NCCN/Pfizer Request for Proposals (RFP) Phase I/II Clinical Trials of Axitinib in the Treatment of Melanoma, Hepatocellular Carcinoma and Colorectal Cancer

I. Introduction

National Comprehensive Cancer Network® (NCCN) and Pfizer Global Medical Grants (Pfizer) are collaborating to offer a new grant opportunity seeking proposals to support NCCN Member Institution faculty utilizing axitinib. The intent of this RFP is to encourage NCCN Member Institutions to submit clinical research proposals specifically in the treatment of melanoma, hepatocellular carcinoma (HCC) and colorectal cancer (CRC).

The National Comprehensive Cancer Network® (NCCN®) is a not-for-profit alliance of 30 leading cancer centers devoted to patient care, research, and education. NCCN is dedicated to improving and facilitating quality, effective, efficient, and accessible cancer care so patients can live better lives. Through the leadership and expertise of clinical professionals at NCCN Member Institutions, NCCN develops resources that present valuable information to the numerous stakeholders in the health care delivery system. By defining and advancing high-quality cancer care, NCCN promotes the importance of continuous quality improvement and recognizes the significance of creating clinical practice guidelines appropriate for use by patients, clinicians, and other health care decision-makers around the world.

The mission of Pfizer Global Medical Grants is to accelerate the translation of science into quality patient care through independent grants, partnerships, and collaborations. Pfizer Global Medical Grants supports the global healthcare community's independent initiatives (e.g., research, quality improvement or education) to improve patient outcomes in areas of unmet medical need that are aligned with Pfizer's medical and/or scientific strategies. For all Investigator Sponsored Research (ISRs) and general research grants, the grant requester (and ultimately the grantee) is responsible for the design, implementation, sponsorship, and conduct of the independent initiative supported by the grant, including compliance with any regulatory requirements. Pfizer will not be involved in any aspect of study protocol or project development, nor the conduct or monitoring of the research program.

This Request for Proposals (RFP) is being issued by both organizations. NCCN is the lead organization for review and evaluation of proposals. A review committee, led by NCCN, will make decisions on which proposals will receive funding. **Grant funding and overall management of the funded studies will be provided directly from Pfizer.**

II. Background

Preclinical data

Overview on role of angiogenesis in cancer and immune modulation

Angiogenesis is a well described hallmark of promoting cancer and inhibition of angiogenesis has proven clinical benefit in many clinical settings. The primary pathway that characterizes angiogenesis is the vascular endothelial growth factor (VEGF) pathway. Vascular endothelial growth factors are involved in angiogenesis, lymphangiogenesis, and vasculogenesis. They are primarily known as mediators of tumor neovascularization. Different isoforms of VEGF (A–F) bind to transmembrane receptors (VEGF-R 1–3),

resulting in dimerization and activation through phosphorylation of tyrosine kinases[1]. VEGF is secreted by most tumors in response to hypoxia-inducible factor (HIF) or upregulation of oncogenes, such as c-myc[2].

In addition to angiogenesis, VEGF also contributes to immune evasion through multiple mechanisms including the promotion and expansion of inhibitory immune cell subsets (regulatory T cells {Tregs} and myeloid-derived suppressor cells {MDSCs}), suppression of dendritic cell maturation, mitigation of effector T-cell response, and alteration of lymphocyte development and trafficking[3]. Increased VEGF serum levels are associated with a poorer prognosis in many tumor types[4,5,6,7,8].

Role of VEGF in melanoma
Melanoma cells demonstrate high levels of VEGF, VEGF-R1, VEGF-R2, and VEGF-R3. Clinically, higher levels of VEGF are associated with poorer prognosis in patients with metastatic melanoma. In addition, high levels of VEGF are associated with lack of response to high dose interlukin-2 (IL-2) and decreased overall survival (OS) with ipilimumab, suggesting that inhibition of VEGF could improve treatment outcomes[9,10].

Role of VEGF in HCC
HCC typically overexpress VEGF-A, PDFG, IGF-1 and TGF-Beta leading to increased neoangiogenesis and tumor proliferation via hepatocyte growth factor secretion and macrophages. Related to this, HCCs are highly vascularized tumors, presumably making them good candidates for both antiangiogenic agents and arterial endovascular local therapy procedures, such as the different forms of embolization.

Role of axitinib in immune modulation
Axitinib can increase in CD8+ T-cells and CD45+ cells with immune-stimulating antigen-presenting phenotype in tumor tissue. In addition, axitinib decreases the accumulation and suppressive capacity of myeloid derived suppressor cells (MDSC) and reduces inflammation through inhibition of phospho-STAT3, Arg1, and iNOS2[11,12,13].

Clinical Data

Pharmacokinetics of axitinib
Axitinib is an oral small molecule indazole derivative inhibitor of VEGF Receptors 1, 2, and 3. The IC50 for axitinib on VEGFR 1, 2, and 3 is very low making it one of the more potent small molecules in this space (in comparison to sorafenib[14,15], cabozantinib[16,17] and lenvantinib[18]). In addition, axitinib possess a much shorter half-life of 2.5-6.1 hours compared to 20-99 hours of most other approved anti-VEGFR TKIs. The shorter half-life allows for rapid reversal of potential adverse events thereby making it ideal to combine with other anti-cancer agents.

Clinical data of axitinib in melanoma
In 2011, Freuhauf et al[19] published a multicenter, open-label, phase II study evaluating the safety and clinical activity of axitinib with metastatic melanoma. The study included 32 patients aged 18 years or older with histologically confirmed metastatic melanoma, who had received no more than one prior systemic therapy for metastatic disease. The objective response rate (ORR) was 18.8% with an additional 18.8% achieving stable disease for an overall clinical benefit rate of 37.5%. Median OS was 6.6 months with 33.9% achieving a six-month progression-free survival.

In 2015, Algazi et al[20] published the results of a clinical/correlative prospective phase II combination study of axitinib followed by paclitaxel/carboplatin which yielded extended survival in advanced BRAF wild-type metastatic melanoma patients with ECOG performance status 0–1 and normal organ function. Up to three prior lines of therapy were enrolled as long as these did not include carboplatin or paclitaxel. Axitinib 5 mg orally twice a day was taken on days 1–14 of each 21-day treatment cycle, and carboplatin (AUC=5) with paclitaxel (175 mg/m^2) was administered on day 1 starting with cycle 2. Among the 36 evaluable patients, nineteen (52.8%) were progression free at 6 months; eight of the 36 patients (22.2%) evaluable for response had confirmed partial responses (PR), and an additional 16 patients (44.4%) had stabilization of disease as the best response for an ORR of 22% and a disease control rate of 66.7%.

In 2019, Sheng et al[21] published the results of a single-center, phase IB trial evaluating the safety and preliminary efficacy of toripalimab, a humanized immunoglobulin G4 monoclonal antibody against PD-1, in combination with the VEGF receptor inhibitor axitinib in patients with advanced melanoma, including patients with chemotherapy-naive mucosal melanomas (88%). Exclusion criteria included history of autoimmune diseases, ongoing infections, or prior anti–PD-1, anti–programmed death ligand-1 (PD-L1), or anti–PD-L2 immunotherapy. Patients received toripalimab at 1 or 3 mg/kg via intravenous infusion every 2 weeks, in combination with axitinib 5 mg orally twice a day. Thirty-three patients were enrolled (mucosal melanoma, n=29; unknown primary, n=2). By the cutoff date, among 29 patients with chemotherapy-naïve mucosal melanoma, fourteen patients (48.3%; 95% CI, 29.4% to 67.5%) achieved an objective response per RECIST v1.1, and the median progression-free survival was 7.5 months (95% CI, 3.7-NE).

Clinical data of axitinib in HCC

In 2015, Kang et al[22] published the randomized phase II study of axitinib versus placebo plus best supportive care in second-line treatment of advanced HCC. All patients progressed on prior anti-angiogenic therapy and were Child-Pugh A/B7. Patients were stratified by tumor invasion and region (Asian/non-Asian) and randomized (2:1) to axitinib/ best supportive care (BSC) or placebo/BSC. There was no statistical difference in OS between the axitinib/BSC and placebo/BSC arms. The median OS was 12.7 months with axitinib/BSC and 9.7 months with placebo/BSC. Most common all-causality adverse events with axitinib/BSC were diarrhea, hypertension, and decreased appetite.

In 2015, McNamara et al[23] published a phase II trial of second-line axitinib following prior antiangiogenic therapy in advanced HCC. This study employed Simon's optimum 2-stage design. The median PFS for all patients was 3.6 months; 4.6 months for Asians versus 3.0 months for non-Asians and 4.1 months for Child-Pugh A versus 2.8 months for Child-Pugh B7. The median OS for all patients was 7.1 months; 9.7 months for Asians versus 6.6 months for non-Asian and 8.2 months for Child-Pugh A versus 3.0 months for Child-Pugh B7. Most common axitinib-related grade 3/4 adverse events were hypertension, thrombocytopenia and diarrhea.

In 2017, Chan et al[24] published a phase II study of the efficacy and biomarker on the combination of transarterial chemoembolization and axitinib in the treatment of inoperable HCC. Among the 44 evaluable patients, 18 patients achieved complete response and 12 patients achieved partial responses. The combination of axitinib and TACE demonstrated an ORR in approximately two thirds of the patients and median OS of 18.8 months.

In 2016, Lo et al[25] published a small study of 20 patients was conducted to evaluate the utility of dynamic contrast-enhanced ultrasound in measuring early tumor response of axitinib in HCC. Median overall survival was 7.1 months and progression free survival was 3.6 months. This was not significantly associated with PFS or progression at 16 week with a borderline statistically significant OS.

Clinical data of axitinib in CRC

In 2010, Sharma et al[26] published a phase I study of axitinib (AG-013736) in combination with bevacizumab plus chemotherapy or chemotherapy alone in patients with metastatic colorectal cancer and other solid tumors. Patients with previously treated solid tumors received axitinib (starting dose 5 mg twice daily) combined with FOLFOX (5-fluorouracil/leucovorin/ oxaliplatin) plus bevacizumab (1, 2, or 5 mg/kg, cohorts 1-3, respectively), FOLFIRI (5-fluorouracil/leucovorin/irinotecan) (cohort 4), or FOLFOX (cohort 5). Thirty patients were enrolled (n = 16, 8, and 6 for cohorts 1-3, 4, and 5, respectively) with ten patients having RECIST-confirmed partial tumor responses (objective response rate: 33.3%).

In 2013, Bendell et al[27] published the result a randomized phase II study of axitinib or bevacizumab plus FOLFIRI or modified FOLFOX-6 after failure of first-line therapy for metastatic colorectal cancer. Patients were randomized 1:1 to axitinib 5 mg twice daily or bevacizumab 5 mg/kg every 2 weeks plus modified FOLFOX-6 (if previously treated with irinotecan) or FOLFIRI (if previously treated with oxaliplatin) and stratified by performance status and prior bevacizumab therapy. Primary endpoint was progression-free survival (PFS). In 171 patients, PFS was 7.6 months with axitinib/FOLFOX versus 6.4 months with bevacizumab/FOLFOX (hazard ratio [HR], 1.04; 95% confidence interval [CI], 0.55-1.96; 1-sided P = .55) and 5.7 months with axitinib/FOLFIRI vs. 6.9 months with bevacizumab/FOLFIRI (HR, 1.27; 95% CI, 0.77-

2.11; 1-sided P = .83). OS was 17.1 vs. 14.1 months with axitinib/FOLFOX and bevacizumab/FOLFOX (HR, 0.69; 95% CI, 0.37-1.27; 1-sided P = .12) and 12.9 vs. 15.7 months with axitinib/FOLFIRI and bevacizumab/FOLFIRI (HR, 1.36; 95% CI, 0.82-2.24; 1-sided P = .88). Compared to bevacizumab, axitinib did not improve outcomes when added to second-line chemotherapy for metastatic colorectal cancer.

In 2013, Infante et al[28] published the results of an open-label, randomized phase 2 trial evaluating axitinib, bevacizumab, or both in combination with chemotherapy as first-line treatment of metastatic colorectal cancer (mCRC). Previously untreated mCRC were randomized 1:1:1 to receive continuous axitinib 5 mg twice daily, bevacizumab 5 mg/kg every 2 weeks, or axitinib 5 mg twice daily plus bevacizumab 2 mg/kg every 2 weeks, each in combination with modified 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX-6). One hundred and thirty-six patients were enrolled. The ORR was numerically inferior in the axitinib arm (n = 42) versus the bevacizumab arm (n = 43; 28.6% vs. 48.8%; 1-sided *P* = .97). PFS (11.0 months vs. 15.9 months; 1-sided *P* = .57) and OS (18.1 months vs. 21.6 months; 1-sided *P* = .69) also were numerically inferior in the axitinib arm. Similarly, efficacy endpoints for the axitinib/bevacizumab arm (n = 41) were numerically inferior (ORR, 39%; PFS, 12.5 months; OS, 19.7 months).

In 2017, Bendell et al[29] published a non-randomized, open-label phase-2 trial designed to examine the efficacy of single agent axitinib as maintenance therapy for patients with mCRC who received first-line treatment with mFOLFOX/bevacizumab. Patients with metastatic colorectal cancer were eligible to receive maintenance axitinib after four cycles of mFOLFOX/bevacizumab. Median PFS was 8.3 months, which was consistent with historical controls of other first-line regimens.

In 2018, Gravalos et al[30] published their work evaluating the efficacy and safety of axitinib as maintenance therapy, compared with placebo, in patients achieving disease control from a first-line induction chemotherapy with or without bevacizumab or cetuximab (KRAS wild-type tumor). This study was a double-blinded, placebo-controlled, multicenter, randomized, phase II trial. Patient were eligible if they achieved a complete response (CR), PR, or stable disease (SD), after 6 to 8 months of standard induction treatment with a regimen containing fluoropyrimidine (5-FU or capecitabine) oxaliplatin (FOLFOX, XELOX) or irinotecan (FOLFIRI, XELIRI), bevacizumab or cetuximab (KRAS wild-type tumors). Forty-nine patients were included with 25 in arm A and 24 in arm B. The median follow-up was 26.1 months (95% confidence interval [CI], 18.4-31.7 months). PFS rate at 6 months was 40% (95% CI, 21.3%-58.1%) in the axitinib arm versus 8.3% (95% CI, 1.4%-23.3%) in the placebo arm (*P* = .0141). The median PFS was statistically significantly longer in the axitinib group than in the placebo group (5.0 vs. 3.2 months; hazard ratio, 0.46; 95% CI, 0.25-0.86; *P* = .0116). Median OS was also longer in the axitinib arm but did not reach statistical significance (27.6 vs. 20.0 months; hazard ratio, 0.7; 95% CI, 0.3-1.5; *P* = .33).

III. Scope

The overall aim is to develop innovative studies to help determine the role of axitinib in the treatment of melanoma, HCC and CRC. It is hoped proposals submitted in response to this RFP will be useful in guiding further development of axitinib in combination with other therapies. Studies with correlative endpoints will be accepted but cannot be the primary endpoint.

Collaboration between NCCN Member Institutions is strongly encouraged in order to foster the interactive sharing of knowledge and expertise, and to utilize the combined clinical strengths of members, particularly in the case of uncommon tumors. Although the submitting investigator must be from an NCCN Member Institution, participating institutions do not need to be an NCCN Member Institution. This can also include cross-institutional collaboration for the conduct of correlative studies.

The NCCN Request for Proposals Development Team (RFPDT) has developed a Request for Proposals (RFP) with a formalized review procedure to accept applications and select the proposals of highest scientific merit. The NCCN RFPDT has overseen the development of the RFP. A NCCN Scientific Review Committee composed of members of this group and others will perform the review of applications.

This RFP is open to investigators from NCCN Member Institutions. Collaboration between NCCN Member Institutions is strongly encouraged in order to foster the interactive sharing of knowledge and expertise, and to utilize the combined strengths of members. Although the submitting applicant must be from an NCCN Member Institution, participating institutions do not need to be NCCN Member Institutions.

Areas of Interest (Phase I/II studies in the identified tumor types):

- Melanoma:
    - Combination or sequencing trials with immunotherapy in the front line or refractory setting
    - Combination or sequencing trial with BRAF/MEK inhibition in the front line or refractory setting
    - Neo-adjuvant combination or sequential therapy approaches in resectable melanoma (pathological responses will be accepted)
    - Trials for melanoma brain metastases (with or without radiation therapy)

- Hepatocellular Carcinoma:
    - Rationally justified studies with local therapy
    - Combination or sequencing trials with immunotherapy for advanced disease
    - Exclusions:
        - Monotherapy for advanced disease will not be considered

- Colorectal Cancer (concepts will need to be novel due to current activity in this space):
    - Neoadjuvant or other settings where the short half-life of axitinib may prove advantageous
    - Rationally designed combination studies with immunotherapy
    - Local liver metastasis disease studies
    - Exclusions:
        - Evaluation of axitinib in a setting where there is already an approved indication for bevacizumab will not be considered (e.g. first-line metastatic disease)

Specific exclusions from this RFP include:

- The following concepts are out of scope:
    - Preclinical or biomarker only studies
    - Purely translational studies
    - Tissue agnostic trials
    - Trials in the adjuvant space
    - Studies in combination with Pfizer investigational products OX40 or RN888

IV. Requirements

Date RFP Issued:	May 20, 2020
Clinical Area:	Melanoma, HCC and CRC
Applicant Eligibility Criteria:	Investigators from NCCN Member Institutions

Budget:	• There is $1.5 Million available for funding. It is anticipated that 2-3 trials will be awarded funding
	• There is a maximum of 28% for indirect costs
	• General Guidance (inclusive of indirects):
	  • $500,000 for a multi-institutional trial
	  • $300,000 for a single institution trial
	  • Additional funding may be available for exceptional concepts with detailed justification within the budget

Estimated Key Dates:	• Proposal Deadline: August 12, 2020 11:59pm Eastern Time • Anticipated Notification Date: Early October
Study Timelines	• Commence, which is defined as the first patient receiving the first dose of study drug(s), no later than 10 months of notice of study approval • Accrual period-within 2 years of commencement • Manuscript submission within 9 months after study endpoint achieved
How to Apply:	Please go to https://www.cybergrants.com/pfizer/Research and sign in. First-time users should click "REGISTER NOW" Requirements for submission: • Select the following Competitive Grant Program Name: 2020 Oncology NCCN Pfizer Axitinib Project • Complete all required sections of the online application. See Appendix A for additional details If you encounter any technical difficulties with the website, please click the "Technical Questions" link at the bottom of the page
Selection Criteria:	Applications will be evaluated on the basis of: 1. Scientific Value 2. Research experience of the Principal Investigator 3. Soundness of study design 4. Feasibility, including reasonable assurance of achieving intended and full accrual 5. Budgetary reasonableness 6. Statistics
Questions:	• Guide for applicants: https://www.cybergrants.com/pfizer/Research/GMG_ResearchApplication_ExternalPreview.pdf • If you have questions regarding this RFP, please direct them in writing to Nicole Kamienski, NCCN Research Study Associate at Kamienski@nccn.org or Pfizer's Grant Officer, Jacqueline Waldrop at Jacqueline.Waldrop@pfizer.com with the subject line "NCCN Pfizer Axitinib Project"

Mechanism by which Applicants will be Notified:	• All applicants will be notified via email by the anticipated dates noted above • Applicants may be asked for additional clarification if needed by the during the review period

IV. References

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APPENDIX A

Applications will be accepted via the online portal. When uploading your Full Proposal/Protocol please ensure it addresses the following:

Goals and Objectives	• Provide the main goal of the study and the study population (if applicable). Provide a detailed definition that is directly linked to the primary objective
Assessment of Need for the Project	• This should reflect your study rationale. Provide a brief description of the medical/scientific question and the rationale of how this trial or study addresses the question
Target Audience	• Describe the primary audience(s) targeted for this project. For Investigator Sponsored Clinical Trials, please specify the age, gender and other demographic information for trial population • Also indicate whom you believe will directly benefit from the project outcomes. Describe the overall population size as well as the size of your sample population
Project Design and Methods	• Describe concisely the research design and methods for achieving the stated goals. For a clinical interventional study, include inclusion/exclusion criteria, treatment plan and statistical plan
Innovation	• Explain what measures you have taken to assure that this project idea is original and does not duplicate other projects. Describe how this project builds upon existing work, pilot projects, or ongoing projects developed either by your institution or other institutions related to this project
Evaluation and Outcomes	• Specify type and frequency of safety, efficacy, and/or outcome measures. Also indicate the method(s) used to assess measures • Provide a publication plan describing intended submission of abstracts to (a) congress(es) or intended submission of (a) publication(s) to peer-reviewed journals. All publications must follow ICH guidelines
Anticipated Project Timeline	• Provide an anticipated timeline for your project including project start/end dates
Additional Information	• If there is any additional information you feel Pfizer should be aware of concerning the importance of this project, please summarize here • Early-career applicants: Letter(s) of support from mentor(s) and collaborators describing how the award will advance the applicant's career.

Organization Detail	• This information is used to assess the capability of the organizational resources available to perform the effort proposed. Identify the facilities to be used [laboratory, animal, clinical and “other”]. If appropriate, indicate their capacities, pertinent capabilities, relative proximity and extent of availability to the project
References	• Bibliography of relevant references.