NCCN Request for Proposals (RFP): Combination Therapy with Relugolix in the Treatment of Advanced Prostate Cancer

Date Issued: March 20, 2023

1.0 Purpose

The National Comprehensive Cancer Network®, Pfizer Global Medical Grants (Pfizer) and Myovant Sciences (Myovant) are collaborating to offer a new grant opportunity seeking proposals for investigator-initiated research with relugolix. Pfizer and Myovant Sciences (hereafter, "Grantor") is providing $5 million in funding to support clinical research studies to further evaluate the effectiveness of relugolix in combination with other therapies for the treatment of advanced prostate cancer. The Grantor will serve as the funding organization. Grants are available to all investigators from institutions within the United States.

2.0 Organization Information

National Comprehensive Cancer Network

The National Comprehensive Cancer Network® (NCCN®) is a not-for-profit alliance of 32 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 and Myovant Sciences

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. Myovant Sciences aspires to redefine care for men and women through purpose-driven science, empowering medicines, and transformative advocacy. 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. Pfizer and Myovant must not be involved in any aspect of study protocol or project development, nor the conduct or monitoring of the research program.

3.0 Background

Mechanism of Action

Relugolix is a nonpeptide gonadotropin-releasing hormone (GnRH) receptor antagonist that competitively binds to pituitary GnRH receptors, thereby reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and consequently

testosterone. Relugolix is currently indicated for the treatment of adult patients with advanced prostate cancer, the only currently approved oral androgen deprivation therapy (ADT) for this indication.

Relugolix is known to have certain drug-drug interactions, since it is metabolized through multiple pathways including cytochrome P450 (CYP) 3A and is a substrate of CYP2C8 and P-glycoprotein (P-gp). Co-administration of relugolix with a P-gp inhibitor increases exposure of relugolix (as measured by both area under curve [AUC] and maximum concentration [C_{max}]), which could in turn increase the risk of adverse reactions from relugolix. As such, oral P-gp inhibitors should be avoided in combination with relugolix, but if this is not possible, relugolix should be administered first, separated by at least 6 hours, before the P-gp inhibitor, and patients should be monitored more frequently for adverse effects. If a short course treatment of a P-gp inhibitor is indicated, relugolix can be held for up to 14 days; if relugolix is held for more than 7 days, a loading dose of relugolix of 360 mg should be administered on the first day, followed by 120 mg once daily thereafter. When relugolix is co-administered with both a P-gp and a strong CYP3A inducer, AUC and C_{max} are decreased, potentially reducing the effects of relugolix. P-gp and CYP3A inducers should be avoided, but, if they must be co-administered, relugolix dosing should be increased to 240 mg once daily.

Clinical Data

Relugolix was studied in the HERO trial, a Phase 3 study, in which patients with advanced prostate cancer were randomized to receive relugolix or leuprolide for 48 weeks [1]. The primary endpoint of the study was sustained testosterone suppression to castrate levels (<50 ng/dL) from day 29 through week 48. Patients enrolled on this study were eligible if they were considered candidates for at least 1 year of continuous ADT and included patients who had evidence of biochemical or clinical recurrence after definitive local therapy, *de novo* androgen-sensitive metastatic disease, or advanced localized disease. A total of 934 patients were randomized in a 2:1 fashion to relugolix (with a loading dose of 360 mg orally (PO) on Day 1 followed by 120 mg PO once daily) or to leuprolide acetate (22.5 mg [or 11.25 mg in Japan and Taiwan] by injection every 3 months) for 48 weeks. Leuprolide acetate 11.25 mg is a dosage regimen that is not recommended for this indication in the US. The study met its primary endpoint, with 96.7% (95% CI 94.9% – 97.9%) of men receiving relugolix maintaining castration through 48 weeks and 88.8% (95% CI 84.6% – 91.8%) of men receiving leuprolide. This finding met prespecified statistical criteria. An exploratory subgroup of 184 patients were followed for testosterone recovery after treatment discontinuation; the mean testosterone level at 90 days was 288.4 ng/dL in the relugolix group and 58.6 ng/dL in the leuprolide group.

While combining additional therapies with ADT has established benefit in the treatment of advanced prostate cancer in the metastatic, non-metastatic, androgen-sensitive, and castration-resistant settings, clinical data is limited regarding relugolix used in combination with other prostate cancer therapies. An exploratory subgroup analysis of the HERO study evaluated 125 patients who took at least one concomitant therapy that could impact testosterone levels [2]. Radiation therapy (RT) was administered to 15.9% and 18.8% of patients in the relugolix and leuprolide groups, respectively. Concomitant enzalutamide was administered in 17 patients on relugolix, and in 6 patients on leuprolide, while docetaxel was administered to 8 patients on relugolix and 5 patients on leuprolide. No clinically relevant differences in adverse events were observed between

patients with or without concomitant therapies, but conclusions are difficult to draw given these small numbers.
A Phase 2 multicenter study (APA-RP) is in progress to evaluate the combination of ADT with apalutamide in patients with high-risk localized prostate cancer after radical prostatectomy to determine the biochemical recurrence-free rate [3]. The primary objective of a substudy to evaluate patients receiving relugolix in combination with apalutamide was to determine if standard maintenance dosing of relugolix in combination with apalutamide sustained castrate testosterone levels. Within 90 days of radical prostatectomy, patients received a loading dose of relugolix 360 mg PO on Day 1, after which relugolix dosing was 120 mg PO once daily. Apalutamide at a dose of 240 mg PO once daily began on Day 14. A total of 12 patients were enrolled and received at least one dose of apalutamide; all achieved castrate testosterone levels after 2 weeks of relugolix monotherapy. All patients with testosterone measured at Day 28 maintained castrate testosterone levels with no relugolix dose adjustments needed. No new safety signals were observed.

Some ongoing studies will provide further data regarding the combination of relugolix with androgen receptor signaling pathway inhibitors (ARSPIs) and other prostate cancer treatments. An ongoing Phase 1 trial will assess the safety and tolerability of relugolix in combination with abiraterone acetate in patients with metastatic androgen-sensitive or metastatic castration-resistant prostate cancer (CRPC) or in combination with apalutamide in patients with androgen-sensitive or non-metastatic CRPC [4]. The OPTYX study, a large, multi-center, prospective, observational trial, is enrolling patients with prostate cancer who are initiating treatment with relugolix within 1 month of enrollment [NCT05467176]. This registry study will collect information about the tolerability of relugolix in combination with other treatments for prostate cancer. In the large REPLACE-CV study, patients who are candidates for at least 1 year of ADT for prostate cancer are randomized to receive either relugolix or leuprolide, with time to a major adverse cardiovascular event as the primary outcome [NCT05605964]. Once enrolled on the study, intensification with ARSPIs is permitted, which will result in additional data on relugolix combination therapy. In the REVELUTION study, 90 patients are being randomized to receive radiation therapy (RT), RT + leuprolide, or RT + relugolix to investigate the impact of ADT on cardiovascular risk [NCT05320406]. In the Phase 2 NRG PROMETHEAN study, 260 patients are being randomized to receive relugolix in combination with stereotactic ablative body radiation therapy (SABR) or placebo in combination with SABR, and the primary outcome is radiologically progression-free survival [NCT05053152].

Beyond the ongoing studies and background information, a need remains to further characterize the efficacy and safety of relugolix in combination with other prostate cancer treatments.

4.0 Aims and Eligibility

Aim:	The overall aim is to develop innovative studies to advance scientific knowledge regarding combination therapies with relugolix in the treatment of patients with advanced prostate cancer, including high-risk or locally advanced primary, recurrent, or metastatic, in any state (androgen-sensitive or castration-resistant). It is hoped that proposals submitted in response to this

	RFP will be useful to guide further development of relugolix. Studies with correlative endpoints are encouraged.
Geographic Scope:	United States
Eligibility Criteria: *Investigators from the following organizations may apply*	• US institutions only. • Academic health care centers. • Community health care centers. • Health care professional organizations and other organizations related to health care improvement. • Health care delivery organizations must serve as the lead applicant, if partnered with health technology companies.
Additional Eligibility Information:	• Collaboration among institutions is strongly encouraged to foster interactive sharing of knowledge and expertise, and to utilize the combined strengths of the involved institutions. • Junior faculty (i.e., Assistant Professors and below) are encouraged to apply. • Trainees may participate as a sub-investigator under appropriate mentorship from a PI.

5.0 Requirements

Clinical Area:	Prostate cancer
Target Audience:	Medical oncologists, urologists, and radiation oncologists.
Funding Considerations:	• A total of $5 million is available to fund all projects. • The intent is to fund 2-5 studies. The main evaluation criteria are clinical relevance and scientific merit. All budgets must include line-item information and a robust justification. • Overhead (indirect cost) rates of up to 28% of the total proposed project budget are allowed and *must* 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:	Combinations of relugolix and ADT that have not been studied extensively. These can include: • Combination studies with ARSPIs or with chemotherapy;

Areas of research interest/emphasis (continued):	• Studies seeking to understand adherence to, or persistence with, oral combination therapies;
	• Combination studies evaluating toxicities including, but not limited to, cardiovascular, bone, mental health, and/or financial toxicities;
	• Studies establishing or increasing the efficacy of combination therapies including, but not limited to, pharmacokinetic evaluation or evaluation of other molecular or metabolic pathways;
	• Combination studies that maximize quality of life, which can include intermittent or shorter duration strategies for ADT;
	• Relugolix combination treatment with novel approaches; These can include:
	  • Studies in combination with newer therapies, such as radiopharmaceuticals, theranostics, or PARP inhibitors, or novel/experimental therapies such as immunotherapy, vaccines, or epigenetic modulators; and
	  • Studies investigating strategies to limit toxicities.

Areas excluded or considered out of scope:	Specific areas considered out-of-scope or excluded include: • Studies in disease other than prostate cancer; • Studies that evaluate relugolix as a monotherapy (including studies of relugolix as a monotherapy in combination with external beam RT); • Studies that are completely preclinical; • Correlative studies or pharmacodynamic studies can be included in the proposal, but should not be the primary objective of the proposal; • Registry studies; • Projects involving opioids; and • Claims-based studies. **Proposals duplicative of completed, ongoing, or planned studies will not be considered. Planned and ongoing studies are outlined in the Clinical Data portion of the Background.**
Study Timeframes for Approved Studies:	• Commencement (defined as first patient receiving first dose of study drug): no later than nine (9) months after notice of study approval. • Complete accrual: within five (5) years of commencement. • Reporting/dissemination of results in manuscript form: no later than nine (9) months after study endpoint achieved. **All studies will require documentation of the feasibility of accruing the targeted study population; studies may be multi-institutional.**

Selection Criteria:	Proposals will be judged based on the following criteria: • Scientific value; • Clinical relevance; • Research qualifications of the applicants; • Soundness of study design, including detailed sample size determination; • Feasibility including reasonable assurance of achieving intended accrual; • If the proposal requires a second investigational drug, applicants are required to include a letter of support for any drug planned for combination with relugolix, or a clear plan for obtaining the companion drug(s). • Appropriateness and transparency of the statistical analysis plan (applicants are encouraged to include a biostatistician as a co-investigator); and • Budgetary completeness and reasonableness. The GRANTOR can reject any study with safety issues or if it is an already studied concept.
Drug Supply:	Relugolix will be supplied by the Grantor for all approved and funded studies. If the proposal requires a second investigational drug, applicants are required to include a letter of support for any drug planned for combination with relugolix, or a clear plan for obtaining the companion drug(s).
Key Dates:	• RFP release date: March 20, 2023 • Proposal submission deadline: May 22, 2023 (Please note submission deadline is 5:00 PM Eastern Time) • Anticipated grant award notification date: June 23, 2023
Questions:	If you have questions regarding this RFP, please direct them in writing to Nicole Zion, Clinical Research Manager, at zion@nccn.org and Dewayne Brumlow, the Pfizer Grant Officer, at dewayne.brumlow@pfizer.com with the subject **"NCCN Pfizer Myovant Relugolix RFP"**.
How to Submit:	• 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: **2023 ONC US NCCN Myovant Advanced Prostate Cancer RES** • Select the following Area of Interest: **Oncology – Genitourinary**

How to Submit:	• Requirements for submission:
	  • 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.

Review and Approval Process:	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.
Mechanism by which Applicants will be Notified:	• 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, Myovant, 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:

Goals and Objectives	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). List the *overall* 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.
Assessment of Need for the Project and Preliminary Data	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. 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.
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 or materials already developed. 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.

Evaluation and Outcomes	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. In terms of the metrics used for the needs assessment, describe how you will determine if the practice gap was addressed for the target group. Describe how you expect to collect and analyze the data. Quantify the amount of change expected from this project in terms of your target audience. Describe how the project outcomes will be broadly disseminated.
Project Timeline	Provide an anticipated timeline for your project including project start/end dates.
Additional Information	If there is any additional information you feel the reviewers should be aware of concerning the importance of this project, please summarize here.
Organization Detail (Environment and Mentors)	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. 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.

Budget Detail	The budget amount requested must be in U.S. dollars (USD). While estimating your budget please keep the following items in mind: • General organizational running costs such as insurances, heating, lighting, rent, building maintenance may be included. 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 project budget. • The inclusion of these costs cannot cause the amount requested to exceed the budget limit set forth in the RFP. It should be noted that grants awarded through GMG cannot be used to purchase Grantor therapeutic agents (prescription or non-prescription). Grantor maintains a company-wide, maximum allowed overhead rate of 28% for independent studies and projects. Please click here for details.

8.0 References

1. Shore ND, Saad F, Cookson MS, George DJ, Saltztstein DR et al. Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer. *N Engl J Med* 2022; 382: 2817-2196
2. George DJ, Shore ND, Saad F, Cookson M, Saltzstein D, et al. Impact of concomitant prostate cancer therapy on efficacy and safety of relugolix versus leuprolide in men with advanced prostate cancer: Subgroup analysis from the phase III HERO study. *J Clin Oncol* 2021; 39: s6 (abstr 106)
3. Brown G, Belkoff L, Hafron JM, Saltzstein DR, Potdar R, et al. Coadministration of Apalutamide and Relugolix in Patients with Localized Prostate Cancer at High Risk for Metastases. *Target Oncol* 2023; 18: 95-103.
4. De La Cerda J, Migoya E, Brown B, Lu S, Zohren F, Tutrone RF, et al. Relugolix in combination with abiraterone acetate, apalutamide, or docetaxel in men with advanced prostate cancer (aPC): a phase 1, three-part, open-label, parallel-cohort study. *J Clin Oncol* 2022; 40: s6 (abstr 207)

9.0 Acronyms

ADT	Androgen Deprivation Therapy
ARSPI	Androgen Receptor Signaling Pathway Inhibitors
AUC	Area Under Curve
C_{max}	Maximum Concentration

CYP	Cytochrome P450
FSH	Follicle-Stimulating Hormone
GMG	Global Medical Grants
GnRH	Gonadotropin-Releasing Hormone
LH	Luteinizing Hormone
NCCN	National Comprehensive Cancer Network
NCCN Guidelines®	NCCN Clinical Practice Guidelines in Oncology
P-gp	P-glycoprotein
PO	Orally
RFP	Request for Proposals
RFPDT	Request for Proposals Development Team
RT	Radiation Therapy
SABR	Stereotactic Ablative Body Radiation
SRC	Scientific Review Committee
USD	United States Dollars