National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

REQUEST FOR PROJECT TEAM MEMBER APPLICATIONS
FOR CONDUCTING CLINICAL TRIALS USING ROGARATINIB (NSC# 804782)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) is accepting Project Team Member Applications for a project using rogaratinib (BAY 1163877), an adenosine triphosphate (ATP)-competitive inhibitor of fibroblast growth factor receptor (FGFR) 1-4 (FGFR1-4) being developed by CTEP as an anticancer therapy in collaboration with Bayer AG (Leverkusen, Germany). Rogaratinib is an orally (PO) available small molecule inhibitor that targets the kinase domain of FGFR1-4 (Collin *et al.*, 2018). As a single agent, it shows potent cytotoxic activity toward cell lines that express constitutively active FGFRs or aberrantly express FGFRs due to gene alteration. Bayer is using an mRNA-based FGFR assay (RNA scope) to pre-select patients for clinical studies with rogaranib.

The role of the CTEP Rogaratinib Project Team will be to evaluate all available evidence to determine whether there is adequate preclinical data to support an early clinical trial with rogaratinib alone or in combination with other agents in cholangiocarcinoma with FGFR2-fusion protein complexes, estrogen receptor (ER)-positive metastatic breast cancer with FGFR1 and FGFR2 gene alterations, and selected sarcomas. The project team may decide to recommend clinical trials or may direct the development of pre-clinical evidence in specific areas. In addition, CTEP is also interested in developing assays that could replace or complement the current FGFR mRNA-based selection biomarker strategy and that could be incorporated into potential early phase clinical trials.

The project team will include:

1. **Clinician Scientists** with expertise in early phase studies and with an interest in solid tumors containing known FGFR aberrations, including cholangiocarcinoma, breast cancer, and sarcoma (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 for incorporation into clinical trials of this FGFR 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 the cancer biology of FGFR inhibitors (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 rogaratinib 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 should they be developed. 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 weeks or less.

Background/Rationale

Fibroblast growth factor (FGF)/FGFR signaling regulates cell proliferation, survival, differentiation, migration, and angiogenesis (Brooks *et al*., 2012; Feng *et al*., 2015; Perez-Garcia *et al.*, 2018). Dysregulation of this pathway has been associated with developmental disorders and cancers in humans. There are five FGFR isoforms, four of which FGFR1-4 are receptor tyrosine kinases (RTKs), whereas FGFR5 lacks the intracellular

kinase motif (Brooks *et al.*, 2012). FGFRs function primarily through the FGF binding to the extracellular domain followed by intracellular recruitment of FRS2 and subsequent activation of downstream signaling pathways (RAS-MAPK, PI3K-AKT, PLCγ-PIP$_2$, and STAT). Among 18 biologically active members of the FGF protein family, there are three hormone-like FGFs (FGF19, 21, and 23), which function in endocrine manner and other 15 "canonical" FGFs (FGF1-10, 16 18, 20, and 22) function as autocrine and paracrine growth factors (Perez-Garcia *et al.*, 2018). Alternatively, ligand-independent activation may arise from activating mutations, aberrant expression, or translocations that lead to permanent dimerization (Brooks *et al.*, 2012). Regulatory mechanisms involved in FGFR signaling appear to be different depending on tumor type and molecular context (Feng *et al.*, 2015; Perez-Garcia *et al.*, 2018).

Genetic and epigenetic alterations of FGFR1-4 genes, including amplifications, activating mutations, gene fusion complexes, DNA methylation, histone remodeling, microRNA regulation, *etc.* were found in human cancers (Feng *et al.*, 2015). The genetic profiling of ~5000 tumor specimens by Next-Generation Sequencing (NGS) identified FGFR aberrations in 7.1%, with the majority being gene amplifications (66%), mutations (26%), and rearrangements (8%) (Helsten *et al.*, 2016). The FGFR alterations were most frequent in *FGFR1* (3.5%) followed by *FGFR3* (2.0%), *FGFR2* (1.5%), and *FGFR4* (0.5%). The most commonly affected tumor histologies were urothelial (32%), breast (18%), endometrial (13%), squamous lung cancers (13%), ovarian cancer (9%), glioma (8%), and cholangiocarcinoma (7%). In a different study of genetic profiling in conjunction with expression and functional analyses of ~100 Ewing sarcoma specimens, activating mutations in *FGFR1* were rare, but the copy number gain in *FGFR1* (either due to gene amplification or trisomy 8) was detected in 31.7% (13/41) of specimens studied (Agelopoulous *et al.*, 2015). FGFR overexpression is a predictor for poor response to endocrine therapy in breast cancer (Turner *et al.*, 2010). Rhabdomyosarcoma (RMS) cells with *FGFR4*-activating mutations and osteosarcoma cells with high *FGFR1* expression are prone to sensitivity with FGFR inhibitors (Taylor 6th *et al.*, 2009; Weekes *et al.*, 2016).

Mechanism of Action

Rogaratinib (Figure 1) is an ATP-competitive inhibitor of FGFR1-4 (Collin *et al.*, 2018). Rogaratinib potently inhibits kinase activity of FGFR1-4 isoforms, with 50% inhibitory concentrations (IC$_{50}$s) of 1.8 nM for FGFR1, <1 nM for FGFR2, 9.2 nM for FGFR3, and 1.2 nM for FGFR4. It also shows the inhibitory potency against vascular endothelial growth factor receptor 2 (VEGFR2) (IC$_{50}$=120 nM).
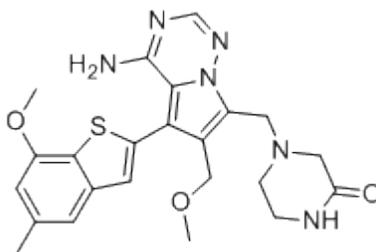

Figure 1: Structure of rogaratinib

Nonclinical Studies of Rogaratinib

In vitro efficacy has been observed in cell lines derived from breast cancer, urothelial bladder cancer (UBC), RMS, and squamous cell carcinoma of the lung, head and neck, or esophagus with FGFR alterations (Héroult *et al.*, 2015; Politz *et al.*, 2017; Politz *et al.*, 2018). Rogaratinib potently inhibited proliferation of bFGF-stimulated HUVEC (IC$_{50}$=16 nM), but VEGF-stimulated HUVEC were inhibited less efficiently (IC$_{50}$=453 nM) (Collin *et al.*, 2018). *In vivo* single-agent efficacy has been observed in xenograft mouse models for SCC, hepatocellular carcinoma, and breast cancer. In combinatorial therapy, rogaratinib re-sensitized xenograft models of antiestrogen-resistant breast cancer with *FGFR1* amplification to fulvestrant (Politz *et al.*, 2017).

The preclinical pharmacokinetic (PK) profile of intravenously (IV) administered rogaratinib exhibited a low blood clearance in rats (0.78 L/hr/kg) and dogs (0.36 L/h/kg), with plasma steady-state volumes of distribution of 0.54 L/kg and 1.2 L/kg, respectively (Collin *et al.*, 2018). Dose-normalized exposures (area under the concentration-time curve [AUC]) of rogaratinib administered PO in rats and dogs were 0.96 kg/h/L and 1.2 kg/h/L, respectively, and oral bioavailability was 46% and 35%, respectively. Terminal half-lives ($t_{1/2}$) for PO administered rogaratinib were 4.5 h and 3.8 h in rats and dogs, respectively.

Clinical Studies of Rogaratinib

The following studies are being conducted as part of the Bayer AG clinical development program for rogaratinib (Table 1):

Table 1: Rogaratinib clinical trial listing on ClinicalTrials.gov							
NCT	Phase	Agent(s)	Disease/Indication	Study Start-End	Status/ Sponsor	Planned Accrual	Abstract*
NCT01976741	1	Rogaratinib	Advanced solid tumors	12/2013 – 07/2019	Active Bayer	224	Joerger *et al.*, 2016; Ellinghaus *et al.*, 2017; Joerger *et al.*, 2017a; Joerger *et al.*, 2017b; Joerger *et al.*, 2018
NCT02592785	1	Rogaratinib	Advanced solid tumors	12/2015 – 12/2017	Complete Bayer	9	Tahara *et al.*, 2018
NCT03410639	2/3	Rogaratinib versus Investigator choice of taxane (docetaxel or paclitaxel) or vinflunine IV	Urothelial carcinoma	07/2018 (Anticipated)	Not yet recruiting Bayer	400	
NCT03473756	1b/2	Rogaratinib + Atezolizumab	Urothelial carcinoma	06/2018 (Anticipated)	Not yet recruiting Bayer	190	

Data from the dose-escalation phase of the ongoing first-in-human phase 1 trial of rogaratinib monotherapy in patients with advanced solid tumors (NCT01976741) suggest that rogaratinib was well-tolerated up to 800 mg PO twice a day (BID), with no dose-limiting toxicities (DLTs) and manageable dose modification (Joerger *et al.*, 2016). The recommended phase 2 dose (RP2D) was 800 mg BID on a 21-day cycle. Rogaratinib was absorbed rapidly and exhibited an average plasma $t_{1/2}$ of 12.7 h. The most common adverse events (AEs) were grade 1/2 diarrhea, hyperphosphatemia, and alopecia. Patients enrolled to three expansion cohorts (non-small-cell lung cancer [NSCLC], UBC + head and neck squamous cell carcinoma [HNSCC], and all-comers) were prescreened for overexpression of *FGFR1-3by* mRNA levels were assigned to cohorts for. Among 44 evaluable patients treated in the expansion phase, 5 (1 each HNSCC, squamous NSCLC, and adenoid cystic carcinoma of tongue, and 2 UBC) had partial response (PR) and 18 had SD >3 months. The majority of the responders (4/5) did not have genetic FGFR alterations (mutation, amplification, or translocation) despite having high FGFR1 or 3 mRNA levels (Joerger *et al.*, 2016 and Ellinghaus *et al.*, 2017).

As of February 2018, the overall response rate in 51 evaluable UBC patients was 24% (12/51, all PRs), and the disease control rate (DCR) was 73% (37/51) (Joerger *et al.*, 2018). Of the 12 responders, 11 were positive for *FGFR3* mRNA, 5 of whom also had *FGFR3* mutations, and 1 was positive for *FGFR1* mRNA. For 10 patients who had prior immunotherapy, overall response rate (ORR) was 30% (3/10), and DCR was 80% (8/10).

Nine patients with advanced solid tumors overexpressing *FGFR* mRNA were enrolled in a phase 1 of rogaratinib monotherapy trial in Japan (NCT02592785) (Tahara *et al.*, 2018). Safety and toxicity of rogaratinib

were similar to the results from NCT01976741. One patient with epipharynx cancer achieved a PR, and the DCR was 56% (5/9).

CTEP's Plans for Rogaratinib Development

At the present time, CTEP plans to develop rogaratinib in a stepwise manner:

Step 1:

Identification of reliable, reproducible, sensitive and specific biomarker or biomarker set able to identify the patient population likely to respond to FGFR inhibition based on molecular features across different tissue histologies.

Review of preclinical data supporting the combination of rogaratinib with other agents, and direct the development of additional preclinical data to help prioritize ETCTN trials with rogaratinib.

Step 2 is contingent upon success of Step 1; and could include early phase clinical trials involving:

1. Cholangiocarcinoma with FGFR2 alterations
2. ER+/HER2- metastatic breast cancer with *FGFR1* or *FGFR2* alterations in patients who have progressed on initial hormone therapy
3. Sarcoma (including pediatric)
4. Solid tumors in combination with immune checkpoint inhibitors

Correlative Studies of Interest to CTEP

Assays for *FGFR* mRNA expression (via RNAscope or other methods) and gene alterations (including mutations, gene amplifications, and translocations) can be used for patient stratification. However, CTEP's goal is to implement a selection strategy that will efficiently identify patients harboring alterations in *FGFR* biology that would render them responsive to FGFR inhibition. This strategy might not only be based on mRNA expression.

Potential pharmacodynamic markers may include, but are not limited to, phosphorylated FGFRs, phosphorylated MAPK pathway proteins, and serum FGF23 (a potential surrogate marker for hyperphosphatemia mediated by renal FGFR1 inhibition) (Yanochko *et al.*, 2013).

Rogaratinib Project Team Selection, Composition, and Tasks

The rogaratinib drug project team will meet regularly by WebEx to review available evidence and 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 early phase studies involving FGFR modulation across tissue types, translational scientists with expertise in biomarker development; and basic scientists with expertise in FGFR biology. 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 pertinent early phase studies.

Questions regarding this request for applications may be addressed to Fernanda Arnaldez, M.D., Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6565; FAX: 240-276-7894; e-mail: fernanda.arnaldez@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.

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 Rogaratinib 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 25, 2018**. 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 <u>Clinician Scientists</u> 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 submit their applications directly to PIO.

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