NCCN Pfizer Request for Proposals (RFP): Development of Talazoparib for Prostate Cancer

National Comprehensive Cancer Network® (NCCN®) and Pfizer Global Medical Grants (Pfizer)

I. Introduction

National Comprehensive Cancer Network® (NCCN) and Pfizer Global Medical Grants (Pfizer) are collaborating to offer a new grant opportunity seeking proposals to advance the understanding of the mechanisms of action, underlying biology, and clinical activity of talazoparib in prostate cancer.

The National Comprehensive Cancer Network® (NCCN®) is a not-for-profit alliance of 31 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 must 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.** A total of $1.5 Million USD is available for award.

II. Background

The intent of the RFP is to encourage organizations to submit letters of intent (LOIs) describing concepts and ideas to promote the further development of talazoparib for the treatment of prostate cancer.

Several poly (ADP-ribose) polymerase inhibitors (PARPi) have demonstrated efficacy in patients with metastatic castration-resistant prostate cancer (mCRPC) with the greatest activity seen in patients with homologous recombination repair (HRR) deficiency.[1] Two PARPi are FDA-approved for the treatment of patients with mCRPC. Olaparib is indicated for the treatment of patients with mCRPC, a deleterious germline or somatic mutation in an HRR gene, and disease progression following prior treatment with enzalutamide or abiraterone.[2,3] Rucaparib is indicated for the treatment of patients with mCRPC, a deleterious germline or somatic BRCA mutation and disease progression following treatment with androgen receptor-directed therapy and a taxane-based chemotherapy. [4,5] There is an ongoing debate regarding the optimal panel of biomarkers to predict response and resistance to PARPi in prostate cancer. Other important gaps in knowledge include the role of PARP inhibitors in other prostate cancer disease states and role of PARP inhibitors in combination with other drugs. Other PARPi currently under investigation for prostate cancer include niraparib, veliparib and talazoparib.

Talazoparib is a PARP inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (*gBRCAm*) human epidermal growth factor receptor 2 (HER2) -negative locally advanced or metastatic breast cancer.[6] Talazoparib is not indicated for the treatment of prostate cancer. In addition to catalytic inhibition, talazoparib and other PARP inhibitors induce PARP trapping at sites of DNA damage. The capacity to trap PARP–DNA complexes varies among PARP inhibitors and is not correlated with PARP enzymatic inhibition.[7,8,9,10] Pre-clinical models suggest that PARP-trapping may be more effective in inducing apoptosis than enzymatic inhibition of PARP alone. [7,8,9,10] In pre-clinical models, talazoparib is a potent PARPi, with both strong catalytic inhibition (half-maximal inhibitory concentration, 4 nM) and PARP-trapping that is approximately 100 times greater than that of other PARP inhibitors.[8] The clinical implications of more potent PARP-trapping are unknown.

The TALAPRO-1 study provides preliminary evidence that talazoparib is active in patient with mCRPC and HRR deficiency.[11] TALAPRO-1 included patients with mCRPC, DDR deficiency, progression following at least one taxane and either abiraterone acetate or enzalutamide. Between July 4, 2017 and March 20, 2020, the study enrolled 128 patients. The median (range) duration of talazoparib treatment was 6.2 (0.5–22.2) months in the efficacy population. TALAPRO-1 met its primary objective with a confirmed objective response rate (ORR) of 29.8%. In patients with BRCA1/2 alterations, the ORR of 45.9% and median rPFS was 11.2 months. Objective responses, PSA responses, circulating tumor cell (CTC) count reductions or stable were observed across DNA mutations. The most common all-grade treatment-emergent adverse events were anemia, nausea, decreased appetite, and asthenia.

Ongoing and planned clinical trials will further evaluate the efficacy and safety of talazoparib in prostate cancer. TALAPRO-2 (NCT03395197) is an ongoing international, phase III, placebo-controlled study of talazoparib and enzalutamide in patients with mCRPC with and without DDR mutations. TALAPRO-3 (NCT04821622) is a phase III, placebo-controlled study of talazoparib with enzalutamide in DDR gene mutated metastatic castration-sensitive prostate cancer (mCSPC).

III. Scope

The overall aim is to develop innovative investigations to help determine the role of talazoparib and foster the development of PARPi in prostate cancer. Proposals should focus on clinical development of talazoparib alone or in combinations, understanding the biologic mechanisms of talazoparib, or defining optimal patient factors and other predictive biomarkers of clinical benefit. Both clinical trials with correlative endpoints and basic research proposals are encouraged.

This RFP is open to investigators from all US institutions. Collaboration between institutions is strongly encouraged in order to foster the interactive sharing of knowledge and expertise, and to utilize the combined strengths of members.

IV. Letters of Intent (LOI)/Proposals

This RFP model employs a 2-stage process using the Pfizer web-based system. Stage 1 is the submission of the 3-page LOI; if an LOI is selected, the applicant will be invited to Stage 2 to submit a full program proposal. Details are provided in Section VII.

The NCCN Scientific Review Committee (SRC) has been formed to oversee this process and will utilize a formalized review procedure to accept LOIs and subsequently select the proposals of highest scientific merit. The NCCN SRC has overseen the development of the RFP and will perform the peer review of applications.

Areas of Interest:

The following areas of pre-clinical research are encouraged:

1. Mechanisms of action of talazoparib
2. Role of PARP trapping in response and resistance
3. Predictors of response and resistance to talazoparib
4. Models of resistance
5. Novel combinations with talazoparib

The following areas of clinical and translational research are encouraged:

1. Clinical trials to understand biomarkers of response to talazoparib
2. Clinical trials to understand and overcome resistance to talazoparib
3. Role of talazoparib in other prostate cancer disease states beyond metastatic CRPC
4. Novel combinations with talazoparib
5. Translational research using existing tissue specimens and/or databases to better understand the role of talazoparib in prostate cancer treatment

Specific Exclusions from this RFP include:

1. Studies that do not include talazoparib
2. Studies in tumor types other than prostate cancer
3. Combinations with chemotherapy or immunotherapy
4. Clinical trials that compare talazoparib to chemotherapy
5. Pediatric studies

V. Requirements

Date RFP Issued:	April 27, 2021
Clinical Area:	Prostate Cancer

Applicant Eligibility Criteria:	To be eligible: • The institution and principal investigator (PI) must be based in the United States. • Only organizations are eligible to receive grants, not individuals or medical practice groups. • The applicant (PI) must have a medical or doctoral degree (MD, PhD, or equivalent), an advanced nursing degree (BSN with a MS/PhD), or a degree in Pharmacy, Physiotherapy, or Social Work. • Applicant must be affiliated with a host institution. • Proposals including mentorship of early career investigators are encouraged.
Budget:	A total of $1.5 Million is available to fund selected projects. It is anticipated that 3-5 projects will be awarded funding but the final number will depend on the quality of the projects and is at the discretion of the review panel. The maximum indirect (overhead) rate is 28% and must be included in the total grant amount requested. Applicants are required to disclose additional sources of funding for this project and demonstrate that funding does not overlap with the scope of this award. Amount requested may not exceed the budget limit set forth in the RFP and the budget submitted must be within fair market value. No funding for capital equipment is allowed.
Estimated Key Dates:	LOI Deadline: **6/21/2021** Please note the deadline is 5:00 pm Eastern Time. Anticipated LOI Notification Date: **8/4/2021** Full Proposal Deadline: * **9/24/2021** *Only accepted LOIs will be invited to submit full proposals. Please note the deadline is 5:00 pm Eastern Time. Anticipated Full Proposal Notification Date: **11/01/2021** Grants distributed following execution of fully signed Letter of Agreement.

Study Timeline:	2 years.
How to Apply:	Please go to www.cybergrants.com/pfizer/loi and sign in. First-time users should click "REGISTER NOW". Requirements for submission: Select the following Competitive Grant Program Name: **2021 Oncology: Talazoparib for Prostate Cancer** Complete all required sections of the online application referring to the guide included in the Appendix If you encounter any technical difficulties with the website, please click the "Need Support?" link at the bottom of the page. **IMPORTANT:** Applications submitted through the wrong application type and/or submitted after the due date will not be reviewed by the committee.
Selection Criteria:	Applications will be evaluated on the basis of: 1. Impact and Scientific Value 2. Feasibility and Institutional Environment 3. Study Design and Scientific Hypotheses 4. Alignment to Areas of Interest outlined in the RFP 5. Budget 6. Appropriateness of Statistical Approach 7. Opportunity for career development and mentorship
Questions:	If you have questions regarding this RFP, please direct them in writing to Nicole Kamienski, NCCN Senior Research Study Associate at Kamienski@nccn.org with the subject line "NCCN Pfizer Talazoparib Project".
Grant Agreements:	If your grant is approved, your institution will be required to enter into a written grant agreement with Pfizer. Please click here to view the core terms of the agreement. Pfizer has drafted the terms of these agreements to be balanced and reasonable and to further the goals of both parties. Negotiating grant agreements requires significant resources, so please ensure that your institution (including your legal department) is able and willing to abide by these terms before proceeding with submission of your application as they will need to be accepted in their entirety.

Review and Approval Process:	Grant requests received in response to a specific RFP are reviewed by a Scientific Review Committee (SRC) to make final grant decisions. The panels are comprised of professionals from the medical community with advanced degrees and expertise in particular clinical areas, or specific needs of a geographic region/learner group, or expertise in research, continuing professional development or quality improvement.
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 or to make a summary presentation during the review period.

VI. Terms and Conditions

1. This RFP does not commit Pfizer or its partners to award a grant or a grant of any particular size if one is awarded, nor to pay any costs incurred in the preparation of a response to this request.

2. Pfizer reserves the right to accept or reject any or all applications received as a result of this request, or to cancel this RFP in part or in its entirety, if it determines it is in the best interest of Pfizer to do so.

3. For compliance reasons and in fairness to all applicants, all communications about the RFP must come exclusively to Pfizer at the email address included in the RFP. Applicants should not contact other departments within Pfizer regarding this RFP. Failure to comply will disqualify applicants.

This RFP does not provide permission and license for the use (including the creation of derivative products) of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for commercial use. Grant recipients will need to maintain a separate end-user or other license agreement directly with NCCN for use of the NCCN Guidelines.

VII. Letter of Intent Submission Requirements

The Letter of Intent (LOI) will be accepted via the online application. When answering the LOI questions in the application please keep the following in mind:

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 patient population 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.

VIII. References

1. Antonarakis ES, Gomella LG, Petrylak DP. When and How to Use PARP Inhibitors in Prostate Cancer: A Systematic Review of the Literature with an Update on On-Going Trials. European Urology Oncology 2020; 3(5); 612-614
2. LYNPARZA [prescribing information]. Wilmington, DE: AstraZeneca 2020.
3. de Bono J et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med 2020; 382:2091-2102
4. RUBRACA [prescribing information]. Boulder, CO: Clovis Oncology, Inc. 2020.

5. Abida W, et al. Rucaparib in Men with Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration. J Clin Oncol. 2020; 38(32):3763-3772
6. TALZENNA [prescribing information]. New York, NY: Pfizer Inc.; 2020.
7. Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res 2012; 72:5588-5599.
8. Murai J, Huang SY, Renaud A, et al. Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. Mol Cancer Ther 2014; 13:433-443
9. Rouleau M, Patel A, Hendzel MJ, Kaufmann SH, Poirier GG. PARP inhibition: PARP1 and beyond. Nat Rev Cancer 2010; 10:293-301
10. Shen Y, Rehman FL, Feng Y, et al. BMN 673, a novel and highly potent PARP1/2 inhibitor for the treatment of human cancers with DNA repair deficiency. Clin Cancer Res 2013; 19:5003-5015
11. De Bono et al. 2021. Proceeding of ASCO GU. Poster 93.