

NCCN Request for Proposals (RFP): Investigator Sponsored Research for Understanding the Mechanisms and Formulating the Optimal Management of Hematological Toxicity of PARPi in the Treatment of Prostate Cancer

Date Issued: May 28, 2024

1.0 Purpose

The National Comprehensive Cancer Network® and Pfizer Global Medical Grants (Pfizer) are collaborating to offer a new grant opportunity seeking proposals for investigator-initiated research for the optimal management of hematologic toxicities of PARP inhibitors (PARPi). Pfizer (hereafter, “Grantor”) is providing \$1 Million in funding to support research studies to advance the understanding of mechanisms and formulating the optimal management of hematologic toxicity of PARPi in the treatment of patients with prostate cancer. The Grantor will serve as the funding organization. Grants are available only to investigators from NCCN Member Institutions.

2.0 Organization Information

National Comprehensive Cancer Network

The National Comprehensive Cancer Network® (NCCN®) is a not-for-profit [alliance of 33 leading cancer centers](#) devoted to patient care, research, and education. NCCN is dedicated to improving and facilitating quality, effective, efficient, and equitable 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.

Pfizer Global Medical Grants

Pfizer Global Medical Grants (GMG) 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.

This RFP is being issued by both organizations. NCCN is the lead organization for review and evaluation of proposals. A Scientific Review Committee (SRC), led by NCCN, will make decisions on which proposals will receive funding. **Grant funding and general oversight of the funded projects will be provided directly from Pfizer.**

For all 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. NCCN and Pfizer must not be involved in any aspect of study protocol or project development, nor the conduct or monitoring of the project.

3.0 Background

Metastatic castration resistant prostate cancer (mCRPC) is associated with poor prognosis and overall survival. Poly-ADP ribose polymerase inhibitors (PARPi) have emerged as effective treatment options, as single agents, or in combination with Novel hormonal therapy (NHT) for patients with germline or somatic mutations of homologous recombination repair (HRR) genes. The prevalence of HRR gene mutations in patients with metastatic prostate cancer (mPC) has been documented to be as high as 20-30% [1]. In men with mCRPC and select HRR pathway alterations, PARPi treatment can induce objective tumor responses as well as improve progression free and overall survival. PARPi are approved as single agents or in combination with NHT for mCRPC. [1].

PARPi treatment is associated with hematologic toxicity, often leading to dose modification, treatment interruption, discontinuation or need for supportive management [2]. Anemia is reported as the most common hematologic toxicity associated with PARPi in mCRPC, with grade ≥ 3 anemia occurring in approximately 25% of patients and often occurring shortly after PARPi initiation [3, 4]. Thrombocytopenia and neutropenia are less frequent but still common [4]. Myelodysplasia (MDS) and acute myeloid leukemia (AML) are rarely reported in PARPi treated prostate cancer but do have higher occurrence in other PARPi treated tumor subtypes, such as ovarian cancer [5]. The latency period between PARPi exposure to diagnosis of MDS or AML ranges between 0.6 to 66.8 months (median 17.8 months) [5]. Myelosuppression by PARPi is consistently noted to be dose dependent in patients with mCRPC thus, dose modification has been the primary strategy to mitigate toxicity. Studies report up to 15-20% of patients manifesting with anemia require a dose reduction [6, 7].

The use of PARPi is expected to rise in the coming years, with their combination with other agents already being examined in earlier disease settings. In the advanced mCRPC population, hematologic derangements present a challenge given this population’s advanced age and frailty, significant bone disease burden, comorbidities, and most importantly, heavy pretreatment, thereby carrying an inherent risk for hematologic toxicity. There is limited data exploring the effect of hematologic toxicity in patient related outcomes. Hematologic safety must become a priority as our use of PARPi grows. This request for proposals seeks to solicit projects that focus on understanding the mechanisms of hematologic toxicity, identification of patients at risk for cytopenias, as well as improving the management PARPi-mediated cytopenias in patients with prostate cancer.

4.0 Aims and Eligibility

Aim:	To advance the understanding and management of hematologic toxicity of PARPi alone or in combination with NHT in the treatment of patients with prostate cancer
Geographic Scope:	United States
Eligibility Criteria: <i>Investigators from the following organizations may apply</i>	<ul style="list-style-type: none"> • NCCN Member Institutions only. • Collaboration between NCCN Member Institutions is strongly encouraged in order to foster the interactive sharing of knowledge and expertise, and to utilize the

	<p>combined clinical strengths of members, particularly in the case of uncommon tumors. Although the submitting investigator must be from an NCCN Member Institution, participating co-investigators do not need to be at an NCCN Member Institution. This can also include cross-institutional collaboration.</p> <ul style="list-style-type: none"> • Proposal submissions from Junior Faculty are encouraged. • Trainees may participate as a sub-investigator under the appropriate mentorship from a PI from a NCCN Member Institution
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5.0 Requirements

Clinical Area:	Prostate cancer
Target Audience:	A multi-disciplinary approach is encouraged. Members may include, but are not limited to: Urologists, Medical Oncologists, Hematologists, Basic Scientists, Radiation Oncologists) and other allied prostate cancer healthcare providers.
Funding Considerations:	<ul style="list-style-type: none"> • A total of \$1 Million is available to fund all projects. • The intent is to fund 2-5 studies. All budgets must include line-item information and a robust justification. <ul style="list-style-type: none"> • Clinical trials will be capped at a maximum of \$500,000.00 (Including direct and indirect costs) • Quality and Pre-clinical will be capped at a maximum of \$250,000.00 (Including direct and indirect costs) • Overhead (indirect cost) rates of up to 28% of the total proposed project budget are allowed and <i>must</i> be included in the total requested amount. • No travel or publication costs will be covered. • Applicants are required to disclose additional sources of funding for the proposed project and demonstrate that funding does not overlap. • Funding decisions are deferred to the members of the Scientific Review Committee (SRC) as chosen by NCCN and are independent of Grantor.
Areas of research interest/emphasis:	<p>This Request for Proposals (RFP) intends to support proposals to optimize the management and minimize the incidence of hematologic toxicity in metastatic prostate cancer patients receiving PARPi. All hematologic toxicities can be investigated, but anemia must constitute the primary focus of the project.</p> <p>Proposals in the following topic areas are strongly encouraged:</p> <ol style="list-style-type: none"> 1. Best practices aimed at risk stratification, diagnosis, and treatment of prostate cancer patients at substantial risk for development of anemia and other hematologic toxicities while using PARPi.

<p>Areas of research interest/emphasis (continued):</p>	<ul style="list-style-type: none"> • Initiatives that focus on the identification of clinical parameters (disease specific or patient specific) that increase the risk of anemia. • Proposals examining biomarkers that identify patients at risk of developing anemia and other hematologic toxicities. Retrospective secondary analysis of completed, well performed clinical trials or institutional databases with biobank access will be permitted. • Initiatives aimed at optimizing drug dosing strategies and monitoring schemas that mitigate PARPi associated hematologic toxicities. • Studies that focus on intervention strategies to minimize risk of anemia. <p>2. Innovative approaches to minimize hematologic toxicity for disparate populations.</p> <ul style="list-style-type: none"> • Studies focusing on barriers to care experienced by disparate populations thereby increasing their risk of hematologic adverse events, specifically anemia. • Initiatives aimed at the optimization of patient adherence to treatment monitoring. <p>3. Integration of technology tools for decision support.</p> <ul style="list-style-type: none"> • Studies capitalizing on the use of remote monitoring and/or telehealth navigation to improve multidisciplinary management of hematologic toxicity. <p>4. Preclinical studies that enhance the understanding of mechanisms and/or mitigation of hematologic toxicities associated with PARPi.</p>
<p>Areas excluded or considered out of scope:</p>	<p>Specific areas considered out-of-scope or excluded include:</p> <ul style="list-style-type: none"> • Any research comparing PARPi. • Projects whose primary endpoint is the diagnosis of MDS/AML due to the expected long latency. • Projects that focus on non-prostate cancer populations. <p>Proposals duplicative of completed, ongoing, or planned studies will not be considered.</p>
<p>Study Timeframes for Approved Studies:</p>	<ul style="list-style-type: none"> • Commencement: no later than 4-6 months after notice of study approval. • Period of performance: up to 2 years • Complete accrual: within 2 years of commencement (if applicable) • Reporting/dissemination of results in manuscript form: no later than 9 months after study endpoint achieved. <p>All studies will require documentation of the feasibility of accruing the targeted study population; studies may be multi-institutional.</p>

<p>Selection Criteria:</p>	<p>Proposals will be assessed using the following criteria:</p> <ul style="list-style-type: none"> • Knowledge of and experience with the area; • Capability of carrying out the work; • Collaboration if appropriate; • Scalability and sustainability; • Potential effect and expected outcomes of the project; and • Dissemination strategies. <p>The Grantor can reject any study with safety issues or if it is an already studied concept.</p>
<p>Drug Supply:</p>	<p>If needed, Talazoparib can be requested from the Grantor for approved and funded studies.</p> <p>If the proposal requires a different PARPi investigational drug, applicants are required to include a letter of support for any drug planned for combination with Talazoparib, or a clear plan for obtaining the companion drug(s).</p>
<p>Key Dates:</p>	<ul style="list-style-type: none"> • RFP release date: May 28, 2024 • Proposal submission deadline: July 23, 2024 (Please note submission deadline is 5:00 PM Eastern Time) • Anticipated grant award notification date: September 19, 2024
<p>Questions:</p>	<p>If you have questions regarding this RFP, please direct them in writing to Nicole Zion, Clinical Research Manager, at zion@nccn.org and Lori Carpenter, Grant Officer at lori.carpenter@pfizer.com with the subject “NCCN Pfizer PARPi RFP”.</p>
<p>How to Submit:</p>	<ul style="list-style-type: none"> • Please go to https://www.cybergrants.com/pfizer/Research and sign in. First-time users should click “REGISTER NOW”. • Select the following Competitive Grant Program Name: 2024 ONC US NCCN Hematological Toxicity in PARPi RES • Select the following Area of Interest: Oncology - Genitourinary – RES • Requirements for submission: <ul style="list-style-type: none"> • 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: Be advised that applications submitted through the wrong application type or submitted after the due date will not be reviewed.

<p>Review and Approval Process:</p>	<p>An NCCN Request for Proposals Development Team (RFPDT) was formed to oversee this process and will utilize a formalized review procedure to select the proposals of highest clinical relevance and scientific merit. The NCCN RFPDT oversaw the development of this RFP and will perform the peer review of applications. All reviews, evaluations, and award decisions are independent of Grantor.</p>
<p>Mechanism by which Applicants will be Notified:</p>	<ul style="list-style-type: none"> • All applicants will be notified via email by the date noted above. • Applicants may be asked for additional clarification during the review period.

6.0 Terms and Conditions

1. This RFP does not commit Pfizer or their 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. 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. These terms have been drafted 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.
3. 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®) or the NCCN Biomarkers Compendium 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 or Biomarkers Compendium.

7.0 Submission Requirements

Applications will be accepted via the online portal listed in the “How to Submit” section. Project Proposals/Protocols should be single-spaced using Calibri 12-point font and 1-inch margins. Note: There is a 15-page limit exclusive of references.

When uploading your Full Proposal please ensure it addresses the following:

<p>Goals and Objectives</p>	<p>Briefly state the overall goal of the project. Describe how this goal aligns with the focus of the RFP and the goals of the applicant organization(s).</p> <p>List the <i>overall</i> objectives you plan to meet with your project both in terms of learning and expected outcomes. Objectives should describe the target population as well as the outcomes you expect to achieve as a result of conducting the project.</p>
<p>Assessment of Need for the Project and Preliminary Data</p>	<p>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.</p>
<p>Target Audience</p>	<p>Describe the primary audience(s) targeted for this project. 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. For Investigator Sponsored Clinical Trials, please specify the age, gender, and other demographic information for trial population.</p>
<p>Project Design and Methods</p>	<p>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.</p>
<p>Innovation</p>	<p>Explain what measures you have taken to ensure that this project idea is original and does not duplicate other projects or materials already developed.</p> <p>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.</p>
<p>Evaluation and Outcomes</p>	<p>Specify type and frequency of safety, efficacy, and/or outcome measures. Also indicate the method(s) used to assess measures.</p> <p>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.</p> <p>In terms of the metrics used for the needs assessment, describe how you will determine if the</p>

	<p>practice gap was addressed for the target group. Describe how you expect to collect and analyze the data.</p> <p>Quantify the amount of change expected from this project in terms of your target audience. Describe how the project outcomes will be broadly disseminated.</p>
<p>Project Timeline</p>	<p>Provide an anticipated timeline for your project including project start/end dates.</p>
<p>Additional Information</p>	<p>If there is any additional information you feel the reviewers should be aware of concerning the importance of this project, please summarize here.</p>
<p>Organization Detail (Environment and Mentors)</p>	<p>Describe the attributes of the institutions/ organizations/associations that will support and facilitate the execution of the project and the leadership of the proposed project. Articulate the specific role of each partner in the proposed project. Letters of support from partner organizations are required to be submitted with the full proposal.</p> <p>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.</p>

<p>Budget Detail</p>	<p>The budget amount requested must be in U.S. dollars (USD).</p> <p>While estimating your budget please keep the following items in mind:</p> <ul style="list-style-type: none"> • General organizational running costs such as legal fees, insurance, heating, lighting, etc. should be included in and Institutional Overhead (if required). These costs are not specific to a grant request and therefore should not appear as line items in budgets. However, costs that are specific to the study (e.g., some countries require insurance to be taken out on a per-study basis for clinical research) would be acceptable to be included as line items. <ul style="list-style-type: none"> ○ The inclusion of these costs cannot cause the amount requested to exceed the budget limit set forth in the RFP. • Grantor does not provide funding for capital purchases (infrastructure expenses such as equipment, purchases of software or software licenses, technology or bricks and mortar). Equipment hire/leasing is acceptable and may be included in the project budget. • It should be noted that grants awarded through GMG cannot be used to purchase Grantor therapeutic agents (prescription or non-prescription). <p>Grantor maintains a company-wide, maximum allowed overhead rate of 28% for independent studies and projects. Please click here for details.</p>
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8.0 References

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2. Maiorano BA, De Giorgi U, Verzoni E, Maiello E, Procopio G, Conteduca V, Di Maio M, Meert UROg: **Hematological Toxicity of PARP Inhibitors in Metastatic Prostate Cancer Patients with Mutations of BRCA or HRR Genes: A Systematic Review and Safety Meta-analysis.** *Target Oncol* 2024, **19**(1):1-11.
3. Wang C, Li J: **Haematologic toxicities with PARP inhibitors in cancer patients: an up-to-date meta-analysis of 29 randomized controlled trials.** *J Clin Pharm Ther* 2021, **46**(3):571-584.
4. Bowling GC, Swargaloganathan P, Heintz C, Madan RA, Eldhose B, Dobi A, Chesnut GT: **Hematological Toxicities with PARP Inhibitors in Prostate Cancer:**

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5. Morice P-M, Leary A, Dolladille C, Chrétien B, Poulain L, González-Martín A, Moore K, O'Reilly EM, Ray-Coquard I, Alexandre J: **Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database.** *The Lancet Haematology* 2021, **8**(2):e122-e134.
 6. Abida W, Patnaik A, Campbell D, Shapiro J, Bryce AH, McDermott R, Sautois B, Vogelzang NJ, Bambury RM, Voog E *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.
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 8. LaFargue CJ, Dal Molin GZ, Sood AK, Coleman RL: **Exploring and comparing adverse events between PARP inhibitors.** *Lancet Oncol* 2019, **20**(1):e15-e28.
 9. Hashimoto K, Kawakami K, Yokokawa T, Shibata N, Soejima A, Sugisaki T, Mori Y, Shimizu H, Yunokawa M, Kanao H *et al*: **Serum Creatinine Elevation as a Risk Factor for Niraparib-induced Hematologic Toxicity.** *Anticancer Research* 2023, **43**(10):4533-4541.
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 11. Xu Z, Vandenberg CJ, Lieschke E, Di Rago L, Scott CL, Majewski IJ: **CHK2 Inhibition Provides a Strategy to Suppress Hematologic Toxicity from PARP Inhibitors.** *Molecular Cancer Research* 2021, **19**(8):1350-1360.