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 ABEMACICLIB (NSC# 783671)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) is accepting Project Team Member Applications (PTMAs) for a project using abemaciclib (LY2835219, Verzenio™), an adenosine triphosphate (ATP)-competitive inhibitor of cyclin-dependent kinase (CDK) 4/6 being developed by CTEP as an anticancer agent in collaboration with Eli Lilly and Company. Abemaciclib is an orally (PO) bioavailable small molecule inhibitor that prevents phosphorylation and subsequent inactivation of the retinoblastoma (Rb) tumor-suppressor protein, inducing $G_1$ cell-cycle arrest and inhibition of cell proliferation (Patnaik *et al.*, 2016). It has been approved for treatment of advanced/metastatic breast cancer both as a single agent and in combination with other agents.

At the present time, the preliminary CTEP drug development plan is to prioritize combination early phase trials of abemaciclib in novel disease areas. 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 3-4 different trials with abemaciclib. The project team will include:

1. **Clinician Scientists** with expertise in early phase studies and with an interest in sarcomas, testicular germ cell tumors, uveal melanomas, lymphoma and gynecologic 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 an interest in biomarker development of CDK4/6 inhibition and cell cycle modulation and mechanisms of acquired resistance to CDK 4/6 inhibitors (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 cell-cycle biology applied to pathogenesis and progression of neoplasia (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 abemaciclib in early phase 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 6-8 weeks or less.

## Background/Rationale

During the cell cycle, the $G_1$ restriction point controls entry into S phase and is essential for maintaining control of cell division (Sherr, 1996; Ortega *et al.*, 2002). CDK4 and CDK6 participate in a complex with D-type cyclins to initiate the transition through the $G_1$ restriction point by phosphorylating and inactivating the retinoblastoma (Rb) tumor-suppressor protein. Alterations in this pathway occur frequently in human cancers and involve loss of CDK inhibitors by mutation or epigenetic silencing, mutation/overexpression of either CDK4 and CDK6 or cyclin D, or inactivation of Rb. These alterations render cells less dependent on mitogenic signaling for proliferation. From a therapeutic standpoint, the goal of inhibiting CDK4 and CDK6 with a

small-molecule inhibitor is to prevent cell cycle progression through the $G_1$ restriction point, thus arresting tumor growth.

Mechanism of Action

Abemaciclib (Figure 1) is an ATP-competitive inhibitor of CDK4 and CDK6. Abemaciclib potently inhibits CDK4 and CDK6 at 50% inhibitory concentrations ($IC_{50}$) of 2 nM and 10 nM, respectively (Gelbert *et al.*, 2014). This inhibits phosphorylation of Rb and thus dissociation of the E2F family of transcription factors, arresting cells in $G_1$ at the restriction point and inhibiting proliferation. Precise dissociation constants for ATP binding ($Ki^{ATP}$) were 0.6 nM and 2.4 nM for CDK4/cyclin D1 and CDK6/cyclin D1, respectively. Minimal activity is observed with CDK9 ($IC_{50}$=57 nM), but this does not translate to significant cellular activity. Activity was also seen against Proviral Integration site of Moloney murine leukemia virus 1 (PIM1) kinase ($IC_{50}$=50 nM).

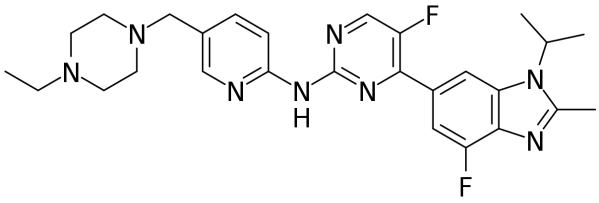


**Figure 1: Structure of abemaciclib**

Nonclinical Studies of Abemaciclib

Abemaciclib has shown nonclinical evidence of antitumor activity in breast cancer (Vidula and Rugo, 2016), colorectal cancer (Gelbert *et al.*, 2014), acute myeloid leukemia (Gelbert *et al.*, 2014), glioblastoma (GBM) (Raub *et al.*, 2015), non-small-cell lung cancer (NSCLC) (Patnaik *et al.*, 2016), lung adenocarcinoma (Litchfield *et al.*, 2018), mantle-cell lymphoma (MCL) (Gelbert *et al.*, 2014), melanoma (Tate *et al.*, 2014), multiple myeloma (Iriyama *et al.*, 2018), Ewing sarcoma (Dowless *et al.*, 2018), and renal cell carcinoma (Small *et al.*, 2017), as a single agent or in combination with other agents.

Clinical Pharmacology of Abemaciclib

In clinical pharmacokinetic (PK) studies, abemaciclib plasma concentrations increased dose-dependently following doses between 50 and 275 mg (Patnaik *et al.*, 2016). The time course was characterized by a slow absorption phase with a median time to maximum plasma concentration ($t_{max}$) ranging from 4 to 6 hours. The mean terminal elimination half-life ($t_{1/2}$) ranged from 17.4 to 38.1 hours, with no apparent dose-dependent change in clearance. Abemaciclib concentrations in the cerebrospinal fluid (range of 2.2-14.7 nM) exceeded the $Ki^{ATP}$ for the CDK4/cyclin D1 complex. In pharmacodynamic analysis, a decrease of ≥60% in Rb separated most patients with stable disease or response from those with progressive disease.

Population PK modeling determined relative bioavailability to be dependent on dose and time parameters in a linear one-compartment model, with serum albumin and alkaline phosphatase concentrations being the only significant covariates (Tate *et al.*, 2018). Based on this analysis, no abemaciclib dose adjustments are currently recommended for adults of different sex, age, or body weight.

Clinical Studies of Abemaciclib

The following active studies are being conducted as part of the Eli Lilly clinical development program for abemaciclib (Table 1):

**Table 1: Active abemaciclib clinical trial listings on ClinicalTrials.gov (not including trials solely in breast cancer)**

| NCT Number | Phase | Agent(s) | Disease/ Indication | Sponsor | Study Start-End | Planned Accrual | Abstract |
|---|---|---|---|---|---|---|---|
| NCT01394016 | 1 | Abemaciclib; abemaciclib + fulvestrant | Advanced cancer | Eli Lilly | 12/2009-10/2019 | 220 | (Patnaik *et al.*, 2016; Tate *et al.*, 2018) |
| NCT01739309 | 2 | Abemaciclib | MCL | Eli Lilly | 3/2013-9/2019 | 28 | |
| NCT02014129 | 1 | Abemaciclib | Metastatic cancer; lymphoma | Eli Lilly | 12/2013-6/2019 | 12 | (Fujiwara *et al.*, 2016) |
| NCT02079636 | 1 | Abemaciclib + pemetrexed; abemaciclib + gemcitabine; abemaciclib + ramucirumab; abemaciclib + LY3023414; abemaciclib + pembrolizumab | NSCLC | Eli Lilly and Merck | 3/2014-7/2020 | 150 | (Kim *et al.*, 2018) |
| NCT02152631 | 3 | Abemaciclib *vs.* erlotinib | NSCLC | Eli Lilly | 10/2014-9/2019 | 453 | (Goldman *et al.*, 2018) |
| NCT02308020 | 2 | Abemaciclib | Breast cancer, NSCLC, or melanoma with brain metastases | Eli Lilly | 4/2015-11/2019 | 247 | (Bachelot *et al.*, 2018) |
| NCT02411591 | 1 | Necitumumab + abemaciclib | NSCLC | Eli Lilly | 6/2015-5/2019 | 70 | (Besse *et al.*, 2018) |
| NCT02450539 | 2 | Abemaciclib *vs.* docetaxel | NSCLC | Eli Lilly | 8/2015-2/2019 | 159 | (Scagliotti *et al.*, 2018) |
| NCT02688088 | 1 | Drug cocktail (caffeine, warfarin, dextromethorphan, and midazolam) +/- abemaciclib (drug-interaction study) | Advanced solid tumors | Eli Lilly | 2/2016-4/2019 | 48 | |
| NCT02745769 | 1 | Ramucirumab + merestinib; ramucirumab + abemaciclib | Advanced cancer; colorectal cancer; MCL | Eli Lilly | 10/2016-1/2019 | 23 | |
| NCT02784795 | 1 | LY3039478 + taladegib; LY3039478 + abemaciclib; LY3039478 + gemcitabine + cisplatin; LY3039478 + gemcitabine+carboplatin; LY3039478 + LY3023414 | Advanced or metastatic solid tumors | Eli Lilly | 11/2016-7/2019 | 163 | |
| NCT02919696 | 1 | Abemaciclib | Advanced or metastatic cancer in native Chinese participants | Eli Lilly | 8/2017-12/2019 | 20 | |

| NCT Number | Phase | Agent(s) | Disease/ Indication | Sponsor | Study Start-End | Planned Accrual | Abstract |
|---|---|---|---|---|---|---|---|
| NCT02981342 | 2 | Abemaciclib *vs.* abemaciclib + LY3023414 *vs.* standard of care (gemcitabine or capecitabine) | Pancreatic ductal adenocarcinoma | Eli Lilly | 1/2017-4/2019 | 231 | (Chiorean *et al.*, 2017) |
| NCT02981940 | 2 | Abemaciclib +/- surgery | GBM | Dana-Farber and Eli Lilly | 2/2017-4/2022 | 42 | |
| NCT01655225 | 1 | LY3023414; LY3023414 + midazolam; LY3023414 + fulvestrant; LY3023414 + pemetrexed + cisplatin; LY3023414 + abemaciclib + letrozole | Advanced or metastatic cancer | Eli Lilly | 7/2012-3/2020 | 130 | (Bendell *et al.*, 2018) |
| NCT02779751 | 1b | Abemaciclib + pembrolizumab; abemaciclib + pembrolizumab + anastrozole | NSCLC; breast cancer | Eli Lilly and Merck | 11/2016-10/2021 | 100 | (Tolaney *et al.*, 2018) |
| NCT02791334 | 1a/1b | LY3300054; LY3300054 + ramucirumab; LY3300054 + abemaciclib; LY3300054 + merestinib; LY3300054 + LY3321367 | Advanced refractory solid tumors | Eli Lilly and Merck | 6/2016-7/2020 | 215 | (Patnaik *et al.*, 2018) |
| NCT02846987 | 2 | Abemaciclib | Liposarcoma | Memorial Sloan-Kettering and Eli Lilly | 7/2016-7/2019 | 33 | |
| NCT02857270 | 1 | LY3214996; LY3214996 + midazolam; LY3214996 + abemaciclib; LY3214996 + nab-paclitaxel + gemcitabine | Advanced or metastatic cancer | Eli Lilly | 9/2016-7/2020 | 252 | |
| NCT02977780 | 2 | Temozolomide *vs.* temozolomide + neratinib + radiation *vs.* CC-115 + radiation *vs.* temozolomide + abemaciclib + radiation | GBM | Dana-Farber, Eli Lilly, Celgene, Puma Biotechnology, and Accelerate Brain Cancer Cure | 2/2017-5/2021 | 280 | (Alexander *et al.*, 2017) |
| NCT03220646 | 2 | Abemaciclib | Primary brain tumor | Memorial Sloan-Kettering and Eli Lilly | 7/2017-7/2020 | 78 | |
| NCT03310879 | 2 | Abemaciclib | Advanced solid tumor of non-breast origin | Dana-Farber and Eli Lilly | 11/2017-4/2025 | 38 | |
| NCT03643510 | 2 | Fulvestrant + abemaciclib | Recurrent endometrial adenocarcinoma | Memorial Sloan-Kettering and Eli Lilly | 8/2018-8/2021 | 25 | |

| NCT Number | Phase | Agent(s) | Disease/ Indication | Sponsor | Study Start-End | Planned Accrual | Abstract |
|---|---|---|---|---|---|---|---|
| NCT03675893 | 2 | Letrozole + LY3023414 + abemaciclib *vs.* LY3023414 + abemaciclib | Endometrial cancer | Dana-Farber and Eli Lilly | 12/2018-12/2020 | 62 | |
| NCT03706365 | 2 | Abemaciclib + abiraterone + prednisone *vs.* placebo + abiraterone + prednisone | Metastatic castrate-resistant prostate cancer | Eli Lilly | 11/2018-2/2024 | 180 | |

Abemaciclib was initially approved by the Food and Drug Administration (FDA) in combination with fulvestrant for women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer with disease progression following endocrine therapy and as monotherapy in patients with disease progression following endocrine therapy and prior chemotherapy (FDA, 2017). It was later approved in combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer (FDA, 2018). Abemaciclib is currently under active investigation in other indications as a monotherapy and in combination with other agents.

## CTEP's Plans for Abemaciclib Development

While CDK4/6 inhibitors have changed the landscape of breast cancer therapy, other less common entities could benefit from abemaciclib therapy as well, based on available preclinical/basic data. These diseases include, but are not limited to, liposarcoma, testicular germ cell tumors, uveal melanoma, diffuse large B-cell lymphoma (DLBCL), multiple myeloma, and gynecologic malignancies.

Correlative Studies of Interest to CTEP

CTEP is committed to biomarker-driven clinical science and has a strong interest in further understanding D-Cyclin Activating Features (DCAF) as related to sensitivity to abemaciclib. Pharmacodynamic markers will also be pursued.

## Abemaciclib Project Team Selection, Composition, and Tasks

The abemaciclib drug project team will meet regularly by WebEx to review available evidence, determine promising strategies, identify biomarkers to evaluate these strategies, and evaluate clinical trial designs to test these strategies. The project team will be composed of intramural and extramural members. The extramural members will include clinician-scientists with experience in early phase studies in areas that include but are not limited to liposarcoma, testicular germ cell tumors, uveal melanoma, DLBCL, multiple myeloma, and gynecologic malignancies; translational scientists with expertise in biomarker development; and basic scientists with expertise in cell cycle modulation and cyclin inhibition. 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 to a variety of early phase studies.

Questions regarding this request for applications may be addressed to Percy Ivy, M.D., Associate Branch Chief, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6565; FAX: 240-276-7894; e-mail: ivyp@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 abemaciclib 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), May 13, 2019**. 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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