreach (e.g., regular pipeline meetings)
  - Offering Agent Prioritization Committee feedback to companies on the potential utility of their agents for pediatric cancers

External Reviewer Feedback (2)

- Enhancing interactions with COG Disease Committees to facilitate identification of disease-specific early phase clinical trials that can be performed through the PEP-CTN
- Need for increased engagement with regulatory agencies to ensure that early phase clinical trials developed by PEP-CTN meet both scientific and regulatory purposes

Purpose of RFA

- To support the PEP-CTN to conduct “first in children” studies (i.e., phase 1 often with phase 2 expansion cohorts) as well as phase 2 and pilot studies of promising agents/regimens
  - Molecularly targeted agents
  - IO agents including bispecific T cell engaging agents, CAR T cells, and antibody-drug conjugates
- To define the pharmacokinetic behavior and key pharmacodynamic effects of novel agents in children
- To augment the ability of PEP-CTN to work with pharmaceutical companies by continuing enhancements to its clinical trials infrastructure

Plans for PEP-CTN

- Structure:
  - Scientific Leadership
  - Operations and Biostatistics Component
  - Member institutions (Core and non-Core)
  - Pharmacokinetic (PK) and Biology Component
  - Imaging Component
- NCI to work with PEP-CTN leadership to enhance capabilities:
  - Streamlining decision-making for agent prioritization
  - Augmenting interactions with pharmaceutical companies, regulatory agencies, & COG Disease Committees to more effectively move agents to testing through PEP-CTN

Budget Considerations

- Budget for Grant Year 1-5 for current PEP-CTN award:

	2018	2019	2020	2021	2022
Approved budget	**$4,739,780**	**$4,783,063**	**$4,729,868**	**$4,204,459**	**$4,237,300**
Less unobligated balance	$0	$0	$834,329	$0	$0
EHR Supplement			$587,952	$638,499	
Total federal award amount	**$4,740,000**	**$4,640,000**	**$4,483,952**	**$4,842,499**	**$4,153,000**

- Propose increase of ~ 8% from FY2022 award to $4.5M total cost for Year 1 (FY2024) with a 5-year cost of $22.5M
- Increase justified by higher cost of research activities and by the anticipated conduct of more complex clinical trials that require additional resources to conduct (e.g., CAR T cell studies)

Summary

- PEP-CTN can accelerate the movement of promising novel agents into clinical testing in children
- Important to continue enhancing the capabilities of PEP-CTN for conducting scientifically sound clinical trials that can be used for regulatory purposes
- PEP-CTN plays a central role in NCI’s pediatric cancer research program

NATIONAL CANCER INSTITUTE

www.cancer.gov

www.cancer.gov/espanol