REQUEST FOR PROJECT TEAM MEMBER APPLICATION FOR CONDUCTING CLINICAL TRIALS USING COPANLISIB (NSC# 784727)

The Cancer Therapy Evaluation Program (CTEP) is accepting Project Team Member applications for a project using copanlisib (BAY 80-6946), a pan-class I PI3K inhibitor being developed by CTEP as an anticancer agent in collaboration with Bayer. Copanlisib exhibits highly potent inhibitory activity against PI3Kα and PI3Kδ isoforms relative to PI3Kβ or PI3Kγ. Copanlisib has shown potent antitumor effect in multiple preclinical models of tumor types with increased PI3K signaling (*e.g.*, HER2-positive and ER-positive breast cancer, aggressive non-Hodgkin's lymphoma [NHL] such as diffuse large B-cell lymphoma [DLBCL], follicular lymphomas, chronic lymphocytic leukemia [CLL], multiple myeloma [MM], and biliary cancer). In addition to anti-proliferative effects, antitumor activity of copanlisib was associated with reduced cell migration and induction of apoptosis. Single-agent copanlisib intravenously (IV) administered at the maximum tolerated dose (MTD) of 0.8 mg/kg weekly for 3 weeks on a 28-day cycle to patients with relapsed/refractory indolent or aggressive lymphomas demonstrated a robust antitumor activity, with a 53% objective response rate (ORR) in indolent NHL (Dreyling *et al.*, 2014a) and a 64% ORR in mantle cell lymphoma (MCL) (Cunningham *et al.*, 2015). The recommended phase 2 dose for copanlisib monotherapy has recently changed to 60 mg (flat dose) IV weekly for 3 weeks on and 1 week off, since no effect of body weight or BSA was found on the clearance of copanlisib.

The current CTEP drug development plan for copanlisib includes a biomarker-driven phase 1b study of copanlisib in combination with the PD-1 inhibitor nivolumab in patients with lymphomas and solid tumors. This trial is being conducted at the Developmental Therapeutics Clinic at NCI to determine the recommended phase 2 dose (RP2D) for this combination as well as to examine pharmacodynamic (PD) and immune target effects. CTEP is also testing copanlisib in cohorts of patients with PIK3CA mutation and PTEN mutation or protein loss who are enrolled in the NCI MATCH trial. In addition, CTEP sponsors a phase 2 evaluation of copanlisib in patients with persistent or recurrent endometrial carcinoma harboring PIK3CA hot-spot mutations (NRG-GY008).

It is anticipated that CTEP will activate up to four new combination trials with copanlisib through the project team process. The project team will include:

1. **Clinician-scientists** with expertise in phase 1b and phase 2 studies and with an interest in PI3K signaling in breast cancer, lymphoma, or other refractory solid tumors (fill out **Part A** of the attached Application);
2. **Translational scientists** with expertise in biomarker development involving the PI3K pathway, estrogen response pathways, or tumor immunology, related to breast cancer, lymphomas, or other advanced malignancies (fill out **Part B** of the attached Application); and
3. **Basic scientists** with expertise in the PI3K pathway and associated signaling, tumor immunology, or tumor growth, progression, and survival pathways (fill out **Part C** of the attached Application).

Prospective project 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 be responsible for prioritizing the research questions regarding copanlisib in 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. The project team should aim to complete its work in three months or less.

Background/Rationale

PI3K transmits signals from receptor tyrosine kinases (RTKs) to numerous cellular targets that are important for cell proliferation, survival, differentiation, and migration (Liu *et al.*, 2013). PI3K/AKT signaling is commonly dysregulated in human cancers *via* various mechanisms, *e.g.*, gene amplification, rearrangement, or activating and/or loss-of-function mutations of the pathway's molecular components (Westin, 2014). Aberrant activation of class I PI3Ks has been associated with intrinsic and acquired resistance of tumors to targeted agents, chemotherapy, and radiotherapy (Liu *et al.*, 2013).

Four PI3K isoforms (PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ), all of which have a catalytic p110 subunit (p110α/β/γ/δ), comprise the class I PI3K subfamily (Liu *et al.*, 2013; Westin, 2014). PI3Kα signaling is frequently active in human malignancies, and tumors with activating mutations in PIK3CA or loss of PTEN have been found to be sensitive to PI3Kα inhibitors. PI3Kδ-specific inhibitors have shown remarkable therapeutic efficacy in some human leukemias and lymphomas (Yang *et al.*, 2015). A major component of the mechanism of action of PI3Kδ inhibition in the B-cell malignancies is to attenuate the responsiveness of the tumor cells to supportive stimuli from the microenvironment(Okkenhaug and Burger, 2016). Inhibition of PI3Kδ has been shown to protect mice against a broad range of cancers, including non-hematological solid tumors (Ali *et al*., 2014). Inactivation of PI3Kδ breaks regulatory T-cell (Treg)-mediated immune tolerance that unleashes a cytotoxic T-cell response and resulting in tumor regression. Copanlisib is a pan-class I PI3K small-molecule inhibitor exhibiting activity predominantly against the PI3Kα and PI3Kδ isoforms. Preclinical data suggest that copanlisib may be more efficient in inhibiting survival of leukemia cells than idelalisib (PI3Kδ inhibitor) or duvelisib (PI3Kα/γ) (Gockeritz *et al.*, 2015).

Mechanism of Action

Copanlisib is a pan-class I PI3K inhibitor that has greater potency against α and δ isoforms of PI3K (IC_{50}=0.5 and 0.7 nmol/L, respectively) than β or γ isoform (IC_{50}=3.7 and 6.4 nmol/L, respectively) (Liu *et al.*, 2013). In comparison, copanlisib was ~10-100-fold weaker inhibitor of mTOR (IC_{50}=45 nmol/L). In the kinase screen, copanlisib at 1 μmol/L failed to achieve a 50% inhibition of PI4K-II, PIP_4-5, PIP_5-4K, or any of the additional 220 kinases tested, which underscores its strong specificity to class I PI3Ks. In tumor cell lines with hyperactive PI3K signaling, copanlisib antitumor activity was paralleled by a robust decrease in basal levels of phosphorylated AKT, at both Ser473 (AKTpS473) and Thr308 (AKTpT308), and by increases in caspase 9 levels, which is suggestive of induction of apoptosis.

Nonclinical Studies of Copanlisib

In vitro antiproliferative activity of copanlisib was evident across multiple solid tumor types, *i.e.*, breast, endometrial, colon, gastric, kidney, lung, pancreas, prostate (Liu *et al.*, 2013), melanoma (Schneider *et al.*, 2014), as well as hematologic cancers such as multiple myeloma [MM] (Glauer *et al.*, 2013), and CLL (Gockeritz *et al.*, 2015); however, its potency varied among cell lines within most tumor types (Liu *et al.*, 2013). For example, in the panel of breast cancer cell lines, copanlisib strongly inhibited HER2-positive cell lines (mean IC_{50}=17 nmol/L) and those with PIK3CA-activating mutations (mean IC_{50}=19 nmol/L), but was about a 40-fold weaker inhibitor (IC_{50}=774 nmol/L) of the HER2-negative/wild-type PIK3CA cell lines. Based on these data, HER2-positive and PIK3CA-mutant status may predict sensitivity of breast cancer to copanlisib. No correlation was found between the mut/null status of *PTEN* and copanlisib activity in breast cancer cell lines. Copanlisib demonstrated activity against breast cancer cell lines resistant to trastuzumab and lapatinib; in addition, when used in combination with trastuzumab or lapatinib, copanlisib restored sensitivity of the cells to these agents, as demonstrated by synergistic antitumor effects when used in combination (Elster *et al.*, 2015). Copanlisib effectively inhibited the growth of hematologic tumor cell lines, which is potentially associated with its strong activity against PI3Kδ (Liu *et al.*, 2013). Against CLL, copanlisib was a more potent inhibitor *in vitro* and *in vivo* than idelalisib or duvelisib, as shown by achieving a 50% growth inhibition at about 10-fold lower concentrations than the other two inhibitors and producing higher levels of apoptosis (Gockeritz *et al.*,

2015). Robust and durable tumor regressions were observed with copanlisib in rat and mouse xenograft models of HER2-positive/mutant PIK3CA breast cancer, mutant PIK3CA/KRAS colon cancer, erlotinib-resistant NSCLC, and patient-derived luminal breast tumor (Liu *et al.*, 2013). All animals bearing HER2-positive/mutant PIK3CA breast tumor xenograft that received five doses of copanlisib 6 mg/kg IV (MTD) or 3 mg/kg IV every second day remained tumor free on day 73 when the study was terminated.

Pharmacokinetics/Pharmacodynamics (PK/PD)

In the single-dose and multiple-dosing studies in the nude rat model, copanlisib administered IV exhibited large volume of distribution (V_{ss}=32 L/kg), high plasma clearance (3.95 L/kg ×h), and half-life ($t_{1/2}$=6 h); no accumulation of copanlisib in the blood was observed (Liu *et al.*, 2013). The PK/PD studies in rats bearing lung tumor xenografts revealed that copanlisib exposure was about 100-fold higher in the tumor than in plasma exposure at 48 h post-dosing; this effect has been attributed to the basicity and large V_{ss} of copanlisib and the acidic environment of the tumor. A potent inhibition of AKTpS473 in the tumor (>90% inhibition at 24 h post-dosing) correlated with high tumor exposure to copanlisib; pAKT was suppressed up to 72 h. In addition, Ki-67 and phospho-histone 3 were reduced by 65% and 75%, respectively. Copanlisib inhibited the tumor uptake of F^{18}-fluoro-2-deoxy-D-glucose (FDG) in a dose-dependent manner with sustained inhibition for 24-48 h post-dosing.

Clinical Studies of Copanlisib

Copanlisib has been under investigation as monotherapy or in combination with other agents in a number of clinical studies for the treatment of advanced oncologic malignancies; a brief outline of studies posted on ClinicalTrials.gov is provided below (the first 6 studies in the table have been restricted to US sites and the remaining 11 studies are international studies).

NCT	Phase	Agent(s)	Disease/Indication	Study Start – End* Sponsor/Country	Active/ Complete	Planned Accrual
NCT00962611	1	copanlisib	adv solid tumors	11/2009– 2/2016 Bayer/USA	complete	57
NCT01460537	1	copanlisib + gemcitabine +/- cisplatin	adv solid tumors	11/2011-12/2015 Bayer/USA	complete	50
NCT01411410	1	copanlisib + paclitaxel	adv solid tumors	8/ 2011-7/2015 Bayer/USA	complete	55
NCT02455297	2	copanlisib	relapsed/refr MCL that failed ibrutinib	8/2015-8/2019 Bayer/USA	active	152
NCT02631590	2	copanlisib + gemcitabine + cisplatin	adv or metastatic cholangiocarcinoma	5/2016-12/2018 Moffitt/USA	active	25
NCT02728258	2	Copanlisib	persistent/recurrent endometrial cancer	9/2016-6/2020 NRG Oncology/USA	Active	84
NCT01392521	1	copanlisib + refametinib	adv solid tumors	7/2011-4/2014 Bayer/ International (USA, Netherland, Germany)	complete	64
NCT02155582	1	copanlisib	adv NHL or solid tumor types with ≥30% frequency of PIK3CA or PTEN aberrations	8/2014-11/2016 Bayer/Europe	active, not recruiting	55
NCT02253420	1	copanlisib + itraconazole + rifampin	adv solid tumors	10/2014-2/2018 Bayer/Health Canada	active	26

NCT	Phase	Agent(s)	Disease/Indication	Study Start – End* Sponsor/Country	Active/ Complete	Planned Accrual
NCT02342665	1b/2	copanlisib	relapsed indolent B-cell NHL	4/2015-3/2019 Bayer/Japan	active	26
NCT01660451 **CHRONOS-1**	2	copanlisib	relapsed indolent or aggressive NHL, 3rd line	11/2012-3/2019 Bayer/International world-wide	active, not recruiting	227
NCT02369016 **CHRONOS-2**	3	copanlisib *vs.* placebo	indolent NHL refr to rituximab, 3rd line	9/2015-10/2019 Bayer/International world-wide	active	189
NCT02367040 **CHRONOS-3**	3	copanlisib + rituximab *vs.* placebo + rituximab	relapsed indolent B-cell NHL	6/2015-12/2020 Bayer/International world-wide	active	514
NCT02626455 **CHRONOS-4**	3	IMCTx +/- copanlisib+	relapsed indolent NHL	1/2016-12/2024 Bayer/International world-wide	active	676
NCT02391116	2	copanlisib	DLBCL (prior therapy for aggressive NHL required)	5/2015-1/2018 Bayer/International world-wide	active, not recruiting	67
NCT02705859	1b/2	copanlisib + trastuzumab	recurrent or metastatic HER^+ breast cancer	4/2016-10/2020 ICORG/Ireland	active	19
NCT02822482	1b/2	copanlisib + cetuximab	squamous cell carcinoma of head and neck	6/2016-6/2020 UNICANCER/France	active	32

* For a study that has yet not been completed (it is in an active status), the end of a study represents anticipated completion
Adv: advanced; refr: refractory; IMCTx: standard immunochemotherapy for NHL

The clinical MTD of copanlisib monotherapy, established in the first-in human phase 1b trial in patients with advanced solid tumors, was 0.8 mg/kg 1-h IV weekly for 3 weeks on a 28-day cycle (Lotze *et al.*, 2012; Patnaik *et al.*, 2016). The mean half-life at the MTD was 38 h. Copanlisib at the MTD was generally well tolerated with grade 2/3 hyperglycemia occurring following each dose. Hypertension lasting <24 hours was common in patients with pre-existing hypertension. Interstitial pneumonitis was seen only in patients with follicular lymphoma (FL).

In the phase 2 study, copanlisib monotherapy administered at the MTD demonstrated robust activity in patients with heavily pretreated relapsed/refractory lymphoma (Dreyling *et al.*, 2014a; Dreyling *et al.*, 2014b). The objective response rates (ORR) were: 53% for indolent NHL (excluding CLL), 38% for CLL (Dreyling *et al.*, 2014a), 29% for aggressive NHL (Dreyling *et al.*, 2014b). Among 11 patients with MCL (all had prior rituximab), 7 achieved objective responses accounting for 64% ORR (Cunningham *et al.*, 2015). Complete responses were observed in FL, MCL, and peripheral T-cell lymphoma. Common (>10%) grade 3-4 adverse events (AEs) included hypertension (43%), hyperglycemia (25%), neutropenia (27%), and anemia (13%) (Dreyling *et al.*, 2014b). There were three drug-related grade 5 events (lung infection, meningitis, and respiratory failure).

Rationale for Proposed PTMA Studies:

CTEP is interested in copanlisib due to its strong activity in B-cell hematologic malignancies and the possibility that it may have a better therapeutic index than older or oral pan-PI3K inhibitors currently in clinical development. Copanlisib has a favorable PK/PD profile *in vivo* with higher exposure in animal tumor *vs.* plasma and profound induction of apoptosis and prolonged inhibition of pAKT in H460 tumor xenografts. The relatively long half-life of copanlisib with weekly administration may also contribute to better tolerability compared to PI3K inhibitors given with daily administration, and may permit copanlisib combination therapy to be tolerated by patients. Pan-class I PI3K inhibitors show serious adverse effects upon long-term continuous dosing, which limits the on-therapy time (Toska and Baselga, 2016). Evidence from preclinical models

suggests that a transient but potent interruption of the PI3K pathway can increase tolerance without compromising therapeutic efficacy (Will *et al.*, 2014; Yang *et al.*, 2016). The IV formulation of copanlisib, while less convenient, may also lead to fewer gastrointestinal side effects than are seen with oral PI3K inhibitors, and may preclude large interpatient variations in absorption, commonly associated with oral PI3K inhibitors.

The activity of copanlisib in FL is presumably due to potent PI3Kδ inhibition by the agent. CTEP believes that this potent PI3Kδ inhibition may also break regulatory T-cell immune tolerance to cancer, leading to the potential for combination therapy with immune checkpoint inhibitors (Ali *et al.*, 2014).

Data from preclinical models suggest that activation of PI3K/AKT can confer resistance to antiestrogens and that there is reciprocal cross-talk between PI3K signaling by PI3K and ER, whereby inhibition of one of the pathways enhances the function of the other (Bosch and Bergamaschi, 2015; Mayer and Arteaga, 2016). One way by which the inhibition of PI3K could lead to sensitization of hormonal therapy is through the induction of estrogen-dependent transcriptional activity and increased ER expression, potentially mediated by increased FOXO3A-mediated transcription (Bosch et al, 2015).

Intermittent high-dose PI3K inhibition is both less toxic and more effective than more continuous daily administration of a drug such as buparlisib (BKM-120 or GDC-0941) in ER+/PIK3CA mutant breast cancer models (Toska and Baselga, 2016; Yang *et al.*, 2016). The BELLE-2 phase 3 trial of buparlisib/fulvestrant *vs.* fulvestrant was positive in ER+, HER2-negative breast cancer (PFS; 6.9 *vs.* 5 months), but demonstrated considerable toxicity and modest clinical benefit, partly because patients could not stay on buparlisib for more than a few months in most cases (Campone, 2016). When considering only those ER+ patients with PIK3CA mutation, the difference in PFS for the combination was more pronounced, *i.e.*, 7 months for the combination *vs.* 3.2 months for fulvestrant.

Copanlisib has selective activity in luminal breast cancer cell lines and demonstrates strong combined activity with hormonal blockade and with CDK-4/6 inhibition in ER-positive breast cancer cell line xenografts (O'Brien *et al.*, 2016). Single agent copanlisib induced significant tumor growth inhibition in ER-positive, HER2-negative xenograft models. Robust tumor regressions were shown with the triple combinations of copanlisib-palbociclib-tamoxifen and copanlisib-palbociclib-fulvestrant.

Pharmaceutical Information

Copanlisib is intended for IV use in humans. Copanlisib is available as a lyophilized product containing 60 mg of the drug powder in a 6 mL injection vial. *In vitro*, copanlisib is metabolized primarily via cytochrome P450 (CYP) isoform CYP 3A4 and to a lesser extent by CYP1A1. It is also a substrate of drug efflux transporters, *i.e.* P-gp and BCRP. Concomitant administration with strong inhibitors or inducers of CYP3A4 should be avoided. Use caution when administered with strong inhibitors and inducers of CYP1A1, P-gp, and BCRP. Copanlisib inhibits P-gp, BCRP, MATE2K, and MATE1; thus, caution is recommended when co-administered with drugs which are substrates of these proteins.

CTEP Plans for Copanlisib Development through the Project Team:

CTEP would like to utilize a copanlisib project team to develop several clinical trials with copanlisib as well as to devise appropriate pharmacodynamic and other biomarker studies for those trials. CTEP would like to utilize the results of the phase 1 study with nivolumab and copanlisib being initiated at NCI to follow up with two separate phase 2 studies of this combination 1) in patients with DLBCL and 2) in patients with non-heme refractory solid tumors. The rationale to focus on one or several solid tumor types in this trial can be discussed within the project team. These trials and their companion biomarkers will be developed through the project team process. In these trials, a run-in period of copanlisib (prior to the initiation of nivolumab) could be considered to permit pre- and post-treatment tumor biopsies, examining the immunomodulation of T-cell subsets with the PI3K inhibitor. The optimal design of these trials will be discussed with the complete project

team, but randomized trials of nivolumab +/- copanlisib may be considered. The development of a triplet therapy with copanlisib/nivolumab plus the CTLA4 inhibitor ipilimumab may also be considered. Correlative studies could focus on evaluating the effects of PI3K inhibition on immunomodulation of T-cell subsets as well as on phosphorylated AKT, S6K, and ERK, and cleaved caspase 3 in tumor biopsies. The role of the project team is to evaluate all available evidence to modify and refine this initial plan.

CTEP would also like to utilize the copanlisib project team to consider the development of a trial of copanlisib with fulvestrant (CF) in advanced ER-positive PIK3CA mutant and PI3KCA wild-type metastatic breast cancer. Bayer has plans for an investigator initiated ER-positive breast cancer neoadjuvant phase 1b/2 trial of letrozole/copanlisib (LC), with reduction of Ki-67 as the primary endpoint, but supports a CTEP-sponsored trial of CF in advanced breast cancer. This phase 2 trial would require a safety run-in or dose escalation, probably starting at the 45 mg weekly flat dose of copanlisib and escalating to the full 60 mg full dose in the combination. This trial might be considered for second-line treatment of ER-positive breast cancer patients progressing on an aromatase inhibitor. Separate cohorts of ER-positive breast cancer patients with PIK3CA-mutant and PIK3CA wild type tumors treated with CF could also be considered in this trial, due to a difference in the PFS of those two groups treated with buparlisib/fulvestrant (Campone, 2016).

CTEP will also consider development of a trial to study triplet therapy with copanlisib, palbociclib and fulvestrant, based on strong preclinical activity of the triplet in ER-positive breast cancer models and potential benefit of copanlisib in palbociclib resistance (O'Brien, 2016). A phase I trial could be considered, using doses and schedule of palbociclib/fulvestrant from the PALOMA-3 trial, with escalation of weekly treatment with copanlisib. Expansion cohorts, to assess safety and preliminary evidence of activity could be considered in ER-positive HER2-negative patients progressing after prior aromatase therapy and after prior treatment with letrozole/palbociclib

CTEP is willing to discuss different or additional copanlisib trials and the copanlisib project team applicants can suggest such studies either in the response to this PTMA or during the project team process if the applicant is accepted to the team. In a similar fashion, applicants for a basic science or translational position on the project team can suggest alternative trials, combinations, or biomarker strategies based on their experience in the field.

Correlative Studies of Interest to CTEP

CTEP is interested in the development of studies to examine the effects of copanlisib on regulatory T-cells, myeloid-derived suppressor cells (MDSCs), and other parameters of antitumor immunity in tumor biopsies and other patient-derived materials obtained from lymphoma and non-heme solid tumor patients receiving the agent. CTEP is also interested in the development of quantitative multiplex immunofluorescence or other assays that can examine the PD effects of copanlisib on PI3K pathway downstream targets from tumor biopsy material and ultimately patient-derived materials from clinical trials using copanlisib. Similar studies of the effect of copanlisib combinations on tumor proliferation and the generation of apoptosis *in vivo* are also of interest.

Limited funding for these biomarker/correlative studies may be available through the CRADA agreement for copanlisib established between NCI and Bayer Pharmaceuticals, and/or through grant mechanisms (UM1, R01, R21, etc.). Applications should specifically state whether correlative funding is available or being requested from NCI within their PTMA applications.

A CTEP project team could make recommendations for limited preclinical studies for copanlisib alone or in combination to examine biomarkers and to justify proposed clinical studies, as well as to plan biomarker studies to occur with the study. If these studies are requested by the project team, a proposal with a budget will be requested from the appropriate project team translational researcher involved, and the studies may be funded through a UM1 supplement.

Copanlisib Project Team Selection, Composition, and Tasks

The copanlisib project team will meet regularly by WebEx to review available evidence, determine promising strategies, examine clinical trial designs to test those strategies, and to identify biomarkers to evaluate those strategies. The project team will be composed of intramural and extramural members. The extramural members will include clinician scientists with experience in phase 1b/2 trial designs in lymphoma, breast cancer, and other refractory solid tumor patients; translational scientists with expertise in PI3K biomarker development; and basic scientists with expertise in the PI3K pathway, tumor immunology, ER signaling, and other aspects of tumor signaling and survival pathways. 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 success in accruing to and/or leading early phase clinical studies in the relevant indications, as represented in the NIH Biosketch.

Questions regarding this request for applications may be addressed to L Austin Doyle, M.D., Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6565; FAX: 240-276-7894; e-mail: doylela@mail.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 as project team members to develop Career Development Letters of Intent (CrDLs). https://ctep.cancer.gov/protocolDevelopment/lois_concepts.htm

Project Team Member Applications (PTMAs) should contain a clear indication of the applicant's desired role on the copanlisib 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), January 17, 2017.** The most recent version of the PTMA form, available on the CTEP Website (http://ctep.cancer.gov), must be used. PTMAs should be submitted electronically to:

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

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