



ALLIANCE FOUNDATION TRIALS (AFT)

PROTOCOL NUMBER

AFT – 47

ARACOG: A Randomized Phase II Study of Androgen Receptor Directed Therapy on COGnitive Function in Patients Treated with Darolutamide or Enzalutamide

Protocol Version: Version 6.0

Protocol Version Date: 28-August-2025

Investigational Product: Darolutamide

Study Sponsor: Alliance Foundation Trials, LLC

IND Exempt

Investigational Product Supplier: Bayer Healthcare

ClinicalTrials.gov Identifier: NCT04335682

This document contains confidential information of Alliance Foundation Trials, LLC. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Alliance Foundation Trials, LLC.

Protocol Contacts

Sponsor Principal Investigator [REDACTED] Alliance Foundation Trials, LLC 221 Longwood Avenue, Suite 122 Boston, MA 02215 [REDACTED] [REDACTED]	
Study Chair [REDACTED] Dana-Farber Cancer Institute 450 Brookline Avenue, Dana 09-930 Boston, MA 02215 [REDACTED] [REDACTED]	Study Co-Chair [REDACTED] University of California San Francisco 505 Parnassus Avenue, M1286C San Francisco, CA 94143 [REDACTED] [REDACTED]
Study Co-Chair [REDACTED] Memorial Sloan Kettering Cancer Center 353 East 68th Street New York, NY 10065 [REDACTED] [REDACTED]	Correlatives Science Co-Chair [REDACTED] University of Minnesota/ Masonic Cancer Center 420 Delaware Street Southeast, MMC 480 Minneapolis, MN 55455 [REDACTED] [REDACTED]
AFT Executive Officer [REDACTED] Dana-Farber Cancer Institute 44 Binney Street, D1230 Boston, MA 02115 [REDACTED] [REDACTED]	Primary Statistician [REDACTED] Mayo Clinic Division of Clinical Trials & Biostatistics 200 First Street Southwest Rochester, MN 55905 [REDACTED] [REDACTED]
Medical Monitor [REDACTED] Alliance for Clinical Trials in Oncology 125 South Wacker Drive, Suite 1600 Chicago, IL 60606 [REDACTED] [REDACTED]	AFT Project Manager [REDACTED] Alliance Foundation Trials, LLC 221 Longwood Avenue, Suite 122 Boston, MA 02115 [REDACTED] [REDACTED]

Study Resources

The following study resource sites are accessible via the AFT website:

<https://alliancefoundationtrials.org/>

Adverse Event Reporting
via Medidata Rave® iMedidata Portal

Protocol-related questions may be directed as follows:

Questions	Contact
Questions related to data submissions, RAVE	Mayo Data and Statistics Center  Data Manager  
Questions related to AE/SAE reporting	IQVIA Clinical Safety Management  
All other questions regarding AFT-47 Study (protocol, assessments, IRB submission, eligibility, etc.)	AFT Clinical Trial Operations 

Synopsis and Study Schema

Study Number/Title	ARACOG: A Randomized Phase II Study of Androgen Receptor Directed Therapy on COGNITIVE Function in Patients Treated with Darolutamide or Enzalutamide
Study Type/Phase	Phase II
Clinical Indication	Advanced prostate cancer: metastatic and non-metastatic castration resistant prostate cancer (CRPC) or metastatic hormone sensitive prostate cancer (HSPC)
Number of Study Participants	132 patients (114 evaluable patients; 57 patients per study arm). We anticipate enrollment at up to 12 sites through the Alliance Foundation Trials network of sites.
Estimated Duration of Study	36 months
Primary Objective	To compare the effects of treatment with enzalutamide (ENZ) versus darolutamide (DARO) on the cognitive function of men with advanced prostate cancer by comparing the change in the maximally changed cognitive domain from baseline in patients in each study arm by 24 weeks.
Secondary Objective	To determine the effects of ENZ or DARO on cognitive function as measured by: • Average decline in maximally changed cognitive domain in patients in each group at 48 weeks. • Cumulative proportion of impaired patients in each group at 24 weeks. • Cumulative proportion of impaired patients in each group at 48 weeks. • Average decline in lowest ranking domain at baseline (in a given individual) at 24 weeks. • Average decline in lowest ranking domain at baseline (in a given individual) at 48 weeks. • Number of patients crossing over from ENZ to DARO and DARO to ENZ by each cause. • Proportion of patients crossing over from each treatment arm based on subjective (self-reported, FACT-Cognitive Function (Version 3). FACT-Cog

	V3, decline by >10 points from baseline score) cognitive effects. • Proportion of patients crossing over from each treatment arm based on objective cognitive effects (the Cambridge Neuropsychological Test Automated Battery [CANTAB] cognition tests, decline by >30% from baseline on any cognitive domain). • Proportion of patient crossing over due to neurologic toxicity (fatigue) with a preference to cross over (ENZ or DARO) or severe neurological toxicity [seizures or posterior reversible encephalopathy syndrome PRES]). Cross over for severe neurologic toxicity is allowed for patients on ENZ only. • Improvement in cognitive function after crossover from each treatment arm. • Time to prostate-specific antigen (PSA) progression. • PSA response rate at 24 weeks (on the basis of a decrease from baseline of $\geq 50\%$). • Progression free survival <u>Exploratory Objectives:</u> • To determine the within treatment association between androgen receptor (AR) CAG repeat length and baseline cognitive function as assessed by CANTAB performance. • To determine the within treatment association between AR CAG repeat length and change in cognitive function at 24 and 48 weeks as assessed by CANTAB performance. • To determine the within treatment association of polygenic hazard scores (PHS) with baseline cognitive function as assessed by CANTAB performance. • To determine the within treatment association of PHS with change in CANTAB performance at 24 weeks or 48 weeks. • To determine the within patient change in financial toxicity in patients undergoing treatment for advanced prostate cancer.
--	--

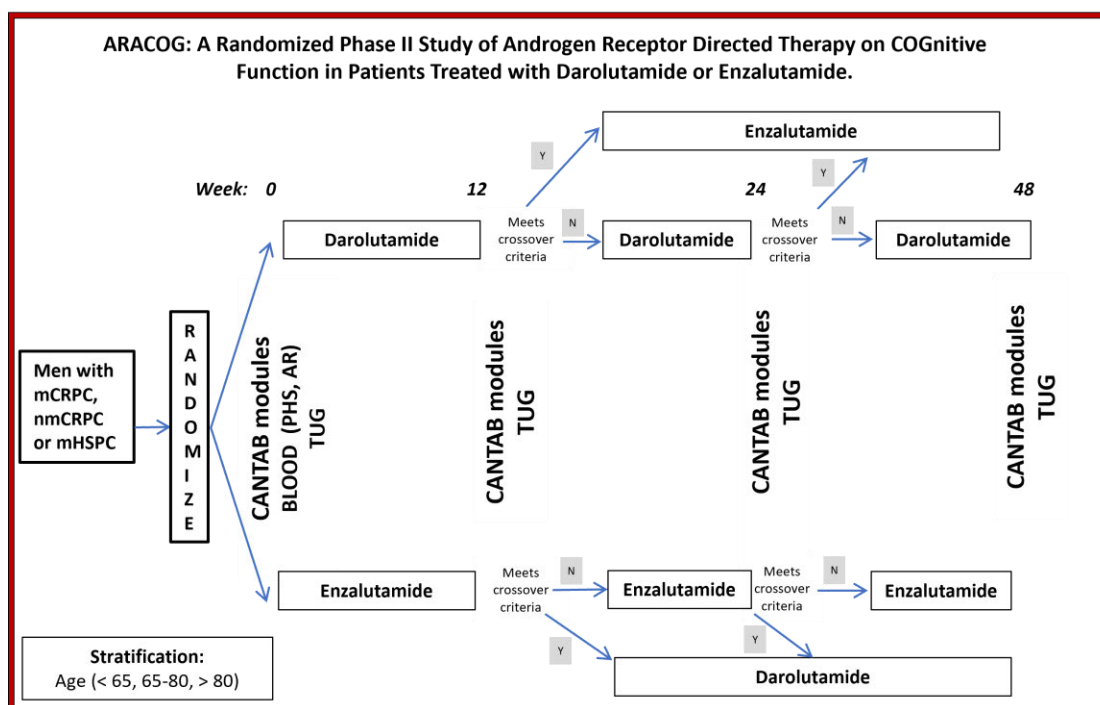
Study Design	This is a prospective, randomized, open-label phase II study comparing cognitive outcomes between men with advanced prostate cancer treated with DARO or ENZ. Approximately 132 patients will be enrolled. After informed consent, screening and baseline evaluations, eligible patients will be randomized in a 1:1 fashion to treatment with ENZ 160 mg PO daily or DARO 600 mg PO twice daily, in combination with standard GnRH antagonist or agonist-based treatment. Analysis will be stratified by age (<65, 65-80, >80). The primary endpoint will be the percent change in the maximally changed cognitive domain by 24 weeks in each study arm. Patients will be allowed to cross over from either treatment to the opposite treatment arm at 12 and 24 weeks if they meet any of the cross-over criteria described in the protocol. These patients will be evaluated based on their treatment assignment for the intent to treat analysis. Note: Patients on ENZ who experience severe neurologic toxicity defined as falls, seizures, or PRES should cross over between time points. Patients experiencing these effects on DARO will not be permitted to cross over but will have an end of treatment visit. Cross over from one treatment arm to the opposite treatment arm can occur at 12 and 24 weeks if participants: a) report subjective cognitive decline on the FACT-Cog (>10 points from baseline) and request crossover; or b) show objective cognitive changes on study assessments (CANTAB, >30% decline in any domain from baseline) and request crossover, or c) have neurologic toxicity (eg grade 2 fatigue, or asthenia, or other grade 2 related adverse events as determined by the treating physician and confirmed by the sponsor) and report a preference to cross over (ENZ or DARO) or experience severe neurologic toxicity (falls, seizure, PRES, applicable for ENZ patients only). DARO patients experiencing falls or severe neurologic toxicity must discontinue treatment. Patients experiencing
----------------------------	---

	falls or severe neurologic toxicity event on DARO at any point will discontinue the study but will not cross over to ENZ and will be removed from the study. Blood samples will be collected for exploratory genomic analyses (AR CAG repeat length, polygenic hazard score). Surveys will be completed for all patient reported outcomes, including financial toxicity. Cognitive assessments will be performed using modules from Cambridge Neuropsychological Test Automated Battery (CANTAB), an internationally recognized software for assessing cognitive function and impairment. Tests include tests of learning and executive function; working memory; visual, verbal and episodic memory; and attention, information and processing time. The maximally changed cognitive domain is defined as the domain most changed from baseline in each individual.
Key Eligibility Criteria	Key inclusion criteria include: • Histologically or cytologically confirmed adenocarcinoma of the prostate • Progressive disease per PCWG3 criteria with EITHER: ○ Metastatic CRPC or non-metastatic CRPC (M0CRPC) ○ For mCRPC: metastatic disease documented by standard or novel imaging techniques ○ OR for M0CRPC: no evidence of metastatic disease on standard imaging. ○ OR mHSPC • Surgically or medically castrated, with testosterone levels of <50 ng/dL. If the patient is medically castrated, continuous dosing with GnRH agonist or antagonist must have been initiated at least 4 weeks prior to randomization and must be continued throughout the study. • Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 • Able to complete cognitive testing and patient reported outcome surveys in English. • Ability to swallow study medications whole.

	• Able to provide informed consent. Key exclusion criteria include: • Prior chemotherapy for treatment of CRPC. Patients who received chemotherapy for HSPC are still eligible provided chemotherapy was completed >6 months prior to study entry. • Use of investigational agents for the treatment of prostate cancer within 2 weeks of study entry. • Prior usage of an androgen receptor pathway inhibitor (ARPI): enzalutamide, darolutamide, apalutamide for greater than 4 weeks. Must have a 2 week washout from the use of prior ARPI before baseline testing completed • Prior use of investigational agents that act on the androgen axis. • Progression during treatment with abiraterone (PSA or radiographic progression). Must have <12 weeks of abiraterone exposure prior to enrollment if given for treatment of CRPC or mHSPC, and patients must have a 2 week washout period before completing baseline testing for this study If abiraterone was used with radiation for high risk localized hormone sensitive disease, patients can enroll if no progression of disease during treatment (PSA or radiographic) and >6 weeks since last dose of abiraterone. • Any active, or prior history of, brain metastasis that have not been treated and stabilized. • Active or history of seizures or seizure disorder. • Prior diagnosis of moderate or severe dementia or other severe neurologic impairment.
--	--

Statistical Methodology	The target sample size is 132, allowing for 15% patient drop-out. Our sample size justification is based on the projection that the most changed cognitive domain among men treated for 24 weeks with DARO will decline on average by 15% from baseline in the population, while the most changed cognitive domain among men treated with ENZ will decline on average by 30% in the population. A sample size of 57 patients per treatment arm has power 0.88 based on the Lehmann alternative, assuming this two- fold effect on the average rate of cognitive decline between treatments and a two-sided 0.05 Wilcoxon rank sum test that will be used to evaluate the primary objective.
---------------------------------------	--

Figure 1: Study Schema



Cross over from one treatment arm to the opposite treatment arm can occur at 12 and 24 weeks if participants experience any one of the following:

- report subjective cognitive changes on a standardized survey (FACT-Cog, decline by >10 from baseline) and request cross-over;
- show objective cognitive changes on study assessments (CANTAB modules, decline by >30% from baseline in any module) and request cross-over;
- or experience neurologic toxicity (consistent with grade 2 fatigue) and request a preference to cross over from ENZ to DARO or DARO to ENZ or experience severe neurologic toxicity (seizure, PRES, or falls- applicable to ENZ to DARO only).

Note: Crossover is allowed to DARO between time points for patients on ENZ that experience severe neurologic toxicity which includes, but is not limited to, falls, seizures, or PRES. If a subject experiences 'other neurologic toxicity deemed severe by the treating clinician,' they may cross over between time points with sponsor approval. Patients experiencing these effects on DARO will not be permitted to cross over to ENZ but will have an end of treatment visit.

Table of Contents

ALLIANCE FOUNDATION TRIALS (AFT).....	1
Protocol Contacts	2
Study Resources.....	3
Synopsis and Study Schema	4
Table of Tables	14
Table of Figures	15
List of Abbreviations and Definition of Terms	15
1. Background Information.....	17
1.1. Overview of Disease and Patient Population	17
1.1.1 Overview of Disease: ADT & AR Directed Therapies in Prostate Cancer.....	17
1.1.2. Current Treatment Approach Indication	17
1.1.3. Study Rationale.....	18
1.1.4. Rationale for Measuring Cognitive Decline in Prostate Cancer Patients Receiving AR- Targeted Therapies	19
1.1.5. Rationale for Assessing Genetic Risk Factors for the Development of Cognitive Dysfunction.....	19
1.1.6. Rationale for Brief Assessment of Financial Toxicity	21
1.2. Study Design	21
1.2.1. Stratification Factors	22
1.3. Study Design Rationale	22
2. Study Agents	23
2.1. Nonclinical studies	23
2.1.1. Clinical studies.....	25
2.1.2. Clinical Pharmacology.....	25
2.1.3. Pharmacodynamics	26
2.1.4. Efficacy and Safety	26
2.2. Enzalutamide	27
2.2.1. Clinical Experience and Side Effects.....	27
3. Objectives and Endpoints	28
3.1. Primary Objectives	28
3.2. Secondary Objectives	28
3.3. Exploratory Objectives.....	29
3.4. Endpoints.....	29
3.4.1. Primary Endpoint.....	29
3.4.2. Secondary Endpoints	29
3.4.3. Exploratory Endpoints	30
4. Eligibility Criteria	30
4.1. Inclusion Criteria.....	30
4.2. Exclusion Criteria.....	32
4.3. Inclusion of Minorities	33
4.4. Subject Withdrawal Criteria	33
4.5. Subject Replacement	34

5.	Site Enrollment Requirements	34
6.	Patient Numbering and Treatment Assignment	34
7.	Treatment Plan and Investigational Agent Information	35
7.1.	Treatment Regimen	35
7.1.1.	Enzalutamide.....	35
7.1.2.	Darolutamide.....	36
7.1.3.	Cross-Overs.....	38
7.1.4.	Duration of Therapy.....	39
7.2.	AR Targeted Treatment Discontinuation.....	39
7.3.	Pregnancy	40
7.4.	Supportive Care and Concomitant Medications.....	40
7.4.1.	Supportive Care	40
7.4.2.	Concomitant Medications	40
7.4.3.	Prohibited Medications	40
7.4.4.	Incompatibilities of Darolutamide	41
7.4.5.	Incompatibilities of Enzalutamide	41
7.4.6.	Permitted Medication.....	42
8.	Dose and Treatment Modifications.....	42
8.1.	Dose Reduction - Darolutamide	43
8.2.	Dose Reduction - Enzalutamide	44
8.3.	Hypertension	44
8.3.1.	Posterior Reversible Encephalopathy Syndrome.....	45
8.3.2.	Falls, Risk of Falls, Fall-related Injuries.....	45
8.3.3.	Seizures	45
9.	Study Assessments and Procedures	45
9.1.	Assessment Types.....	45
9.1.1.	Efficacy Assessment – Cognitive Testing.....	45
9.1.2.	Safety and Tolerability Assessments.....	46
9.1.3.	Biomarkers/Correlative Studies	46
9.1.4.	Patient Reported Outcomes.....	48
10.	Study Assessment Table.....	48
11.	Adverse Events	53
11.1.	Adverse Events.....	53
11.2.	Adverse Event Reporting Exceptions.....	53
11.3.	Serious Adverse Events	54
11.3.1.	Life-threatening.....	54
11.4.	Suspected Unexpected Serious Adverse Reaction (SUSAR).....	54
11.5.	Adverse Events of Special Interest.....	54
11.6.	Overdose.....	55
11.6.1.	Darolutamide Overdose	55
11.6.2.	Enzalutamide overdose	55
11.7.	Adverse Event Reporting	55
11.7.1.	Serious Adverse Event Reporting.....	56
11.7.2.	Events of Special Interest Reporting.....	56

11.7.3.	Assessment of Severity of Adverse Events.....	56
11.7.4.	Assessment of Causality of Adverse Events.....	57
11.7.5.	Expedited Safety Reporting to Regulatory Agencies.....	58
11.8.	Data Collection and Submission	58
12.	Correlative Science	58
12.1.	Future Biomedical Research	58
13.	Measurement of Effect/ Efficacy Assessments.....	59
13.1.	Patient Disease-Related Outcome Measures.....	59
13.1.1.	The Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog)	59
13.1.2.	Functional Assessment of Cancer Therapy – Prostate Version (FACT-P).....	59
13.1.3.	PHQ-9: Patient Health Depression Questionnaire.....	59
13.1.4.	Sleep Scale from Medical Outcomes Study.....	60
13.1.5.	Functional Activities Questionnaire (FAQ)	60
13.1.6.	COMprehensive Score for financial Toxicity (COST).....	60
13.1.7.	Health Literacy.....	60
13.2.	Assessments based on PSA	60
13.3.	Radiographic Assessments:	61
13.3.1.	Definition of Radiographic Progression	61
13.3.2.	PSA Progression within 48 weeks of study initiation.....	61
13.3.3.	PSA Progression beyond 48 weeks of study initiation	61
14.	Statistical Considerations.....	61
14.1.	Overview of the Study Design	61
14.1.1.	Definitions.....	62
14.2.	Sample Size, Accrual Time and Study Duration	62
14.3.	Stratification Factors	62
14.4.	Statement for Primary Endpoint.....	62
14.5.	Interim Analysis Design for Primary Endpoint.....	62
14.6.	Supplementary/Secondary Analysis Plans	62
14.7.	Treatment Switching/Missing Data Analyses	63
14.8.	Early Discontinuation of the Study	64
14.9.	Criteria for Taking a Patient Off Protocol Therapy	64
14.10.	Criteria for Taking a Patient Off Study	64
15.	General Regulatory Considerations	65
15.1.	Compliance with Study Enrollment and Results Posting Requirements	65
15.2.	Regulatory and Ethical Compliance.....	65
15.3.	Informed Consent	65
15.4.	Responsibilities of the Site Investigator/IRB/IEC/REB.....	65
15.5.	Financial Disclosures	66
15.6.	Protocol Deviations	66
15.7.	Protocol Amendments	66
15.8.	Retention of Records (Study Documentation, Record Keeping)	66
15.8.1.	Retention of Records.....	66
15.9.	Data Confidentiality	67

15.10. Database Management and Quality Control	67
15.11. Site Monitoring.....	68
15.12. Data and Safety Monitoring Board (DSMB)	68
15.13. Regulatory Reporting	68
15.14. Audits and Inspections	68
15.15. Early Discontinuation of the Study	68
15.16. Publication of Study Protocol and Results	69
16. References.....	70
Appendix 1: ECOG Performance Status.....	73
Appendix 2: New York Heart Association Classification of Heart Failure (NYHA CHA).....	74
Appendix 3: Common Terminology Criteria for Adverse Events v5.0 (CTCAE).....	75
Appendix 4: CYP3A4 Inducers and Inhibitors	76
Appendix 5: FACT-COG	77
Appendix 6: FACT-P.....	80
Appendix 7: PHQ-9	84
Appendix 8: Sleep Scale from the Medical Outcomes Study.....	86
Appendix 9: FAQ	88
Appendix 10: COST Survey	89
Appendix 11: Health Literacy	90

Table of Tables

Table 1: Treatment Administration Summary	35
Table 2: Prohibited Medications While on Enzalutamide	41
Table 3: Dose modification and/or delay for toxicities considered related to study treatment (darolutamide)	43
Table 4: Darolutamide Dose Reduction for Toxicity Other than those associated with endpoints (fatigue, cognition, mood, neurologic toxicity)	43
Table 5: Enzalutamide - Dose Reduction for Toxicity	44
Table 6: Schedule of Assessments	49
Table 7: Adverse Event Severity Grading Scale	57
Table 8: Guidelines for Determining the Relationship Between Adverse Event and the Study Drug.....	58

Table of Figures

Figure 1:	Study Schema	10
Figure 2:	Hypthesized Effect of AR CAG Length and Cognitive Impairment With AR Blockade	20
Figure 3:	Human plasma NDE levels	47

List of Abbreviations and Definition of Terms

AD	Alzheimer's Disease
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AR	Androgen Receptor
AST	Aspartate Aminotransferase
BBB	Blood Brain Barrier
BCRP	Breast Cancer Resistance Protein
CANTAB	Cambridge Neuropsychological Test Automated Battery
CITI	Collaborative Institute Training Initiative
CNS	Central Nervous System
CRPC	Castration Resistant Prostate Cancer
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DARO	Darolutamide
DEA	Drug Enforcement Agency
DCMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
DHT	Dihydrotestosterone
ECOG	Eastern Cooperative Oncology Group
ENZ	Enzalutamide
FAQ	Functional Activities Questionnaire
FDA	Federal Drug Administration
GCP	Good Clinical Practice
GnRH α	Gonadotrophin-Releasing Hormone Agonists or Antagonists
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HGB	Hemoglobin
HIPPA	Health Insurance Portability and Accountability Act
HP	Hippocampus

HP-PFC	Hippocampus-Prefrontal Cortex
IB	Investigator Brochure
ICF	Informed Consent Form
IRB	Institutional Review Board
IND	Investigational New Drug
INR	Prothrombin Time
IUD	Intrauterine Device
IUS	Intrauterine System
LHRH	Luteinizing Hormone Releasing Hormone
MCI	Mild Cognitive Impairment
mHSPC	metastatic Hormone-Sensitive Prostate Cancer
M0 CRPC	Non-Metastatic Castration-Resistant Prostate Cancer
mCRPC	Metastatic Castration-Resistant Prostate Cancer
PCa	Prostate Cancer
PCCTC	Prostate Cancer Clinical Trials Consortium
PCWG3	Prostate Cancer Working Group 3
PFC	Prefrontal Cortex
P-gp	P0-glucoprotein
PHS	Polygenic Hazard Score
PO	Per Oral
PRC	Protocol Review Committee
PRES	Posterior Reversible Encephalopathy Syndrome
PSA	Prostate Specific Antigen
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SOC	Standard of Changes
SOP	Standard Operating Procedure
SPE	Single Patient Exception
TSH	Thyroid Stimulating Hormone
TUG	Timed up-and-go

1. Background Information

1.1. Overview of Disease and Patient Population

1.1.1 Overview of Disease: ADT & AR Directed Therapies in Prostate Cancer

Prostate cancer (PCa) is the most common non-cutaneous cancer among American men, and the second leading cause of cancer death in the United States (US).¹ Approximately 40-50% of the nearly 161,360 men diagnosed with PCa each year will receive treatment with androgen deprivation therapy (ADT) at some point during the course of their disease.² The ADT, accomplished by medical or surgical castration lowering testosterone to <50 ng/dL, inhibits signaling through the androgen receptor (AR), disrupting tumor progression. It is considered the backbone of treatment of metastatic PCa.

Although a majority of men will respond to treatment with ADT, men who are exposed for long periods of time eventually develop castration-resistant disease with progression of tumor growth despite maintaining low levels of testosterone. Perhaps surprisingly, work completed during the past decade demonstrated that further suppression of AR signaling can provide disease control and prolong life among men with metastatic castration-resistant prostate cancer (mCRPC).³⁻⁶

These novel AR-directed therapies (enzalutamide [ENZ] and darolutamide [DARO]) accomplish this by directly antagonizing the AR. ENZ is Food and Drug Administration (FDA) approved for treatment across the disease spectrum of metastatic hormone sensitive prostate cancer (mHSPC) and CRPC (metastatic and non-metastatic castration resistant prostate cancer).⁷ DARO received FDA approval for treatment in patients with non-metastatic castration-resistant prostate cancer on July 30, 2019.⁸

1.1.2. Current Treatment Approach Indication

1.1.2.1. Cognitive Effects of Cancer Therapy: Hormonal and Genetic Mechanisms

The cognitive effects of exposure to cancer treatments have been evaluated for decades.⁹⁻¹² The constellation of effects, typically attributed to exposure to chemotherapy, includes poor short-term memory, impaired multi-tasking, poor concentration and attention, and word-finding difficulties, among others. These changes can negatively impact interactions with family and loved ones, work performance, and continued access to health services.^{9,13,14} Although there is a robust literature describing these complications among patients with some solid tumors, such as breast cancer, there is a relative paucity of literature describing the cognitive effects of cancer treatment among men with PCa.^{12, 15-20}

In addition to chemotherapy, changes in hormonal signaling during cancer treatment may also contribute to cognitive dysfunction.²¹⁻²³ This has been demonstrated multiple times among breast cancer patients. For example, women with breast cancer treated with tamoxifen, an estrogen receptor antagonist, in addition to chemotherapy displayed greater cognitive dysfunction than women treated with chemotherapy alone.²³ In a separate investigation, treatment with tamoxifen alone was associated with worse visual and verbal memory and processing speed when compared with no treatment.²² Finally, there is a suggestion that direct estrogen receptor antagonist activity with tamoxifen may be associated with worse verbal memory and executive

function when compared with post-menopausal breast cancer patients treated with the aromatase inhibitor, exemestane, which reduces the production of estrogen.²¹

1.1.2.2. Systemic Effects of Low Testosterone

The side effects of inducing castrate levels of testosterone have been well described among men with PCa. Some early effects include hot flashes, erectile dysfunction, loss of libido, fatigue, depression, impaired glucose tolerance, loss of muscle mass and bone density, and weight gain.²⁴ Many of these effects, including fatigue, depression, and hot flashes, can raise the risk of cognitive dysfunction or compound cognitive deficits that already exist.²⁵⁻²⁷

1.1.2.3. Complex Role of Testosterone in Development of Dementia

In non-cancer populations, a decline in circulating testosterone into the low or clinically hypogonadal range in men has been associated with the development of Alzheimer's Disease (AD).^{28, 29, 30, 31} In recent studies of aging men, testosterone levels are significantly lower in men with AD compared to non-demented, age-matched controls.²⁸⁻³⁰ Evidence suggests that low testosterone increases β -amyloid ($A\beta$) production and tau phosphorylation, both of which contribute to the development of mild cognitive impairment (MCI) and AD.²⁶⁻³²

Whether low testosterone due to ADT is associated with cognitive decline in men with PCa has been controversial.^{11-14, 28-32} While several studies failed to demonstrate an association between exposure to ADT and cognitive decline, multiple recent prospective and population-based studies suggest an association.^{28, 30, 31, 33} In clinical practice, cognitive change associated with ADT appears to span the spectrum of cognitive dysfunction, from subtle impairment in specific domains, to severe dementia including Alzheimer's disease. To more completely define the effects of low testosterone on the cognitive function of men with prostate cancer, a prospective study that quantifies the range of cognitive decline that we see clinically, from mild cognitive impairment to overt dementia, is imperative.

1.1.3. Study Rationale

1.1.3.1. Biological Rationale for AR Modulation of Dementia-Associated Plaque

The androgen receptors (AR) is highly expressed in hippocampal and forebrain neuron cell bodies, dendritic spines, and synapses where AR signaling promotes neuronal growth, spinal density, synaptic function, and axonal regeneration.^{33, 34, 35} Multiple cellular and animal studies strongly suggest that testosterone is a negative regulator of β Amyloid plaque formation, a process that couples with abnormal hyperphosphorylation of tau to lead to neurofibrillary tangles in patients with AD.^{36, 37, 38, 39} Treatment of male 3xTg-AD mice, a transgenic model of AD, with leuprolide increased levels of β Amyloid within the hippocampus and subiculum.³⁶ Conversely, exposure of castrated male 3xTg-AD mice to testosterone reduced brain β Amyloid, with leuprolide increased levels of β Amyloid within the hippocampus and subiculum.³⁶

Conversely, exposure of castrated male 3xTg-AD mice to testosterone reduced brain β Amyloid deposition, confirming that androgens can regulate the amyloidogenic pathway.³⁶

1.1.4. Rationale for Measuring Cognitive Decline in Prostate Cancer Patients Receiving AR- Targeted Therapies

1.1.4.1. Enzalutamide

Enzalutamide (ENZ) is a small molecular AR antagonist, which inhibits AR activity by blocking nuclear translocation of the AR as well as DNA binding. Based on its efficacy in mCRPC as demonstrated by the AFFIRM⁴ and PREVAIL⁴⁰ studies, ENZ is a standard of care treatment for patients with mCRPC. Based on the PROSPER study, ENZ is also approved for treatment of M0CRPC.⁴¹ Based on the ARCHES and ENZAMET studies, ENZ is approved for treatment of mHSPC.^{58,59}

However, ENZ is known to cross the blood-brain barrier (BBB), and the side effects of ENZ, as recognized in the product label, include seizure and a neurological disorder known as posterior reversible encephalopathy syndrome (PRES).⁴² Since the approval of ENZ, there has been a growing concern about cognitive, attention, and memory impairment in ENZ-treated patients (these AEs occurred in 4.6-5.7% of ENZ-treated patients versus 1.4-1.8% of placebo-treated patients in two large studies). ENZ is also associated with an increased risk of falls (9% in ENZ-treated patients versus 4% of placebo-treated patients). We hypothesize that these neurologic-related side effects of ENZ are due to brain exposure to the drug.

1.1.4.2. Darolutamide

Darolutamide (DARO; previously known as ODM-201) is a novel nonsteroidal AR antagonist indicated for castration-resistant prostate cancer (CRPC), jointly developed by Bayer AG and Orion Corporation. DARO received FDA approval on July 30, 2019 for the treatment of non-metastatic castration-resistant prostate cancer based on results from the randomized, multicenter phase III study, ARAMIS. In a separate phase III study for mHSPC, ARASENS,⁵⁷ there was a benefit in overall survival in patients treated with ADT plus docetaxel with darolutamide versus ADT plus docetaxel with placebo.

DARO and its metabolites have negligible brain penetration, suggesting the potential for neurologic-related toxicities is much lower than similar drugs that cross the BBB. We hypothesize that there will be fewer neurologic-related side effects of DARO compared to ENZ due to reduced BBB penetration.

1.1.5. Rationale for Assessing Genetic Risk Factors for the Development of Cognitive Dysfunction

1.1.5.1. Genetic Polymorphisms, AR Genotype and Risk of Cognitive Dysfunction

Clinical experience and existing data suggest that the cognitive decline associated with ADT may occur in a currently unidentified vulnerable population of individuals in which genetic, biologic, and environmental factors combine to increase the risk of this complication.^{15, 18, 28, 29, 30, 31, 32} At present, the population of PCa survivors at greatest risk of cognitive change in the setting of ADT has not been identified, and no interventions to prevent or reverse cognitive change are available. Methods to identify at-risk individuals and provide interventions to prevent cognitive decline are critical to preserving the mental health and quality of life of the vulnerable members

of the population, while ensuring men who are not vulnerable can proceed with treatment with less risk of these complications.

In addition, there are polymorphisms in the promoter region of the AR that vary in the length of a repeating CAG nucleotide sequence and polyglutamine ‘tail’ (**Figure 2**). Longer CAG repeats have been associated with cognitive impairment. Yaffe and colleagues evaluated the association between length of CAG repeats and cognitive function measured by the Mini Mental Status Exam (MMSE). They found that elderly men with long CAG repeats in the promoter region of the AR gene scored lower on the MMSE than men with shorter CAG repeats, suggesting an interaction between androgen signaling and neuroprotection.⁴³ We will evaluate the association between AR CAG repeats, change in CANTAB score, and PCa disease-specific biomarkers.

Figure 2: Hypthesized Effect of AR CAG Length and Cognitive Impairment With AR Blockade

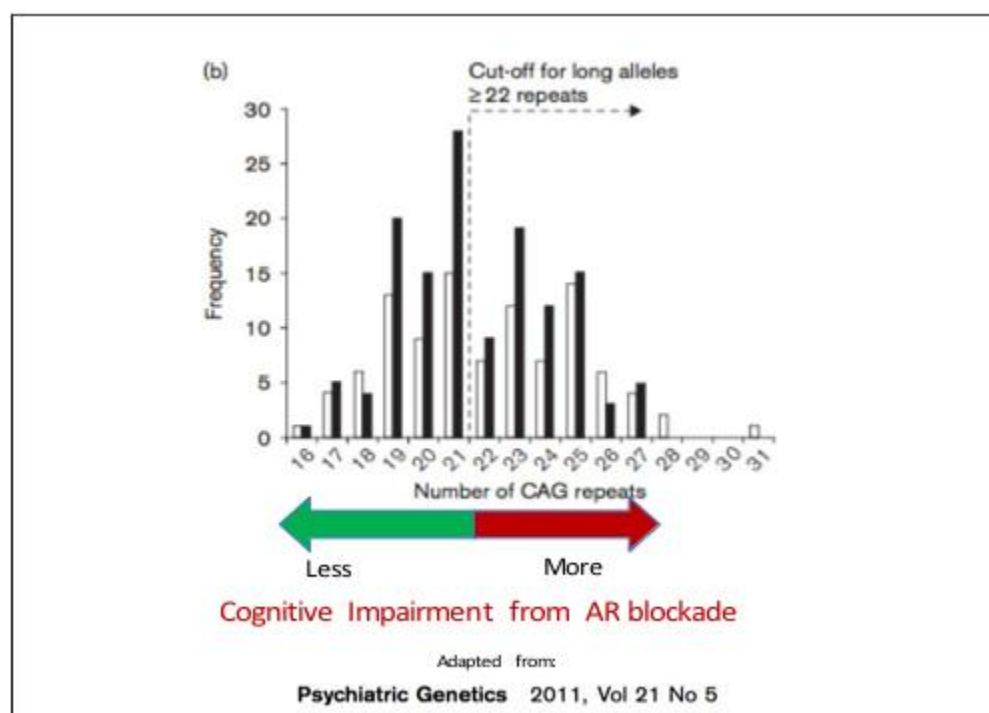


Fig. 1. Hypothesized effect of AR poly CAG length and results of cognitive testing. The graph shown displays the population distribution of men in India although these data and the Gaussian distribution it displays has been reproduced in other populations. Although men with prostate cancer may have a slightly different distribution, this pattern is expected to persist

1.1.5.2. Polygenic Hazard Score for Dementia

Desikan et al recently published a polygenic hazard score (PHS) to predict age-associated risk of AD44. This score takes into account genetic variation beyond the primary risk factor for AD, APOE-ε4, and is predictive of age of AD onset and longitudinal progression from normal aging to AD, as well as in vivo markers of AD-related neurodegeneration. We hypothesize that the

same genetic variants that predict risk for AD may predict risk of cognitive decline with AR antagonism; a patient in the highest risk quartile of the PHS, for example, would be most likely to develop cognitive decline with AR antagonism. We will evaluate the association between PHS score, change in CANTAB score, and plasma biomarkers.

1.1.6. Rationale for Brief Assessment of Financial Toxicity

Financial toxicity is an increasingly recognized risk of cancer treatment and can be particularly important for patients receiving oral treatments for their cancer due to co-pay requirements.

Patients with a cancer diagnosis are at an increased risk of bankruptcy compared to the general population.⁴⁶ Nipp and colleagues have demonstrated that patients may alter prescription medication dosing, split pills, and engage in alter their lifestyles in order to afford cancer therapy.⁴⁷ To date, no standard strategy for screening for financial risk has been implemented routinely in clinical practice. Moreover, prospective therapeutic clinical trials do not collect measures related to financial toxicity, albeit may indirectly ascertain financial risk through Quality of Life patient reported outcome measures. This study will collect financial toxicity measures at baseline and at the time of the primary endpoint using the only validated short patient reported outcome form for measuring financial toxicity among solid tumors.⁴⁸

Understanding the financial toxicity experienced by patients on the trial, including patients who pay co-payments for their treatment and those that do not, will enable clinicians and researchers to develop enhanced strategies to support patients and optimize care delivery and may help address a frequently unmeasured confounding variable in the comparison of oral drug therapies.

1.2. Study Design

The goal of the trial is to assess cognitive and QOL outcomes over the 48-week period of the trial. This is a prospective, randomized, open-label phase II study comparing cognitive outcomes between men with advanced prostate cancer who have mHSPC or metastatic or non-metastatic CRPC (mCRPC or M0CRPC) treated with DARO or ENZ. This will be a multicenter trial conducted at 12 sites across the US.

A total of 132 subjects will be enrolled for this trial. Approximately 20 potentially eligible patients are anticipated to be seen per month, and it is anticipated that at least 6 per month will be accrued (once all sites are activated).

After informed consent, screening and baseline evaluations, eligible patients will be randomized in a 1:1 fashion to treatment with ENZ 160 mg PO daily or DARO 600 mg PO twice daily, in combination with standard GnRH antagonist or agonist-based treatment. Patients will be stratified by age (<65, 65-80, > 80).

The primary endpoint will be the percent change in the maximally changed cognitive domain by 24 weeks in each study arm.

Patients will be allowed to cross over from either treatment to the opposite treatment arm at 12 and 24 weeks if they meet any of the cross-over criteria described below:

- a) report subjective cognitive changes on a standardized survey (FACT-Cog, decline by >10 from baseline) and request cross-over;

- b) show objective cognitive changes on study assessments (CANTAB) modules, decline by >30% from baseline in any module) and request cross-over;
- c) or experience neurologic toxicity (consistent with grade 2 fatigue) and request a preference to cross over from ENZ to DARO or DARO to ENZ) or experience severe neurologic toxicity (seizure, PRES, or falls- applicable for ENZ to DARO only).

Note: Cross over is allowed to DARO between time points for patients on ENZ that experience severe neurologic toxicity. Severe neurologic toxicity includes, but is not limited to, falls, seizures, or PRES. If a subject experiences 'other neurologic toxicity deemed severe by the treating clinician,' they may cross over between time points with sponsor approval. Patients experiencing these effects on DARO will not be permitted to cross over to ENZ, but will have an end of treatment visit.

Patients randomized to the DARO arm who report falls, experience witnessed falls, show an increased risk of falls, or have severe neurologic toxicity will be removed from the study without crossing over, and will complete an end of treatment visit. Blood samples will be collected for exploratory genomic analyses (AR CAG repeat length, PHS).

Cognitive assessments will be performed using Cambridge Neuropsychological Test Automated Battery (CANTAB), an internationally recognized software for assessing cognitive function and impairment. Tests available in the CANTAB battery include tests of learning and executive function; working memory; visual, verbal and episodic memory; and attention, information and processing time. The battery will include the One Touch Stockings of Cambridge, Spatial Working Memory, Paired Associates Learning, Rapid Visual Information Processing, and Spatial Span tests. The maximally changed cognitive domain is defined as the domain most changed from baseline in each individual.

Patients will have the option to opt into an additional separate sub-study.

In addition, health literacy will be assessed in the patients participating in this study to test the following hypotheses:

- Low baseline health literacy is independently associated with decline in cognitive function.
- High baseline financial toxicity is independently associated with decline in cognitive function.
- Increase in reported financial toxicity during study is associated with decline in cognitive function.

1.2.1. Stratification Factors

Analysis will be stratified by patient age (< 65, 65-80, >80) as there is an association between increasing age and risk of developing cognitive impairment in the general population.

1.3. Study Design Rationale

The goal of the trial is to assess cognitive outcomes over the 48-week period of the trial. This is a prospective, randomized, open-label phase II study comparing cognitive outcomes between men with advanced prostate cancer with mHSPC or metastatic or non-metastatic CRPC (mCRPC or

M0CRPC), who will receive treatment with DARO or ENZ. These medications are both AR antagonists, a class of medications that can provide disease control in men with prostate cancer, but that has also been implicated in potentially being associated with cognitive decline. Pre-clinical data suggests that ENZ crosses the BBB, potentially acting as an AR antagonist in the central nervous system. Similar models suggest that DARO may have 30-50 times less penetration of the CNS than ENZ. Given this, in this study we are assessing cognitive function and patient reported outcomes among men receiving treatment with ENZ or DARO to see if there is evidence of cognitive change or other patient reported symptoms during treatment. We are also assessing blood and imaging correlatives to define the biology of differences in patient reported outcomes or findings of cognitive change during treatment.

2. Study Agents

Darolutamide

Darolutamide (DARO) is a nonsteroidal antiandrogen – specifically, a selective antagonist of the androgen receptor – was developed by Orion and Bayer HealthCare for the treatment of advanced, castration-resistant prostate cancer.

2.1. Nonclinical studies

Darolutamide, both its diastereomers and its major metabolite were found to possess antiandrogenic as well as antitumor activity both in in vitro and in vivo models of CRPC, and the molecule was found to be safe and well-tolerated in non-clinical studies. Current clinical data indicate that darolutamide exhibits a good safety and tolerability profile and promising antitumor activity in male subjects with CRPC.

Darolutamide binds with a high affinity and selectivity to the AR with potent and improved antagonism for human androgen receptor (hAR) in vitro. The affinity to the AR and antagonistic properties of the two diastereomers and the major circulating metabolite keto-darolutamide are similar. In AR overexpressing human embryonic kidney cells (HS-HEK293), darolutamide showed significant and better antagonism than bicalutamide.

In a cell line derived from a bone metastasis of a patient with CRPC (VCaP) with endogenous AR gene amplification and AR overexpression, darolutamide suppressed dose-dependently androgen-induced VCaP cell proliferation more efficiently than bicalutamide. Darolutamide shows strong antagonism for several AR mutants (W742L, F877L) identified in patients with resistance to approved AR antagonists. In pharmacological studies in vivo, oral darolutamide showed an antiandrogenic activity in the immature rat assay. Darolutamide also showed a significant antitumor activity in the castration-resistant VCaP xenograft mouse model as well as in the orthotopic VCaP tumors both in intact and castrated mice. In invitro studies evaluating secondary pharmacodynamic effects, darolutamide was observed to inhibit 5-hydroxytryptamine (5-HT), i.e., serotonin, uptake and type-A γ -aminobutyric acid receptors (GABAA) receptors with half-maximal inhibitory concentration (IC₅₀) values of over 50- and 80-fold higher, respectively, compared to hAR blocking IC₅₀ value.

Due to the low brain/plasma ratio, central nervous system (CNS) effects via 5-HT uptake and GABAA inhibition are not expected. In transactivation assays, darolutamide functioned as a

weak human progesterone receptor (hPR) antagonist, giving AR potency selectivities greater than 78-fold. In safety pharmacology studies in rats with single dosing, darolutamide had no biologically relevant CNS effects or effects on respiratory function. Darolutamide, at high local doses/concentrations, led to a decrease in gastric emptying and intestinal propulsion after single oral dosing to rats. Studies to address the risk for QT prolongation in humans were performed in vitro (human ether-à-go-go-related gene [hERG] K⁺ channel and L-type Ca⁺⁺ voltage clamp assays) and in vivo (QT/QTc intervals in electrocardiogram [ECG] recordings of Beagle dogs). The hERG K⁺ and L-type Ca⁺⁺ current were blocked with IC₅₀ concentrations of about 40- to 100-fold higher than the plasma free peak concentrations (C_{max}) observed at 700mg twice daily (b.i.d.) dose level in the Phase I/II clinical study in metastatic castration-resistant prostate cancer (mCRPC) subjects.

In ECG recordings of conscious and anesthetized beagle dogs, no prolongation of QT/QTc intervals was seen. Hence, it can be assumed that darolutamide has no potential for delayed repolarization at clinically relevant plasma concentrations. After single intravenous administration of darolutamide to anesthetized dogs, vasodilation, associated with a decrease in arterial blood pressure (BP), was observed at high plasma concentrations of darolutamide. This is not regarded to be of biological relevance as this was observed at free peak plasma concentrations of ≥ 3 -fold higher than the plasma free C_{max} observed at 700mg b.i.d. dose level in the Phase I/II clinical study in mCRPC subjects.

The drug substance darolutamide is a 1:1 mixture of two diastereomers, (S,R)-darolutamide and (S,S)-darolutamide. After peroral administration, in humans (S,S)-darolutamide is the main diastereomer (about 85%) in terms of area under the plasma concentration-time curve (AUC). Keto-darolutamide is the major metabolite in plasma of all species. After repeated administration, keto-darolutamide/parent darolutamide ratio was close to 1 in dogs. In rodents and humans, the metabolite plasma concentrations were higher than darolutamide. No human-specific disproportionate metabolites have been found.

In vitro, oxidative metabolism of darolutamide involves human cytochrome P450 (CYP) 3A4. Glucuronidation is catalyzed by several uridine-5'-diphospho glucuronosyltransferase (UGT) isoforms. In vitro experiments indicate a low risk for drug-drug interactions (DDIs) resulting from inhibitory effects of darolutamide on CYP and UGT isoforms in humans. Based on in vitro results, a risk to observe weak to moderate CYP3A4 induction cannot be ruled out. The clinical significance of these potential interactions is not known. In vitro plasma protein binding of darolutamide and keto-darolutamide with fraction unbound of 8% and 0.2% in human is moderate and high, respectively. There are no differences in protein binding between the two diastereomers.

After a 7-day oral administration of 50mg/kg darolutamide in mice, the highest tissue/plasma ratio for (S,R)-, (S,S)-darolutamide and keto-darolutamide was found in liver and kidney. The brain/plasma ratio was very low indicating low or negligible possibility of drug related CNS effects, including seizures, which were observed in humans during treatment with other antiandrogens. In vitro, darolutamide was a substrate and inhibitor of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) as well as an inhibitor of the uptake transporters OATP1B1 and OATP1B3. Interaction with BCRP has been confirmed by

clinical study results (Study17723). For P-gp, a drug interaction at intestinal level cannot be ruled out. In vitro, keto-darolutamide was a substrate and an inhibitor of the efflux transporters P-gp and BCRP. In addition, it inhibited MATE2K. However, due to similar permeability and transporter affinity, in vivo studies with the parent compound are expected to cover clinical effects of both parent and metabolite.

The toxicity of darolutamide was assessed in repeated dose toxicity studies up to 26-week duration in the rat and up to 39-week duration in the dog. Darolutamide was well tolerated up to the highest dose levels tested ($2 \times 500 \text{ mg/kg/day}$ in rats and $2 \times 200 \text{ mg/kg/day}$ in dogs). Darolutamide is not considered to represent a genotoxic risk for man. An invitro3T3 neutral red uptake phototoxicity study with darolutamide demonstrated that it is not phototoxic. No stand-alone developmental and reproductive toxicity studies have been conducted with darolutamide. Based on the known pharmacologic effects of antiandrogens, a decrease in fertility in males and developmental toxicity would be expected.

2.1.1. Clinical studies

As of data cut-off date of 04-Jan-2019, darolutamide has been given to 173 subjects with mCRPC. For the 164 subjects from the studies 17829, 18035 and 17830, the median duration of treatment was of 214 days, ranging from 1 to 2063 days and the total exposure to darolutamide was 143.6 patient-years(PY). The median duration of treatment in the 9 Japanese mCRPC subjects in Study17719 was 84.0 days (range: 31-328 days).

As of 04-Jan-2019, 1509 subjects including placebo (in a 2:1 randomization) and 1306 subjects have been randomized in the two double-blind Phase III Studies 17712 and 17777, respectively.

2.1.2. Clinical Pharmacology

Results of 12-week change from baseline in serum prostate-specific antigen (PSA), soft-tissue and bone lesions and circulating tumor cells (CTC) count show that darolutamide has significant antitumor activity in subjects with mCRPC.

The higher doses seemed to have a numerically better response than the lower doses particularly in chemotherapy-naïve CYP17i-naïve subjects. Effects on the CNS triggered via 5-HT uptake and GABAA inhibition are not expected, due to the low brain/plasma ratio observed in preclinical studies.

After oral administration of darolutamide given as a tablet together with food, approximately 60-75% of the administered compound is absorbed and becomes bioavailable. Following repeated oral administration of 600mg (2 tablets of 300 mg) BID to nmCRPC patients in Study17712, peak plasma concentrations of darolutamide of 4.79mg/L (coefficient of variation: 30.9%) were reached around 4 hours after administration.

Steady-state of (S,R)-darolutamide and (S,S)-darolutamide are reached after 2 and 4 days, respectively. Darolutamide is eliminated with an effective half-life of 20 hours.

After intravenous. administration of 100 μg of [^{14}C] darolutamide on top of an oral dose of 300mg darolutamide to healthy male volunteers, the volume of distribution (V) was estimated to be 119L. The mean fraction of unbound darolutamide and its major metabolite keto-darolutamide

in plasma was 8% and 0.2%, respectively. Darolutamide is subject to oxidation as well as to glucuronidation. CYP3A4 is the main enzyme involved in oxidation. Keto-darolutamide is the only major metabolite in plasma with 1.7-fold higher concentrations compared to darolutamide. Darolutamide and its metabolites are mainly excreted with urine (63.4% of dose) and a smaller portion with the feces (32.4% of dose). Approximately 7% and 30% of the administered dose were excreted unchanged as darolutamide in urine and feces, respectively. There is no indication for dose adjustments in patients with mild, moderate or severe renal impairment or in patients with mild or moderate hepatic impairment based on available data to date.

2.1.3. Pharmacodynamics

Results of 12-week change from baseline in serum prostate-specific antigen (PSA), soft-tissue and bone lesions and circulating tumor cells (CTC) count show that darolutamide has significant antitumor activity in subjects with mCRPC.

2.1.4. Efficacy and Safety

NUBEQA[®] (darolutamide) tablets is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer, has been approved by FDA in July 2019.

Serious adverse reactions occurred in 25% of patients receiving NUBEQA[®] and in 20% of patients receiving placebo. Serious adverse reactions in $\geq 1\%$ of patients who received NUBEQA[®] were urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA[®] and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA[®]. Adverse reactions occurring more frequently in the NUBEQA[®] arm ($\geq 2\%$ over placebo) were fatigue (16% vs. 11%), pain in extremity (6% vs. 3%) and rash (3% vs. 1%).

Clinically significant adverse reactions occurring in $\geq 2\%$ of patients treated with NUBEQA[®] included ischemic heart disease (4.0% vs. 3.4% on placebo) and heart failure (2.1% vs. 0.9% on placebo). Safety and efficacy of NUBEQA[®] have not been established in females and it can cause fetal harm and loss of pregnancy. Males with female partners of reproductive potential should use effective contraception during treatment with NUBEQA[®] and for 1 week after the last dose.

Study 17712 (ARAMIS) met its primary efficacy objective, with darolutamide treatment providing a statistically significant improvement in metastasis-free survival (MFS).

A treatment benefit in MFS was seen for darolutamide compared with placebo with a hazard ratio of 0.413 (95% confidence interval [CI]: [0.341; 0.500]), signifying superiority of darolutamide and a 58.7% reduction in the risk of metastasis or death ($p < 0.000001$). Median MFS was 40.37 months (95% CI: [34.33; A1]) in the darolutamide arm compared with 18.43 months (95% CI: [15.51; 22.34]) in the placebo arm.

Treatment with darolutamide also resulted in a positive trend in overall survival (OS) (median was not reached in either arm at the time of the interim OS analysis, hazard ratio=0.706, $p=0.045210$) and a delay in time to pain progression (median 40.3 vs. 18.4 months, hazard

ratio=0.413, $p<0.000001$) compared to placebo. Time to initiation of first cytotoxic chemotherapy (hazard ratio=0.433, $p<0.000001$) and time to first symptomatic skeletal event (SSE) (hazard ratio=0.428, $p=0.011262$) were not mature at the time of primary analyses.

2.2. Enzalutamide

Enzalutamide, sold under the brand name Xtandi[®], is a nonsteroidal antiandrogen medication which is used in the treatment of prostate cancer. It is indicated for use in conjunction with castration in the treatment of mHSPC and metastatic castration-resistant prostate cancer and non-metastatic castration-resistant prostate cancer.

2.2.1. Clinical Experience and Side Effects

Seizure: Seizure occurred in 0.4% of patients receiving enzalutamide in clinical studies, however, in a study of patients with predisposing factors for seizure, 2.2% of enzalutamide - treated patients experienced a seizure. Patients should be cautioned about the risk of developing a seizure while taking enzalutamide and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Posterior Reversible Encephalopathy Syndrome (PRES): In post approval use, there have been reports of PRES in patients receiving enzalutamide. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. Enzalutamide should be discontinued in patients who develop PRES.

Hypersensitivity: Reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with enzalutamide in clinical trials. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue enzalutamide and promptly seek medical care. Enzalutamide should be permanently discontinued for serious hypersensitivity reactions.

Ischemic Heart Disease: In the placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the enzalutamide arm compared to patients on the placebo arm (2.7% vs 1.2%). Grade 3-4 ischemic events occurred in 1.2% of patients on enzalutamide versus 0.5% on placebo. Ischemic events led to death in 0.4% of patients on enzalutamide compared to 0.1% on placebo. Patients should be monitored for signs and symptoms of ischemic heart disease. Cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia should be managed and enzalutamide should be discontinued for Grade 3-4 ischemic heart disease.

Falls and Fractures: In the placebo-controlled clinical studies, patient reported falls occurred in 10% of patients treated with enzalutamide compared to 4% of patients treated with placebo.

Fractures occurred in 8% of patients treated with enzalutamide and in 3% of patients treated with placebo. Patients should be evaluated for fracture and fall risk. Patients who are at risk for fractures should be monitored and managed according to established treatment guidelines and consider use of bone-targeted agents.

Adverse Reactions: The most common adverse reactions ($\geq 10\%$) that occurred more frequently ($\geq 2\%$ over placebo) in the enzalutamide patients from the randomized placebo-controlled trials were asthenia/fatigue, decreased appetite, hot flush, arthralgia, dizziness/vertigo, hypertension, headache and weight decreased.

Lab Abnormalities: In the two placebo-controlled trials in patients with mCRPC, Grade 1-4 neutropenia occurred in 15% of enzalutamide patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). In the placebo-controlled trial in patients with nmCRPC, Grade 1-4 neutropenia occurred in 8% of patients receiving enzalutamide (0.5% Grade 3-4) and in 5% of patients receiving placebo (0.2% Grade 3-4).

Hypertension: In the two placebo-controlled trials in patients with mCRPC, hypertension was reported in 11% of enzalutamide patients and 4% of placebo patients. Hypertension led to study discontinuation in $< 1\%$ of patients in each arm. In the placebo-controlled trial in patients with nmCRPC, hypertension was reported in 12% of patients receiving enzalutamide and 5% of patients receiving placebo.

3. Objectives and Endpoints

3.1. Primary Objectives

The primary objective of this study is to compare the effects of treatment with enzalutamide (ENZ) versus darolutamide (DARO) on the cognitive function of men with advanced prostate cancer by comparing the change in the maximally changed cognitive domain from baseline in patients in each study arm by 24 weeks.

3.2. Secondary Objectives

To determine the effects of ENZ or DARO on cognitive function as measured by:

- Average decline in maximally changed cognitive domain in patients in each group at 48 weeks.
- Cumulative proportion of impaired patients in each group at 24 weeks.
- Cumulative proportion of impaired patients in each group at 48 weeks.
- Average decline in lowest ranking domain at baseline (in a given individual) at 24 weeks.
- Average decline in lowest ranking domain at baseline (in a given individual) at 48 weeks.
- Number of patients crossing over from ENZ to DARO and DARO to ENZ by each cause:
 - Proportion of patients crossing over from each treatment arm based on subjective (self-reported, FACT-Cognitive Function [Version 3], FACT-Cog V3, decline by >10 points from baseline score) cognitive effects.
 - Proportion of patients crossing over from each treatment arm based on objective cognitive effects (the Cambridge Neuropsychological Test Automated Battery [CANTAB] cognition test, decline by $> 30\%$ from baseline on any cognitive domain).
 - Proportion of patient crossing over due to neurologic toxicity (fatigue) with a preference to cross over (ENZ or DARO) or severe neurological toxicity [seizures]

or posterior reversible encephalopathy syndrome PRES)). Cross over for severe neurologic toxicity is allowed for patients on ENZ only.

- Improvement in cognitive function after crossover from each treatment arm.
- Time to prostate-specific antigen (PSA) progression.
- PSA response rate at 24 weeks (on the basis of a decrease from baseline of $\geq 50\%$).
- Progression free survival

3.3. Exploratory Objectives

- To determine the within treatment association between androgen receptor (AR) CAG repeat length and baseline cognitive function as assessed by CANTAB performance.
- To determine the within treatment association between AR CAG repeat length and change in cognitive function at 24 and 48 weeks as assessed by CANTAB performance.
- To determine the within treatment association of polygenic hazard scores (PHS) with baseline cognitive function as assessed by CANTAB performance.
- To determine the within treatment association of PHS with change in CANTAB performance at 24 weeks or 48 weeks.
- To determine the within patient change in financial toxicity in patients undergoing treatment for advanced prostate cancer.
- To assess the relationship between baseline health literacy and average decline in maximally changed cognitive domain at 48 weeks.
- To assess the relationship between baseline financial toxicity and average decline in maximally changed cognitive domain at 48 weeks.
- To assess the relationship between average increase in financial toxicity and average decline in maximally changed cognitive domain at 48 weeks.

3.4. Endpoints

3.4.1. Primary Endpoint

The primary endpoint is a comparison of the change in the maximally changed cognitive domain from baseline in patients in each study arm at 24 weeks. Any patient who has remained on treatment (cross-over or remaining on initial treatment) for 24 weeks are eligible for this endpoint and analyzed according to the treatment they were assigned (intent to treat).

3.4.2. Secondary Endpoints

- The average decline in the maximally changed cognitive domain at 48 weeks within treatment.
- Cumulative proportion of impaired patients in each treatment group at 24 weeks.
- Cumulative proportion of impaired patients in each treatment group at 48 weeks.
- The average decline in the baseline lowest ranking domain at 24 weeks within each treatment arm.
- The average decline in the baseline lowest ranking domain at 48 weeks within each treatment arm.
- The proportion of patients crossing over from each treatment arm

- The proportion of patients crossing over from each treatment arm based on subjective (self-reported, FACT-Cog) cognitive effects.
- Proportion of patients crossing over from each treatment arm based on objectively measured cognitive effects (CANTAB modules).
- Proportion of patients crossing over due to neurologic toxicity (fatigue and severe neurologic toxicity [seizure or PRES]).
- Percentage of patients with improvement in cognitive function after crossover from each treatment arm.
- Time to PSA progression.
- PSA response rate at 24 weeks (on the basis of a decrease from baseline of $\geq 50\%$).
- Progression free survival.

3.4.3. Exploratory Endpoints

- To determine the within treatment arm association between AR CAG repeat length and baseline cognitive function as assessed by CANTAB performance.
- To determine the within treatment arm association of AR CAG repeat length with change in the maximally changed cognitive domain by CANTAB testing at 24 and 48 weeks.
- To determine the within treatment arm association of polygenic hazard scores (PHS) with baseline CANTAB performance.
- To determine the within treatment arm association of PHS with change in CANTAB performance at 24 and 48 weeks.
- To prospectively assess distress from financial toxicity in patients undergoing treatment for advanced prostate cancer.

4. Eligibility Criteria

Eligibility will be evaluated by the study team according to the following criteria. Subjects must meet all of the inclusion and none of the exclusion criteria to be randomized into the study. Study treatment may not begin until a subject is randomized. Please refer to [Section 6](#) for complete instructions regarding randomization procedures.

The AFT does not grant eligibility waivers. Investigators must carefully consider any condition that in the opinion of investigator would interfere with participation in the study. Please contact the study chairs for eligibility questions.

4.1. Inclusion Criteria

1. Patients must be age ≥ 18 years.
2. Patients must exhibit an ECOG performance status of ≤ 2 (see [Appendix 1](#)).
3. Patients must have histologically or cytologically confirmed adenocarcinoma of the prostate.
4. Progressive disease per PCWG3 criteria with EITHER:
 - a. Metastatic CRPC or non-metastatic CRPC (M0CRPC)
 - b. For mCRPC: metastatic disease documented by standard or novel imaging techniques

- c. OR for M0CPRC: no evidence of metastatic disease on standard imaging (bone scan, CT scans, or MRI scans).
5. Metastatic HSPC demonstrated by standard or novel imaging techniques
 6. Patients must be surgically or medically castrated, with serum testosterone levels per LCMS of <50 ng/dL at the time of enrollment. If the patient is medically castrated, continuous dosing with GnRH agonist or antagonist must have been initiated at least 28 days prior to randomization and must be continued throughout the study.
 7. Patients must not have had a major surgical procedure or significant traumatic injury within 6 weeks prior to study enrollment and must have fully recovered from any such procedure.
 8. Patient's physician must have the intent to treat with study therapy for 12 months or greater.
 9. Patients must have adequate organ and bone marrow function within 28 days prior to randomization, as defined below:

Platelets	$\geq 100,000/\mu\text{L}$
HGB	$\geq 9 \text{ g/dL}$
Total Bilirubin	$\leq 1.5 \times \text{institutional upper limits of normal (ULN)}^*$
AST (SGOT)	$\leq 2.5 \times \text{institutional ULN}$
ALT (SGPT)	$\leq 2.5 \times \text{institutional ULN}$
Creatinine OR Creatinine clearance	$\leq 1.5 \times \text{institutional ULN}$ OR $\geq 30 \text{ mL/min}$ using modified Cockcroft/Gault formula or institutional standard.

10. Men of reproductive potential and their partners must agree to use adequate contraception during treatment and for 3 months following discontinuation of study drug. Adequate contraception includes:
 - True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
 - Sterilization: Female partners have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks prior to enrollment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
 - Male participant sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
 - Use of a combination of any two methods from each of the following categories:
 - Female partner with prior placement of an intrauterine device (IUD) or intrauterine system (IUS).
 - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
 - Oral contraception use by female partners, injected or implanted hormonal methods are not sufficient.

- Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment and for 3 months following discontinuation.
- 11. Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.
- 12. Patients must have the ability to complete cognitive testing and patient reported outcome surveys in English without the use of an interpreter.
- 13. Patients must have access to internet at home to complete the cognitive testing, either on a CANTAB compliant home device or site provided iPad.
- 14. Patients must have the ability to swallow study agents whole in a capsule or tablet form.
- 15. Patients must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
- 16. Able to obtain enzalutamide through standard of care-insurance coverage with an acceptable co-payment (as assessed by the patient) and willingness to pay co-payment for the duration of the study. Patients must agree to this prior to randomization.

4.2. Exclusion Criteria

1. Patients who have had prior chemotherapy for treatment of CRPC.
2. Chemotherapy is allowed in the mHSPC setting provided chemotherapy was completed >6 months prior to study entry.
3. Use of investigational agents for the treatment of prostate cancer within 2 weeks of study entry.
4. Patients who have had prior use of an ARPI: apalutamide, ENZ or DARO for >4 weeks. If they have stopped prior treatment within this exposure window, they must have a 2 weeks washout before completing baseline testing for the study.
5. Patients with progression of disease on abiraterone are not eligible. Must have < 12 weeks of abiraterone exposure prior to enrollment. If used with radiation for high risk localized hormone sensitive disease, can enroll if no progression of disease during treatment with abiraterone (PSA or radiographic) and > 6 weeks since last exposure to abiraterone. If abiraterone was used immediately prior to enrollment, patients must have a 2 weeks washout before completing baseline testing for this study.
6. Patients with any active, or prior history of, brain metastasis that have not been treated and stabilized.
7. Patients who have active or history of seizures or seizure disorders.
8. Patients with a prior diagnosis of moderate or severe dementia or severe cognitive impairment, or other neurologic impairment consistent with a severe cognitive disorder.
9. Patients with inadequately controlled hypertension (defined as a blood pressure of
10. ≥ 160 mmHg systolic and/or ≥ 95 mmHg diastolic), or any prior history of hypertensive crisis or hypertensive encephalopathy are not eligible unless blood pressure is adequately controlled ($< 160/95$) prior to randomization.
11. Patients with symptomatic congestive heart failure (NYHA class ≥ 2 congestive heart failure; see [Appendix 2](#)).

12. Patients who have an uncontrolled intercurrent illness including, but not limited to any of the following:
- Unstable angina pectoris
 - Untreated/uncontrolled cardiac arrhythmia
 - Psychiatric illness/social situations that would limit compliance with study requirements
 - Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient's safety or study endpoints.

4.3. Inclusion of Minorities

Men of all races and ethnic groups are eligible for this study.

4.4. Subject Withdrawal Criteria

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons.

The reason(s) for study treatment discontinuation must be clearly documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted).
- Patient is unable to comply with protocol requirements.
- Patient demonstrates disease progression.
- Patient experiences unacceptable toxicity.
- Treating physician determines that continuation on study treatment would not be in the patient's best interest.
- Patient develops a second malignancy that requires treatment which would interfere with this study.

Following treatment discontinuation, patients will be followed by routine clinic visit (or telephone call, if appropriate) every 3 months for a maximum of 1 year unless patient withdraws consent before that.

The reason(s) for study discontinuation must be clearly documented on the appropriate eCRF and may include:

- Patient withdraws consent (no follow-up permitted).
- Treating physician determines that continuation on the study would not be in the patient's best interest.
- Patient becomes lost to follow-up (LTF).

Crossover will be allowed from ENZ or DARO to the other treatment arm as specified in [Section 7.1.3](#) (Cross-Overs). Agreement to cover co-pay for standard of care enzalutamide is required prior to randomization, therefore cross-over due to unwillingness to pay the enzalutamide co-payment is not permitted.

4.5. Subject Replacement

Any patient who signs consent but does not begin study treatment can be replaced.

5. Site Enrollment Requirements

Before a site can receive authorization to screen a patient, sites must submit all required essential documents to the sponsor including:

- AFT Investigator Agreement.
- Curriculum Vitae(s) of the Principal Investigator.
- Medical License(s).
- Completed Financial Disclosure Form(s) from all investigators.
- Investigator Brochure Signature Page(s).
- Documentation of Good Clinical Practice (GCP) Training.
- Protocol Signature Page.
- A copy of the dated and signed, written IRB approval of the protocol, amendments, ICF, and any recruiting materials, if applicable. This approval must clearly identify the specific protocol by title and number and must be by the IRB Chair or authorized designee.
- Name and address of the IRB, including a current list of the IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Documentation of protocol training.
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable.
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.
- Any other documentation required by local regulations.
- Sites will receive site selection correspondence with detailed requirements for site activation.

6. Patient Numbering and Treatment Assignment

Patient enrollment and randomization will be facilitated using the Medidata Rave® iMedidata Portal, accessible via the AFT Web site: <https://alliancefoundationtrials.org/>. After written informed consent has been obtained, the study site will obtain a unique patient identifier by entering the patient in Medidata Rave®. The patient identifier will stay the same throughout the entire study. Patients must receive this identifier prior to submission of bio-specimens.

Prior to accessing the patient enrollment system, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes
- All patients have signed an appropriate consent form and HIPAA authorization form
- Patient agrees to cover copay for standard of care enzalutamide if randomized to the ENZ arm

The Medidata Rave® iMedidata Portal will provide the site with a confirmation of enrollment and treatment randomization information.

Patients enrolled but not randomized for any reason, such as failing study entry criteria, should be documented as a screen failure in Medidata Rave®.

7. Treatment Plan and Investigational Agent Information

This is a prospective, randomized, open-label phase II study to compare cognitive outcomes in men with advanced prostate cancer treated with DARO or ENZ. Treatment with DARO or ENZ will begin within 28 days of patient enrollment and will be administered on an outpatient basis. Questions regarding treatment should be directed to the Study Chairs. Patient with or without metastatic disease can participate in this study, if eligible otherwise. Patient enrolled in one treatment arm can cross-over to the other treatment arm, if eligible according to the cross-over criteria. See [Section 7.1.3](#) for details.

7.1. Treatment Regimen

Patients will take DARO at a dose of 600 mg (300 mg × 2 tablets) by mouth (PO) twice daily (BID; with food), or ENZ at a dose of 160 mg PO once daily (QD), beginning on Day 1, of Week 1. Patients will take DARO or ENZ throughout planned treatment period or withdrawal of consent or progression of disease requiring change in therapy. Refer to [Section 7.1.1](#) and [Section 7.1.2](#) for additional details.

Table 1: Treatment Administration Summary

Treatment Administration Summary					
Agent	Premedication's	Dose	Route	Schedule	Supportive Therapies
ENZ	None	160 mg (4 x 40 mg capsules or 2x80mg tablets)	PO	QD	in combination with standard GnRH antagonist or agonist-based treatment
DARO	None	600 mg (2 x 300 Mg tablets)	PO	BID	

Abbreviations: BID = twice daily; ENZ = enzalutamide; DARO = darolutamide; PO = by mouth; QD=once daily

7.1.1. Enzalutamide

Enzalutamide (ENZ; also known as XTANDI®) is an anti-androgen and acts as an antagonist of the androgen receptor. ENZ is an AR inhibitor that acts on different steps in the AR signaling pathway. ENZ has been shown to competitively inhibit androgen binding to androgen receptors and inhibit AR nuclear translocation and interaction with DNA. A major metabolite, N-desmethyl ENZ, exhibited similar in vitro activity to ENZ. ENZ decreased proliferation and induced cell death of PCa cells in vitro, and decreased tumor volume in a mouse PCa xenograft model.

7.1.1.1. Storage and Stability

ENZ will be stored by the patient as per package insert instructions, at 20°C to 25°C (68°F to 77°F) in a dry place and the container should be kept tightly closed. Excursions permitted from 15°C to 30°C (59°F to 86°F).

7.1.1.2. Availability

ENZ is available commercially and will be prescribed to the patient at a dose of 160 mg daily.

7.1.1.3. Administration

ENZ will be self-administered by the patient at a dose of 160 mg (four 40 mg capsules or two 80mg tablets) once daily for continuous daily dosing. These capsules are white to off-white oblong soft gelatin capsules imprinted in black ink with ENZ. Equivalent tablet doses are acceptable.

Enzalutamide can be taken with food or without food. Enzalutamide pills should be swallowed whole. Patients should swallow capsules or tablets whole. Do not chew, dissolve, or open the capsules. Do not cut, crush, or chew the tablets.

If the patient forgets to take the dose before 6:00 pm, then the dose should be withheld that day and the enzalutamide should be restarted the following day.

At each new cycle, patients will be prescribed sufficient supplies until the next visit. Patients will be asked to fill out medication diary and will be required to bring it to each visit for the study staff to review.

Enzalutamide drug compliance will be assessed at the beginning of a new cycle. ENZ should not be used after the expiration date.

7.1.1.4. Side Effects of Enzalutamide

Likely side effects include: fatigue, hot flashes, neuromuscular pain (including back pain and arthralgias), diarrhea, peripheral edema, neutropenia, headache, and upper respiratory infection. Serious potential side effects include infections, falls and fall-related injuries, and hypertension. Rare but a serious potential side effects (<1%) include seizure or PRES. See [Section 2.2.1](#) for details.

7.1.2. Darolutamide

Darolutamide (DARO; also known as NUBEQA®) is a selective antagonist of the androgen receptor.

7.1.2.1. Storage and Stability

Darolutamide will be delivered packed in wide-necked plastic bottles (150 ml PE white opaque closed with Screw cap closure PP/PP white opaque with children proof and sealing insert) each containing 140 tablets of BAY 1841788 TABL 0.3G 002 COAT and should be stored below 30°C.

7.1.2.2. Availability

Alliance Foundation Trials (AFT) will obtain DARO directly from Bayer as study supply.

All participating sites will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. Each site will maintain written records of any disposition of the study drugs.

The Site Investigators shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Site Investigators will not allow the investigational drug to be used in any manner other than that specified in this protocol.

7.1.2.3. Administration

DARO will be administered at the standard dose of 1200 mg by mouth daily (300 mg × 2 tablets twice daily). DARO must be taken with food, as recommended by the IB.

7.1.2.4. Side Effects of Darolutamide

According to the Phase III (ARAMIS) study, adverse events was generally similar in the darolutamide and placebo groups; with the exception of fatigue, all adverse events that occurred or worsened during the treatment period that had a frequency of 5% or greater occurred in less than 10% of the patients in either group. Key adverse events that are known to be associated with next-generation androgen-receptor inhibitors, such as fracture, falls, seizures, and weight loss, were analyzed after grouping of synonymous or pathophysiologically related adverse events that occurred or worsened during the treatment period; most showed small or no differences in incidence between the darolutamide group and the placebo group. The incidence of seizures was 0.2% in both groups. Incidences of other adverse events of interest, including hypertension, rash, dizziness, and cognitive disorder, differed only slightly between the darolutamide group and the placebo group. After adjustment for duration of the treatment or observation period, the between-group differences in the incidences of adverse events of interest either decreased or disappeared.⁵⁰

7.1.2.5. Ordering

The procedure to determine initial and re-supply of DARO will be finalized and provided to sites separately from the protocol.

7.1.2.6. Accountability

Site investigators or designated responsible parties must maintain a record of the inventory of distribution of the study drug using the appropriate documentation method (eg, drug accountability log).

The investigator is responsible for keeping accurate records of the clinical supplies received from AFT or designee, the amount dispensed to patients and the amount remaining at the conclusion of the study.

7.1.2.7. Destruction and Return

Sites may destroy unused study drug according to their institutional policies. If any study drug is lost or damaged, its disposition should be documented in the source documents. Patients will be instructed to return empty containers (if applicable) and unused investigational product to the clinic site.

7.1.3. Cross-Overs

Patients will be allowed to cross over to the opposite treatment arm at 12 and 24 weeks if they meet any of the cross-over criteria at the testing time points. Crossover between time points will be allowed only for patients with falls, seizures, PRES, or another neurologic toxicity deemed severe by the treating clinician and confirmed by sponsor, on ENZ. There is no other allowable reason for crossover between visits, and there is no crossover before treatment after randomization. Cross-over for patients unwilling to pay the co-payment for standard of care ENZ is prohibited. Patients must agree to pay co-payment for ENZ prior to enrolling on the trial.

Between visit events that merit crossover or discontinuation of either agent before 24 weeks will be included in the primary endpoint analysis. Between visit events that merit crossover or discontinuation of treatment that occur after 24 weeks will be documented as trial data but will not be incorporated in the primary endpoint analysis. All other cross-overs will occur at 12 or 24 weeks, and data from the time of crossover will be included in the primary endpoint analysis.

Patients experiencing falls (witnessed or self-reported) or severe neurologic toxicity event on DARO at any point will discontinue the study but will not cross over to ENZ. Between visit events that merit crossover includes fall, seizure, or PRES on ENZ (these events require study discontinuation if they occur on DARO). If these occur before 24 weeks the events will be included in the primary endpoint analysis.

7.1.3.1. Subjective Cognitive Decline and Patient Preference

If patients on either arm reports subjective cognitive decline on their FACT-COG questionnaire (as measured by a decrease of >10 points from a patient's own baseline score) and respond yes to the follow-up question of "Do you think this change is related to your systemic therapy?" and express a preference to the treating physician to cross over to the other treatment arm, they will be allowed to switch to the other treatment.

7.1.3.2. Objectively Measured Cognitive Decline and Patient Preference

If patients on either arm experience a decrease >30% on any cognitive domain from their own baseline performance as measured by CANTAB module assessments at any study visit, and they express a preference to the study physician to cross over to the other arm, they will be allowed to switch to the other treatment arm.

7.1.3.3. Increased Risk of Falls

If patients on the ENZ arm have experienced falls between clinic visits or a fall presumed possibly related to study drug exposure by the treating physician, or an increased risk of falls deemed associated with study drug as assessed by the treating physician, they will be required to cross-over from ENZ to DARO.

If they are on the DARO arm, they will discontinue the study and complete an end of treatment visit (will not cross over to ENZ).

Continuation of ENZ treatment will not be allowed in any patients who experience a fall or have a newly increased risk of falls even if the patient does not wish to cross-over to DARO arm. Experiencing a fall at any point will induce cross-over from ENZ to DARO, even if not at 12 or 24 weeks. Increased risk of fall merits cross-over at 12 or 24 weeks.

7.1.3.4. Neurologic Toxicity Event

Patients treated with ENZ or DARO experiencing the neurologic toxicity event of fatigue of $\geq$ grade 2 and is worse than baseline can cross-over to treatment with the opposite treatment at 12 and 24 weeks if they express a preference to the study physician to cross over to the other arm. Patients experiencing severe neurologic toxicity events, defined as any seizure, falls, PRES, or another neurologic toxicity deemed severe by the treating clinician and confirmed by sponsor can cross-over between time points if treated with ENZ, or will discontinue the study if treated with DARO and complete all assessments required for the end of treatment visit. See [Section 7.1.3](#) for further details.

7.1.4. Duration of Therapy

Duration of treatment requires intent to treat with study therapy for 48 weeks or greater.

Patients responding to treatment will be allowed to continue therapy beyond the 12-month primary data collection period for up to 52 weeks of follow-up or when the trial concludes the treatment phase, whichever comes sooner. After the treatment phase concludes, patients may continue treatment off study for as long as deemed appropriate by their treating physician, but treatment will occur using commercial supply per standard of care. Patients will return for the End of Treatment visit 30 days (± 3 days) after the last dose of study treatment of the primary data collection period or prior to initiating new therapy. Patients will be followed by routine clinic visit (or telephone call, if appropriate) every 3 months for a maximum of 1 year unless patient withdraws consent before that. Patients removed from study for unacceptable treatment-related adverse event(s) will be followed until resolution of stabilization of the adverse event.

7.2. AR Targeted Treatment Discontinuation

One of the following scenarios will be applicable to the patients participating in this trial:

- They will continue undergoing assessments through 48 weeks without a cognitive event or treatment change.
- They will cross-over prior to 48 weeks due to cognitive decline or a cross-over event and remain on the alternate treatment arm through the 48-week visit.
- They will cross-over from one drug to the other and subsequently discontinue AR targeted therapy due to persistent or recurrent cognitive decline or cross-over events, with or without disease progression.
- They will experience disease progression without cognitive events.

When at all possible, patients should complete all scheduled assessments according to the timeline of the trial, even if on alternate therapies such as chemotherapy or other systemic therapies, or local treatments or metastasis directed treatments like radiation.

If a patient withdraws from the study, sites should encourage the patient to complete an end of treatment visit with cognitive and patient reported outcome tests. The purpose is to determine whether there is an association between cognitive and QOL outcomes and withdrawing consent.

7.3. Pregnancy

Safety and efficacy of enzalutamide have not been established in females. Enzalutamide can cause fetal harm and loss of pregnancy when administered to a pregnant female. Males with female partners of reproductive potential are advised to use effective contraception during treatment with enzalutamide and for 3 months after the last dose of enzalutamide. Enzalutamide should not be handled by females who are or may become pregnant.

There is no current clinical data of the use of darolutamide in pregnant women. Darolutamide is not to be used in women who are, or may be, pregnant or breast-feeding. In the ongoing studies in subjects with prostate cancer, a barrier method of contraception is required during and up to 4 weeks after treatment with darolutamide if the patient is engaged in sexual activity with a pregnant woman since maternal exposure to an AR antagonist could affect development of the fetus. If the patient is engaged in sexual activity with a woman of childbearing potential, highly effective contraception should be used during and up to 4 weeks after treatment to prevent pregnancy.

7.4. Supportive Care and Concomitant Medications

7.4.1. Supportive Care

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate.

7.4.2. Concomitant Medications

Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic or for adrenal insufficiency.

Other than LHRH agonists that are required to maintain castrate levels of testosterone, anti-cancer therapies are excluded during this study. These include chemotherapy, radiotherapy, immunotherapy, ketoconazole, diethylstilbestrol, PC-SPES, and other experimental anticancer medications, such as herbal preparations. Bisphosphonates or denosumab can be started or discontinued during the study at the discretion of the treating physician.

7.4.3. Prohibited Medications

No other investigational therapy should be given to patients. No anticancer agents other than the study medications should be given to patients. If such agents are required for a patient, then the

patient must first be withdrawn from the study. Other restrictions are described below in [Section 7.4.4](#) and [Section 7.4.5](#).

7.4.4. Incompatibilities of Darolutamide

Drugs that are substrates for BCRP should be avoided if possible; if concomitant BCRP or Pg-p substrates are necessary, patients should be monitored for signs and symptoms of increased exposure to BCRP substrates when given concomitantly with DARO.

Clinical studies have confirmed that DARO is a substrate and an inhibitor of BCRP, and co-administration may increase serum concentrations of other drugs that are BCRP substrates (e.g., methotrexate, sulfasalazine, fluvastatin, atorvastatin). Therefore, combination with BCRP substrates should be avoided, if possible.

Drugs that inhibit or induce CYP3A4 should be avoided if possible. Repeated co-administration of strong or moderate CYP3A4 inducers (e.g. carbamazepine, phenobarbital, St. John's Wort) with darolutamide is expected to reduce darolutamide plasma concentrations. Therefore, concomitant intake of these substances during study treatment should be avoided.

7.4.5. Incompatibilities of Enzalutamide

In particular, concomitant use of ENZ with drugs with a narrow therapeutic index metabolized by CYP3A4 (eg, cyclosporine, ergotamine, fentanyl, quinidine, sirolimus, tacrolimus) should be avoided as ENZ may decrease their exposure. A list of CYP3A4 inducers and inhibitors are listed in [Appendix 4](#).

Additionally, concomitant use of drugs with a narrow therapeutic index that are metabolized by CYP2C9 (eg, phenytoin, warfarin) and CYP2C19 should be avoided, as ENZ may decrease their exposure. See package insert for full details. Enzalutamide (ENZ) is a strong inducer of CYP3A4 and may decrease serum concentrations of drugs that are substrates. Therefore, combination with CYP3A4 substrates should be avoided. Concomitant use of strong CYP2C8 inhibitors should be avoided.

The following drugs are prohibited from 30 days prior to enrollment and throughout the study period while the patient is taking ENZ ([Table 2](#):). These drugs are excluded because they are known to lower the seizure threshold or prolong the QT interval.

Table 2: Prohibited Medications While on Enzalutamide

Prohibited Medications while on Enzalutamide
Aminophylline/theophylline
Atypical antipsychotics, including: Clozapine Olanzapine Risperidone Ziprasidone
Bupropion
Class IA and III antiarrhythmics, including: Amiodarone Bretylium Disopyramide

Ibutilide
Procainamide
Quinidine
Sotalol
Dolasetron
Droperidol
Gatafloxacin/moxifloxacin
Lithium
Macrolide antibiotics, including: Erythromycin Clarithromycin
Pethidine
Phenothiazine antipsychotics, including: Chlorpromazine Mesoridazine Thioridazine
Pimozide
Tricyclic and tetracyclic antidepressants, including: Amitriptyline Desipramine Doxepin Imipramine Maprotiline Mirtazapine
Venlafaxine

7.4.6. Permitted Medication

Calcium and Vitamin D are allowed at any point on study.

8. Dose and Treatment Modifications

Any patient who receives at least one dose of study therapy will be evaluable for toxicity endpoints. Each patient will be assessed for the development of toxicity according to the timeframe referenced in the Schedule of Events table. Toxicity will be assessed according to CTCAE v 5.0 (See [Appendix 3](#)). Dose adjustments should be avoided, but if necessary, will be made according to the system showing the greatest degree of toxicity.

Patients experiencing unacceptable toxicity that constitutes cross over criteria should cross-over per instructions. Investigators should contact one of the Study Chairs or designee for requests for dose reductions for non-cross-over reasons (liver, renal, heme toxicity). Dose modifications are listed below, but dose reductions are discouraged without consultation with study chairs. Holding drug for up to 14 days is allowed.

Because the primary endpoint of the study is driven by adverse events associated with either drug, dose reductions will not be permitted with either darolutamide or enzalutamide in response to subjective adverse events (e.g. fatigue). Furthermore, certain adverse events that are not subjective (e.g. Hypertension) may impact performance on cognitive tests – and the response to hypertension is detailed below in [Section 8.3](#). All other adverse events can be managed through holding medications with resumption at a reduced dose as described below.

8.1. Dose Reduction - Darolutamide

Patients who experience self-reported or witnessed falls or protocol-defined increased risk of falls or seizure events on DARO will discontinue study drug. Adverse events that do not impact cognition or quality of life reporting per study questionnaires (e.g. diarrhea) that are deemed, in the opinion of the investigator, to be related to study treatment, can be addressed via dose reductions after discussing with a Study Chair or designee.

Table 3: Dose modification and/or delay for toxicities considered related to study treatment (darolutamide)

Severity grade (NCI-CTCAE v 5.0)	Dose modifications	Study treatment withdrawal
Grade 0-2	Treat on time. Per investigator's decision to interrupt or reduce study treatment. ^{a, b}	-
Grade 3 or 4	Delay until $\leq$ grade 2. ^a When the severity is grade $\leq$ 2, restart at a reduced dose of 300 mg bid. ^{b, c}	If the dosing of the study treatment is temporally or permanently reduced to 300 mg bid and a grade 3 or higher treatment-related AE occurs while the patient is on a dose of 300 mg bid, the patient must cross over.

Excludes clinically non-significant and asymptomatic laboratory abnormalities

Abbreviations: NCI-CTCAE v 5.0 = National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0.

^a If there is no recovery after 28 consecutive days, treatment should be permanently discontinued.

^b When AE returns to baseline or is resolved, dose escalation to 600 mg bid may be considered at the discretion of the investigator.

^c If dose is re-escalated to 600 mg bid and a second treatment-related AE with a severity of grade 3 or higher occurs, a permanent dose reduction is required. A third occurrence of a grade 3 or higher treatment-related AE requires permanent discontinuation of study treatment.

For patients who experience grade 3 or 4 adverse events of this type, DARO may be held for up to 14 days until toxicity improves to $\leq$ grade 1 after discussion with one of the study chairs and must then be resumed at 300 mg bid and can be re-escalated up to 600 mg bid at the discretion of the treating physician.

If the grade 3 or 4 adverse event recurs, DARO dose should be reduced to -1 dose level. If the toxicity recurs to grade 3 or 4, the patient can cross over when this occurs (level -2). If that occurs, the patient can cross over to ENZ at full dose or discontinue study medications and continue on study follow-up per study protocol (**Error! Reference source not found.**). Dosing delays for grade 1 or 2 adverse events for up to 14 days are as per the Investigator's discretion.

Table 4: Darolutamide Dose Reduction for Toxicity Other than those associated with endpoints (fatigue, cognition, mood, neurologic toxicity)

Level	Daily Dose
1 (starting dose)	600 mg bid
-1	300 mg bid – discuss with a study chair

-2	Cross over to ENZ at full dose or discontinue study medications and continue on study follow-up only but discontinue treatment per study protocol
----	---

8.2. Dose Reduction - Enzalutamide

Patients who experience a neurologic toxicity or other drug intolerance will be eligible to cross over to the DARO arm. Neurologic toxicities include as falls, seizures, fatigue, development of cognitive impairment, as described in [Section 7.1.3](#) (Cross-Overs).

Adverse events that do not impact cognition, energy, or patient reported outcomes as detailed in quality of life surveys (e.g. diarrhea) that are deemed, in the opinion of the investigator, to be related to study treatment, can be addressed via dose reductions after discussion with the study chairs and PI. For patients who experience grade 3 or 4 adverse events of this type, ENZ may be held for up to 14 days until toxicity improves to $\leq$ grade 1 after discussion with the sponsor, and must then be resumed at the standard dose. If the grade 3 or 4 adverse event recurs, ENZ dose should be reduced to -1 dose level. If the toxicity recurs to grade 3 or 4, the patient can cross over when this occurs. If the grade 3 or 4 adverse event does not resolve to $\leq$ grade 1 toxicity by 14 days after initially holding the dose for a grade 3 or 4 toxicity, the dose can be reduced to dose -1 level. This should continue unless the patient experiences a recurrence of the grade 3 or 4 toxicity. If that occurs, the patient must cross over can cross over to DARO at full dose or discontinue study medications and continue study follow-up per study protocol. Dosing delays for grade 1 or 2 adverse events for up to 14 days are as per the Investigator's discretion.

Table 5: Enzalutamide - Dose Reduction for Toxicity

Level	Daily Dose
1 (starting dose)	160 mg
-1	120 mg – discuss with a study chair
-2	Cross over to DARO at full dose or discontinue study medications and continue on study follow-up only but discontinue treatment per study protocol

8.3. Hypertension

For grade 1-2 hypertension, management will be per study investigator discretion and institutional guidelines. Treatment spironolactone should be avoided due to the potential to contribute to PCa progression. No dose reduction or interruption will be mandated for grade 1 or 2 hypertension.

For an initial episode of grade 3 hypertension, ENZ will be held until hypertension is grade $\leq$ 1 in severity, at which point ENZ will be restarted at 160 mg/day. The BP will be monitored at the investigator's discretion. If there is a recurrence of grade 3 hypertension, ENZ will be held until grade $\leq$ 1 in severity, and then restarted at 160 mg/day. If there is a second recurrence of grade 3 hypertension, ENZ will be permanently discontinued, and crossover to DARO may be considered. If grade 4 hypertension occurs during study treatment, ENZ will be permanently discontinued. If there is a greater than 4-week delay in treatment, ENZ will be permanently discontinued.

8.3.1. Posterior Reversible Encephalopathy Syndrome

If patients choose not to cross over after posterior reversible encephalopathy syndrome (PRES; (headache, confusion, visual loss among other symptoms, with MRI correlate), then ENZ must be discontinued, and reported as per protocol guidelines.

8.3.2. Falls, Risk of Falls, Fall-related Injuries

Due to safety concerns, patients must cross over from ENZ to DARO if they have a fall that the treating physician deems potentially related to treatment during the study.

Patients experiencing a self-reported or witnessed fall on DARO that they treating physician deems related to study treatment, the patient must stop DARO treatment per study protocol but should continue with follow up per protocol.

If patients are at increased risk of falls during treatment with ENZ, they may cross from ENZ to DARO.

If patients are at increased risk of falls during treatment with DARO (experience a self-reported or witnessed fall regardless of fall-related injuries), DARO must be discontinued and they will not cross-over to ENZ. Follow up testing should continue per protocol.

8.3.3. Seizures

If patients choose not to cross over after seizure or possible seizure event, then ENZ must be discontinued, and reported as per protocol guidelines.

9. Study Assessments and Procedures

The study-specific assessments are detailed in this section and outlined below. Screening assessments must be performed within 28 days prior to the first dose of DARO or ENZ. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed a **window of ± 7 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before study registration. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered the data monitoring system for AFT. The system is password protected and meets HIPAA requirements.

9.1. Assessment Types

9.1.1. Efficacy Assessment – Cognitive Testing

Patients enrolled on the study will undergo cognitive testing remotely using select CANTAB modules at baseline and between 7-14 days prior to all study visits following baseline assessment. Patients will perform the CANTAB modules via web-based testing, either using their own CANTAB capable device or via a supplied device. The testing battery should be completed

with a site representative on video conference or phone with the patient to instruct the patient on completing the CANTAB modules remotely.

The maximally changed cognitive domain is defined as the domain most changed from baseline in each individual; this value will be averaged across all individuals in a study arm at 24 weeks to calculate the primary endpoint. For individuals that cross over prior to 24 weeks, their score will be from the time of cross-over, not the 24-week assessment. For example, if a patient experienced a self-reported or witnessed fall within 9 weeks, that patient should discontinue study drug and then be tested with cognitive testing and PRO surveys by 9 weeks before crossing over, and the cognitive and PRO data at the time of cross-over would count towards the primary endpoint analysis.

For secondary endpoints, cognitive impairment, as specified by the International Cognition and Cancer Task Force guidelines, is defined as meeting one of the following: 1) ≥ 1.5 SDs below (age- and education-adjusted) norm on ≥ 2 cognitive domain modules; or 2) ≥ 2 SDs below norm on ≥ 1 cognitive domain module.

9.1.2. Safety and Tolerability Assessments

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v5.0 for reporting of adverse events.

9.1.3. Biomarkers/Correlative Studies

9.1.3.1. Genetic polymorphisms associated with androgen receptor targeted cognitive effects (ARTACE).

Patient derived samples will be utilized to evaluate the association between development of ARTACE and a dementia-associated polygenic hazard score (PHS) in advanced prostate cancer patients receiving treatment with AR antagonist therapy. The hypothesis is that genetic variants that are associated with an increased risk of Alzheimer's disease as quantified in the PHS are associated with ARTACE at 24 or 48 weeks.

With this investigation, we will perform a first-in-field investigation of cognitive function in AR targeted therapy -treated patients assessed according to PHS, a validated genetic risk score for the development of dementia to identify genetic factors associated with populations of men at highest risk of cognitive decline on ADT.

DNA will be collected at baseline. Assays will be performed at the University of Minnesota Genomics Center, the core genomics resource at the University of Minnesota and data analysis will be performed through a collaboration with UCSF.

The relationship of PHS to CANTAB modules will be the primary deliverable of this correlative proposal. Spearman's rank correlation statistic and its attendant 95% confidence interval will be computed to evaluate:

- Within-treatment association of polygenic hazard scores (PHS) with baseline CANTAB performance.
- Within-treatment association of polygenic hazard scores (PHS) with change in CANTAB performance at 24 and 48 weeks.

9.1.3.2. Germline AR genotype and development of ARTACE in advanced prostate cancer patients receiving treatment with AR antagonist therapy.

We hypothesize that longer AR CAG repeat length will be associated with a greater degree of ARTACE at baseline and greater change in cognitive function during treatment.

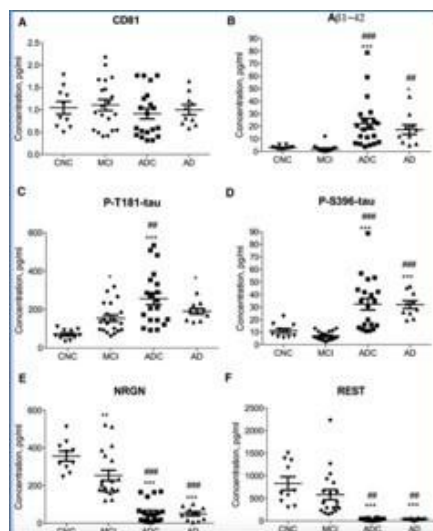
Blood collected from patients at baseline will be sent to the genotyping shared resource at the University of Minnesota Masonic Cancer Center. Sanger sequencing will be performed to elucidate the number of CAG repeats in the germline AR of patients.

Patients will undergo CANTAB cognitive evaluations. CAG repeat data will be expressed as a discrete variable (as the number of repeats, typically ranging from 15-30 with an expected median of approximately 21). The group median and range will be described.

Spearman's rank correlation statistic and its attendant 95% confidence interval will be computed to evaluate:

- Within-treatment association of AR CAG repeat length with baseline CANTAB performance.
- Within-treatment association of AR CAG repeat length with change in CANTAB performance at 24 and 48 weeks.

Figure 3: Human plasma NDE levels



Human plasma NDE levels of P-T181-tau, P-S396-tau, Aβ1-42, NRG1 (neurogranin), and REST (Repressor element 1-silencing transcription factor) and their associations with stages of dementia: CNC = cognitively normal controls, MCI = mild cognitive impairment, ADC = progression from MCI to Alzheimer's disease AD = Alzheimer's disease

Comparisons will be made between baseline samples and 1) time of crossover samples for patients meeting criteria for crossover OR at 2) 48 weeks for patients not experiencing crossover. Data will be expressed as a dot plot indicating the concentrations of target protein in pg/mL concentrations as in **Figure 3** above.

9.1.4. Patient Reported Outcomes

Patient reported outcome measures include:

- FACT-COG: patient perception of cognitive function ([Appendix 5](#))
- FACT-P: patient perception of well-being ([Appendix 6](#))
- PHQ-9: patient health depression questionnaire ([Appendix 7](#))
- Sleep scale from Medical Outcomes Study ([Appendix 8](#))
- Informant survey by Functional Activities Questionnaire (FAQ) ([Appendix 9](#))
- Comprehensive Score for financial Toxicity (COST) ([Appendix 10](#))
- Health Literacy 3 item ([Appendix 11](#))

10. Study Assessment Table

Please refer to **Table 6** for the planned assessments for the study.

Table 6: Schedule of Assessments

Time Period	Screening ¹	Remote Testing Pre-Week 1	Week 1 (Baseline) (±7 days)	Remote Testing (+7-14 Days of Week 12)	Week 12 (±7 days)	Remote Testing (+7-14 Days of Week 24)	Week 24 (±7 days)	Week 36 (±7 days)	Remote Testing (+7-14 Days of Week 48)	Week 48 (±7 days)	Remote Testing (+7-14 Days of Early ET or Crossover)	Early ET or Crossover	End of Treatment ⁷	Follow-up ⁷
Assessment or Activity														
Informed Consent	X													
Medical history (including family history of dementia)	X													
Physical exam ¹	X		X		X		X	X		X		X	X	
Prostate Cancer Diagnosis (histologically confirmed)	X													
Prior Cancer Treatment	X													
Genetic Testing (CAG repeat and DNA sequencing) ¹⁰			X											
ECOG status	X		X		X		X	X		X		X	X	
Toxicity					X		X	X		X		X	X	X
Concurrent Medications	X		X		X		X	X		X		X		X ⁸

Time Period	Screening ¹	Remote Testing Pre-Week 1	Week 1 (Baseline) (±7 days)	Remote Testing (+7-14 Days of Week 12)	Week 12 (±7 days)	Remote Testing (+7-14 Days of Week 24)	Week 24 (±7 days)	Week 36 (±7 days)	Remote Testing (+7-14 Days of Week 48)	Week 48 (±7 days)	Remote Testing (+7-14 Days of Early ET or Crossover)	Early ET or Crossover	End of Treatment ⁷	Follow-up ⁷
Fall Assessment (Timed Up and Go) ²			X		X		X			X		X		
Comorbid Illness Assessment ³	X									X		X		
Labs ⁴	X		X		X		X	X		X		X	X	
PSA ⁵	X		X		X		X	X		X		X	X	X
CANTAB ⁶		X		X		X			X		X			
Informant survey by FAQ			X		X		X			X		X	X	
COST questionnaire			X							X		X	X	
Health Literacy ³	X													
FACT-Cog			X		X		X			X		X	X	
FACT-P			X		X		X			X		X	X	
PHQ-9			X		X		X			X		X	X	
Sleep Scale from MOS			X		X		X			X		X	X	
Medication Diary Review					X		X	X		X		X	X	

Time Period	Screening ¹	Remote Testing Pre-Week 1	Week 1 (Baseline) (±7 days)	Remote Testing (+7-14 Days of Week 12)	Week 12 (±7 days)	Remote Testing (+7-14 Days of Week 24)	Week 24 (±7 days)	Week 36 (±7 days)	Remote Testing (+7-14 Days of Week 48)	Week 48 (±7 days)	Remote Testing (+7-14 Days of Early ET or Crossover)	Early ET or Crossover	End of Treatment ⁷	Follow-up ⁷
Adverse Event Assessment	X		X		X		X	X		X		X	X	X ⁹
Radiological evaluations				Participants with PSA progression during the 48 week will have radionuclide bone scan and CT or MRI scan of the chest, abdomen, and pelvis)										
Survival Status												X	X	X

Abbreviations: CANTAB = Cambridge Neuropsychological Test Automated Battery; ET = early termination; COST = Comprehensive Score for financial Toxicity

- ¹ The screening procedures and assessments must be completed within 28 days of the Day 1, Week 1 Visit (baseline). Screening labs do not need to be repeated if treatment starts within 2 weeks of screening.
- ² TUG testing is only required for patients without mobility limitations that preclude interpretation in the opinion of the treating physician. Examples of mobility limitations include patients requiring a wheelchair for assistance while in the clinic or at home, patients with walkers, canes or other mobility supports, patients with severe arthritis that causes mobility limitations due to pain or limitations in range of motion, and others at the discretion of the treating physician.
- ³ Comorbidity assessment for dementia, stroke, and cardiovascular disease by patient report.
- ⁴ Laboratory assessment will include serum: testosterone, albumin, ALT, AST, total bilirubin, creatinine, sodium, potassium, bicarbonate, chloride, BUN, calcium and complete blood count with differential.
- ⁵ PSA and testosterone to be drawn each visit until Week 48. PSA required every 12 weeks (±7 days). Other labs and scans as clinically indicated.
- ⁶ CANTAB: These assessments should be performed remotely 7-14 days prior to the patient's in clinic visit, with a site representative on video conference or on the phone for the patient. CANTAB assessments do not have to be repeated at ET or at the cross-over visit, if done within the past 14 days.
- ⁷ Patients responding to treatment will be allowed to continue therapy beyond the 12-month primary data collection period for up to 52 weeks of follow-up or when the trial concludes the treatment phase, whichever comes sooner. After the treatment phase concludes, patients may continue treatment off study for as long as deemed appropriate by their treating physician, but treatment will occur using commercial supply per standard of care. Patients will return for the End of Treatment visit 30 days (±3 days) after the last dose of study treatment of the primary data collection period or prior to initiating new therapy. Patients will be followed by routine clinic visit (or telephone call, if appropriate) every 3 months for a maximum of 1 year unless patient withdraws consent before that. Patients removed from study for unacceptable treatment-related AEs will be followed until resolution of stabilization of the AE.
- ⁸ Only collecting whether or not a patient continues on DARO/ENZ during follow-up. No other medications need to be collected. If patient discontinued DARO/ENZ, no additional information on medications needs to be collected.
- ⁹ AE/SAE information only need to be collected for patients continuing on DARO/ENZ during the follow-up period. Patients removed from study for unacceptable treatment-related AEs will be followed until resolution of stabilization of the AE.



- ¹⁰. The Genetic Testing (CAG repeat and DNA sequencing) should be collected at baseline to ensure collection. However, if the samples is missed or inadequate at baseline, it may collected at any point throughout the study period. Only one sample is required per patient.

11. Adverse Events

11.1. Adverse Events

Per the International Conference of Harmonisation (ICH) guidelines, an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure.

It may include a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patient's health, regardless of etiology.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

11.2. Adverse Event Reporting Exceptions

The following are NOT considered AEs:

- **Baseline condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form (ICF) is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
- **Disease Progression:** The term "disease progression" should not be reported as an adverse event term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

11.3. Serious Adverse Events

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death.
- Life-threatening adverse event.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.3.1. Life-threatening

An adverse event or suspected adverse reaction is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

11.4. Suspected Unexpected Serious Adverse Reaction (SUSAR)

- An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of an SAE/Reaction
- Qualifies for expedited IND safety reporting to the FDA, Competent Authorities and other regulatory bodies by meeting all three definitions of suspected adverse reaction, serious, and unexpected.
- As this study is IND exempt, no SUSARs will be sent to the FDA.

11.5. Adverse Events of Special Interest

Adverse Events of special interest are events that the drug manufacturer or the Sponsor of the study, AFT, are actively monitoring as a result of a previously identified signal (even if non-serious). An AE of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor’s product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted.

AEs of special interest by CTCAE are as follows and should be assessed:

- Fall
- Seizure
- Fracture
- Fatigue
- Amnesia
- Memory impairment
- Cognitive disturbance
- Concentration impairment
- Depressed level of consciousness

11.6. Overdose

11.6.1. Darolutamide Overdose

The highest dose of darolutamide studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose. Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to toxicity in patients with intact hepatic and renal function. In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt darolutamide treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, darolutamide treatment can be continued with the next dose as scheduled. In the event of intake of a higher than recommended dose, darolutamide treatment can be continued with the next dose as scheduled. There is no specific antidote for darolutamide and symptoms of overdose are not established.

11.6.2. Enzalutamide overdose

In the event of an overdose, stop treatment with enzalutamide and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at < 240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizures following an overdose.

11.7. Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical study are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs will be recorded from the time of signing consent through 30 days following cessation of treatment of the primary data collection period. Patients removed from study for unacceptable treatment-related AEs will be followed until resolution or stabilization of the AE. Any increase of a documented baseline condition from screening/history will be reported as an adverse event. Adverse events are entered into the eCRF in Rave Electronic Data Capture (EDC) system.

11.7.1. Serious Adverse Event Reporting

SAEs must be entered into the eCRF on the Serious Adverse Event form in Rave EDC within 24 hours of learning of the event. Serious adverse events will be recorded from the time of the first study related procedure through 30 days following cessation of treatment of the primary data collection period.

All serious adverse events that meet criteria in [Section 11.3](#) must be reported to the AFT via Rave EDC within 24 hours of the site's knowledge of the event. AFT will send SAE reports to BMS within 24 hours of becoming aware of the event.

Note: All deaths on study require reporting via Rave EDC. Attribution to treatment or other cause should be provided.

11.7.2. Events of Special Interest Reporting

11.7.2.1. Pregnancy Reporting

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the AFT immediately.

All initial reports of pregnancy must be reported to AFT using the Serious Adverse Event form within 24 hours of becoming aware of the event.

AFT will submit pregnancy reports to Bayer within 24 hours from AFT's first awareness date.

Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event form.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the approved form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported by sites within 24 hours of their knowledge of the event using the Pregnancy case report form within Rave EDC. AFT will report to Bayer within 24 hours of the receipt of the event.

11.7.2.2. Overdose Reporting

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

11.7.3. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v 5.0) will be used for assessing AE severity.

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as none, mild, moderate or severe.

Table 7 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Table 7: Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated.
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living. ^a
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living. ^{b, c}
4	Life-threatening consequences or urgent intervention indicated Assessment of Severity of Adverse Events.
5	Death related to adverse event. ^d

NCI CTCAE National Cancer Institute Common Terminology Criteria for AEs. Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

^a Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

^b Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

^c If an event is assessed as a "significant medical event," it must be reported as a SAE (see [Section 11.7.1](#) for reporting instructions), per the definition of SAE in [Section 11.3](#).

^d Grade 4 (only if immediately life threatening) and Grade 5 events must be reported as SAEs (see [Section 11.7.1](#) for reporting instructions), per the definition of SAE in [Section 11.3](#).

11.7.3.1. Follow-up of Adverse Events

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to AFT (or designee) using the same procedure used for transmitting the initial SAE report.

All AEs should be followed with appropriate medical management to resolution or stabilization. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

11.7.4. Assessment of Causality of Adverse Events

An assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must document the causal relationship in the eCRF and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable. A suspected adverse reaction is any AE for which there is reasonable possibility that the investigational product caused the AE. An investigator's causality assessment should determine if there exists a reasonable possibility that the investigational product caused or contributed to an AE.

The relationship of the AE to the study treatment will be assessed following the classifications below:

Table 8: Guidelines for Determining the Relationship Between Adverse Event and the Study Drug

AE Relationship	Definition
Definite	This relationship suggests that a definite causal relationship exists between treatment administration and the AE, and that other conditions (concurrent illness, progression/progression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study treatment is re-administered.
Probable	This relationship suggests that a reasonable temporal sequence of the event with treatment administration exists and, based upon the known pharmacological action of the treatment, known or previously reported adverse reactions to the treatment or class of treatment, or judgment based on the Investigator's clinical experience, the association of the event with the study treatment seems likely. The event disappears or decreases on cessation of study treatment.
Possible	This relationship suggests that the study treatment caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of treatment administration or follows a known response pattern to the study treatment, but could also have been produced by other factors.
Unlikely Related	This relationship suggests an improbable (but not impossible) association between the study medication and the reported event. The adverse event severity grading scale for the NCI CTCAE (v 5.0) will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm .
Not Related	This relationship suggests no association between the study treatment and the reported event.

11.7.5. Expedited Safety Reporting to Regulatory Agencies

As this study is IND exempt, AFT will not be submitting SUSAR reports to the FDA or other regulatory authorities. However, AFT will send safety reports to Bayer following the FDA SUSAR timelines within 15 calendar days of AFT awareness of the event and all SUSARs resulting in life-threatening, or death within 7 calendar days of AFT awareness.

11.8. Data Collection and Submission

Data collection for this study will be done through the Medidata Rave EDC system.

12. Correlative Science

12.1. Future Biomedical Research

All collected biospecimens will be stored at the University of Minnesota, until biospecimen accrual and clinical follow-up is sufficiently complete to allow for the design and execution of specific correlative analyses using analytical platforms that will be available at that time.

Such biomarker research will address emergent questions not described elsewhere in this protocol and will only be conducted on specimens from appropriately consented patients. The objective of collecting specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of disease and/or their therapeutic treatments in the context of this study. Proposals for future correlative research will undergo rigorous scientific, programmatic, and statistical review by AFT, and biospecimens will only be released to those investigators who have obtained appropriate regulatory approval and demonstrate adequate funding to successfully complete proposed research aims. AFT will ensure that all collected specimens are used only for approved research protocols.

Anonymized (de-identified) data generated from biospecimens used for future correlative research, including somatic and constitutional (germline) genomic data, may be shared with other researchers or deposited in a publicly accessible or controlled-access data repositories. Correlative study results and data will never be returned to individual patients.

13. Measurement of Effect/ Efficacy Assessments

13.1. Patient Disease-Related Outcome Measures.

13.1.1. The Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog)

The Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog), the only self-report questionnaire that has specifically assessed cognition, was developed from interviews with expert clinicians and oncology patient focus groups.^{54, 55} It is the first patient-reported outcome measure evaluating cognitive impairment to be validated with cancer patients and can potentially be used in standard clinical practice as a tool for evaluating patients' cognitive complaints before, during and after chemotherapy. This questionnaire evaluates patients' self-reported perceptions of their cognitive abilities and the effects of these cognitive changes on their HRQOL. The FACT-Cog distinguishes itself from other available subjective neuropsychological tests because the questionnaire focuses on the noticeability and functional interference of the multiple specific domains associated with perceived cognitive functioning.

13.1.2. Functional Assessment of Cancer Therapy – Prostate Version (FACT-P)

The FACT-P is a 12-item prostate cancer-specific scale that supplements the general version (FACT-G). Scores can be produced from the 12 condition-specific items, the Prostate Cancer Score (PCS) and a Treatment Outcome Index (TOI) can be calculated by summing the FACT-G Physical and Functional domains and the PCS.

13.1.3. PHQ-9: Patient Health Depression Questionnaire

The PHQ-9 is a 9-question instrument given to patients in a primary care setting to screen for the presence and severity of depression. It is the 9-question depression scale from the Patient Health Questionnaire. The Patient Health Questionnaire (PHQ-9) is a brief, 9-item self-report screening tool that may help identify symptoms that could relate to depression. The PHQ-9 was developed for use in primary care settings.

13.1.4. Sleep Scale from Medical Outcomes Study

Sleep is an important element of functioning and well-being. The Medical Outcomes Study Sleep Scale (MOS-Sleep) includes 12 items assessing sleep disturbance, sleep adequacy, somnolence, quantity of sleep, snoring, and awakening short of breath or with a headache. A sleep problems index, grouping items from each of the former domains, is also available.

13.1.5. Functional Activities Questionnaire (FAQ)

The Functional Activities Questionnaire (FAQ) serves a screening tool for evaluating ADI's independence. The instrument was intended for community studies of normal aging and moderate senile dementia.

In order to take the FAQ, a lay informant (i.e. spouse, friend, or relative) must administer it. The participant must respond to 10-items pertaining to daily tasks needed when living independently. A scale ranging from independence (0) to dependence (3) is used for responses. Approximately 10 minutes is required for completion. The FAQ is an informant-based measure of functional abilities. Informants (i.e., family members, caregivers) rate the patient's performance of 10 complex, higher order activities. This is to be completed by an informant who is present at follow up, if someone is present. If no one is present, the patient can designate someone to complete it by phone and the study coordinator can call this person to complete it within 7 days of the study visit. If no one is available or has this knowledge, that would be marked as n/a for the patient.

13.1.6. Comprehensive Score for financial Toxicity (COST)

Financial toxicity (FT) has a negative impact on the quality of life and survival of patients with cancer. The comprehensive score for FT (COST) questionnaire is a tool to measure FT which has already been validated in patients with cancer in the United States. The Comprehensive Score for financial Toxicity (COST) patient-reported outcome measure (PROM) was previously developed to assess financial toxicity in patients with cancer. The COST questionnaire is short and includes 11 brief statements about costs, resources, and concerns. For each question, patients were asked to circle 1 of 5 possible responses that helped determine their level of concern.

13.1.7. Health Literacy

Limited health literacy (HL) contributes to poor health outcomes and disparities, and direct measurement is often time-intensive. In this study, patients will be asked 3 health literacy questions.

13.2. Assessments based on PSA

- **Prostate Specific Antigen Response Rate (PSARR)** is defined as the proportion of participants with a reduction in PSA level of $\geq 50\%$ from baseline, confirmed with a second assessment conducted at least 2 weeks later.
- **PSA Change** from Baseline to 12 Weeks is defined as the individual proportion of rise or fall in PSA at 12 weeks relative to baseline.
- **Maximum PSA Change** is defined as the individual maximum proportion of rise or fall in PSA from baseline occurring at any time point

- **Time to PSA Progression** is defined as the time from the date of randomization to the date of first observation of PSA progression. The PSA progression is defined as a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir (or baseline value if baseline is the smallest on study), which is confirmed by a second value obtained at least 2 weeks later.

13.3. Radiographic Assessments:

Patients experiencing radiographic progression prior to 48 weeks should discontinue treatment and complete an early termination assessment prior to transitioning to the next treatment per standard of care. Treatment beyond radiographic progression after 48 weeks is at the physician's discretion.

13.3.1. Definition of Radiographic Progression

Progression of disease in soft tissue is per RECIST criteria. Progression of disease by bone per PCWG3 is defined as the appearance of at least 2 new lesions on a post-treatment scan, with at least 2 additional lesions on the next scan (2+2 rule) with the initial two lesions that are persisting on a confirmatory subsequent scan (at least 6 weeks later or at the next scheduled assessment).

The date of progression is the date of the first scan when the first 2 (or more) new lesions are documented.

Changes in intensity of uptake alone do not constitute either progression or regression.

13.3.2. PSA Progression within 48 weeks of study initiation

Patients with advanced prostate cancer who experience PSA progression during the 48-week study period will be required to undergo imaging studies (radionuclide bone scan and CT or MRI scan of the chest, abdomen, and pelvis) locally to confirm if radiographic progression has occurred. If radiographic progression has occurred during that time study treatment will be discontinued. Patients who experience PSA progression but do NOT have radiographic progression may continue study therapy up to 48 weeks per protocol.

13.3.3. PSA Progression beyond 48 weeks of study initiation

Imaging studies (radionuclide bone scan and CT or MRI scan of the chest, abdomen, and pelvis) are recommended for patients experiencing PSA progression beyond 48 weeks. Discontinuation of study therapy is recommended for patients experiencing radiographic progression (defined as >2 new metastatic lesions for patients with previous negative imaging, however treatment beyond 48 weeks will be per treating physician's discretion.

14. Statistical Considerations

14.1. Overview of the Study Design

This is a prospective, randomized, phase 2 clinical trial, designed to compare the cognitive function of men with advanced prostate cancer treated with DARO or ENZ. After informed consent, screening and baseline evaluations, eligible patients will be randomized in a 1:1 fashion to treatment with ENZ or DARO. The randomization will be stratified by age (<65 , $65-80$, >80).

The primary endpoint of the study is the percent change in the maximally changed cognitive domain by 24 weeks.

14.1.1. Definitions

- Maximally changed cognitive domain

Defined as the domain (eg, executive, memory, visuospatial) that changes the most from baseline in each individual; this value will be averaged across all individuals in a study arm at 24 weeks to calculate the primary endpoint. For individuals that cross over prior to 24 weeks, their score will be from the time of cross-over, not the 24-week assessment.

For secondary endpoints, cognitive impairment, as specified by the International Cognition and Cancer Task Force guidelines, is defined as meeting one of the following: 1) ≥ 1.5 SDs below (age- and education-adjusted) norm on ≥ 2 cognitive domain modules; or 2) ≥ 2 SDs below norm on ≥ 1 cognitive domain module.

14.2. Sample Size, Accrual Time and Study Duration

The target sample size is 132, allowing for 15% overall drop-out for a final sample size of 114. Our sample size justification is based on the projection that the most changed cognitive domain among men treated for 24 weeks with DARO will decline on average by 15% from baseline in the population, while the most changed cognitive domain among men treated with ENZ will decline on average by 30% in the population. A sample size of 57 patients per treatment has power 0.88 based on the Lehmann alternative, assuming a two-fold effect on the average rate of cognitive decline between treatments and a two-sided 0.05 Wilcoxon rank sum test.⁵⁶

It is estimated that approximately 6 patients will be accrued per year at each of 12 sites. The estimated time to achieve total accrual is 22 months. It is anticipated that the analyses for this component will commence approximately 36 months from the start of the study.

14.3. Stratification Factors

Randomization will be stratified by age (<65, 65-80, >80).

14.4. Statement for Primary Endpoint

The primary objective, to assess the maximum change in cognitive domain between treatments will be evaluated with the Wilcoxon rank sum statistic.

14.5. Interim Analysis Design for Primary Endpoint

There is no interim analysis planned for this study.

14.6. Supplementary/Secondary Analysis Plans

The following outcomes from the secondary objectives will be summarized within treatment and 95% confidence intervals for their corresponding parameter values will be computed.

- The average decline in the maximally changed cognitive domain at 48 weeks.
- The cumulative proportion of impaired patients at 24 weeks.
- The cumulative proportion of impaired patients at 48 weeks.

- The average decline in the baseline lowest ranking domain at 24 weeks.
- The average decline in the baseline lowest ranking domain at 48 weeks.

The following cross over outcomes will be summarized and 95% confidence intervals for their corresponding parameter values will be computed.

- The proportion of patients crossing over from each treatment arm based on subjective (self-reported, FACT-Cog V3) cognitive effects.
- The proportion of patients crossing over from each treatment arm based on objectively measured cognitive effects (CANTAB modules).
- The proportion of patients crossing over due to neurologic toxicity (fatigue and severe neurologic toxicity [seizure or PRES]); Cross over for severe neurologic toxicity is allowed for patients on ENZ only.
- The proportion of patients with improvement in cognitive function after crossover from each treatment arm.

Additional secondary objectives include:

- Estimation of the proportion PSA responses at 24 weeks (on the basis of a decrease from baseline of $\geq 50\%$)
- Estimation of the probability of PSA progression over time using the cumulative incidence function.

Spearman's rank correlation statistic will be computed within treatment to evaluate the following exploratory objectives.

- The within treatment arm association of AR CAG repeat length with baseline CANTAB performance.
- The within treatment arm association of AR CAG repeat length with change in CANTAB performance at 24 and 48 weeks.
- The within treatment arm association of polygenic hazard scores (PHS) with baseline CANTAB performance.
- The within treatment arm association of polygenic hazard scores (PHS) with change in CANTAB performance at 24 and 48 weeks.

The sign test will be applied to assess:

- The within patient change in financial toxicity.

14.7. Treatment Switching/Missing Data Analyses

For all post-baseline data analyses, an initial intent to treat analysis will be performed where all randomized patients are analyzed according to the treatment they were originally assigned. Subsequent to the intent to treat analyses, sensitivity analyses will be employed to evaluate the effect of treatment switching and missing data on the observed outcomes.

14.8. Early Discontinuation of the Study

Early trial termination will be the result of the criteria specified below:

1. Poor adherence to protocol and regulatory requirements.
2. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to patients.
3. Plans to modify or discontinue the development of the study drug.

14.9. Criteria for Taking a Patient Off Protocol Therapy

Duration of treatment requires intent to treat with study therapy for 48 weeks or greater.

Discontinuation of study drug during the period of on-study evaluation, for whatever reason including disease progression, will be noted as study data and such patients will not be replaced. Patients discontinuing should complete an end of treatment visit including study testing.

Patients meeting criteria for crossover who are on either DARO or ENZ will be permitted to cross over to the alternate drug, unless the reason for crossover is falls or neurologic toxicity (only cross-over from ENZ to DARO in that situation). Patients experiencing falls, PRES, or seizure on DARO will be discontinued from study therapy but will continue to be followed through 48 weeks with cognitive testing.

Patients may continue to receive cycles of treatment until any of the following occur:

- Disease progression
- Development of an inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Patient decides to withdraw from either study treatment or the as a whole study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Following treatment discontinuation, patients will be followed by routine clinic visit (or telephone call, if appropriate) every 3 months for a maximum of 1 year unless patient withdraws consent before that.

14.10. Criteria for Taking a Patient Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- Completion of required follow up

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

15. General Regulatory Considerations

15.1. Compliance with Study Enrollment and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, <http://www.clinicaltrials.gov>. Information posted will allow patients to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

15.2. Regulatory and Ethical Compliance

This study will be conducted in compliance with the study protocol, subsequent amendment(s) and with the study-specific manuals/guidelines, if applicable. These documents ensure that the ICH E6 guideline for Good Clinical Practice is maintained as well as compliance with the principles of the Declaration of Helsinki (World Medical Association), or the laws and regulations of the country in which the research is conducted, whichever afford the greater protection to the individual.

Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulation and applicable local, state and federal laws.

15.3. Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written Informed Consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. This information must be provided to the patient prior to undertaking any trial-related procedure which is not part of the routine clinical management of the patient (i.e. would not be indicated outside the study). The proposed Informed Consent Form and consenting process must comply with the GCP guidelines, regulatory requirements and be consistent with IRB/institutional policies.

15.4. Responsibilities of the Site Investigator/IRB/IEC/REB

The regulatory requirements for the Investigator can be found in Subpart D of 21CFR312 (21CFR 312.60: General Responsibilities of Investigators) and in ICH E6 Section 4.

Additional requirements are also outlined in the Statement of Investigator Responsibilities (Form FDA 1572) and the Site Services Agreement. Alliance Foundation Trials, LLC (AFT) will supply the protocol and subsequent amendments.

The Site Investigator is responsible for overall study compliance, execution, oversight and management of the study at their site, and satellite sites, if applicable.

As specified in 21CFR 312.62 (Investigator Record Keeping and Record Retention) and ICH E6 Section 4.9 and Section 8, the Site Investigator is responsible for ensuring that their study staff maintains and retains all study related documentation, including but not limited to: signed

Informed Consent forms, source documents, protocol documents, Institutional Review Board (IRB) approvals, relevant IRB and Sponsor correspondence, and associated regulatory documents. The Site Investigator is responsible for retaining and keeping safe all patient related documentation. In order to do this, the site staff will complete electronic case report forms (eCRFs) in a timely manner.

15.5. Financial Disclosures

Site Investigators will provide AFT with adequate and accurate financial information in accordance with local regulations and laws in order to allow AFT to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing updated information on financial interests during the course of the study as well as for 1 year after completion of the study.

15.6. Protocol Deviations

The Site Investigator is responsible to document and explain any deviations from the approved protocol. The investigator should promptly report any deviations that might impact patient safety and data integrity to AFT and if locally applicable, to the respective IRB in accordance with local IRB policies and procedures.

A deviation is a departure from the protocol. If deviations are discovered by the monitor or data manager, other member of study staff or otherwise, they will be discussed with the Site Investigator and study staff. AFT does not provide waivers for protocol deviations.

15.7. Protocol Amendments

Any modifications to the protocol or the Informed Consent Form which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendments will be released by AFT, agreed by the investigator(s) and approved by relevant IRBs prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents and the Informed Consent Form have been approved by relevant IRBs must be provided to AFT before the study is initiated. Because administrative processing of amendments may take time which could impact study conduct, AFT may release operational memos to allow such changes to the protocol conduct to occur prior to the formal amendment review without being considered a protocol deviation. This is particularly true for changes which impact patient safety. Such memos should be processed per local IRB/institutional standard.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the AFT, agreed by the investigator(s) and notified to the IRB as per institutional guidelines.

15.8. Retention of Records (Study Documentation, Record Keeping)

15.8.1. Retention of Records

Any records and documents relating to the conduct of this study and the distribution of investigational product must be retained by the investigator until notification by AFT, or for the

length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of AFT. Written notification should be provided to AFT prior to transferring any records to another party or moving them to another location.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), AFT should be prospectively notified. The study records must be transferred to a designee acceptable to AFT, such as another investigator, another institution, or to AFT itself.

15.9. Data Confidentiality

Patient medical information, including information associated with biologic specimens, is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) which has been signed by the patient, unless permitted or required by law. Data derived from biologic specimen analysis on individual patients will not be provided to study investigators unless a request for research use is granted. The overall results of any research conducted using biologic specimens will be available in accordance with the effective AFT policy on study data publication.

Data collected during this study may be used to support the development, registration or marketing of an investigational product. All data collected during the study will be controlled by the Sponsor, AFT. AFT will abide by all relevant data protection laws. After a patient has consented to take part in the study, their medical records and the data collected during the study will be reviewed by representatives of the Sponsor to confirm that the data collected are accurate and for the purpose of analyzing the results. These records and data may be additionally reviewed by auditors or by regulatory authorities. The patient's name, however, will not be disclosed outside the hospital. They will be known by a unique patient number.

Written Authorization is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (e.g. Health Insurance Protection and Portability Act [HIPAA]), and any other state and country privacy requirements.

15.10. Database Management and Quality Control

The Site Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study.

Rave EDC will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF. eCRFs will be completed in a timely manner.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto eCRFs.

At study completion, when the database has been declared to be complete and accurate, the database will be locked.

AFT will review eCRFs for accuracy and completeness; any discrepancies will be resolved with the investigator or designee, as appropriate. Queries are entered, tracked, and resolved through the EDC system directly. All changes to the study database will be documented.

15.11. Site Monitoring

Monitoring visits will be conducted by representatives of the Alliance Foundation according to the US CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to AFT (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.12. Data and Safety Monitoring Board (DSMB)

The Alliance Foundation Trials Data Safety Monitoring Board will be monitoring this study to ensure objectivity and the safety of participants.

The DSMB will meet twice a year either at a face-to-face meeting or by teleconference. At each meeting, the study will be reviewed for safety and progress toward completion. When appropriate, the DSMB will also review formal interim analyses of the outcome data. If necessary, the DSMB will recommend study closure or modifications. Any DSMB recommendations for changes to the study will be circulated to investigators.

15.13. Regulatory Reporting

Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32, as applicable.

It is the responsibility of the investigator and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines, AFT's guidelines, and Institutional Review Board (IRB) policy.

15.14. Audits and Inspections

Investigator sites may be audited by AFT under the AFT site audit program. Affiliate and satellite sites are subject to audit by AFT but in most cases will be centrally audited at the main member site. To enable evaluations and/or audits from health authorities or AFT, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed informed consent forms, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). In the event that the investigator or other site personnel are notified of a Health Authority's intent to inspect the site(s), notification will be sent to compliance@alliancefoundationtrials.org immediately upon awareness.

15.15. Early Discontinuation of the Study

Early study termination will be the result of the criteria specified below:

- Poor adherence to protocol and regulatory requirements
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects



- Plans to modify or discontinue the development of the study drug

15.16. Publication of Study Protocol and Results

Alliance Foundation Trials, LLC prioritizes the timely presentation and publication of study results. Publications and any kind of presentations of results from the study shall be in accordance with accepted scientific practice, academic standards and customs and must be approved in writing by AFT as the sponsor of this study. No investigator may present or publish any portion of this study without written approval from AFT.

16. References

1. Society AC. Prostate Cancer Statistics. 2017.
2. Howlader N NA KM, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, November 2014 SEER data submission posted to the SEER web site, April 2015. 2015.
3. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433.
4. Scher HI FK, Saad F, Taplin ME, Sternberg CN, Miller K, De Wit R, Mulders P, Hirmand M, Selby B, de Bono JS. Effect of MDV3100, an androgen receptor signaling inhibitor (ARSI), on overall survival in patients with prostate cancer postdocetaxel: Results from the phase III AFFIRM study. *J Clin Oncol* 30, 2012 (suppl 5; abstr LBA1). 2012.
5. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.
6. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197.
7. Xtandi (Enzalutamide) package insert. Northbrook IAPU, Inc; July 2018.
8. Nubeqa (Darolutamide) package insert. Whippany NBHPI, July 2019
9. Janelins MC, Kohli S, Mohile SG, Usuki K, Ahles TA, Morrow GR. An update on cancer- and chemotherapy-related cognitive dysfunction: current status. *Semin Oncol*. 2011;38(3):431-438.
10. Ahles TA, Saykin AJ, Furstenberg CT, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol*. 2002;20(2):485-493.
11. Brezden CB, Phillips KA, Abdoell M, Bunston T, Tannock IF. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol*. 2000;18(14):2695-2701.
12. Ahles TA, Root JC, Ryan EL. Cancer- and cancer treatment-associated cognitive change: an update on the state of the science. *J Clin Oncol*. 2012;30(30):3675-3686.
13. Reid-Arndt SA, Yee A, Perry MC, Hsieh C. Cognitive and psychological factors associated with early posttreatment functional outcomes in breast cancer survivors. *J Psychosoc Oncol*. 2009;27(4):415-434.
14. Wefel JS, Lenzi R, Theriault RL, Davis RN, Meyers CA. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. *Cancer*. 2004;100(11):2292-2299.
15. McGinty HL, Phillips KM, Jim HS, et al. Cognitive functioning in men receiving androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. *Support Care Cancer*. 2014;22(8):2271-2280.
16. Alibhai SM, Breunis H, Timilshina N, et al. Impact of androgen-deprivation therapy on cognitive function in men with nonmetastatic prostate cancer. *J Clin Oncol*. 2010;28(34):5030-5037.
17. Joly F, Alibhai SM, Galica J, et al. Impact of androgen deprivation therapy on physical and cognitive function, as well as quality of life of patients with nonmetastatic prostate cancer. *J Urol*. 2006;176(6 Pt 1):2443-2447.
18. Jim HS, Small BJ, Patterson S, Salup R, Jacobsen PB. Cognitive impairment in men treated with luteinizing hormone-releasing hormone agonists for prostate cancer: a controlled comparison. *Support Care Cancer*. 2010;18(1):21-27.
19. Yamada TH, Denburg NL, Beglinger LJ, Schultz SK. Neuropsychological outcomes of older breast cancer survivors: cognitive features ten or more years after chemotherapy. *J Neuropsychiatry Clin Neurosci*. 2010;22(1):48-54.
20. Jenkins V, Shilling V, Deutsch G, et al. A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. *Br J Cancer*. 2006;94(6):828-834.
21. Schilder CM, Seynaeve C, Beex LV, et al. Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with breast cancer: results from the neuropsychological side

- study of the tamoxifen and exemestane adjuvant multinational trial. *J Clin Oncol*. 2010;28(8):1294-1300.
22. Palmer JL, Trotter T, Joy AA, Carlson LE. Cognitive effects of Tamoxifen in pre-menopausal women with breast cancer compared to healthy controls. *J Cancer Surviv*. 2008;2(4):275-282.
 23. Castellon SA, Ganz PA, Bower JE, Petersen L, Abraham L, Greendale GA. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *J Clin Exp Neuropsychol*. 2004;26(7):955-969.
 24. Saylor PJ, Smith MR. Adverse effects of androgen deprivation therapy: defining the problem and promoting health among men with prostate cancer. *J Natl Compr Canc Netw*. 2010;8(2):211-223.
 25. Lee M, Jim HS, Fishman M, et al. Depressive symptomatology in men receiving androgen deprivation therapy for prostate cancer: a controlled comparison. *Psychooncology*. 2015;24(4):472-477.
 26. Gonzalez BD, Jim HS, Donovan KA, et al. Course and Moderators of Hot Flash Interference during Androgen Deprivation Therapy for Prostate Cancer: A Matched Comparison. *The Journal of Urology*. 2015;194(3):690-695.
 27. Storey DJ, McLaren DB, Atkinson MA, et al. Clinically relevant fatigue in men with hormone-sensitive prostate cancer on long-term androgen deprivation therapy. *Ann Oncol*. 2012;23(6):1542-1549.
 28. Gonzalez BD, Jim HS, Booth-Jones M, et al. Course and Predictors of Cognitive Function in Patients With Prostate Cancer Receiving Androgen-Deprivation Therapy: A Controlled Comparison. *J Clin Oncol*. 2015;33(18):2021-2027.
 29. Gunlusoy B, Ceylan Y, Koskderelioglu A, et al. Cognitive Effects of Androgen Deprivation Therapy in Men With Advanced Prostate Cancer. *Urology*. 2017;103:167-172.
 30. Nead KT, Gaskin G, Chester C, et al. Influence of age on androgen deprivation therapy-associated Alzheimer's disease. *Sci Rep*. 2016;6:35695.
 31. Nead KT, Gaskin G, Chester C, Swisher-McClure S, Leeper NJ, Shah NH. Association Between Androgen Deprivation Therapy and Risk of Dementia. *JAMA Oncol*. 2017;3(1):49-55.
 32. Cherrier MM, Aubin S, Higano CS. Cognitive and mood changes in men undergoing intermittent combined androgen blockade for non-metastatic prostate cancer. *Psychooncology*. 2009;18(3):237-247.
 33. Verdile G, Laws SM, Henley D, et al. Associations between gonadotropins, testosterone and beta amyloid in men at risk of Alzheimer's disease. *Mol Psychiatry*. 2014;19(1):69-75.
 34. Sar M, Stumpf WE. Androgen concentration in motor neurons of cranial nerves and spinal cord. *Science*. 1977;197(4298):77-79.
 35. Tabori NE, Stewart LS, Znamensky V, et al. Ultrastructural evidence that androgen receptors are located at extranuclear sites in the rat hippocampal formation. *Neuroscience*. 2005;130(1):151-163.
 36. Rosario ER, Pike CJ. Androgen regulation of beta-amyloid protein and the risk of Alzheimer's disease. *Brain Res Rev*. 2008;57(2):444-453.
 37. Rosario ER, Carroll JC, Pike CJ. Evaluation of the effects of testosterone and luteinizing hormone on regulation of beta-amyloid in male 3xTg-AD mice. *Brain Res*. 2012;1466:137-145.
 38. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol*. 2011;70(11):960-969.
 39. Lim YY, Pietrzak RH, Ellis KA, et al. Rapid decline in episodic memory in healthy older adults with high amyloid-beta. *J Alzheimers Dis*. 2013;33(3):675-679.
 40. Evans CP, Higano CS, Keane T, et al. The PREVAIL Study: Primary Outcomes by Site and Extent of Baseline Disease for Enzalutamide-treated Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer. *Eur Urol*. 2016;70(4):675-683.
 41. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med*. 2018;378(26):2465-2474.
 42. Xtandi (Enzalutamide) package insert. Northbrook, IL: Astellas Pharma US, Inc; July 2018.
 43. Yaffe K, Edwards ER, Lui LY, Zmuda JM, Ferrell RE, Cauley JA. Androgen receptor CAG repeat polymorphism is associated with cognitive function in older men. *Biol Psychiatry*. 2003;54(9):943-946.

44. Desikan RS, Fan CC, Wang Y, et al. Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score. *PLoS Med.* 2017;14(3):e1002258.
45. Wang L, Apple AC, Schroeder MP, et al. Reduced prefrontal activation during working and long-term memory tasks and impaired patient-reported cognition among cancer survivors postchemotherapy compared with healthy controls. *Cancer.* 2016;122(2):258-268.
46. Ramsey SD, Bansal A, Fedorenko CR, et al. Financial Insolvency as a Risk Factor for Early Mortality Among Patients With Cancer. *J Clin Oncol.* 2016;34(9):980-986.
47. Ryan David Nipp LLZ, Gregory Samsa, Jeffrey M. Peppercorn, Deborah Schrag, Donald H. Taylor, Amy Pickar Abernethy, and Yousuf Zafar. Coping with cancer treatment-related financial burden. *Journal of Clinical Oncology.* 2014;32. 31_suppl:161-161.
48. de Souza JA, Yap BJ, Wroblewski K, et al. Measuring financial toxicity as a clinically relevant patient-reported outcome: The validation of the COMprehensive Score for financial Toxicity (COST). *Cancer.* 2017;123(3):476-484.
49. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc.* 1991;39(2):142-148.
50. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med.* 2019;380(13):1235-1246.
51. Apple AC, Ryals AJ, Alpert KI, et al. Subtle hippocampal deformities in breast cancer survivors with reduced episodic memory and self-reported cognitive concerns. *Neuroimage Clin.* 2017;14:685-691.
52. Li P, Kaslan M, Lee SH, Yao J, Gao Z. Progress in Exosome Isolation Techniques. *Theranostics.* 2017;7(3):789-804.
53. Winston CN, Goetzl EJ, Akers JC, et al. Prediction of conversion from mild cognitive impairment to dementia with neuronally derived blood exosome protein profile. *Alzheimers Dement (Amst).* 2016;3:63-72.
54. Wagner LI, Sweet, J., Butt, Z., Lai, J. S., Cella, D. Measuring Patient Self-Reported Cognitive Function: Development of the Functional Assessment of Cancer Therapy–Cognitive Function Instrument. *The Journal of Supportive Oncology.* 2009; 7:W32-W39.
55. Wagner H, Jr. Postoperative radiation therapy for patients who have resected non-small cell lung cancer. *Hematol Oncol Clin North Am.* 2005;19(2):283-302, vi.
56. Heller G. Power calculations for preclinical studies using a K-sample rank test and the Lehmann alternative hypothesis. *Stat Med.* 2006;25(15):2543-2553.
57. Smith, Matthew R., et al. "Darolutamide and survival in metastatic, hormone-sensitive prostate cancer." *New England Journal of Medicine.* 386.12 (2022): 1132-1142.
58. Armstrong, Andrew J., et al. "ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer." *Journal of Clinical Oncology.* 37.32 (2019): 2974.
59. Davis, I. D., et al. "ENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group. Enzalutamide with standard first-line therapy in metastatic prostate cancer." *N Engl J Med.* 381.2 (2019): 121-131.

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
*As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

Appendix 2: New York Heart Association Classification of Heart Failure (NYHA CHA)

Class	Symptomatology
I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea
II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.



Appendix 3: Common Terminology Criteria for Adverse Events v5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting.
(https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm)

Appendix 4: CYP3A4 Inducers and Inhibitors

CYP3A4 Inducers		CYP3A4 Inhibitors	
1.	Efavirenz	1.	indinavir
2.	nevirapine	2.	nelfinavir
3.	barbiturates	3.	ritonavir
4.	carbamazepine	4.	clarithromycin
5.	glucocorticoids	5.	itraconazole
6.	modafinil	6.	ketoconazole
7.	oxcarbazepine	7.	nefazodone
8.	phenobarbital	8.	saquinavir
9.	phenytoin	9.	telithromycin
10.	rifabutin	10.	aprepitant
11.	rifampin	11.	erythromycin
12.	St. John's wort	12.	fluconazole
		13.	grapefruit juice
		14.	verapamil
		15.	diltiazem
		16.	cimetidine
		17.	amiodarone
		18.	delaviridine
		19.	fluvoxamine
		20.	imatinib
		21.	mifepristone
		22.	star fruit
		23.	voriconazole

Appendix 5: FACT-COG

FACT-Cognitive Function (Version 3)

Below is a list of statements that other people with your condition have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
<u>PERCEIVED COGNITIVE IMPAIRMENTS</u>						
CogA1	I have had trouble forming thoughts	0	1	2	3	4
CogA3	My thinking has been slow	0	1	2	3	4
CogC7	I have had trouble concentrating	0	1	2	3	4
CogM9	I have had trouble finding my way to a familiar place.....	0	1	2	3	4
CogM10	I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
CogM12	I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
CogV13	I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
CogV15	I have had trouble finding the right word(s) to express myself	0	1	2	3	4
CogV16	I have used the wrong word when I referred to an object	0	1	2	3	4
CogV17b	I have had trouble saying what I mean in conversations with others	0	1	2	3	4
CogF19	I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
CogF23	I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
CogF24	I have forgotten names of people soon after being introduced	0	1	2	3	4

FACT-Cog (Version 3)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Some- what	Quite a bit	Very much
<u>PERCEIVED COGNITIVE ABILITIES</u>						
Cog PC1	I have been able to concentrate	0	1	2	3	4
Cog PV1	I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
Cog PM1	I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
Cog PM2	I have been able to remember to do things, like take medicine or buy something I needed.....	0	1	2	3	4
Cog PF1	I am able to pay attention and keep track of what I am doing without extra effort.....	0	1	2	3	4
Cog PCH 1	My mind is as sharp as it has always been	0	1	2	3	4
Cog PCH 2	My memory is as good as it has always been	0	1	2	3	4
Cog PMT 1	I am able to shift back and forth between two activities that require thinking	0	1	2	3	4
Cog PMT 2	I am able to keep track of what I am doing, even if I am interrupted	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Some- what	Quite a bit	Very much
<u>IMPACT ON QUALITY OF LIFE</u>						
CogQ35	I have been upset about these problems.....	0	1	2	3	4
CogQ37	These problems have interfered with my ability to work	0	1	2	3	4
CogQ38	These problems have interfered with my ability to do things I enjoy.....	0	1	2	3	4
CogQ41	These problems have interfered with the quality of my life	0	1	2	3	4

FACT-Cog (Version 3)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogF25	My reactions in everyday situations have been slow.....	0	1	2	3	4
CogC31	I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
CogC32	My thinking has been slower than usual	0	1	2	3	4
CogC33a	I have had to work harder than usual to express myself clearly	0	1	2	3	4
CogC33c	I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
CogMT1	I have trouble keeping track of what I am doing if I am interrupted.....	0	1	2	3	4
CogMT2	I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
<u>COMMENTS FROM OTHERS</u>						
CogO1	Other people have told me I seemed to have trouble <u>remembering information</u>	0	1	2	3	4
CogO2	Other people have told me I seemed to have trouble <u>speaking clearly</u>	0	1	2	3	4
CogO3	Other people have told me I seemed to have trouble <u>thinking clearly</u>	0	1	2	3	4
CogO4	Other people have told me I seemed <u>confused</u>	0	1	2	3	4

Appendix 6: FACT-P

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>PHYSICAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

<u>SOCIAL/FAMILY WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>EMOTIONAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

<u>FUNCTIONAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4



221 Longwood Avenue
Ste. 122
Boston, MA 02115
www.AllianceFoundationTrials.org

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>ADDITIONAL CONCERNS</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
C2	I am losing weight.....	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me.....	0	1	2	3	4
P2	I have certain parts of my body where I experience pain....	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level.....	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels.....	0	1	2	3	4
P7	I have difficulty urinating.....	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities.....	0	1	2	3	4
BL5	I am able to have and maintain an erection.....	0	1	2	3	4

Appendix 7: PHQ-9

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: _____ DATE: _____

Over the last 2 weeks, how often have you been
bothered by any of the following problems?

(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3

add columns

_____ + _____ + _____

(Healthcare professional: For interpretation of TOTAL, TOTAL: _____
please refer to accompanying scoring card).

10. If you checked off <i>any</i> problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	_____
	Somewhat difficult	_____
	Very difficult	_____
	Extremely difficult	_____

Copyright © 1999 Pfizer Inc. All rights reserved. Reproduced with permission. PRIME-MD® is a trademark of Pfizer Inc.
A2663B 10-04-2005

PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.

Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying PHQ-9 Scoring Box to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every ✓ Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

PHQ9 Copyright © Pfizer Inc. All rights reserved. Reproduced with permission. PRIME-MD ® is a trademark of Pfizer Inc.

A2662B 10-04-2005

Appendix 8: Sleep Scale from the Medical Outcomes Study

Sleep Scale from the Medical Outcomes Study

1. How long did it usually take for you to fall asleep during the past 4 weeks?

(Circle One)

0-15 minutes.....1

16-30 minutes.....2

31-45 minutes.....3

46-60 minutes.....4

More than 60 minutes 5

-
2. On the average, how many hours did you sleep each night during the past 4 weeks?

Write in number
of hours per night:

--	--

How often during the past 4 weeks did you...

(Circle One Number On Each Line)

	All of the Time ▼	Most of the Time ▼	A Good Bit of the Time ▼	Some of the Time ▼	A Little of the Time ▼	None of the Time ▼
3. feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	1	2	3	4	5	6
4. get enough sleep to feel rested upon waking in the morning?	1	2	3	4	5	6
5. awaken short of breath or with a headache?	1	2	3	4	5	6
6. feel drowsy or sleepy during the day?	1	2	3	4	5	6
7. have trouble falling asleep?	1	2	3	4	5	6
8. awaken during your sleep time and have trouble falling asleep again?	1	2	3	4	5	6
9. have trouble staying awake during the day?	1	2	3	4	5	6
10. snore during your sleep?	1	2	3	4	5	6
11. take naps (5 minutes or longer) during the day?	1	2	3	4	5	6
12. get the amount of sleep you needed?	1	2	3	4	5	6

Copyright, 1986, RAND

Hays, R. D., & Stewart, A. L. (1992). Sleep measures. In A. L. Stewart & J. E. Ware (eds.), Measuring functioning and well-being: The Medical Outcomes Study approach (pp. 235-259), Durham, NC: Duke University Press.

Appendix 9: FAQ

Functional Activities Questionnaire

Administration

Ask informant to rate patient's ability using the following scoring system:

- Dependent = 3
- Requires assistance = 2
- Has difficulty but does by self = 1
- Normal = 0
- Never did [the activity] but could do now = 0
- Never did and would have difficulty now = 1

Writing checks, paying bills, balancing checkbook	
Assembling tax records, business affairs, or papers	
Shopping alone for clothes, household necessities, or groceries	
Playing a game of skill, working on a hobby	
Heating water, making a cup of coffee, turning off stove after use	
Preparing a balanced meal	
Keeping track of current events	
Paying attention to, understanding, discussing TV, book, magazine	
Remembering appointments, family occasions, holidays, medications	
Traveling out of neighborhood, driving, arranging to take buses	
TOTAL SCORE:	

Evaluation

Sum scores (range 0-30). Cutpoint of 9 (dependent in 3 or more activities) is recommended to indicate impaired function and possible cognitive impairment.

Pfeffer RI et al. Measurement of functional activities in older adults in the community. J Gerontol 1982; 37(3):323-329. Reprinted with permission of The Gerontological Society of America, 1030 15th Street NW, Suite 250, Washington, DC 20005 via Copyright Clearance Center, Inc.

These guidelines/tools are informational only. They are not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners considering each patient's needs on an individual basis. Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients. For more information, visit our Web site at www.aviviahealth.com. To contact our Chief Medical Officer, please call 1-888-4AVIVIA (1-888-428-4842).

Appendix 10: COST Survey

COST – FACIT (Version 2)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Some- what	Quite a bit	Very much
FT1	I know that I have enough money in savings, retirement, or assets to cover the costs of my treatment.....	0	1	2	3	4
FT2	My out-of-pocket medical expenses are more than I thought they would be.....	0	1	2	3	4
FT3	I worry about the financial problems I will have in the future as a result of my illness or treatment	0	1	2	3	4
FT4	I feel I have no choice about the amount of money I spend on care.....	0	1	2	3	4
FT5	I am frustrated that I cannot work or contribute as much as I usually do.....	0	1	2	3	4
FT6	I am satisfied with my current financial situation.....	0	1	2	3	4
FT7	I am able to meet my monthly expenses	0	1	2	3	4
FT8	I feel financially stressed.....	0	1	2	3	4
FT9	I am concerned about keeping my job and income, including work at home.....	0	1	2	3	4
FT10	My cancer or treatment has reduced my satisfaction with my present financial situation	0	1	2	3	4
FT11	I feel in control of my financial situation.....	0	1	2	3	4
FT12	My illness has been a financial hardship to my family and me	0	1	2	3	4

Appendix 11: Health Literacy

*Scores range from 3-15 with higher scores reflecting worse self-reported health literacy.

1. How confident are you filling out medical forms by yourself?
 - Not at all (5)
 - A little (4)
 - Somewhat (3)
 - Quite a bit (2)
 - Extremely (1)

2. How often do you have problems learning about your medical condition because of difficulty understanding written information?
 - Never (1)
 - Rarely (2)
 - Sometimes (3)
 - Often (4)
 - Always (5)

3. How often do you have someone like a family member, friend, hospital or clinic worker or caregiver, help you read hospital materials?
 - Never (1)
 - Rarely (2)
 - Sometimes (3)
 - Often (4)
 - Always (5)

Reference: **Sarkar et al. (2010) Validation of Self-Reported Health Literacy Questions Among Diverse English and Spanish-Speaking Populations.**