DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

REQUEST FOR PROJECT TEAM MEMBER APPLICATIONS FOR CONDUCTING CLINICAL TRIALS USING IPATASERTIB (NSC 781451)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) is accepting Project Team Member Applications for a project assessing ipatasertib, a protein kinase B (AKT) inhibitor being evaluated by CTEP as an anticancer agent in collaboration with Genentech Inc. Ipatasertib is a small-molecule adenosine triphosphate (ATP)-competitive inhibitor that targets all three isoforms of AKT (Saura *et al*., 2017). It has been shown to block the phosphoinositide 3-kinase (PI3K)/AKT pathway in a dose-dependent manner in a variety of cell line and xenograft models (Lin *et al*., 2013). Mutations resulting in increased PI3K/AKT activity, including phosphatase and tensin homolog (PTEN) loss, high baseline phosphorylated AKT, amplification of human epidermal growth factor receptor 2 (*HER2*), and *PIK3CA* kinase domain mutations, are correlated with greater sensitivity to ipatasertib. These cells exhibit dose-dependent block of cell cycle progression at the G1 phase, as well as an increase in apoptotic and necrotic cell populations.

Clinical studies have found ipatasertib to be generally well tolerated. Used as a single-agent, the maximum tolerated dose (MTD) was determined to be 600 mg orally (PO) once daily (QD) on a 21 days on/7 days off (21/7) dosing schedule (Saura *et al*., 2017). The maximum administered dose (MAD) was 400 mg PO QD both on a continuous dosing schedule when ipatasertib was given in combination with abiraterone (1,000 mg QD) and on a 21/7 dosing schedule when ipatasertib was given in combination with chemotherapy like paclitaxel (Doi *et al*., 2019). Pharmacokinetic analysis showed that at 600 mg, mean half-life was 45.8 hours (range, 36.7–55.0 hours) (Saura *et al*., 2017). Among patients who received ipatasertib as a single agent, those patients who experienced stable disease (SD) or incomplete response (IR) were more likely to have mutations in PTEN, *PIK3CA*, or *AKT* indicative of elevated PI3K/AKT activity, whereas those who experienced progressive disease were less likely to have these mutations.

As outlined in this PTMA request, the planned CTEP drug development program for ipatasertib will include monotherapy or combination phase 1 or 2 trials. Combination regimens with hormonal therapy, targeted therapy, and immunotherapy for the treatment of cancers where the PI3K pathway is expected to drive resistance are high priority. The PI3K/AKT pathway is one of the most frequently altered pathways in cancer, critical for survival and growth of many tumors. Early preclinical and clinical data suggest that ipatasertib is most effective when mutations which activate the PI3K/AKT pathway are present. The role of the project team is to evaluate all available evidence to define an initial clinical development program.

It is anticipated that CTEP will activate 3 – 4 different monotherapy or combination trials with ipatasertib as part of the project team. This project team will include:

1. **Clinician Scientists** with expertise in phase 1 and phase 2 studies and with an interest in cancers where the PI3K pathway is expected to drive resistance (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 an interest in biomarker development in the PI3K signaling pathway (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 the PI3K signaling pathway (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 ipatasertib in combination trials, including prioritization of biomarker studies. It is anticipated that the clinicians on the drug project team will be expected to write 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 remain involved in the subsequent design and execution of the proposed trials. It is anticipated that the project team will complete its work in twelve weeks or less.

Background/Rationale

The AKT pathway is frequently activated in human cancers, where it plays a critical role in promoting tumor growth, proliferation, survival, and resistance to treatment (Saura *et al*., 2017). In cancer, it can be activated by multiple pathways, including activating mutations in PI3K, *PIK3CA*, increased receptor tyrosine kinase signaling, and loss of PTEN. AKT acts on a number of molecular targets, including forkhead box O3a (FoxO3a), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mammalian target of rapamycin (mTOR), and vascular endothelial growth factor (VEGF), which regulate cell proliferation, apoptosis, and/or survival (Sun *et al*., 2019). Because of these factors, AKT is a logical target for novel therapeutics for human cancers.

Previous small-molecule inhibitors of AKT have had safety and toxicity issues because of problems with selectivity (Lin *et al*., 2013). Ipatasertib is a novel ATP-competitive AKT inhibitor highly selective for activated AKT. Preclinical models indicate ipatasertib exhibits differential activity in cells with and without activated AKT signaling that is distinct from PI3K inhibitors. This observation suggests ipatasertib could prove effective in treating cancers where resistance is driven by the PI3K/AKT pathway.

Mechanism of Action

Ipatasertib selectively inhibits the active conformation of AKT. When AKT interacts with phospholipids such as PIP3, it undergoes a conformational shift, which allows PDK1 and mTORC2 to phosphorylate T308 and S473, respectively (Lin *et al*., 2012). This conformational shift allows the binding of both ATP, which stabilizes the active form and allows its enzymatic activity, and ipatasertib, which blocks the activity of AKT. The structure of ipatasertib is shown in Figure 1. Ipatasertib is equipotent against all three AKT isoforms, with potencies ranging from 5 to 18 nmol/L (Lin *et al*., 2013).

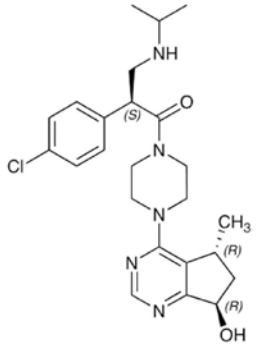

Figure 1: Structure of ipatasertib

Nonclinical Studies of Ipatasertib

The activity of ipatasertib has been evaluated in numerous *in vitro* models. Ipatasertib demonstrated the greatest degree of dose-dependent increase in AKT phosphorylation and growth inhibition in cell lines in which the PI3K/AKT pathway was most active (Lin, *et al*. 2013). This included PC-3 (*PTEN* homozygous deletion mutant, prostate), BT474M1 (*PIK3CA*^{K111N} mutant and *HER2*-amplified, breast), and IGROV-1 (*PTEN*$^{T319fsX1/Y155C}$ and *PIK3CA*^{1069W}, ovarian). In these cell lines, ipatasertib resulted in a dose-dependent block of cell cycle progression at the G1 phase.

Ipatasertib has also been tested *in vivo* in mouse xenograft models with human cancer types including prostate, breast, ovarian, colorectal, non–small cell lung (NSCLC), glioblastoma, and melanoma (Lin *et al*., 2013). Ipatasertib was most effective in xenograft models with AKT activation, whether due to *PTEN* loss, HER2 overexpression, or *PI3KCA* mutation or amplification. Tumor growth delay, stasis, or regression occurred at or below 100 mg/kg daily oral dose in these xenograft models. The viability of two *PIK3CA*-mutant cell lines decreased after treatment (MDA-MB-361 IC_{50}=2.83 mcmol; MDA-MB-453 IC_{50}=0.322 mcmol), however two wild type (WT) *PIK3CA* cell lines (MDA-MB-231 and BS-004) showed only a minor reduction in viability (Ippen *et al*., 2019). Ipatasertib efficacy was also compared in *PIK3CA*-mutant *vs*. WT breast cancer brain metastasis xenograft models. In the *PIK3CA*-mutant model, ipatasertib resulted in a significant inhibition of tumor growth in treated mice, whereas in contrast, sham-treated tumors continued to grow more rapidly. No differences in tumor growth and survival were detected in *PIK3CA*-WT intracranial tumors over the course of treatment.

Clinical Studies of Ipatasertib

As of March 10, 2020, ipatasertib has been evaluated in 29 completed or ongoing clinical trials. An outline of these trials is shown below:

NCT Number	Status	Conditions	Treatments	Ph	Enroll	Start	Completion
NCT04253561	Recruiting	Metastatic Breast Cancer	Ipatasertib| Trastuzumab| Pertuzumab	1	25	Feb-20	Sep-23
NCT03341884	Completed	Hepatic Insufficiency	Ipatasertib	1	29	Nov-17	Jun-18
NCT03222310	Completed	Healthy Volunteers	Ipatasertib| Itraconazole	1	15	Jul-17	Sep-17
NCT03840200	Recruiting	Breast Cancer| Prostate Cancer| Ovarian Cancer	Ipatasertib| Rucaparib	1|2	54	Jun-19	Nov-21
NCT03853707	Recruiting	Breast Cancer	Carboplatin| Ipatasertib| Paclitaxel	1|2	28	Mar-19	Jun-22
NCT03673787	Recruiting	Solid Tumor |Glioblastoma Multiforme| Prostate Cancer	Ipatasertib| Atezolizumab	1|2	51	Aug-18	Nov-20
NCT02536391	Completed	Cancer	Ipatasertib	1	18	Oct-15	Nov-15
NCT02063581	Completed	Healthy Volunteer	Ipatasertib	1	16	Feb-14	Mar-14
NCT02301988	Completed	Breast Cancer	Ipatasertib| Paclitaxel| Placebo	2	151	Feb-15	Aug-17
NCT03072238	Active, not recruiting	Metastatic Prostate Cancer	Ipatasertib| Abiraterone| Placebo	3	1101	Jun-17	Oct-23
NCT02162719	Completed	Breast Neoplasms	Ipatasertib| Paclitaxel| Placebo	2	124	Sep-14	Aug-19
	Recruiting	Breast Cancer	Ipatasertib| Fulvestrant| Aromatase Inhibitor| Palbociclib	1	60	May-19	Jun-24
NCT03337724	Recruiting	Breast Cancer	Ipatasertib| Paclitaxel| Placebo	2|3	450	Jan-18	Dec-21
NCT02390492	Completed	Healthy Volunteer	Period 1 treatment|Period 2 treatment	1	8	Mar-15	Apr-15
NCT04060862	Recruiting	Breast Cancer	Ipatasertib| Placebo| Palbociclib| Fulvestrant	1b/ 3	370	Nov-19	Jan-26
NCT01896531	Active, not recruiting	Gastric Cancer	5-Fluorouracil| Ipatasertib| Leucovorin| Oxaliplatin| Placebo	2	154	Aug-13	Jan-21
NCT04177108	Recruiting	Triple-Negative Breast Cancer	Atezolizumab| Ipatasertib| Paclitaxel |Placebo	3	1155	Nov-19	Oct-25

NCT Number	Status	Conditions	Treatments	Ph	Enroll	Start	Completion
NCT03800836	Recruiting	Breast Cancer	Ipatasertib| Paclitaxel| Atezolizumab| Nab-Paclitaxel|AC	1	202	Feb-18	Oct-22
NCT01485861	Recruiting	Prostate Cancer	Abiraterone| Apitolisib| Ipatasertib| Placebo| Prednisone| Prednisolone	1|2	295	Jan-12	Apr-21
NCT01362374	Active, not recruiting	Neoplasms	5-FU|Docetaxel|Enzalutamide|Ipatasertib|Leucovorin| Oxaliplatin| Paclitaxel	1	123	Jul-11	Jan-20
NCT01562275	Completed	Neoplasms	Ipatasertib| Cobimetinib	1	67	Apr-12	Jan-15
NCT03395899	Recruiting	Breast Cancer	Atezolizumab| Cobimetinib| Ipatasertib| Bevacizumab	2	160	Dec-17	Dec-20
NCT02430363	Unknown status	Glioblastoma	MK - 3475|Biological: Suppressor of the PI3K/Akt pathways	1|2	58	Mar-13	Jun-18
NCT03280563	Recruiting	Breast Neoplasms	Atezolizumab (MPDL3280A), an engineered anti-programmed death-ligand 1 (PD-L1) antibody| Bevacizumab| Entinostat| Exemestane| Fulvestrant| Ipatasertib| Tamoxifen| Abemaciclib	1|2	126	Dec-17	Oct-22
NCT03424005	Recruiting	Triple Negative Breast Cancer	Capecitabine|Atezolizumab|Ipatasertib|SGN-LIV1A|Bevacizumab|Cobimetinib| Chemotherapy (Gemcitabine + Carboplatin or Eribulin)|RO6874281|Selicrelumab	1|2	310	Apr-18	Aug-21
NCT03337698	Recruiting	Carcinoma, Non-Small-Cell Lung	Atezolizumab|Cobimetinib|RO6958688|Docetaxel|CPI-444| Pemetrexed| Carboplatin| Gemcitabine| Linagliptin| Tocilizumab| Ipatasertib| Idasanutlin	1|2	250	Jan-18	Apr-22
NCT03385655	Recruiting	Prostate Cancer	Adavosertib| Savolitinib| Darolutamide| CFI-400945| Ipatasertib| Durvalumab and Tremelimumab	2	500	Dec-17	Dec-21
NCT03498521	Recruiting	Cancer of Unknown Primary Site	Alectinib| Vismodegib| Ipatasertib| Olaparib| Erlotinib| Bevacizumab| Vemurafenib| Cobimetinib| Trastuzumab Subcutaneous (SC)| Pertuzumab| Atezolizumab| Carboplatin| Paclitaxel| Cisplatin| Gemcitabine| Entrectinib	2	790	Jul-18	Jun-22

NCT Number	Status	Conditions	Treatments	Ph	Enroll	Start	Completion
NCT02465060	Recruiting	Advanced Malignant Solid Neoplasm| Bladder Carcinoma| Breast Carcinoma| Cervical Carcinoma| Colon Carcinoma| Colorectal Carcinoma| Endometrial Carcinoma| Esophageal Carcinoma| Gastric Carcinoma| Glioma| Head and Neck Carcinoma| Kidney Carcinoma| Liver and Intrahepatic Bile Duct Carcinoma| Lung Carcinoma| Lymphoma| Malignant Uterine Neoplasm| Melanoma| Ovarian Carcinoma| Pancreatic Carcinoma| Plasma Cell Myeloma| Prostate Carcinoma| Rectal Carcinoma| Myeloma| Skin Carcinoma| Thyroid Gland Carcinoma| Uterine Corpus Cancer	Adavosertib| Afatinib| Afatinib Dimaleate| Binimetinib| Capivasertib| Copanlisib| Copanlisib Hydrochloride| Crizotinib| Dabrafenib| Dabrafenib Mesylate| Dasatinib| Defactinib| Defactinib Hydrochloride| Erdafitinib| FGFR Inhibitor AZD4547| Ipatasertib| Larotrectinib| Larotrectinib Sulfate|Nivolumab| Osimertinib| Palbociclib| Pertuzumab| PI3K-beta Inhibitor GSK2636771| Sapanisertib| Sunitinib Malate| Taselisib| Trametinib| Trastuzumab| Trastuzumab Emtansine| Ulixertinib| Vismodegib	2	6452	Aug-15	Jun-22

CTEP's Plan for Ipatasertib Development

CTEP would like to employ an ipatasertib project team to develop a clinical trials program that complements the company's development program. The first area to address are populations known to be enriched for alterations in the PI3K/AKT pathway, particularly ovarian, endometrial, cervical, and head and neck cancers. Possible clinical investigations include phase 2 studies using ipatasertib in combination with hormonal therapy or bevacizumab in recurrent endometrial cancer, in combination with immune

checkpoint inhibitors (ICIs) in metastatic melanoma, or in combination with taxane chemotherapy in head and neck squamous cell carcinoma (HNSCC) after progression on platinum and/or ICI therapies.

The second area of interest is the exploration of ipatasertib in tumors where the PI3K pathway is expected to drive resistance (*i.e.* epidermal growth factor receptor [EGFR]). Possible clinical investigations include phase 1b trials of ipatasertib in combination with osimertinib in NSCLC with EGFR mutation, in combination with a poly (ADP-ribose) polymerase (PARP) inhibitor in recurrent ovarian cancer, or in combination with a BCL-2 inhibitor in relapse/refractory acute myeloid leukemia (AML). Possible investigations include phase 1 trials of ipatasertib in combination with bevacizumab. Other possible investigations include ipatasertib in combination with endocrine therapy (e.g., fulvestrant, oral SERDs, or aromatase inhibitors) in hormone receptor (HR)+ breast cancer, or other ER+ tumors (e.g., ovarian or endometrial), or in combination with taxane chemotherapy outside of breast cancer.

The third main area of interest is exploring ipatasertib combinations in early stage or high-risk breast cancer. One possible clinical investigation is adding ipatasertib to adjuvant therapy in triple-negative breast cancer (TNBC) or HR+/HER2- patients that are at high risk of recurrence based on the presence of circulating tumor DNA (ctDNA) post-surgery or during adjuvant treatment. Another possible investigation is a phase 1b/2 study of ipatasertib combined with eribulin in TNBC patients that relapse within 1 year of adjuvant therapy.

A fourth area of interest is exploring ipatasertib combinations in prostate cancer, including in early or locally advanced settings. Possible clinical investigations include a phase 1b/2 study of ipatasertib and androgen blockade in metastatic hormone-sensitive prostate cancer patients at a high risk of progression.

A fifth area that CTEP is interested in evaluating is the combination of ipatasertib and radiation therapy, based on preclinical data indicating that ipatasertib and other AKT inhibitors enhance the effects of radiotherapy (Eke *et al*., 2018; Narayan *et al*., 2017; Oeck *et al*., 2017; Searle *et al*., 2017).

An additional high priority area of interest for the CTEP program is developing biomarker-driven studies to explore the role of PI3K/AKT signaling in cancer driven survival and adaptive immunity. Possible clinical investigations include examining how ipatasertib impacts immune cell infiltration and activation, tumor cell immune checkpoint expression, or differentiation of immune cells.

Ipatasertib Project Team Selection, Composition, and Tasks

The ipatasertib drug project team will meet regularly by WebEx to review available evidence and determine promising strategies, identify appropriate biomarkers, prioritize 3-4 initial strategies, and develop efficient clinical trial designs to test these strategies. Non-prioritized trial concepts may be further developed and independently submitted to CTEP by clinicians following the completion of the project team, as appropriate. The project team will be composed of intramural and extramural members. The extramural members will include clinician-scientists with experience in phase 1 - 2 studies in cancers where the PI3K pathway is expected to drive resistance; translational scientists with expertise in biomarker development; and basic scientists with expertise in PI3K signaling pathways. Since the clinician scientists selected for the project team will be expected to lead the clinical trials that emerge from this process, the evaluation criteria for the clinician scientists will include not only clinical trial expertise but also their documented record of accrual to early phase trials of cancer histologies where the PI3K pathway is expected to drive resistance.

Questions regarding this request for applications may be addressed to Dr. John Wright, M.D., PhD, Associate Branch Chief, Investigational Drug Branch (IDB), CTEP, DCTD, NCI (phone: 240-276-6105; FAX: 240-276-7894; e-mail: wrightj@ctep.nci.nih.gov) or to Dr. John Torsten Sandlund, M.D., Medical Officer, IDB, CTEP, DCTD, NCI (phone: 240-276-6565; e-mail: john.sandlund@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 Ipatasertib 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), June 10, 2020**. 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. All submissions funded by NCTN organizations should include a Letter of Support from the Group Chair. 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 submit their applications directly to PIO.

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