



NCCN/Pfizer/Astellas Request for Proposals (RFP): Enzalutamide in the Treatment of Prostate Cancer

I. Introduction

In order to promote the advancement of scientific knowledge concerning the mechanisms of action, underlying biology, and clinical effectiveness of enzalutamide in prostate cancer, the National Comprehensive Cancer Network® (NCCN), Pfizer Global Medical Grants (Pfizer) and Astellas Pharma Global Development (Astellas) are collaborating.

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 to improve outcomes of cancer patients. 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.

Astellas and its alliance partners are committed to supporting investigator sponsored research studies that promote the advancement of medical and scientific knowledge and innovation involving Astellas products and therapeutic areas of interest. Investigator Sponsored Research (ISR) is proposed by a Sponsor-Investigator or institution for which support is requested to obtain an Astellas compound, and/or funding to perform specific research. The Investigator assumes full responsibilities for the research/study as the Sponsor. Astellas is interested in supporting studies that are innovative and contribute to scientific knowledge of a product, a disease state, medical condition or advancing technology.

Pfizer and Astellas 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 all three 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 support of the funded studies will be provided directly from Astellas and Pfizer. Collectively, \$2 Million USD is available for award to fund all projects under this RFP.

II. Scope

The overall aim is to develop innovative, novel, and impactful studies that address unmet needs as well as support the design and performance of enzalutamide research in the treatment of prostate cancer. Clinical trials, prospective studies, and retrospective correlative studies of enzalutamide treatment trials or datasets are encouraged. It is hoped proposals submitted in response to this RFP will guide development of enzalutamide and its combination with other therapies. Studies with correlative endpoints will be accepted, and studies that retrospectively analyze biomarkers (tissue, liquid biopsy, and other approaches) within prospective trials or datasets will be accepted.

The NCCN Request for Proposals Development Team (RFPDT) has developed an 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 (SRC) composed of members of this group and others will perform the review of applications.

This RFP is open to investigators from all US institutions and organizations. 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.

Areas of Interest:

The following are selected priority areas to encourage the development of novel treatment approaches because of their ability to impact the unmet needs for patients with potentially lethal prostate cancer:

1. Earlier disease states
2. Treatment and biology of oligometastatic disease
3. Populations with unique vulnerabilities
4. Innovative treatment strategies
5. Specific disease settings in which enzalutamide may offer value
6. Next generation imaging
7. Biomarkers of enzalutamide response (including imaging)
8. Strategies to improve the therapeutic index of enzalutamide

Specific exclusions from this RFP include:

The goal of this RFP is to focus on impactful studies of enzalutamide that can be completed within three years. Given this constraint, the following are discouraged:

1. Phase III trials or larger multicenter trials
2. Trials unlikely to complete within three-year time frame
3. Trials beyond the requested budget

4. Funding of institutions outside the US
5. Proposals not focused on enzalutamide

III. Letters of Intent (LOI)/Proposals

This RFP model employs a 2-stage process: Stage 1 is the submission of a 4-page LOI or high-level study plan (refer to attachment A), Curriculum Vita, high level budget and Letter of Request, to the Astellas ISR portal. If an LOI is selected, the applicant will be invited to Stage 2 to submit a full program proposal with a more detailed protocol and budget into Astellas’ web-based system for consideration by the NCCN RFPDT. (See Section VII)

The NCCN RFPDT 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 for funding. The NCCN SRC has overseen the development of the RFP and will perform the peer review of applications.

IV. Requirements

Date RFP Issued:	April 5, 2021
Clinical Area:	Prostate
Applicant Eligibility Criteria:	Restricted to US institutions
Budget:	<p>There is \$2 Million available for funding of all projects.</p> <p>It is anticipated that 2-5 projects will be awarded funding but the final number will depend on the quality of the projects and the specific decisions of the review panel.</p> <p>The maximum indirect (overhead) rate is 28% and must be included in the total grant request amount.</p> <p>Applicants are required to disclose additional sources of funding for this project and demonstrate that funding does not overlap.</p> <p>Amount requested may not exceed the budget limit set forth in the RFP and the budget submitted must be within fair market value.</p> <p>No funding for capital equipment is allowed.</p>

<p>Estimated Key Dates:</p>	<p>LOI Deadline: May 14, 2021 Please note the deadline is 5:00 pm Eastern Time.</p> <p>Anticipated LOI Notification Date: June 23, 2021</p> <p>Full Proposal Deadline: *August 4, 2021 *Only accepted LOIs will be invited to submit full proposals. Please note the deadline is 5:00 pm Eastern Time.</p> <p>Anticipated Full Proposal Notification Date: September 29, 2021</p> <p>Grants distributed following execution of fully executed study agreement.</p>
<p>Study Timelines</p>	<p>Commence, which is defined as the first patient receiving the first dose of study drug(s), no later than 3 months after contract execution.</p> <p>Projects to be completed within 3 years of approval.</p> <p>Manuscript submission within 6 months after the study endpoint is achieved</p>
<p>How to Apply:</p>	<p>Please go to the Astellas online portal at https://globalisrportal.force.com and register. Once registered, you can submit a new study request.</p> <p>If you encounter any technical difficulties with the website, please send a message or call as directed on the ISR portal landing page.</p> <p>Help can be obtained, once registered in the portal via ISR Portal Message Center on the Home Page Messages Tab.</p>
<p>Selection Criteria:</p>	<p>Applications will be evaluated on the basis of:</p> <ol style="list-style-type: none"> 1. Impact and Scientific Value 2. Feasibility and Institutional Environment 3. Study Design and Underlying Objective Hypothesis 4. Alignment to Areas of Interest outlined in the RFP 5. Budgetary 6. Statistics
<p>Questions:</p>	<p>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 "Enzalutamide 2021 Project".</p>

Mechanism by which Applicants will be Notified:	<p>All applicants will be notified via email by the anticipated dates noted above.</p> <p>Applicants may be asked for additional clarification, if needed, by the during the review period.</p>
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V. Terms and Conditions

This RFP does not commit Pfizer, Astellas, or its partners to award a grant, 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.

Pfizer and Astellas reserve 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 and Astellas to do so.

For compliance reasons and in fairness to all applicants, all communications about the RFP must come exclusively to Astellas via the ISR submission portal. Applicants should not contact other departments within Pfizer and/or Astellas 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.

VI. Letter of Intent Submission Requirements

The LOI will be accepted via the Astellas ISR Portal online. Applicants will be required to:

1. Register in the portal <https://globalisrportal.force.com>
2. Complete the required fields regarding the proposed study concept within the portal
 - When entering the concept title, please start with **“NCCN Pfizer Astellas Enzalutamide”**
3. Upload a letter of request, signed on institutional letterhead
4. Upload the LOI document using the **“NCCN Pfizer/Astellas Enzalutamide Letter of Intent (LOI) template” (Attachment A)**.
 - The LOI will not exceed 4 pages
 - **Curriculum Vitae will be required for upload**

Failure to include all documents listed above will disqualify your submission.

VII. References

1. Scher HI, et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. N Engl J Med 2012; 367:1187-97.
2. Beer TM, et al. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. N Engl J Med 2014; 371:424-433.

3. Armstrong AJ, et al. Five-year Survival Prediction and Safety Outcomes with Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer from the PREVAIL Trial. *Eur Urol.* 2020;78(3):347-357.
4. Shore ND et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomized, double-blind, phase 2 study. *Lancet Oncol.* 2016; 17(2): 153-163.
5. Penson DF, et al. Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial. *J Clin Oncol.* 2016 Jun 20;34(18):2098-106
6. Sternberg CN, et.al. Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med.* 2020; 382:2197-2206
7. Armstrong AJ, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy with Enzalutamide or Placebo in Men with Metastatic Hormone-Sensitive Prostate Cancer. *J Clin Oncol.* 2019; 37:2974-2986.
8. Davis ID, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *N Engl J Med.* 2019; 381:121-131.
9. Hussain M, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med.* 2018; 378: 2465-2474.
10. Scher, H, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med.* 2012; 367(13): 1187-1197.
11. Lortot Y, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. *Lancet Onc.* 2015; 16(5) 509-521.
12. Tomball B, et al. Patient-reported outcomes following enzalutamide or placebo in men with non-metastatic, castration-resistant prostate cancer (PROSPER): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2019; 20(4): 556-569.
13. Stenzl A, et al. Effect of Enzalutamide plus Androgen Deprivation Therapy on Health-related Quality of Life in Patients with Metastatic Hormone-sensitive Prostate Cancer: An Analysis of the ARCHES Randomised, Placebo-controlled, Phase 3 Study. *Eur Urol.* 2020; 78(4): 603-614.
14. Safety and Efficacy Study of Enzalutamide Plus Leuprolide in Patients with Nonmetastatic Prostate Cancer (EMBARK). NCT02319837
15. A Study of Salvage Radiotherapy with or Without Enzalutamide in Recurrent Prostate Cancer Following Surgery (STEEL) (RTOG 3506). NCT03809000
16. Localized Prostate Cancer Studies – Active Surveillance: A Randomized Study of Enzalutamide in Patients with Localized Prostate Cancer Undergoing Active Surveillance (ENACT). NCT02799745
17. Enzalutamide in Androgen Deprivation Therapy with Radiation Therapy for High Risk, Clinically Localized, Prostate Cancer (ENZARAD). NCT02446444

ATTACHMENT A

NCCN Pfizer/Astellas Enzalutamide Letter of Intent (LOI) template Not to exceed 4 pages

1. Title

- The study title must start with “NCCN Pfizer Astellas Enzalutamide”

2. Investigators and Institutional Affiliations

- Describe the attributes of the institutions and investigators that will support and facilitate the execution of the study

3. Concept

- Overview/Impact Statement
 - Describe how success in the proposed study will move the field forward, benefit patients or promote or validate new ideas that may impact the field. Define the metrics for success of the proposed work
- Objectives
 - Briefly state the objectives (primary, secondary and exploratory) of the study
 - Describe how these objectives aligns with the focus of the RFP

4. Background/Rationale

- Pertinent and succinct background Information or preliminary data

5. Research Design

- Describe concisely the research design and methods for achieving the stated goals including whether prospective or retrospective
 - If retrospective, please provide details of the patient population under study, whether follow up is complete and event rates, and available tissues/samples in order to determine feasibility
- Include the following:
 - Patient Population
 - Inclusion/Exclusion Criteria
 - Treatment Plan
 - Statistical Design and Endpoints (including metrics for determining success)
 - Correlatives

6. Feasibility

- The estimated number of patients seen at all participating institutions
- Anticipated research timelines

7. **Budget**

- A total amount requested is the only information needed for the LOI stage. **Full Budget is not required.** This amount can be adjusted at the Full Proposal stage as applicable
- The budget amount requested must be in U.S. dollars (USD)
- While estimating your budget please keep the following items in mind:
 - A maximum of 28% indirect costs may be included within the request
 - Amount requested may not exceed the budget limit set forth in the RFP
 - No funding for capital equipment is allowed

8. **Additional Information**

- Any additional information you feel is of importance of this study, please summarize it in within the page limitations

9. **References**

- References are not included in four-page limit

Additional Documentation:

1. CV (for PI only)
2. Formal Letter of Request on institutional letterhead

ATTACHMENT B – BACKGROUND

Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors; and consequently, inhibits nuclear translocation of androgen receptors and their interaction with DNA. A major metabolite, N-desmethyl enzalutamide, exhibited similar in vitro activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells in vitro, and decreased tumor volume in a mouse prostate cancer xenograft model.

ROLE OF ENZALUTAMIDE IN METASTATIC CASTRATE RESISTANT PROSTATE CANCER (mCRPC)

Enzalutamide was FDA approved for the treatment of advanced prostate cancer following the results of AFFIRM, a phase III international randomized trial in patients with mCRPC who had disease progression after having received docetaxel chemotherapy.

In the AFFIRM study, enzalutamide demonstrated an overall survival (OS) advantage for these patients with a 37% relative hazard reduction of death (hazard ratio (HR) = 0.63, 95% confidence interval (CI); 0.53, 0.75; $p < 0.001$) and with a median OS in the enzalutamide arm of 18.4 months compared with placebo 13.6 months.¹

The PREVAIL study was a similar phase III trial of enzalutamide plus androgen deprivation therapy (ADT) compared with placebo plus ADT in patients with chemotherapy-naïve mCRPC who had progressed on ADT. Enzalutamide has demonstrated long-term survival advantage over placebo despite the majority of placebo-treated men (68%) receiving subsequent enzalutamide or abiraterone. Median OS for enzalutamide was 36 months (95% CI 34-38) versus 31 months for placebo (95% CI 29-34), HR 0.83 (95% CI 0.75-0.93; $p = .0008$).^{2,3}

TERRAIN was a randomized phase II study in chemotherapy naïve mCRPC comparing enzalutamide plus ADT to bicalutamide plus ADT again demonstrating significantly improved progression free survival (PFS).⁴ In this study, the median PFS with enzalutamide was 15.7 months versus 5.8 months with bicalutamide (HR 0.44 95% CI 0.34-0.57 $p < 0.0001$). These results were similar in the randomized phase II STRIVE trial, where time to PSA progression was improved with enzalutamide over bicalutamide (HR 0.19 $p < 0.001$) accompanied by improved PSA responses and delays in radiographic progression free survival (HR 0.32 $p < 0.001$).⁵

ROLE OF ENZALUTAMIDE IN NON-METASTATIC CASTRATE RESISTANT PROSTATE CANCER (nmCRPC)

Because of the observed life prolonging effects in patients with mCRPC, the role of enzalutamide in nmCRPC has been evaluated in a phase III randomized, double-blind, placebo-controlled study (PROSPER). In this study, patients were required to have no evidence of metastatic disease on conventional imaging (cross sectional computer tomography and nuclear bone scans) and have a prostate-specific antigen (PSA) doubling time of ≤ 10 months. Median OS was significantly higher in the enzalutamide group: 67.0 months (95% CI: 64–NR) versus 56.3 months (95% CI: 54.4–63.0) in the placebo group (HR: 0.73, $P = 0.001$).

ROLE OF ENZALUTAMIDE IN METASTATIC CASTRATE SENSITIVE PROSTATE CANCER (mCSPC)

Patients with mCSPC have radiographically visible metastatic disease (again, traditionally defined with conventional imaging) but have normal testosterone levels. These patients represent a heterogeneous

group; patients with mCSPC may present with either an untreated primary and *de novo* metastatic disease or patients may progress to this state after failing local therapy and going on to develop metastatic lesions without receiving ADT.⁷

ARCHES was a phase III, double-blind, placebo-controlled trial in which mCSPC patients were randomized to receive enzalutamide plus ADT versus placebo plus ADT. The study demonstrated a reduction in radiographic disease progression of 61% for the enzalutamide group (HR 0.39 (95%CI 0.3-0.5; P<0.001).⁸ ENZAMET was also a phase III, randomized, double-blind trial but with an active comparator. In this case patients with mCSPC were randomized to receive enzalutamide plus ADT or a non-steroidal anti-androgen plus ADT. This study demonstrated an OS benefit for enzalutamide HR 0.67 (95%CI 0.52-0.86; p=0.002). In both ARCHES and ENZAMET, the studies demonstrated an overall OS benefit.

RISKS AND BENEFITS OF ENZALUTAMIDE

The balance between the benefits and risks of all therapeutics approaches need to be weighed carefully. Though generally well tolerated, enzalutamide has been associated with adverse events including fatigue, falls, non-pathological fractures, hypertension, cardiovascular events and mental impairment disorders.⁹ The oncological benefits including overall survival advantage with enzalutamide outweigh the risks of treatment in most cases and particularly in more advanced disease states. Indeed, the quality of life outcomes (as measured by patient reported outcomes (PROs) from validated questionnaires) favor treatment regimens which include enzalutamide in advanced disease. In the AFFIRM trial for example, significant improvements in FACT-P quality of life responses were seen for men taking enzalutamide over placebo (43% vs. 18%, P<0.001).¹⁰ Similarly, in the PREVAIL study of chemotherapy-naïve men with mCRPC, enzalutamide treatment extended time to deterioration in FACT-P and improved general health as measured by EQ-5D.¹¹ The quality of life improvements with enzalutamide are slightly muted in earlier disease settings. In the PROSPER study for example, enzalutamide significantly delayed time to pain progression, symptom worsening and decreased functional status compared to placebo but these effects were not as pronounced and time to overall FACT-P deterioration were similar between study arms.^{9,12} In ARCHES, which examined metastatic hormone sensitive disease, benefits in quality of life were mostly evident for men with high volume disease. Indeed, among men with low volume metastatic disease, time to first deterioration in quality of life was modestly shorter if enzalutamide was added to the treatment regimen.¹³

The therapeutic index of enzalutamide can be increased by either identifying men who would respond more robustly to therapy or by selecting individuals for treatment who are less prone to toxicities. Additionally, approaches to reduce drug toxicity and maintain or improve quality of life on therapy can be employed. Understanding strategies to maintain quality of life and to prevent enzalutamide associated toxicities, particularly in earlier disease states is of high significance.

SUMMARY OF PUBLISHED ENZALUTAMIDE TRIALS:

- Enzalutamide has demonstrated improved survival in multiple patient populations from earlier patient types/indications to metastatic disease
- Enzalutamide has shown to provide broad clinical benefits versus ADT in certain populations.
- Enzalutamide offers survival benefit over older-generation agents, such as bicalutamide, in select studies

UNPUBLISHED ONGOING TRIALS INVESTIGATING THE USE OF ENZALUTAMIDE IN EARLIER DISEASE SETTINGS

The role of enzalutamide in early stage prostate cancer is of high interest and is an area of unmet need. A variety of trials, both industry and investigator-initiated sponsored, are underway. The below list is not comprehensive but includes some key ongoing trials.

ONGOING TRIALS FOR ENZALUTAMIDE IN nmCSPC CLINICAL RESEARCH OVERVIEW:

- 1. Safety and Efficacy Study of Enzalutamide Plus Leuprolide in Patients with Nonmetastatic Prostate Cancer (EMBARK):** A phase III, randomized, efficacy, and safety study of enzalutamide plus leuprolide, enzalutamide monotherapy, and placebo plus leuprolide in men with high-risk non-metastatic prostate cancer progressing after definitive therapy (radical prostatectomy or radiotherapy or both).¹⁴
 - Primary outcome: Metastasis-free survival (MFS)
 - Secondary outcomes: OS, time to castrate resistance, safety, MFS time frame, time to PSA progression, and others
- 2. A Study of Salvage Radiotherapy with or Without Enzalutamide in Recurrent Prostate Cancer Following Surgery (STEEL) (RTOG 3506):** A Randomized Phase II Trial of Salvage Radiotherapy with Standard versus Enhanced Androgen Deprivation Therapy (with Enzalutamide) in Patients with Post-Prostatectomy PSA Recurrences with Aggressive Disease Features.¹⁵
 - Primary Objective: Determine whether, in men w/post-prostatectomy PSA recurrence with aggressive disease features, salvage radiotherapy (SRT) w/enhanced ADT will improve PFS compared to SRT with standard ADT.
 - Primary outcome measure: Progression-free Survival (PFS).
- 3. Localized Prostate Cancer Studies – Active Surveillance: A Randomized Study of Enzalutamide in Patients with Localized Prostate Cancer Undergoing Active Surveillance (ENACT)¹⁶**
 - Hypothesis: One year of enzalutamide monotherapy may alter rates of progression for men with low and intermediate risk prostate cancer electing active surveillance.
- 4. Enzalutamide in Androgen Deprivation Therapy with Radiation Therapy for High Risk, Clinically Localized, Prostate Cancer (ENZARAD)¹⁷**
 - Rationale: Adjuvant ADT with a luteinizing hormone releasing hormone analog (LHRHA) given before, during and after radiotherapy (RT) is standard of care for high risk localized prostate cancer.
 - Hypothesis: The addition of enzalutamide to adjuvant ADT and RT will improve outcomes. The aim is to determine the efficacy of enzalutamide compared with NSAA as part of adjuvant ADT with LHRHA in men planned for RT for localized high risk or node-positive prostate cancer.