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|  | **PEP-CTN Agent Prioritization Proposal**  **Form v1.3 Version** |
| National Cancer Institute (NCI)  Division of Cancer Treatment and Diagnosis (DCTD)  Cancer Therapy Evaluation Program (CTEP)  Pediatric Early Phase Clinical Trials Network (PEP-CTN)  Agent Prioritization Committee (APC) |

**PAGE LIMIT: Please limit your submission to no more than 15 pages.**

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| * Please email your completed Agent Prioritization Proposal to [NCI-PEP-CTN@nih.gov](mailto:NCI-PEP-CTN@nih.gov). * Questions regarding the submission process may be emailed to [NCI-PEP-CTN@nih.gov](mailto:NCI-PEP-CTN@nih.gov). * Pre-submission consultation is highly encouraged and can be arranged by emailing [NCI-PEP-CTN@nih.gov](mailto:NCI-PEP-CTN@nih.gov). * Submission of the Investigator’s Brochure for the agent is strongly encouraged, if available. | | | | |
| **Original Submission or Revision?**  **Submission Date:**  **Title (optional):** | | [Click and enter Original or Revision]  [Click and enter Submission Date]  [Click and enter Title] | | |
| **Requestor/Primary Investigator Name:** | | [Click and enter Name] | | |
| Requestor Company/Institution: | | [Click and enter Company/Group/Institution] | | |
| Requestor Street Address: | | [Click and enter Room/Suite/Dept.]  [Click and enter Street Address]  [Click and enter City, State, Postal Code] | | |
| Requestor Phone: | | [Click and enter Phone No.] | | |
| Requestor Email: | | [Click and enter Email Address] | | |
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| Co-investigator Name:  Co-investigator Company/Institution:  Co-Investigator Email: | | [Click and enter Name]  [Click and enter Company/Group/Institution]  [Click and enter Email Address] | | |
| **Proposed Agent(s)1:** | Agent Name | | NSC #1 | Source of Agent |
| Primary Agent: | [Click and enter Agent Name] | | [Click and enter NSC] | [CTEP or Company] |
| Other Agent #1: | [Click and enter Agent Name] | | [Click and enter NSC] | [CTEP or Company] |
| Other Agent #2: | [Click and enter Agent Name] | | [Click and enter NSC] | [CTEP or Company] |
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1 List of Agents Available Under CTEP Collaborative Agreements for Clinical and Non-clinical Studies: <https://ctep.cancer.gov/industryCollaborations2/agreements_agents_table.htm>.

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| **Tumor Type:** | [ ] Solid Tumor  [ ] Hematologic Malignancy (NOS)  [ ] Disease-Specific:  [ ] Biomarker selected cohort |
| Disease-Specific2:  *(Specify Name and Code of the Disease*2*)* | 1. [Click and enter Disease Name] [Click and enter Disease Code]  2. [Click and enter Disease Name] [Click and enter Disease Code]  3. [Click and enter Disease Name] [Click and enter Disease Code] |

2 Disease Names and Disease Codes are available on the CTEP website at <http://ctep.cancer.gov/protocolDevelopment/codes_values.htm>

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| **Rationale and Background (10-page limit, not including tables and figures):**  *(This section should provide the rationale for prioritizing the agent(s) for testing in children with cancer. It should provide supporting preclinical and clinical data and should clearly address why the agent or agent combination was chosen for the specified patient population, any potential safety concerns with the agent or agent combination for this patient population, and how the requested clinical trial of the agent might impact future trials/practice. NOTE: Please include relevant tables, figures, etc., as appropriate to best present the preclinical and clinical rationale for evaluating the agent in the proposed pediatric cancer population.)*  ***Introduction****: Sufficient information to identify and clarify the scientific and medical context from which the opportunity emerges.*  [Click and enter background information]  ***Preclinical molecular target (mechanism of action):*** *Sufficient information should be provided to document the degree of specificity of the agent for its claimed molecular target(s) or mechanism of action. The known or potential relevance of the agent’s target or mechanism of action to childhood cancers should be summarized. For agents with putative genomic biomarkers, provide a description of the Level of Evidence for the agent and its putative predictive molecular biomarker (see Appendix I).*  [Click and enter molecular target]  ***Preclinical in Vitro Studies:*** *Summary of relevant data from both single agent in vitro studies and combination in vitro studies, if performed, should be provided.*  [Click and enter in vitro studies]  ***Preclinical in Vivo Studies:*** *Summary of relevant data concerning the in vivo anticancer activity of the agent should be summarized. Of particular interest is the availability of pharmacokinetic data from preclinical models used to demonstrate efficacy to allow comparisons between the drug exposures effective in preclinical models and those achievable in humans. Relevant results from in vivo toxicology studies should also be described.*  [Click and enter in vivo studies]  ***Clinical Development:*** *Information concerning clinical experience with the agent should be provided, along with any plans for pediatric development of the agent. Sufficient information should be provided to justify the proposed dose(s) and schedule to be evaluated in children.*  [Click and enter status of clinical development]  ***Agent Formulation:*** *Information concerning the available formulations of the agent should be provided. Of particular importance for orally administered agents is the size of capsules/tablets that can be provided and a description of any available formulations that are suitable for young children unable to swallow capsules or tablets.*  [Click and enter agent formulation information]  ***Intellectual Property (to be addressed by pharmaceutical company applicants):*** *The application should indicate the willingness of the developer of the agent to provide sufficient regulatory support to sponsor the study under its own IND, or to allow the PEP-CTN to sponsor the study under an investigator-initiated IND, or to allow CTEP to sponsor the study through an existing (or anticipated) CRADA.*  [Click and enter intellectual property]  **References (Limit to < 30)**  [Click and enter References] |
| **Objectives:**  *(List the primary and secondary objectives for the proposed study of the agent. See Appendix II for a listing of study objectives used in the PEP-CTN protocol template)*  **Primary Objectives:**  [Click and enter Primary Objectives]  **Secondary Objectives:**  [Click and enter Secondary Objectives] |

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| **Requested Abbreviated Eligibility Criteria:**  **Integral Biomarkers (if applicable; i.e., molecular/genomic/proteomic biomarkers required for study conduct):** [Click and enter Integral Markers]  **Patient Age:** [Click and enter Patient Age]  **Non-Standard Inclusion Criteria** (for standard PEP-CTN inclusion criteria, see *Appendix III*): [Click and enter Non-Standard Inclusion Criteria]  **Non-Standard Exclusion Criteria** (for standard PEP-CTN exclusion criteria, see *Appendix III*): [Click and enter non-Standard Exclusion Criteria] |
| **Proposed Study Design:**  **Phase of Study:** *[Options for phase of study include: 1) Phase 1 study; 2) Phase 1 study with a phase 2 expansion cohort (include tumor types for expansion cohorts); 3) Phase 2 study with dose confirmation in the initial cohort of patients (include tumor types); 4) Phase 2 study without dose finding or dose confirmation (include tumor types); 5) Pilot/feasibility study; and 6) Other (explain). For proposals for phase 2 components, describe the diseases that will be studied and the target response rates that will be of interest for the treatment for the proposed patient population(s).]*  [Click and enter study design and diseases to be studed in phase 2 components]  **Estimated Sample Size (with explanation for estimate)**: [Click and enter Estimated Sample Size with explanation for how this sample size was derived] |
| **Treatment Plan:**  *(State the dose, method of administration, and schedule of each agent. State the duration of treatment, the duration of the study, and the duration of follow-up. For agents requiring phase 1 components, provide the proposed dose levels.)*  [Click and enter Treatment Plan] |

**Requested Biomarker Assays for Correlative and PK/PD Studies\*** (including genomics)

| **Biomarker Name** | **Assay** | **Purpose of Assay in this Proposed Study** | **Tissue/Body Fluid Tested and**  **Timing of Assay** | **Mandatory or Optional?** | **CLIA?\*\***  **(yes / no)** |
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*\* PK/PD: Pharmacokinetics/pharmacodynamics*

*\*\* If the assay result will be reported to the patient/patient’s family or the patient’s physician at any time, on or off study, the assay must be performed at a CLIA-approved laboratory.*

**Describe laboratory that will be performing the biomarker assays and indicate source of funding for performance of the assays. Indicate whether any biomarker assays are requested to be performed by PEP-CTN:** [Click and provide information requested for biomarker assays]

**Requested Imaging Correlates** (if applicable)

| **Imaging Correlative Objective** | **Imaging Technique** | **Organ(s) Scanned and  Timing of Scans** | **Mandatory or Optional?** |
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**Other**

**Resources Offered:** *(Describe any resources that the proposing entity is able to offer the PEP-CTN to enrich the proposed testing. Examples include drug labeling and distribution, pharmacokinetic analysis, testing of tissues for specific biomarkers, etc. Limit to one page.)*

[Click and enter Plan]

**Targeted Project Begin Date (Note: 9 months is the target time from Agent Prioritization Proposal submission until protocol activation for agents approved for protocol development)**:

[Click and enter Targeted Project Begin Date]

**Attachments**

* *Letter of support from pharmaceutical collaborator (if proposal is from an academic team and for an agent that is not in the CTEP portfolio). The entity that will be holding the IND (e.g., CTEP, PEP-CTN, or company) should be described in the letter.*
* *Submission of the Investigator’s Brochure for the agent is encouraged, but not required.*

***Information about the PEP-CTN is available at the*** [***PEP-CTN website***](https://ctep.cancer.gov/initiativesPrograms/pep-ctn.htm)***.***

**Appendix I – Level of Evidence for Agents with Putative Genomic Targets**

**Levels of evidence for Agent and Its Putative Predictive Molecular Biomarker**

1. The drug is FDA approved for a malignant indication and there is a molecular abnormality that can serve as a valid predictive marker.
2. The drug is investigational, but met a clinical endpoint (PFS, response) in any malignancy, has evidence of target inhibition and has evidence of a predictive molecular marker.
3. The drug is investigational, but has demonstrated clinical activity in any malignancy and evidence of target inhibition, and has evidence of a predictive molecular marker.

**Levels of Evidence for Actionable Variants Within a Gene**

In order to use a **given variant** (mutation, insertion, deletion, amplification, translocation, protein expression) as a potential predictor of effect of a targeted treatment, the variant must meet one of the levels of evidence below:

**Level 1:** Gene variant credentialed for selection of an approved drug (e.g. BRAF V600E and vemurafenib in melanoma); such a variant will be considered level 1 in any tissue

**Level 2:**  Gene variant is eligibility criterion for an ongoing clinical trial for that treatment OR gene variant has been identified as etiology of N of 1 response

**Level 3:** Preclinical inferential data (in vitro or in vivo models) providing biological evidence to support use of the variant for treatment selection.  E.g.:

* Models with variant respond to the drug while models without the variant do not
* Gain of function mutations demonstrated in a preclinical model; e.g. D769H variant of ERBB2 results in increased tyrosine kinase-specific activity and upregulates pathway signaling (clinical evidence not required)
* Loss of function genes, tumor suppressor or pathway inhibitor (e.g. NF1) – variant produces a stop codon including frameshift or demonstrated loss of function of resultant protein in preclinical model (clinical evidence not required)

**Appendix II – Study Objectives Included in the PEP-CTN Protocol Template**

**Primary Objectives:**

1. To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of AGENT administered as a (ROUTE OF ADMINISTRATION AND SCHEDULE OF ADMINISTRATION) to children with recurrent or refractory solid tumors or leukemia.
2. To define and describe the toxicities of AGENT administered on this schedule.
3. To characterize the pharmacokinetics of AGENT in children with recurrent or refractory cancer.
4. To define antitumor activity of AGENT in pediatric patients with recurrent or refractory [insert disease types being studied].

**Secondary Objectives:**

1. To define the antitumor activity of AGENT a biomarker selected cohort.
2. To assess the biologic activity of AGENT by (STATE METHOD FOR ASSESSING BIOLOGIC ACTIVITY OF INTEREST)

**Appendix III – Standard Inclusion and Exclusion Criteria in PEP-CTN Protocol Template**

**Inclusion Criteria**:

1. Age: Patients must be ≥ 12 months and ≤ 21 years of age at the time of study enrollment.
2. Diagnosis: *(specific to the investigational agent)*
3. Disease Status: (*add additional disease status criteria that is dependent on investigational agent, if applicable*)

* Solid tumors: Patients must have either measurable or evaluable disease.
* Leukemia: Patients with leukemia must have an M3 marrow.

1. Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age. [***NOTE*:** Neurologic deficits in patients with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score].
2. Prior Therapy:

Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and meet minimum durations from prior anticancer therapy prior to enrollment.

1. Patients must not have received prior exposure to the specific *investigational agent.*
2. Organ Function Requirements
3. Adequate Bone Marrow Function Defined as:

* For patients with solid tumors without known bone marrow involvement:
* Peripheral absolute neutrophil count (ANC) ≥ 1000/mm3

Platelet count ≥ 100,000/mm3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)

* For patients with leukemia:
* Platelet count ≥ 20,000/mm3 (may receive platelet transfusions). These patients must not be known to be refractory to red cell or platelet transfusion.

1. Adequate Renal Function Defined as:

* Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m2 or
  + - A serum creatinine based on age/gender as follows:

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| **Age** | **Maximum Serum**  **Creatinine (mg/dL)** | |
|  | **Male** | **Female** |
| 1 to < 2 years | 0.6 | 0.6 |
| 2 to < 6 years | 0.8 | 0.8 |
| 6 to < 10 years | 1 | 1 |
| 10 to < 13 years | 1.2 | 1.2 |
| 13 to < 16 years | 1.5 | 1.4 |
| ≥ 16 years | 1.7 | 1.4 |

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

1. Adequate Liver Function Defined as:

* Patients with solid tumors:
* Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age.
* ALT (SGPT) ≤ 135 U/L. For the purpose of this study, the ULN for ALT is 45 U/L.
* Serum albumin ≥ 2 g/dL.
* Patients with leukemias:
* Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
* ALT (SGPT) ≤ 225 U/L. For the purpose of this study, the ULN for ALT is 45 U/L.
* Serum albumin ≥ 2 g/dL.

1. Other Specific Organ Function is to be determined based on agent specific toxicities:
2. Informed Consent: All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

Exclusion Criteria

* + - 1. Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies, *OR* because there is yet no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use two effective methods of birth control, including a medically accepted barrier or contraceptive method (e.g., male or female condom) for the duration of the study. Abstinence is an acceptable method of birth control.

* + - 1. Concomitant Medications
         1. Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid).
  1. Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.
  2. Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible [except leukemia patients receiving hydroxyurea, which may be continued until 24 hours prior to start of protocol therapy].
  3. Anti-GVHD agents post-transplant:

Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial.

Study Specific:

1. Infection: Patients who have an uncontrolled infection are not eligible.
2. Patients who have received a prior solid organ transplantation are not eligible.
3. Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.