DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

REQUEST FOR JOINT PROJECT TEAM MEMBER APPLICATION FOR CONDUCTING CLINICAL TRIALS USING IXAZOMIB AND PEVONEDISTAT

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) is accepting Joint Project Team Member Applications for a project assessing ixazomib and pevonedistat, two protein homeostasis−modulating agents being developed by CTEP as anticancer agents in collaboration with Millennium-Takeda. Ixazomib (Ninlaro®, MLN2238) is the first orally bioavailable small-molecule proteasome inhibitor with an improved pharmacologic profile compared with bortezomib (Kupperman *et al.*, 2010). Ixazomib is being developed for the treatment of a broad range of human malignancies. In the double-blind, placebo-controlled, phase 3 study of patients with multiple myeloma (MM), the addition of ixazomib to a regimen of lenalidomide and dexamethasone was associated with significantly longer progression-free survival (PFS) (20.6 *vs*. 14.7 months, *P*=0.01), and limited additional toxic effects (Moreau *et al.*, 2016). In November 2015, ixazomib in combination with lenalidomide and dexamethasone received FDA approval for patients with MM who have received at least one prior therapy. Pevonedistat (TAK-294, MLN4924) is a first-in-class NEDD8-activating enzyme (NAE) inhibitor (Soucy *et al.*, 2009). Pevonedistat inhibited NAE *in vitro* and *in vivo*, and displayed anti-tumor activity in xenograft mouse model of solid tumors, lymphomas, and AML (Soucy *et al.*, 2009; Milhollen *et al.*, 2010; Swords *et al.*, 2010). Three phase 1 studies have confirmed its pharmacodynamic effect in the clinical setting in patients with solid tumors and hematologic malignancies (Swords *et al*., 2015; Shah *et al.*, 2015; Sarantopoulos *et al*., 2016). Single-agent pevonedistat has shown potential for anti-tumor activity in relapsed/refractory AML and lymphoma (Shah *et al.*, 2015; Swords *et al.*, 2015). At the present time, the preliminary CTEP drug development plan for ixazomib and pevonedistat is to open single agent or combination early phase trials for the treatment of solid tumors and hematologic malignancies. Since these two agents share common pathway targets, they may have complementary mechanisms of action and common translational assays may be appropriate; thus, a single project team is being organized to provide direction in generating a CTEP clinical development program for these two agents. The role of the project team is to evaluate all available evidence to modify and refine this initial plan.

It is anticipated that CTEP will activate 3-5 different trials with ixazomib or pevonedistat alone or in combination with other treatments. The project team will include:

1. **Clinician scientists** with expertise in phase 1 and 2 studies and with an interest in solid tumors or hematologic malignancies (fill out **Part A** of the attached Application; Clinician Scientists must belong to a qualifying NCI grant funded institution as defined at the end of this letter);
2. **Translational scientists** with knowledge of appropriate biomarkers for incorporation into clinical trials of this proteasome inhibitor and neddylation inhibitor (fill out **Part B** of the attached Application and see the submission instructions at the end of this letter); and
3. **Basic scientists** with expertise in cancer biology of protein-homeostasis inhibitors that is relevant to designing clinical trials of this proteasome inhibitor and neddylation inhibitor (fill out **Part C** of the attached Application and see the submission instructions at the end of this letter).

Prospective team members may apply for multiple roles using a single application form by completing all the appropriate Parts. The project team will be recruited nationally and will prioritize the research questions regarding ixazomib and pevonedistat in single-agent and combination trials, including prioritization of biomarker studies. It is anticipated that the clinicians on the drug project team will be tasked with writing the Letters of Intent describing the study design, based upon the team's recommendations, for CTEP approval, and that these clinicians will ultimately lead the clinical studies. It is also anticipated that other extramural

members of the drug project team will stay involved in the subsequent design and execution of the proposed trials. It is anticipated that the project team will complete its work in 8-10 weeks or less.

Background/Rationale

Targeting the ubiquitin‑proteasome system (UPS) is an effective therapeutic approach in human cancers, as demonstrated by the clinical development of proteasome inhibitors (Shah *et al*., 2016). Other therapeutic targets within the UPS are being investigated with the aim of affecting specific substrate proteins and signaling pathways of importance in human cancers. The therapeutic potential of targeting the UPS in cancer has been demonstrated by the proteasome inhibitor bortezomib (Velcade®; Millennium Pharmaceuticals), which was approved by the FDA in 2003. Ixazomib is a small molecule 20S proteasome inhibitor and is the first orally bioavailable proteasome inhibitor tested in the clinic (Kumar *et al.*, 2014). Ixazomib showed greater tumor pharmacodynamic responses in human lymphoma WSU-DLCL2 xenografts compared with bortezomib (Kupperman *et al.*, 2010). Ixazomib had a greater pharmacodynamic effect in tumor compared with blood, whereas the opposite was true for bortezomib. Ixazomib showed activity in both solid tumor and hematologic preclinical xenograft models, and antitumor activity correlated with greater pharmacodynamics responses. Ixazomib has been studied in a number of clinical trials and has received FDA approval for the treatment of relapsed MM in combination with lenalidomide and dexamethasone in 2015.

Pevonedistat is a small-molecule inhibitor of the NAE, an E1 enzyme of the neddylation pathway, also known as the NEDD8 conjugation pathway. NAE is an essential component of this pathway, which controls neddylation of cullin proteins and thereby regulates the activity of the cullin-RING ligases (CRLs), a subtype of ubiquitin ligases (Soucy *et al.*, 2009). In HCT-116 cells, approximately 20% of proteasome-dependent protein degradation is mediated by CRL-ubiquitinylation. Substrates of CRLs have important roles in cellular processes associated with cancer cell growth and survival pathways (Soucy *et al.*, 2009), and include p21, p27, cyclin D, β-catenin, and Iκβα (Bedford *et al.*, 2011). NAE inhibition with pevonedistat resulted in disruption of S-phase regulation in HCT-116 cells leading to cellular death, and pevonedistat treatment of other human-tumor-derived cell lines, including Calu-6 (lung), SKOV-3 (ovarian), H460 (lung), DLD-1 (colon), CWR22 (prostate) and OCI-LY19 (lymphoma), also resulted in S-phase-defective phenotypes (Soucy *et al.*, 2009) In mice bearing HCT-116 xenografts, pevonedistat administration significantly inhibited tumor growth at various doses and schedules with peak tumor volume reduction observed with the 60 mg/kg BID schedule (tumor volume ratio [treated/control]: 0.15, $P<0.001$).

Mechanism of Action

Ixazomib is an N-capped dipeptidyl leucine boronic acid that preferentially binds to the chymotrypsin-like proteolytic (β5) site of the 20S proteasome with an IC_{50} of 3.4 nmol/L (Kupperman *et al.*, 2010). At higher concentrations, ixazomib also inhibited the caspase-like (β1) and trypsin-like (β2) proteolytic sites (IC_{50} of 31 and 3,500 nmol/L, respectively). Although the selectivity and potency of ixazomib were similar to that of bortezomib, the proteasome binding kinetics for these two molecules are different. The proteasome dissociation half-life for ixazomib is approximately 6-fold faster than that of bortezomib (18 and 110 minutes, respectively), which is believed to be critical for its improved distribution into tissues. Improved *in vivo* pharmacokinetics and tolerability permit administration of ixazomib at higher doses, resulting in greater blood and plasma exposures. Data generated from both subcutaneous and disseminated xenograft efficacy studies show that ixazomib has greater antitumor activity when administered on intermittent or continuous dosing regimens, and improves overall survival compared with bortezomib in these preclinical models.

Pevonedistat is an adenosine sulphamate analogue that binds to the nucleotide-binding pocket of the NAE and forms a covalent adduct with NEDD8 by a mechanism referred to as ‘substrate-assisted inhibition’ (Bedford *et al.*, 2011). Because NEDD8 conjugation of cullin proteins is required for the ubiquitin ligase activity of the

CRLs, blocking NAE results in the inhibition of CRL activity and the stabilization of CRL substrates, some of which are important for cancer cell growth and survival.

Clinical Studies of Ixazomib

There are 47 active or approved studies of ixazomib currently listed in ClinicalTrials.gov in which the compound is being evaluated as a single agent or in combination with various chemotherapies such as alkylating agents, antimetabolites, topoisomerase inhibitors, mitotic inhibitors, corticosteroids, immunomodulators, and other classes of agents. Planned CTEP-sponsored studies include solid tumors (glioblastoma, breast cancer, bladder cancer, renal cancer) and hematologic malignancies (e.g., AML, ALL, B-cell ALL, Burkitt lymphoma, CLL, DLBCL, FL).

Clinical Studies of Pevonedistat

The following studies are being conducted as part of the Millennium-Takeda clinical development program for pevonedistat:

Study NCT	Phase	Agents	Disease/Indication	Study Start-End	Status/Sponsor	Planned Accrual
NCT03057366	1	Pevonedistat; Docetaxel; Carboplatin; Paclitaxel	Advanced Solid Tumors	5/17 - 5/19	Not yet recruiting/ Millennium Pharmaceuticals, Inc.	6
NCT03009240	1	Decitabine; Pevonedistat	Recurrent AML, Secondary AML, Untreated AML	6/17 - 6/19	Not yet recruiting/ City of Hope Medical Center	30
NCT02782468	1	Pevonedistat; Azacitidine	AML, MDS	5/16 - 9/19	Recruiting/ Millennium Pharmaceuticals, Inc.	37
NCT01814826	1	Pevonedistat; Azacitidine	AML	4/13-11/15	Recruitment completed/ Millennium Pharmaceuticals, Inc.	64
NCT01862328	1	Pevonedistat; Docetaxel; Carboplatin; Paclitaxel	Advanced Solid Tumors	7/13-5/15	Recruitment completed/ Millennium Pharmaceuticals, Inc.	64
NCT02122770	1	Pevonedistat; Docetaxel; Carboplatin; Paclitaxel	Advanced Solid Tumors	5/14-7/16	Recruitment completed/ Millennium Pharmaceuticals, Inc.	51
NCT02610777	2	Azacitidine; Pevonedistat	AML, CMML, MDS	4/16 - 3/19	Recruitment completed/ Millennium Pharmaceuticals, Inc.	117

CTEP's Plans for Ixazomib Project Team Development

1) Investigators may propose Phase 1 or phase 1/2 studies that are multiple myeloma-focused trials investigating ixazomib doublet or triplet combinations with other MM therapies (*e.g.*, cyclophosphamide, thalidomide, pomalidomide, daratumumab, immunotherapy, or others)
2) Investigators may propose a trial of ixazomib in the treatment of patients with tumors selected for immunoproteasome expression (phase 2 basket trial for patients with various malignancies)

3) Preclinical studies to evaluate activity of ixazomib in combination with other therapies, including consideration of an ixazomib and pevonedistat combination in various malignancies

CTEP's Plans for Pevonedistat Project Team Development

1) Phase 2 randomized study of pevonedistat with azacitidine vs. azacitidine in adult relapsed or refractory AML
2) Phase 1 study of pevonedistat in combination with HDACi (*e.g.*, belinostat) in adult AML
3) Phase 2 study of the combination of pevonedistat, carboplatin, and paclitaxel in NSCLC

Ixazomib and Pevonedistat Project Team Selection, Composition, and Tasks

The ixazomib and pevonedistat drug project team will meet regularly by WebEx to review preclinical and clinical data supporting trial proposals for the project team, devise clinical trial designs appropriate for studies including a basket trial, and discuss applicable biomarkers to incorporate in these trials. The project team will be composed of intramural and extramural members. The extramural members will include clinician-scientists with experience in early phase clinical trials studies in hematologic malignancies and solid tumors; translational scientists with expertise in biomarker development; and basic scientists with expertise of the cancer biology of this class of agents. Since the clinician scientists selected for the project team will be expected to lead the clinical trials that come out of this process, the evaluation criteria for the clinician scientists will include not only clinical trial expertise but also their documented record of accrual of patients with hematologic malignancies and/or solid tumors in early phase studies.

Questions regarding this request for applications may be addressed to John J. Wright, M.D., Ph.D., Associate Branch Chief, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6105; FAX: 240-276-7894; e-mail: wrightj@ctep.nci.nih.gov).

CTEP recognizes the importance of encouraging and supporting young investigators as they embark upon a clinical cancer research career. CTEP highly encourages Career Development Applications (CrDAs) from these investigators and their mentors to participate as Project Team members and to develop Career Development Letters of Intent (CrDLs) after conclusion of Project Team activities.

Project Team Member Applications (PTMAs) should contain a clear indication of the applicant's desired role on the Ixazomib and Pevonedistat Joint Project Team (clinician scientist, translational scientist or basic scientist). The PTMA should also be accompanied by an NIH Biosketch containing a personal statement customized to this project. The PTMAs should be sent to the Protocol and Information Office (PIO) at the address below by **5:00 PM Eastern Time (ET), August 7, 2017**. The most recent version of the PTMA form, which has been distributed with this communication, must be used. PTMAs should be submitted electronically to:

PIO, CTEP/DCTD/NCI
E-mail: CTEPPTMASubmissions@mail.nih.gov

Please note that Clinician Scientists may only participate through association with the ETCTN, an NCTN Group, or a consortium (see below), and will need to submit the PTMA through their ETCTN LAO's Coordinating Center or the Group/Consortium Operations office, as applicable. That organization will then need to submit the Clinician's application to PIO on your behalf to confirm that they are in support of the proposal. Please allow sufficient time for your organization's review. Qualifying clinical institutions include:

- ETCTN Participating Institution (under UM1 grant)

- NCTN Group member institution (under U10 grant; Alliance, COG, ECOG-ACRIN, NRG Oncology, or SWOG)
- Institutional affiliation with the Pediatric Brain Tumor Consortium (PBTC), Adult Brain Tumor Consortium (ABTC), or Cancer Immunotherapy Trials Network (CITN)

Basic and **Translational Scientists** who belong to a participating ETCTN institution (Lead Academic Organization [LAO] or Affiliated Organization [AO]) **must** submit applications through your LAO's Coordinating Center. Please allow sufficient time for your organization's review. Basic and Translational Scientists from non-ETCTN-affiliated institutions may directly submit their applications to PIO.

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