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Clinical Protocol

Erdafitinib plus Abiraterone Acetate or Enzalutamide in Double Negative Prostate Cancer

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

Status: Approved
Date: 26 August 2022
Prepared by: **Michael T. Schweizer**

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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Erdafitinib plus Abiraterone Acetate or Enzalutamide in Double Negative Prostate Cancer

Background

Many of the treatments for metastatic castration-resistant prostate cancer (mCRPC) are directed at suppressing the androgen receptor (AR)-signaling axis. While AR-directed therapies are initially effective, resistance inevitability occurs. The continued lethality of this disease underscores the importance of testing therapeutics aimed at alternate pathways. Mechanistic studies have revealed that MAPK-signaling, which is activated by FGF/FGFR signaling, is an important AR bypass mechanism in men with late stage, double negative prostate cancer (DNPC). Importantly, targeting FGF/FGFR-signaling with pan-FGFR inhibitors results in significant tumor growth inhibition in both engineered LNCaP^{APIPC} cells and DNPC LuCaP 173.2 PDX models[1]. It is important to note that unlike other malignancies (e.g. bladder and lung cancer), patients with a DNPC phenotype usually do not harbor genomic alterations in FGFR, and over-activation of FGF/FGFR-signaling is primarily driven by autocrine/paracrine activation of this pathway. In total, this data demonstrates that FGF/FGFR-signaling is a critical driver of late stage CRPC, and supports testing FGFR inhibitors in DNPC patients.

On this basis, we are launching a phase II trial testing the pan-FGFR inhibitor erdafitinib in men with metastatic CRPC who have previously progressed on either abiraterone acetate or enzalutamide and who have exhibited a DNPC phenotype on biopsy. Patients will continue on the most recent next- generation AR-directed therapy they progressed on (i.e. either abiraterone acetate or enzalutamide) in order to maintain suppression of AR-signaling, and erdafitinib will be added to their regimen. Erdafitinib will be dosed at the recommended Phase II dose, and abiraterone acetate or enzalutamide will be administered at their respective FDA approved dose. Study subjects will continue on erdafitinib plus either abiraterone acetate or enzalutamide until radiographic progression or intolerable toxicity. *We hypothesize that erdafitinib in combination with a next-generation AR-directed therapy will show clinical efficacy in men with mCRPC with a DNPC phenotype who have progressed on abiraterone* acetate *or enzalutamide*

Objectives

Primary Objective: To determine the objective tumor response rate in subjects with measurable lesions as defined by RECIST v1.1 criteria in mCRPC patients with a DNPC molecular phenotype receiving either enzalutamide or abiraterone acetate in combination with erdafitinib.

Secondary Objectives

1. Determine the radiographic PFS in patients using RECIST 1.1 criteria for soft tissue metastases and Prostate Cancer Working Group 3 (PCWG3) criteria for bone metastases[2,3]
2. Determine the time to response using RECIST 1.1 criteria[2]
3. Determine the overall survival defined as the time interval from C1D1 to the date of death

4. PSA response, defined as >50% reduction in PSA compared with baseline at any point during treatment
5. Assess the incidence and severity of adverse events according to National Cancer Institute- Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

Planned Exploratory Objectives

Correlative work will be performed in order to determine biomarkers predictive of response to combination therapy. Examples of correlative work may include, but will not be limited to:

1. Immunohistochemistry (IHC) for phosphorylated FGFR and FGFR substrate 2 (FRS2) in tumor tissue
2. IHC for PSA and AR expression in tumor tissue
3. Tumor tissue transcript profiling studies to assess candidate biomarkers for response/resistance to FGFR inhibitor therapy and to evaluate core signaling program for FGF/FGFR, MAPK, and AR.
4. Next-generation sequencing of pre-treatment tumor biopsies and cell-free circulating tumor DNA (ctDNA) to identify genomic alterations correlating with response or resistance to treatment, and confirm FGFR alteration status
5. Serial blood (baseline, 12-weeks, progression) will be obtained in order to develop a blood-based gene expression response signature
6. Serum FGF ligand levels (FGF8, FGF9, FGF19) will be drawn at baseline, 12-weeks and at progression

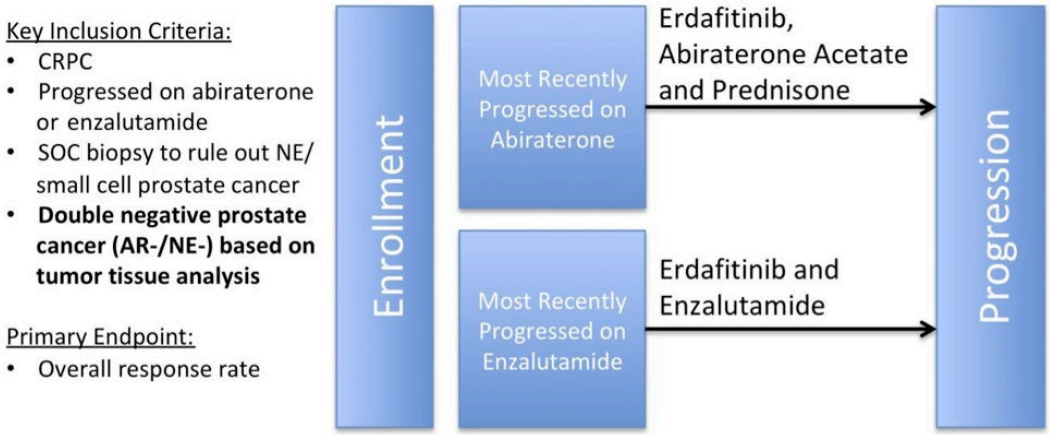
Study Design

This will be a phase II trial testing the pan-FGFR inhibitor, erdafitinib, in men with metastatic CRPC who have progressed on either abiraterone acetate or enzalutamide (Fig 6). Eligible patients must have CRPC (defined as disease progression in spite of a castrate serum testosterone [≤50 ng/dl]), and evidence of RECIST evaluable disease to enroll[2]. Given that the patient population of interest will be heavily pre-treated, and likely enriched for both small cell/NE and double negative prostate cancer, it is recommended that patients undergo a baseline metastatic biopsy prior to enrolling to rule out predominate small cell/NE variant prostate cancer. Patients with DNPC defined by IHC criteria will be eligible to enroll (see Section 9.2.1.1). Transcript profiling methods for identifying DNPC may also be accepted for determining trial eligibility at the PI's discretion. This is based on data showing that transcriptional signatures can accurately define the various prostate cancer subtypes, including DNPC[4,5]. Eligible patients must have demonstrated evidence of active progression per Prostate Cancer Working Group 3 (PCWG3) criteria while on enzalutamide or abiraterone acetate at any time prior to enrollment[3]. If not surgically castrated, participants must be maintained on an LHRH analogue (e.g. leuprolide, goserelin)

Eligible patients will continue on the next-generation AR-directed therapy they most recently progressed on (i.e. either abiraterone acetate or enzalutamide) in order to maintain suppression of AR-signaling, and erdafitinib will be added to their regimen. If a trial subject is not currently on abiraterone or enzalutamide at the time of screening, they must restart the AR-

directed therapy most recently received and demonstrate two successive PSA rises or other evidence of progression prior to starting treatment per protocol. Erdafitinib will be administered at 8 mg once daily orally, with pharmacodynamic uptitration to 9 mg if serum phosphate was below 5.5mg/dL in absence of significant toxicity on cycle 1 day 14 (see Section 6.1).
Abiraterone acetate or enzalutamide will be administered at their respective FDA approved dose (i.e. abiraterone acetate 1000 mg PO daily; enzalutamide 160 mg PO daily). Subjects continuing on abiraterone acetate will also be required to receive prednisone 5 mg PO twice daily in order to blunt mineralocorticoid symptoms associated with abiraterone acetate. Study subjects will continue on erdafitinib plus either abiraterone acetate or enzalutamide until radiographic progression, intolerable toxicity or two-years of treatment, whichever comes first.

Study Schema



Eligibility

Inclusion Criteria:

1. Patients must be ≥ 18 years of age prior to signing informed consent

2. History of histologically diagnosed prostatic adenocarcinoma

3. Participants must have evidence of castration resistant prostate cancer as evidenced by a confirmed rising PSA or radiographic progression (per Prostate Cancer Working Group 3 [PCWG3] criteria) and a castrate serum testosterone level (i.e. ≤ 50 ng/dL)[3]

4. Participants must have previously progressed on abiraterone acetate and/or enzalutamide, with PSA or radiographic progression on the most recent agent per PCWG3 criteria. If the most recent agent received was abiraterone or enzalutamide, there should be no washout prior to initiating erdafitinib per protocol[3]

5. Measurable disease as defined per RECIST v1.1 criteria[2]

6. Subjects who have progressed on only one next-generation AR-directed therapy (e.g. abiraterone, enzalutamide) and who have not received taxane chemotherapy will be required to have evidence of double-negative prostate cancer as defined by immunohistochemistry (see Section 9.2.1.1) on biopsy. A fresh metastatic biopsy within 8 weeks is preferred; however, any archival tissue showing a DNPC phenotype will be acceptable for determining eligibility. Patients who have received two prior lines of AR-directed therapy and at least one prior taxane do not require histologic confirmation of DNPC. Note: transcript profiling methods for defining DNPC may be accepted per the PI's discretion

7. ECOG performance status score $\leq$2

8. Clinical and laboratory values and cardiovascular measurements at screening:

Hematology	
Hemoglobin	$\geq$ 8 g/dL ($\geq$5 mmol/L) (must be without red blood cell [RBC] transfusion within 7 days prior to the laboratory test)
Platelets	$\geq$ 75 x 10^9/L
Absolute Neutrophil Count (ANC)	$\geq$ 1.5 x 10^9/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
Chemistry	
AST and ALT	$\leq$ 2.5 x upper limit of normal (ULN) or $\leq$ 5 x ULN for subjects with liver metastases
Creatinine clearance	$\geq$40 mL/min/1.73 m^2 based upon Modified Diet in Renal Disease formula calculation
Total bilirubin	$\leq$ 1.5 x ULN; except in subjects with congenital bilirubinemia, such as Gilbert's syndrome
Cardiovascular	
Corrected QT interal (QTcF or QTcB)	$\leq$480 msec based on the average of triplicate assessments performed approximately 5 minutes apart
ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; GFR = glomerular filtration rate; QTcB = QT corrected interval by the Bazett's formula; QTcF = QT corrected interval by the Fridericia's formula; ULN = upper limit of normal	
IF Glibert's disease is present, direct bilirubin can be measured	

9. Subjects must agree to use acceptable contraception (see Section 11.3 for requirements)

10. Must sign an informed consent form (ICF) indicated that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study

Exclusion Criteria

1. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 14 days prior to enrollment

2. Active malignancies (i.e. requiring treatment change in the last 24 months) other than malignancy under study (except skin cancers within the last 24 months that are considered completely cured)

3. Evidence of predominant small cell or neuroendocrine variant prostate cancer (see section 9.2.1.1) on most recent standard of care metastatic biopsy

4. Symptomatic central nervous system (CNS) metastases. Treated CNS metastases will be allowed if these are stable for at least 8 weeks prior to enrollment

5. Received prior FGFR inhibitor treatment or if the subject as known allergies, hypersensitivity, or intolerance to erdafitinib or its excipients

6. Current central serous retinopathy (CSR) or retinal pigment epithelial detachment of any grade

7. Has persistent phosphate level >ULN during screening (on 2 consecutive assessments at least 1 week apart, within 14 days of treatment and prior to Cycle 1 Day 1) and despite medical management

8. Has a history of current uncontrolled cardiovascular disease including:

    a. Unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes, cardiac arrest, or known congestive heart failure Class III-V within the preceding 3 months; cerebrovascular accident or transient ischemic attack within the preceding 3 months

    b. Pulmonary embolism or other VTE (venous thromboembolism) within the preceding 2 months

9. Has known active AIDS (human immunodeficiency virus (HIV) infection)

10. Hepatitis B infection as defined according to the American Society of Clinical Oncology guidelines. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status. Hepatitis C (anti-hepatitis C virus [HCV] antibody positive or HCV-RNA quantitation positive) or known to have a history of hepatitis C. If positive, further testing of quantitative levels to rule out positivity is required

11. Has not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are not clinically significant such as alopecia, skin discoloration, hot flashes, Grade 1 neuropathy, Grade 1-2 hearing loss)

12. Has impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions

13. Major surgery within 2 weeks of the first dose, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration (Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate)

14. Any serious underlying medical conditions, such as:
    a. Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection
    b. Active autoimmune or a documented history of autoimmune disease

Statistical Considerations

Sample Size Justification

Although there are no published data on ORR among patients with progressive disease on both abiraterone acetate and enzalutamide, several small studies have explored the objective response rates of abiraterone acetate following enzalutamide and *vice versa* in the post-docetaxel setting: with ORRs ranging from 3-8%[6,7]. Therefore, if we assume a historical-control ORR (H0) of 5% and an alternative hypothesis of a 25% ORR (H1), a sample size of 23 patients gives 86% power to detect a difference in ORR of the hypothesized magnitudes with a type-1 error of 3% based on an exact binomial test. We will therefore plan to enroll up to 25 patients to account for 10% dropout.

Analysis Plan

The primary objective will be to determine the ORR, which will be calculated as the percentage of patients, with 95% confidence intervals, achieving a complete response (CR) or partial response (PR) across the entire study population at any time. On the basis of an exact binomial test, 4 responses are needed to reject the null hypothesized 5% historical control ORR in favor of the alternative at a significance level of p=0.026. Secondary objectives will include determining: radiographic progression free survival (PFS) in patients using RECIST 1.1 criteria for soft tissue metastases and Prostate Cancer Working Group 3 (PCWG3) criteria for bone metastases; time to response using RECIST 1.1 criteria; overall survival (OS) defined as the time interval from C1D1 to the date of death; PSA response, defined as >50% reduction in PSA compared with baseline at any point during treatment; and the incidence and severity of adverse events according to National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[2,3]. Survival endpoints (e.g. PFS, OS) will be presented with Kaplan-Meier curves, and the median survival with 95% CI will be calculated. Rates will be reported as percentages with 95% CI. We will characterize AEs by type and grade. Safety will be summarized as the severity and frequency of a given AE.

TIME AND EVENTS SCHEDULE

	Pre-Screening[e]	Screening	Treatment Cycles						End of Treatment
Treatment Cycle	**Pre-Screening[e]**	**Screening**	**Cycle 1**		**Cycle 2**	**Cycle 3**	**Cycle 4**	**After Cycle 4**	**Discontinue**
Cycle Day	**Day -56 to 0**	**Day -30 to 0**	**Day 1 ± 7 days[f]**	**Day 14 ± 2 days**	**Day 1 ± 7 days**				**Within 14 days[g]**
Administrative Procedures									
Informed Consent		X							
Inclusion/Exclusion Criteria		X							
Demographics and Medical History		X							
Prior and Concomitant Medication Review		X	X		X	X	X	Q1C	X
Erdafitinib Dispensation			X		X	X	X	Q1C	
Clinical Assessments									
Review Adverse Events			X		X	X	X	Q1C	X
ECOG Performance Status		X	X		X	X	X	Q1C	X
Vital Signs and Weight		X	X		X	X	X	Q1C	X
Ophthalmic exam		X							
Physical Examination[a]		X	X		X	X	X	Q1C	X
EKG		X							
Laboratory Assessments									
PSA		X					X	Q3C	X
Testosterone Level		X							

	Pre-Screening[e]	Screening	Treatment Cycles						End of Treatment
Treatment Cycle	**Pre-Screening[e]**	**Screening**	**Cycle 1**		**Cycle 2**	**Cycle 3**	**Cycle 4**	**After Cycle 4**	**Discontinue**
Cycle Day	**Day -56 to 0**	**Day -30 to 0**	**Day 1 ± 7 days[f]**	**Day 14 ± 2 days**	**Day 1 ± 7 days**				**Within 14 days[g]**
Phosphate Level		X	X	X	X	X	X	Q1C	X
CBC with Differential	X	X	X		X	X	X	Q1C	X
Comprehensive Serum Chemistry Panel		X	X		X	X	X	Q1C	X
PT/INR and PTT	X	X							
Correlative Studies Blood Collection[b]			X				X		X
Research biopsy	X								X[h]
Pathologic evaluation[c]	X	X							
Radiographic assessments[d]		X					X	Q3C	X[i]

a. Full physical exam is required at screening. Subsequent physical exams may be targeted.
b. Refer to Laboratory Manual for details on correlative blood sample processing.
c. Pathologic assessment of a biopsy demonstrating DNPC at any point in the patient's treatment history is a pre-screening requirement. However, a fresh biopsy within 8 weeks of enrollment is recommended to rule out predominate small cell/NE variant prostate cancer. Research biopsy will only occur if considered safe by the treatment team.
d. Radiographic assessments should include a CT chest/abdomen/pelvis and bone scan.
e. If archival metastatic tissue previously obtained is already available and suitable for pathologic evaluation, another metastatic biopsy will not be mandated. CBC with Differential, PT/INR and PTT will only be obtained if metastatic biopsy is planned.
f. Assessments done during the screening period do not need to be repeated if within 7 days.
g. Assessments do not need to be repeated if within 7 days.
h. Research biopsy will be performed only if feasible (i.e. safe and metastatic lesion amenable to biopsy is present).
i. Radiographic assessments do not need to be repeated if within 8 weeks.

ABBREVIATIONS

ADT	Androgen Deprivation Therapy
AE	Adverse Event
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AR	Androgen Receptor
AR-V	Androgen Receptor Splice Variant
AR^{FL}	Full Length Androgen Receptor
ARV7	Androgen Receptor Splice Variant 7
BID	Twice Daily
CR	Complete Response
CRPC	Castration-Resistant Prostate Cancer
CTC	Circulating Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Cell-Free Circulating Tumor DNA
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FFPE	Formalin-Fixed Paraffin Embedded
FHCRC	Fred Hutchinson Cancer Research Center
HSPC	Hormone-sensitive Prostate Cancer
IF	Immunofluorescence
IHC	Immunohistochemistry
INR	International Normalized Ratio
IV	Intravenous
LHRH	Luteinizing Hormone-Releasing Hormone
mCRPC	Metastatic Castration-Resistant Prostate Cancer
NCI	National Cancer Institute
OTC	Over-The-Counter
PC	Prostate Cancer
PCWG	Prostate Cancer Working Group
PD	Progressive Disease
PD	Pharmacodynamic
PDX	Patient Derived Xenograft
PK	Pharmacokinetic
PO	By Mouth
PR	Partial Response
PSA	Prostate Specific Antigen
PSA_{50}	50% Decline in PSA from Baseline
PT	Prothrombin Time
Q1C	Every 1 Cycle

Q3C	Every 3 Cycles
Q3W	Every 3 weeks
qPCR	Quantitative Real-Time PCR
RNA-Seq	RNA Sequencing
SD	Stable Disease
T	Testosterone
ULN	Upper Limit of Normal
UW	University of Washington

1. INTRODUCTION

1.1. Background

Prostate cancer is the second leading cause of cancer death among American men[8]. It is primarily an androgen driven malignancy, with treatment of metastatic disease aimed at removing androgen stimulus. Since the 1940s, the backbone of treatment for men with newly diagnosed advanced prostate cancer has entailed either surgical or medical castration (i.e. androgen deprivation therapy; ADT). While ADT is initially highly effective in men with metastatic prostate cancer, resistance invariably develops, with disease progression despite castrate levels of serum testosterone (i.e. ≤50 ng/dL) signifying the emergence of a disease state known as castration resistant prostate cancer (CRPC).

Metastatic CRPC (mCRPC) remains a fatal disease despite six treatments approved by the FDA since 2004, which have been shown to extend survival[9-17]. The first of these agents to be approved was docetaxel, a semisynthetic taxane which inhibits microtubule synthesis. The landmark TAK-327 and SWOG-9916 trials reported that docetaxel had an overall survival benefit in mCRPC when compared to mitoxantrone[14,17]. Since then, a second taxane, cabazitaxel has been shown to have a survival benefit in men with mCRPC who had progressed after docetaxel treatment and was approved for use in this setting[11]. There has also been a radiopharmaceutical and an immunotherapeutic agent which have gained approval for mCRPC. Radium-223 is an alpha emitting calcium mimetic which prolongs survival in men with mCRPC that is predominately metastatic to the bones[13]. Sipuleucel-T is an immunotherapy in which autologous peripheral blood monocytes (PBMCs) are activated by a recombinant fusion protein consisting of the prostate antigen prostatic acid phosphatase fused to granulocyte-macrophage colony-stimulating factor[12].

The observation that AR regulated genes (e.g. PSA) remain expressed in a castrate state led to the further exploration of the AR-signaling axis as a therapeutic target in men with mCRPC and have resulted in the development of effective new AR-directed agents like abiraterone acetate and enzalutamide. Both of these drugs inhibit AR-signaling in men with mCRPC through disrupting the ligand-AR interaction (abiraterone acetate through ligand depletion and enzalutamide through receptor antagonism)[9,10,15] These agents are unfortunately not curative, however, and resistance typically occurs within 1-2 years. In addition, given the considerable mechanistic overlap between abiraterone acetate and enzalutamide, it is not surprising that clinical evidence of cross-resistance between these agents has begun to emerge[6,7] Recent work by our group has shown that in the face of chronic AR-signaling inhibition, a subset of these patients will develop androgen pathway-independent prostate cancer (APIPC) – a molecular prostate cancer subset defined by no AR-signaling activity and the absence of neuroendocrine features (i.e. double negative prostate cancer; DNPC)[1].

Mechanistic studies have revealed that MAPK-signaling, which is activated by the fibroblast growth factor (FGF)/FGF receptor (FGFR) pathway, is an important AR bypass mechanism in men with DNPC. Importantly, targeting FGF/FGFR-signaling with pan-FGFR inhibitors results in significant tumor growth inhibition in both engineered APIPC cells and DNPC patient derived xenograft (PDX) models[1]. In contrast to other malignancies (e.g. bladder and lung cancer), patients with DNPC usually do not harbor genomic alterations in FGFR, and over-activation of

FGF/FGFR-signaling is primarily driven by autocrine/paracrine activation of this pathway. In total, this data demonstrates that FGF/FGFR-signaling is a critical driver of late stage mCRPC and supports our hypothesis that the pan-FGFR inhibitor erdafitinib in combination with abiraterone acetate or enzalutamide will be effective in men with multi-drug resistance mCRPC.

1.2. Double Negative Prostate Cancer

Despite multiple effective therapies, mCRPC remains an invariably fatal disease with resistance to currently available therapies occurring in 1-2 years in most cases. Various pathways to resistance have been described, many of which still rely on the androgen axis[18]. Recent work, however, has demonstrated that a subset of these cancers become completely independent of AR-signaling, without expressing classic neuroendocrine (NE) or small cell markers (e.g. synaptophysin) – a disease state herein referred to as double negative prostate cancer (DNPC) or androgen pathway independent prostate cancer (APIPC). Additional work has shown that DNPC, as well as other prostate cancer subtypes (e.g. AR+/NE-, AR-/NE+ and AR+/NE+) are associated with reproducible transcriptional profiles, which accurately define these molecular subtypes[4,5]. The emergence of DNPCs has become more prevalent with the widespread use of the next-generation AR-signaling inhibitors abiraterone acetate and enzalutamide. As an example, there has been a shift toward more tumors demonstrating a DNPC phenotype following the approval of abiraterone acetate in 2011 compared to the pre-abiraterone acetate era, and data from our rapid autopsy program has shown that 23.3% of mCRPC patients will die with DNPC compared to only 5% prior to 2011[1].

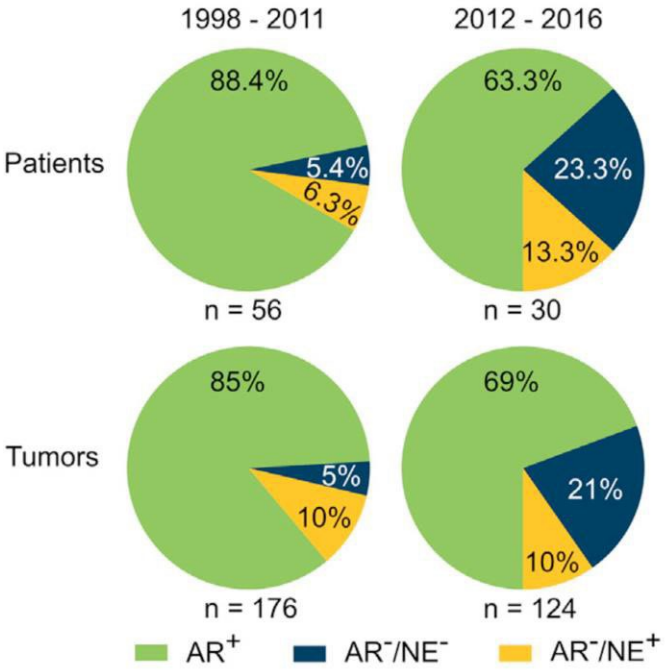


Figure 1. The incidence of AR-null/NE-null prostate cancers has increased since approval of abiraterone acetate in 2011.

Given that nearly 1/4 mCRPC patients will die of DNPC – a clinical state with no proven therapies – new therapeutic approaches for these men are sorely needed. In order to study the molecular drivers of DNPC, our group created an AR-null/NE-null engineered cell-line model from parental LNCaP cells (Fig 2)[1]. LNCaP prostate cancer cells were transduced with an

inducible anti-AR short hairpin RNA (shRNA) as well as an androgen response element-driven suicide gene (LNCaP$^{shAR/pATK}$). LNCaP$^{shAR/pATK}$ cells were then subjected to increasingly severe AR pathway suppression. After 2 weeks of androgen deprivation in charcoal stripped serum(CSS), medium was supplemented with 1 mg/mL doxycycline (Dox) to induce the anti-AR shRNA, which produced >99% cell death. After 5 months, a residual population of viable cells remained. This colony was treated with a 2-week course of ganciclovir to eliminate cells expressing functional AR. Surviving cells were designated LNCaP-AR Program-Independent Prostate Cancer (LNCaP^{APIPC}).

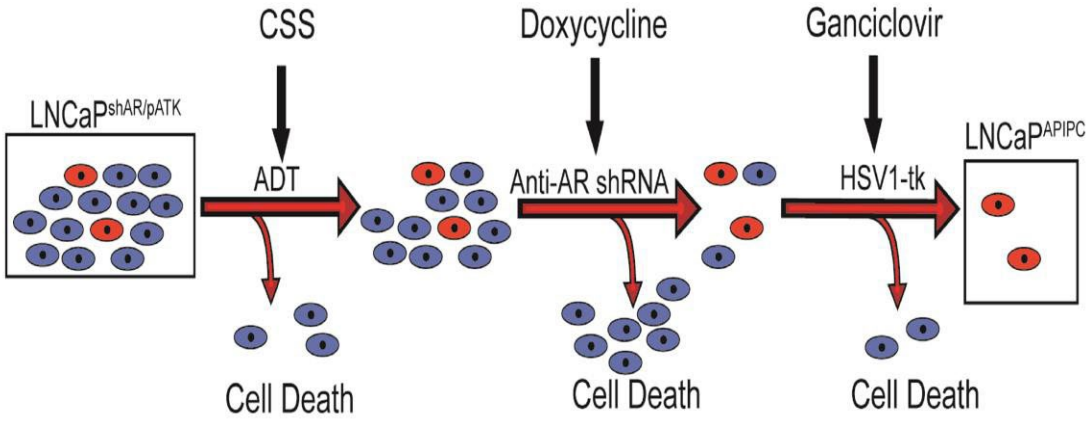


Figure 2. Development of a cellular model of APIPC. LNCaP cells with a doxycycline (Dox)-inducible shRNA targeting the AR (shAR) and an androgen-driven thymidine kinase gene (pATK) were depleted of androgens using ADT then treated with Dox to induce the AR-directed shRNA, then treated with ganciclovir to eliminate cells with AR-driven thymidine kinase expression.

AR and PSA were nearly undetectable in LNCaP^{APIPC} and transcripts comprising an AR activity signature were substantially decreased compared to the parental cell line (Fig 3A). Likewise, there was no AR or PSA protein expression in LNCaP^{APIPC} grown *in vivo* as subcutaneous xenografts[24]. Importantly, NE-associated genes were not upregulated in LNCaP^{APIPC} cells grown with or without androgen supplementation (Fig 3B). Furthermore, LNCaP$^{shAR/pATK}$ and LNCaP^{APIPC} grown as murine xenografts do not express the NE markers chromogranin or synaptophysin. Studies examining the drivers of LNCaP^{APIPC} cell growth found that an autocrine FGF signaling program is likely activated in LNCaP^{APIPC} in the absence of AR to maintain cell survival and growth via MAPK (Fig 3C and D). Importantly, RNA-seq data from our rapid autopsy program demonstrates that DNPC patients have a similar transcriptional program to our LNCaP^{APIPC} model, with overexpression of FGF ligands, FGF receptors and genes comprising the MEK/ERK activity signature[1].

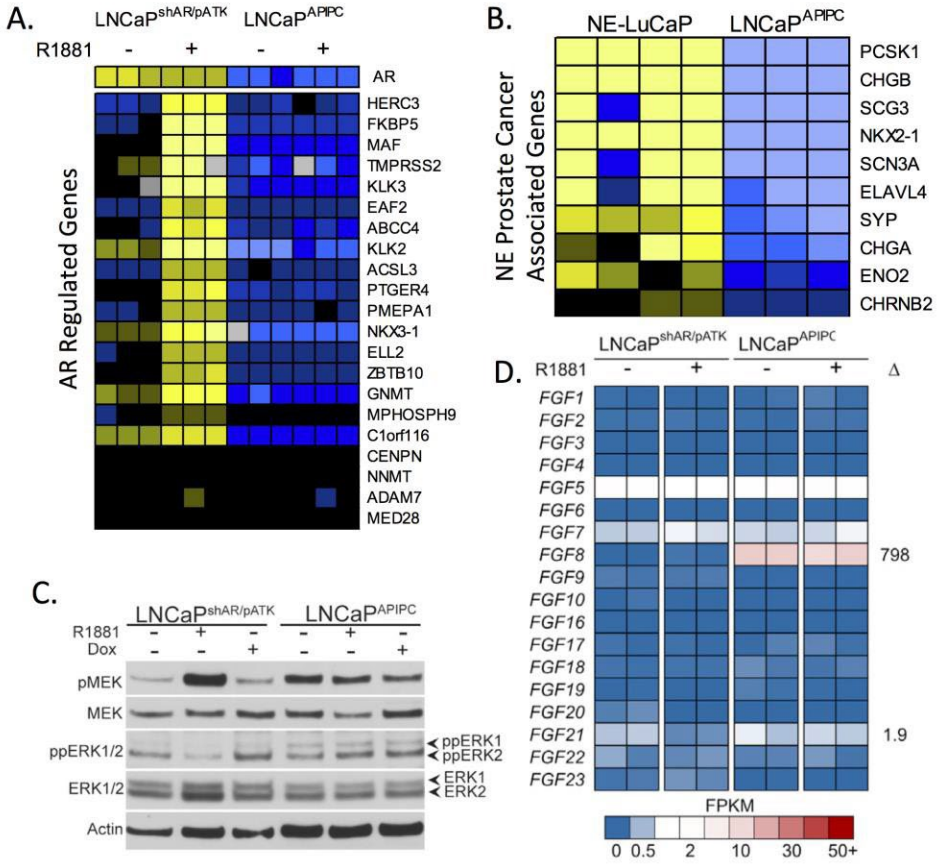


Figure 3. LNCaP^{APIPC} cells demonstrate an AR-null/NE-null transcriptional program, with activation of MAPK signaling and overexpression of FGF8. **A.** LNCaP^{APIPC} demonstrate differential expression of AR regulated genes compared to LNCaP$^{shAR/pATK}$. **B.** LNCaP^{APIPC} dp not demonstrate expression of NE prostate cancer genes. NE-LuCaP PDX gene expression is provided for reference. **C.** Phosphorylated MEK and dually phosphorylated ERK1/2 (ppERK1/2) are elevated in LNCaP^{APIPC} compared with LNCaP$^{shAR/pATK}$. **D.** FGF8 is overexpressed in LNCaP^{APIPC} compared to LNCaP$^{shAR/pATK}$.

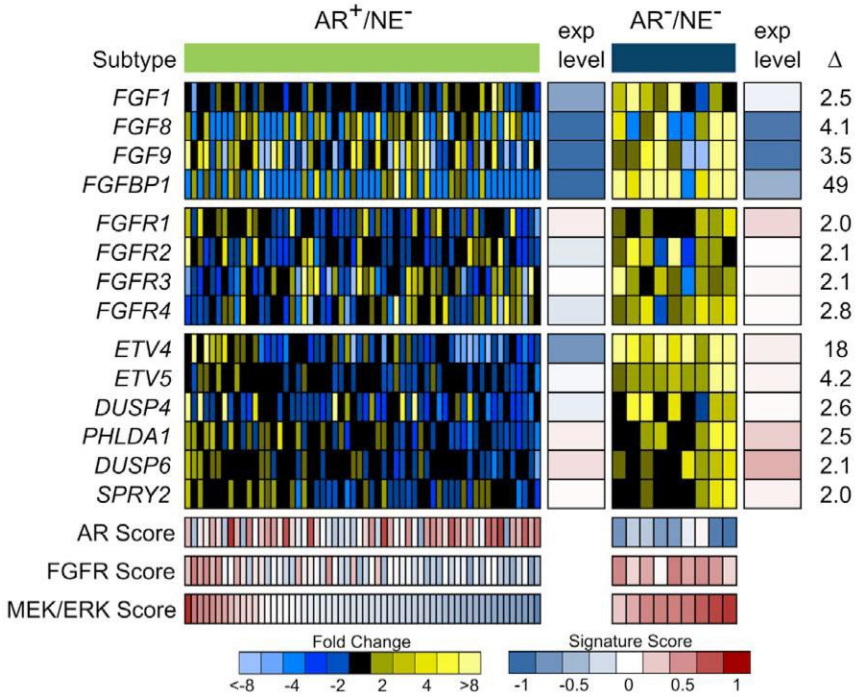


Figure 4. Expression of FGF ligands, FGF receptors, and genes comprising an MEK/ERK activity signature. Relative ratios of RNA-seq transcript abundances are shown, along with mean FPKM values and signature scores (AR+/NE , n = 58 tumors from 35 men; AR /NE , n = 9 tumors from 5 men).

To demonstrate that FGF8 was sufficient to promote the growth of cells cultured under total AR pathway suppression, we treated parental LNCaP$^{shAR/pATK}$ grown in androgen-deprived conditions with Dox to suppress AR expression, and added FGF8b[1]. FGF8b maintained cell proliferation during AR pathway ablation (Fig 5A). Of note, the addition of the FGFR antagonist, PD173074, to cells treated with Dox and FGF8 was growth inhibitory. LNCaP^{APIPC} murine xenografts were also inhibited by PD173074 (Fig 5B). We also tested whether FGFR inhibition was an effective strategy in a patient derived xenograft (PDX) model of DNPC, the LuCaP 173.2 model, and found that treatment with the FGFR antagonist CH-5183284 did indeed result in significant growth inhibition (Fig 5C). Finally, we compared the growth inhibitory effects of erdafitinib (a potent pan-FGFR inhibitor) vs. CH-5183284 in LNCaP^{APIPC} cells grown in androgen-deprived culture conditions and found that erdafitinib was a more potent inhibitor of LNCaP^{APIPC} growth. These data indicate that pharmacologic inhibition of FGFR activity is likely to be effective in men with DNPC.

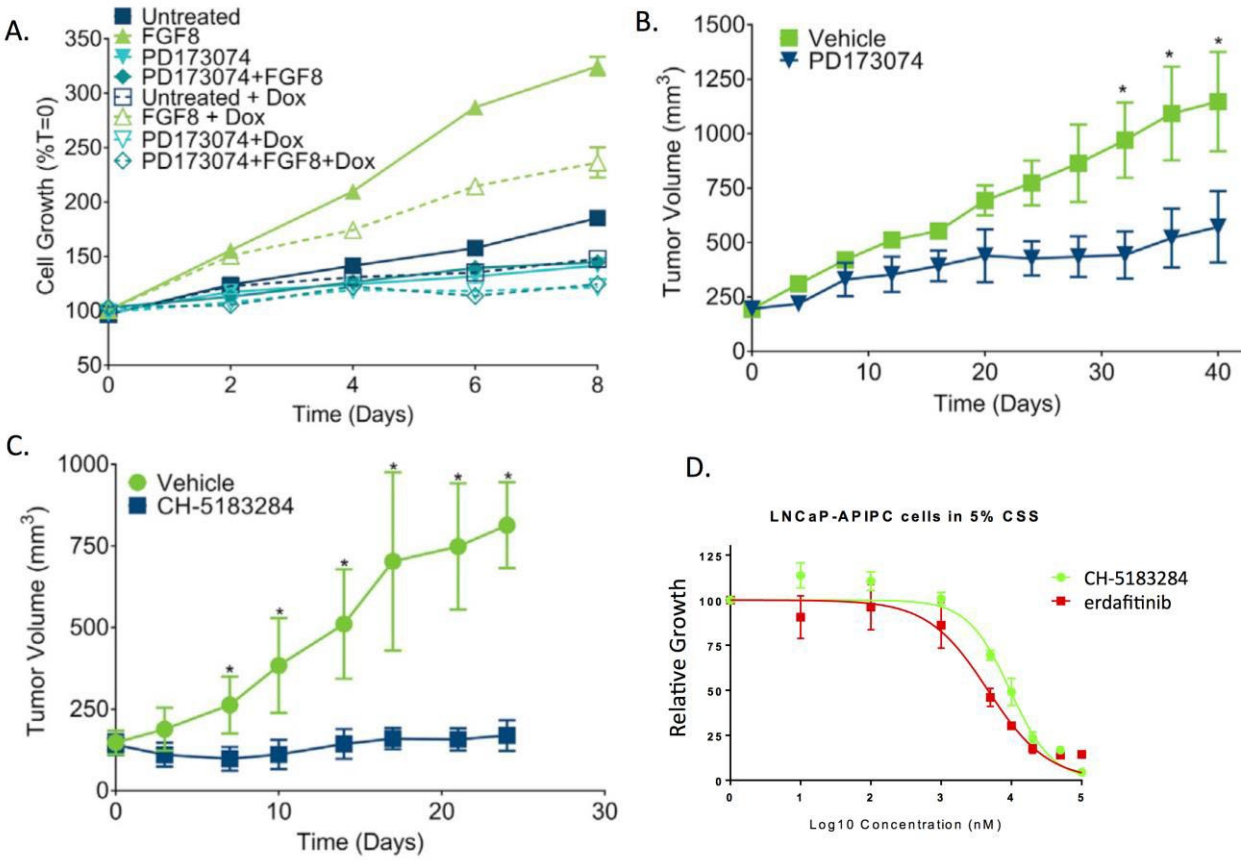


Fig 5. FGF signaling can rescue prostate cancer cell growth following AR-signaling ablation and targeting the FGF receptor is effective in DNPC models. **A.** LNCaP$^{shAR/pATK}$ cells were cultured in androgen-depleted medium ±25 ng/mL FGF8, ±1 mM PD173074 (FGFR inhibitor), and ±1 mg/mL Dox. Solidlines, no Dox; dotted lines, with Dox. Cell number was determined using Cyquant, and values were normalized to day 0. Note: Addition of Dox results in AR knockdown via an inducible AR shRNA (see Fig 2). **B.** LNCaP^{APIPC} cells were inoculated subcutaneously in castrate SCID mice receiving Dox-supplemented feed. When tumors reached 200 mm3 in size, treatment was initiated with the FGFR antagonist PD173074 or vehicle control. Tumor volumes were measured every 2 days (n = 5). *p < 0.01. **C.** LuCaP173.2 tumors were implanted subcutaneously in castrate SCID mice. When tumors reached 200 mm3 in size, treatment was initiated with the FGFR antagonist CH-5183284 or vehicle control. Tumor volumes were measured every 2 days (n = 15). *p < 0.01. **D.** LNCaP$^{shAR/pATK}$ cells were cultured in androgen-depleted medium with either erdafitinib or CH-5183284. Cell growth was significantly (P<0.05) inhibited with erdafitinib compared to CH-5183284.

More recent data has broadly implicated a FGFR signaling as a key mediator of lineage plasticity, which typically accompanies resistance to AR-signaling inhibitors and occurs increasingly in late stage prostate cancer[19,20]. This work has shown that erdafitinib may also be able to reprogram CRPC toward a more differentiated phenotype. Indeed, additional unpublished work from our group has demonstrated that FGFR inhibition may exert an anti-tumor effect across a variety of prostate cancer phenotypes (Figure 6). These data support using erdafitinib more broadly iin the treatment of late stage prostate cancer. In addition, we have observed marked phenotypic heterogeneity in men with late stage prostate cancer, indicating that metastatic biopsies targeting a single lesion may fail to appreciate lineage plasticity at other sites of disease and/or emergence of DNPC phenotypes[20-22].

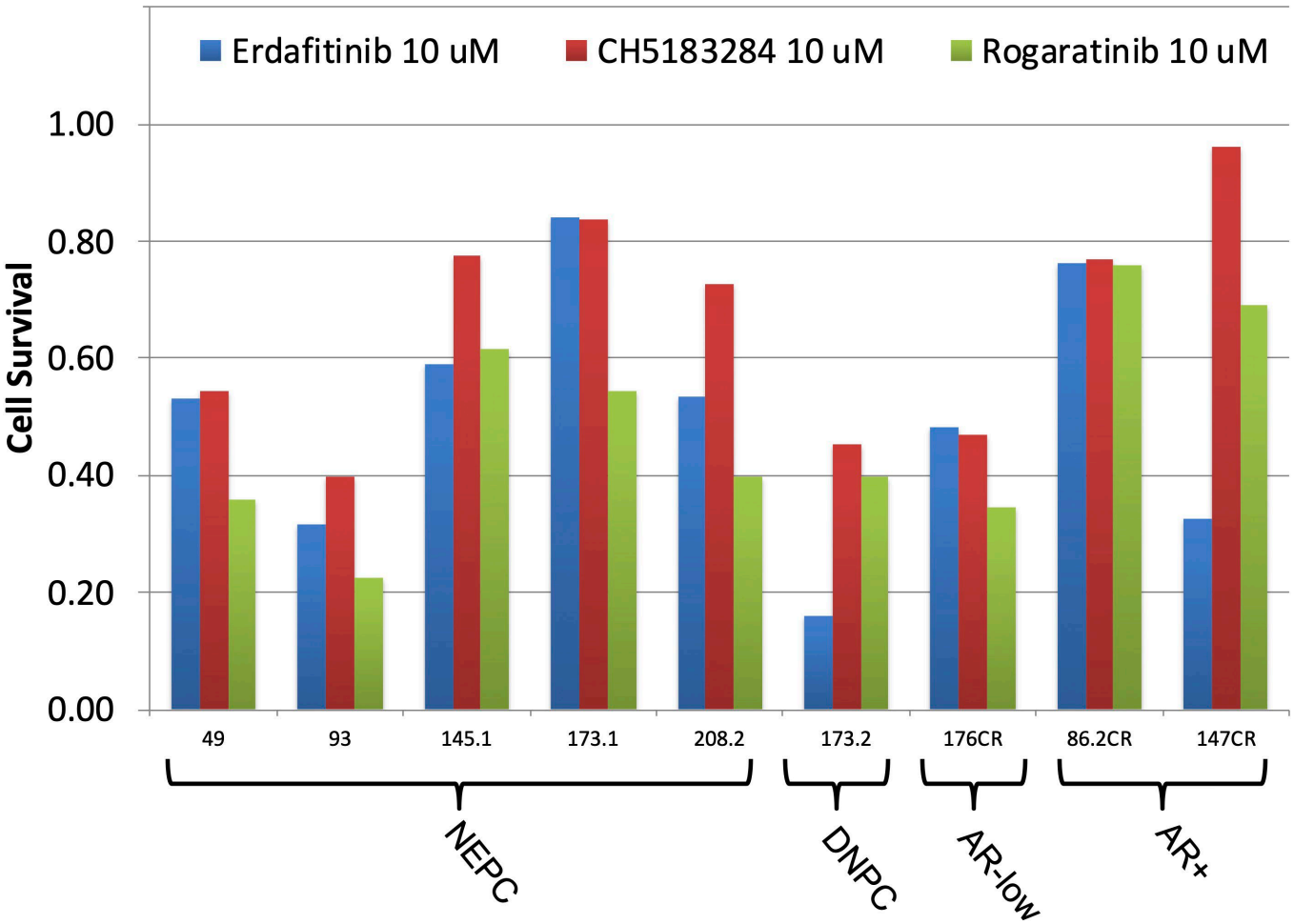


Figure 6. Response to FGFRi in LuCaP PDX cells. Tumors were dissociated and then cells were treated for 3-days in vitro. Viability was assessed by CellTitre Glo. Neuroendocrine (NEPC), DNPC, AR-low and AR+ PDX cell survival data is provided

1.3. Fibroblast Growth Factor Receptors and Erdafitinib

1.3.1. Fibroblast Growth Factor Receptors

The family of fibroblast growth factor receptors (FGFRs) consists of four highly conserved transmembrane receptors tyrosine kinases, namely FGFR1 to 4 and a 5th receptor, which lacks the intracellular kinase domain (FGFR5, also known as FGFRL1). Together, these receptors are able to bind to over 20 different fibroblast growth factor (FGF) ligands. FGFR signaling has been shown to be enhanced by genetic alterations such as gene amplification, mutation or chromosomal translocation, thereby affecting various cellular mechanisms such as angiogenesis, anti-apoptosis, cell migration and proliferation in a variety of cancer entities.

1.3.2. Erdafitinib

Erdafitinib is a highly selective and potent oral pan-FGFR tyrosine kinase inhibitor with high affinity and low nanomolar inhibitory activity for all FGFR family members, FGFR 1, 2, 3 and 4. In FGFR pathway activated cancer cell lines, the concentration required for 50% inhibition (IC_{50}) is in the low nanomolar range 0.1 to 129.2 nM. It has demonstrated activity in FGFR pathway-activated cancer cell lines including squamous non-small cell lung cancer (NSCLC), gastric, breast, hepatocellular cancer (HCC), endometrial, bladder, multiple myeloma, and acute myeloid leukemia. Non-FGFR driven cell lines require significantly higher drug concentration for inhibition of cell proliferation to be observed. Target inhibition and pathway modulation have been demonstrated in cellular models at active cellular concentrations. Brief exposure to erdafitinib has been demonstrated to result in long-term target inhibition. Erdafitinib has been shown to have in vivo antitumor activity in mouse xenograft models of FGFR-driven gastric, bladder, and squamous NSCLC tumor models, and in patient-derived xenografts from squamous NSCLC, gastric, breast, and hepatocellular tumors.

In humans, absorption of erdafitinib was estimated to be near complete. Following single and multiple once-daily administration, erdafitinib exposure (Cmax and AUC) increased in a dose-proportional manner across the dose range of 0.5 to 12 mg. Multiple dose erdafitinib PK was time independent and steady state was achieved after 2 weeks of daily administration. With a once daily dose regimen, mean (coefficient of variation [CV%]) steady state accumulation ratio for AUC from time 0 to 24 hours after daily dosing (AUC_{τ}) was 4.07 (32.0%), corresponding to a mean effective half-life (t1/2) of 58.9 hours.

For the most comprehensive nonclinical and clinical information regarding erdafitinib, refer to the latest version of the Investigator's Brochure and Addenda for erdafitinib (Erdafitinib IB).

1.3.2.1. Erdafitinib Efficacy

Study BLC2001:

This is an ongoing Phase 2, multicenter, open-label study to evaluate the efficacy and safety of single- agent erdafitinib in subjects with advanced ie, metastatic or surgically unresectable urothelial carcinoma and whose tumors had certain FGFR genetic alterations.

Key efficacy results are based on response for the 87 chemo-relapsed/refractory subjects in the 8-mg daily regimen. Responses were assessed using Response Evaluation Criteria in Solid Tumors (RECIST), (version 1.1). Investigator assessed response indicated that the primary objective had been met (objective response rate [ORR] of 40% and the lower bound of the 95% CI exceeding 25%). IRRC assessment of response for subjects treated in the 8-mg daily regimen was comparable to that reported by investigator. Responses were rapid and durable, with a median time to first response of 1.41 months and median duration of response (DOR) of 5.98 months. An estimated 30% of responders had response for more than 1 year. Median progression-free survival (PFS) was 5.52 months, with a median follow up of 11.2 months. Median overall survival (OS) was 13.8 months and the 12-month survival rate was 53%.

Study EDI1001:

This was a Phase 1, first-in-human, open label, multicenter, 4-part, dose escalation study to explore the safety, PK, and pharmacodynamics (PD) of erdafitinib administered orally to adult subjects with advanced or refractory solid malignancies or lymphoma.

Of the 187 subjects treated in this study, 30 subjects had urothelial carcinoma. The 10 subjects treated with erdafitinib 9 mg once daily who responded to treatment with erdafitinib all carried mutations or translocations in FGFR. The ORR for response-evaluable urothelial subjects with FGFR mutations or translocations was 70.0% which included 7 subjects with PR.

All 9 subjects with cholangiocarcinoma carried mutations or translocations of FGFR. The ORR for response-evaluable subjects with cholangiocarcinoma was 27.3%; 3 subjects achieved PR.

Study HCC1001:

Study HCC1001 is an open-label, multicenter, 2-part, Phase 1/2a study to evaluate the safety, PK, PD, and clinical responses of erdafitinib administered orally to Asian subjects ≥18 years of age and with advanced HCC.

Of the 53 subjects treated, 52 subjects with advanced HCC were evaluable for response. The best response to treatment was PR, for 2 subjects in the 10-mg intermittent group. The ORR was 3.8% for all response-evaluable subjects, and 4.8% for 42 response-evaluable subjects with FGF19 amplification. This low response rate led to the discontinuation of recruitment to the study.

Study LUC1001:

Study LUC2001 is an open-label, multicenter, phase 2a clinical study to evaluate the clinical efficacy, safety, and PK of erdafitinib in Asian subjects with selected FGFR translocations or mutations, RET activating mutations or translocations, or other evidence of FGFR pathway activation.

Of the 24 subjects treated, 23 subjects were evaluable for response. The ORR was 26.1%; 6 subjects had a PR. For the 11 subjects with cholangiocarcinoma, all of whom were treated with 8-mg daily and who had an FGFR2 mutation of translocation, 5 subjects had a confirmed PR, for an ORR of 45.5% and 9 subjects had at least SD, for a disease control rate (DCR) of 81.8%.

1.3.2.2. Erdafitinib Safety

In pooled analyses for subjects who received erdafitinib doses of 8 or 9 mg once daily in Studies EDI1001, BLC2001, and GAC1001, all 164 subjects experienced at least 1 adverse event (AE). The most frequently reported adverse events were hyperphosphatemia (81.7%), stomatitis (56.1%), dry mouth (45.7%), diarrhea (41.5%), decreased appetite (37.8%), constipation (35.4%), dysgeusia (35.4%), and dry skin (31.7%). Grade 3 or higher treatment-emergent adverse events (TEAEs) were reported for 66.5% of subjects. The most frequently reported Grade 3 or worse AEs were stomatitis (10.4%), hyponatremia (9.8%), asthenia (6.1%), anemia (5.5%), fatigue (4.3%), and dyspnea (3.7%). Serious adverse events (SAE) were reported for 40.9% of subjects. Thirty subjects (18.3%) had TEAEs that resulted in discontinuation of treatment. A total of 11 subjects

(6.7%) had AEs that were fatal and included general physical health deterioration (2.4%) and asthenia (1.2%) in the context of disease progression. None of the fatal AEs were considered drug-related.

Central serous retinopathy (CSR; inclusive of chorioretinopathy, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, retinal detachment, retinal edema, retinopathy, and vitreous detachment) is an adverse event of special interest. Adverse events of clinical importance include other eye disorders (excluding CSR), skin and nail changes, hyperphosphatemia, and arrhythmias. Adverse drug reactions include hyperphosphatemia, nail disorders, skin disorders, palmar-plantar erythrodysesthesia syndrome (PPES), and central serous retinopathy.

1.4. Enzalutamide

Enzalutamide works through competitive AR inhibition and, unlike the older anti-androgens (e.g. bicalutamide, nilutamide), is a pure AR antagonist. It additionally has the ability to prevent AR nuclear translocation and DNA binding to nuclear response elements[23]. It was approved in 2012 for men with mCRPC post-docetaxel[16] It has also gained approval for men who are docetaxel-naïve given that a recently completed Phase III study showed OS improvements in a pre-chemotherapy population as well[9] In that patient population enzalutamide was shown to result in a 37% reduced risk of death compared to placebo (HR 0.63, 95% CI, 0.53-0.75; P<0.001)[9].

Enzalutamide was initially tested in a Phase I/II dose escalation trial[24]. In that study enzalutamide was tested at doses ranging from 30 mg to 600 mg by mouth daily. It was found to exert an antitumor effect at all doses tested, with a PSA response rate (i.e. ≥50% PSA declines) in 78 out of 140 enrolled subjects (56%). Fatigue was the most common adverse event (AE) and generally occurred following 30-days of treatment. At doses ≥240 mg daily, an increasing proportion of patients required dose reductions secondary to fatigue. Overall grade 3-4 AEs included: fatigue (11%), anemia (3%), arthralgia (2%), asthenia (2%) and seizures (2%). Overall mild (i.e. grade 2) AEs included: fatigue (27.1%), nausea (8.6%), dyspnea (7.9%), anorexia (5.7%) and back pain (5.7%). Two witnessed seizures and one questionable seizure occurred in patients receiving doses of 600 mg, 360 mg and 480 mg, respectively. Only 1/87 patients treated at a daily dose of ≤240 mg discontinued treatment for an AE, compared to 7/53 at doses ≥360 mg. While 240 mg daily was deemed the maximum tolerated dose, it was noted that extent and proportion of patients achieving PSA decreases plateaued somewhere between 150 mg and 240 mg daily. As such, enzalutamide 160 mg by mouth daily was ultimately selected for further investigation.

On the basis of the aforementioned Phase I/II results, the AFFIRM trial, a large randomized Phase III study powered to detect differences in survival, was launched[16] This enrolled men with CRPC who had already progressed on docetaxel. Subjects were randomized 2:1 between enzalutamide 160 mg daily (N=800) and placebo (N=399). This study met its primary endpoint, demonstrating a median OS of 18.4 months with enzalutamide compared to 13.6 months with placebo (HR for death, 0.63; 95% CI, 0.53 to 0.75; P<0.001). The rate of AEs between enzalutamide and placebo were similar. Enzalutamide had a lower rate of grade 3 or higher AEs compared to placebo (45.3% vs 53.1%, respectively). Rates of fatigue, diarrhea and hot flashes

were higher with enzalutamide (Table 1). There were notably 5 patients (0.6%) that experienced a seizure in the enzalutamide arm compared to zero in the placebo arm. One of these seizure required medical intervention, the others were self-limited. Predisposing factors were present in several patients, and included: two subjects with brain metastases, one subject inadvertently received IV lidocaine prior to the seizure and one subject had brain atrophy and a history of heavy alcohol use. The results from this study ultimately lead to the approval of enzalutamide in men with CRPC who had already received prior docetaxel.

More recently, the results of another randomized Phase III study, the PREVAIL trial, were released[9] This study randomized men with CRPC who were docetaxel naïve between enzalutamide 160 mg daily (N=871) and placebo (N=844). As was the case with AFFIRM, the PREVAIL trial demonstrated an OS advantage with enzalutamide. The median OS improved from 30.2 months to 32.4 months with enzalutamide treatment (HR for death, 0.706; 95% CI, 0.60 to 0.84; P<0.0001). While improvement in survival is modest, it should be noted that those in the placebo group received other proven prostate cancer therapies at a higher rate than those on the enzalutamide arm (e.g. 32.8% vs 56.7% received docetaxel and 20.5% vs 45.6% received abiraterone acetate). AEs occurred at comparable rates between the enzalutamide and placebo arms.

Refer to Enzalutamide's FDA label for additional pharmacology and clinical data.

Adverse Event	PREVAIL				AFFIRM			
	Enzalutamide (N=871)		Placebo (N=844)		Enzalutamide (N=800)		Placebo (N=399)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)	All Grades	Grade 3-4	All Grades	Grade 3-4
Fatigue	35.6	1.8	25.8	1.9	34	6	29	7
Back pain	27	2.5	22.2	3				
Constipation	22.2	0.5	17.2	0.4				
Diarrhea					21	1	18	0.3
Hot flashes					20	0	10	0
Arthralgias / musculoskeletal pain	20.3	1.4	16	1.1	14	1	10	0.3
Headache					12	0.8	6	0
Cardiac event/disorder	10.1	2.8	7.8	2.1	6.3	1.1	8	2.5
Hypertension	13.4	6.8	4.1	2.3	6.6		3.3	
Abnormal liver function testing	0.9	0.2	0.6	0.1	1	0.4	2	0.8
Seizure	0	0	0.1	0	0.6	0.6	0	0

Table 1: Adverse events associated with enzalutamide. Data from the AFFIRM and PREVAIL trials[9,16]

1.5. Abiraterone Acetate

Developed through rational design based on a parent pregnenolone structure, abiraterone acetate functions through inhibition of cytochrome P450-17 (CYP-17), a key family of enzymes involved in gonadal, adrenal and intratumoral androgen synthesis[25-27] When given in conjunction with a GnRH analogue, it has the ability to rapidly drive castrate level testosterone (i.e. <20-50 ng/dL) to undetectable[28,29] Unlike ketoconazole, another CYP-17 inhibitor used in the CRPC setting, abiraterone acetate is highly specific for the CYP-17 family of enzymes, making it generally better tolerated than ketoconazole[27,29,30]. It can lead to mineralocorticoid excess, however, through a compensatory elevation in adrenocorticotropic hormone (ACTH) that occurs in response to depressed cortisol levels. When prednisone is co-administered with abiraterone acetate, mineralocorticoid associated side effects (e.g. fluid retention, hypokalemia and hypertension) are mostly prevented, although these are observed more frequently in those receiving abiraterone acetate compared to placebo[10,15,31] Abiraterone acetate is currently FDA approved for the treatment of CRPC in patients who are either pre-

or post-docetaxel.

Two dose escalation Phase I studies were completed utilizing abiraterone acetate[28,32]. Neither study documented dose-limiting toxicities, however, side effects of note included: hypertension (12-29%), hypokalemia (24-48%) and peripheral edema (5-24%). This side effect profile was felt most likely to be a result of mineralocorticoid excess secondary to a compensatory elevation in ACTH occurring in the context of partially blocking adrenal steroid synthesis. These side effects were managed with eplerenone, beta-blockers, diuretics and/or corticosteroids. Furthermore, these studies provided preliminary evidence for abiraterone acetate's efficacy in men with chemotherapy naïve CRPC.

A subsequent Phase II study evaluated abiraterone acetate in men with CRPC post-docetaxel treatment[33]. This study incorporated prednisone 5 mg twice daily into the treatment regimen in an effort to mitigate the aforementioned mineralocorticoid associated side effects. At a dose of 1000 mg daily, abiraterone acetate was found to produce PSA declines of at least 50% in 22/58 (36%) men. Partial responses by Response Evaluation Criteria in Solid Tumors (RECIST) criteria were seen in 4/22 (18%) patients with evaluable tumors. Importantly, no significant hypertension or hypokalemia was noted – likely due to the co-administration of prednisone.

Proof of principle that further androgen suppression is effective in controlling CRPC was provided for in the landmark Phase III COU-AA-301 trial. In that study it was demonstrated that abiraterone acetate, when given to men with CRPC previously treated with docetaxel, resulted in a significant reduction in the risk of death compared to placebo (HR 0.65, 95% CI, 0.54-0.77; $P<0.001$)[10]. Subsequently the COU-AA-302 trial demonstrated similar efficacy in men with CRPC pre-docetaxel (HR 0.79, 95% CI, 0.66-0.96; $P < .0151$)[15]. These two trials demonstrated a higher incidence of mineralocorticoid associated side effects in spite of the co-administration of prednisone. Hypokalemia, peripheral edema and hypertension occurred at approximate rates of 17%, 28-31% and 10-22% in the abiraterone acetate cohorts respectively. Other adverse events observed were generally low grade. Of note there did appear to be higher rates of fatigue, arthralgias, aminotransferase abnormalities and non-fatal cardiac events with abiraterone acetate. Overall, abiraterone acetate was felt to be generally well tolerated, however. A summary of the adverse events observed in these two Phase III trials are listed in Table 1. Ultimately, on the basis of the COU-AA-301 and COU-AA-302 trials abiraterone acetate was approved in the post- and pre-docetaxel setting respectively.

Adverse Event	COU-AA-301				COU-AA-302			
	Abiraterone acetate + Prednisone (n=791)		Placebo + Prednisone (n=394)		Abiraterone acetate + Prednisone (n=542)		Placebo + Prednisone (n=540)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Anemia	23	7.5	26	7.4	-	-	-	-
Thrombocytopenia	4	1.4	3	0.5	-	-	-	-
Neutropenia	1	0.1	0.3	0.3	-	-	-	-
Febrile neutropenia	0	0	0	0	-	-	-	-
Diarrhea	18	0.6	53	1.3	22		18	
Fatigue	44	8.3	169	9.9	39		34	
Asthenia	13	2.3	52	2	-	-	-	-
Back pain	30	5.9	129	9.6	32		32	
Nausea	30	1.6	124	2.5	-	-	-	-
Vomiting	21	1.8	97	2.8	-	-	-	-
Hematuria	8	1.4	31	2.3	-	-	-	-
Abdominal pain	12	2	44	1.5	-	-	-	-
Pain in arm or leg	17	2.4	79	5	17		16	
Dyspnea	13	1.3	46	2.3	-	-	-	-
Constipation	26	1	120	1	23		19	
Pyrexia	9	0.4	35	1.3	-	-	-	-
Arthralgia	27	4.2	89	4.1	28		24	
Urinary tract infection	12	2.1	28	0.5	-	-	-	-
Pain	2	0.6	19	1.8	-	-	-	-
Bone pain	25	5.6	110	7.4	20		19	
Fluid retention or edema	31	2.3	88	1	28	0.7	24	2
Hypokalemia	17	3.8	33	0.8	17	2	13	2
Cardiac disorder*	13	4.1	42	2.3	19	6	16	3
Liver-function test abnormalities or Hepatotoxicity	10	3.4	32	3	4.2	8	9.8	3

Hypertension	10	1.3	31	0.3	-	-	-	-
Hot flush	-	-	-	-	22		18	
Muscle spasm	-	-	-	-	14		20	
Cough	-	-	-	-	17		14	

Table 2: Adverse events observed on the COU-AA-301[10] and COU-AA-302[34] trials.
*Cardiac disorders included: ischemic heart disease, myocardial infarction, supraventricular tachyarrhythmias, ventricular tachyarrhythmias, cardiac failure and possible arrhythmia-related tests, signs and symptoms

Abiraterone acetate plus the GnRH agonist leuprolide have also been tested in the neoadjuvant setting. Taplin and colleagues recently reported on the results of a randomized Phase II study[35] In that trial men were randomized between 24 weeks of neoadjuvant GnRH agonist plus 12 weeks of abiraterone acetate (N=28) and 24 weeks of both neoadjuvant GnRH plue abiraterone acetate (N=30). That trial demonstrated a negative margin rate of 90% and pCR rate of 10% in the cohort receiving 24 weeks of both leuprolide and abiraterone acetate, with an additional 14% of patients achieving a near pCR (defined as ≤5 mm residual tumor). The cohort receiving 24 weeks of GnRH agonist and 12 weeks of abiraterone acetate achieved a negative margin rate of 81%, a pCR rate of 4% and a near pCR rate of 0%. Differences in pathologic outcomes between cohorts were not statistically significant; although, the trial was not powered to detect these differences.

1.6. Overall Rationale for the Study

Many of the treatments for mCRPC are directed at suppressing the AR-signaling axis. While AR-directed therapies are initially effective, resistance inevitability occurs. The continued lethality of this disease underscores the importance of testing therapeutics aimed at alternate pathways. As outlined above, mechanistic studies have revealed that MAPK-signaling, which is activated by FGF/FGFR signaling, is an important AR bypass mechanism in men with late stage, DNPC. Importantly, targeting FGF/FGFR-signaling with pan-FGFR inhibitors results in significant tumor growth inhibition in both engineered LNCaP^{APIPC} cells and DNPC LuCaP 173.2 PDX models[1]. It is important to note that unlike other malignancies (e.g. bladder and lung cancer), patients with a DNPC phenotype usually do not harbor genomic alterations in FGFR, and over-activation of FGF/FGFR-signaling is primarily driven by autocrine/paracrine activation of this pathway. In total, this data demonstrates that FGF/FGFR-signaling is a critical driver of late stage CRPC, and supports testing FGFR inhibitors in DNPC patients.

On this basis, we are launching a phase II trial testing the pan-FGFR inhibitor erdafitinib in men with metastatic CRPC who have previously progressed on abiraterone acetate and/or enzalutamide and exhibit a DNPC phenotype on biopsy. Patients will continue on the most recent next-generation AR-directed therapy they progressed on (i.e. either abiraterone acetate or enzalutamide) in order to maintain suppression of AR-signaling, and erdafitinib will be added to their regimen. Erdafitinib will be dosed at the recommended Phase II dose, and abiraterone acetate or enzalutamide will be administered at their respective FDA approved dose. Study subjects will continue on erdafitinib plus either abiraterone acetate or enzalutamide until radiographic progression or intolerable toxicity. *We hypothesize that erdafitinib in combination with a next-generation AR-directed therapy will show clinical efficacy in men with mCRPC with a DNPC phenotype who have progressed on abiraterone* acetate *or enzalutamide*

2. OBJECTIVE AND ENDPOINTS

2.1. Primary Objective

To determine the objective tumor response rate in subjects with measurable lesions as defined by RECIST v1.1 criteria in mCRPC patients with a DNPC molecular phenotype receiving either enzalutamide or abiraterone acetate in combination with erdafitinib.

2.2. Secondary Objectives

1. Determine the radiographic PFS in patients using RECIST 1.1 criteria for soft tissue metastases and Prostate Cancer Working Group 3 (PCWG3) criteria for bone metastases[2,3]
2. Determine the time to response using RECIST 1.1 criteria[2]
3. Determine the overall survival defined as the time interval from C1D1 to the date of death
4. PSA response, defined as >50% reduction in PSA compared with baseline at any point during treatment
5. Assess the incidence and severity of adverse events according to National Cancer Institute- Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

2.3. Planned Exploratory Objectives

Correlative work will be performed in order to determine biomarkers predictive of response to combination therapy. Examples of correlative work may include, but will not be limited to:

1. Immunohistochemistry (IHC) for phosphorylated FGFR and FGFR substrate 2 (FRS2) in tumor tissue
2. IHC for PSA and AR expression in tumor tissue
3. Tumor tissue transcript profiling studies to assess candidate biomarkers for response/resistance to FGFR inhibitor therapy and to evaluate core signaling program for FGF/FGFR, MAPK, and AR.
4. Next-generation sequencing of pre-treatment tumor biopsies and cell-free circulating tumor DNA (ctDNA) to identify genomic alterations correlating with response or resistance to treatment, and confirm FGFR alteration status
5. Serial blood (baseline, 12-weeks, progression) will be obtained in order to develop a blood-based gene expression response signature
6. Serum FGF ligand levels (FGF8, FGF9, FGF19) will be drawn at baseline,12-weeks and at progression

3. STUDY DESIGN AND RATIONALE

This will be a phase II trial testing the pan-FGFR inhibitor, erdafitinib, in men with metastatic CRPC who have previously progressed on abiraterone acetate and/or enzalutamide (Fig 7). Eligible patients must have CRPC (defined as disease progression in spite of a castrate serum testosterone [≤50 ng/dl]), and evidence of RECIST evaluable disease to enroll[2]. Given that the patient population of interest will be heavily pre-treated, and likely enriched for both small cell/NE and double negative prostate cancer, it is recommended that patients undergo a baseline biopsy prior to enrollment to rule out predominate NE/small cell variant prostate cancer. Patients with DNPC as defined by IHC criteria will be eligible to enroll (see Section 9.2.1.1). Transcript profiling methods for identifying DNPC may also be accepted for determining trial eligibility at the PI's discretion. This is based on data showing that transcriptional signatures can accurately define the various prostate cancer subtypes, including DNPC[4,5]. Eligible patients must have demonstrated evidence of progression per Prostate Cancer Working Group 3 (PCWG3) criteria while on enzalutamide or

abiraterone acetate at any time prior to enrollment[3]. If not surgically castrated, participants must be maintained on an LHRH analogue (e.g. leuprolide, goserelin).

Eligible patients will continue on the most recent next-generation AR-directed therapy they progressed on (i.e. either abiraterone acetate or enzalutamide) in order to maintain suppression of AR-signaling and erdafitinib will be added to their regimen. If a trial subject is not currently on abiraterone or enzalutamide at the time of screening, they must restart the AR-directed therapy most recently received and demonstrate two successive PSA rises or other evidence of progression prior to starting treatment per protocol. Erdafitinib will be administered at 8 mg once daily orally, with pharmacodynamic uptitration to 9 mg if serum phosphate was below 5.5mg/dL in absence of significant toxicity on cycle 1 day 14 (see Section 6.1).

Abiraterone acetate or enzalutamide will be administered at their respective FDA approved dose (i.e. abiraterone acetate 1000 mg PO daily; enzalutamide 160 mg PO daily). Subjects continuing on abiraterone acetate will also be required to receive prednisone 5 mg PO twice daily in order to blunt mineralocorticoid symptoms associated with abiraterone acetate. Study subjects will continue on erdafitinib plus either abiraterone acetate or enzalutamide until radiographic progression, intolerable toxicity or two-years of treatment, whichever comes first.

The primary objective will be to determine the objective tumor response rate in measurable lesions as defined by RECIST v1.1 criteria. For the purpose of defining objective response rate, confirmation of response will not be required. If a patient drops out of the study prior to first on-study radiographic assessment, they will be considered a non-responder for the purpose of the primary analysis; however, an additional subject will be accrued to account for early dropouts. Key secondary objectives will include determining: radiographic progression free survival (PFS) in patients using RECIST 1.1 criteria for soft tissue metastases and Prostate Cancer Working Group 3 (PCWG3) criteria for bone metastases; time to response using RECIST 1.1 criteria; overall survival (OS) defined as the time interval from C1D1 to the date of death; PSA response, defined as >50% reduction in PSA compared with baseline at any point during treatment; and the incidence and severity of adverse events according to National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[2,3].

This study will also include a number of correlative studies aimed at identifying candidate biomarkers for response/resistance to FGFR inhibitor therapy. We will plan to obtain pre- and post-treatment biopsies as well as serial blood samples in order to develop blood-based biomarkers for response/resistance to erdafitinib. Given our rapidly evolving understanding of prostate cancer biology, it is impossible to prospectively define all the relevant biomarkers for the patient population enrolled on this study. Examples of the studies to be conducted may include, but will not be limited to the following. Protein expression studies at baseline and at the time of progression, including IHC for AR, PSA, phospho-FRS2 and phosphor-FGFR. Transcript profiling studies (RNA-seq) on metastatic biopsies to assess activation of the core AR-, MAPK- and FGF/FGFR-signaling programs, and to identify unknown pathways involved in mediating response/resistance to treatment. Next-generation sequencing to assess for FGFR mutations. Baseline protein and transcript expression, as well as changes in these parameters with treatment will be correlated with clinical outcomes. This information will be used to develop a gene expression *response-signature*, which we will be assessed in blood samples.

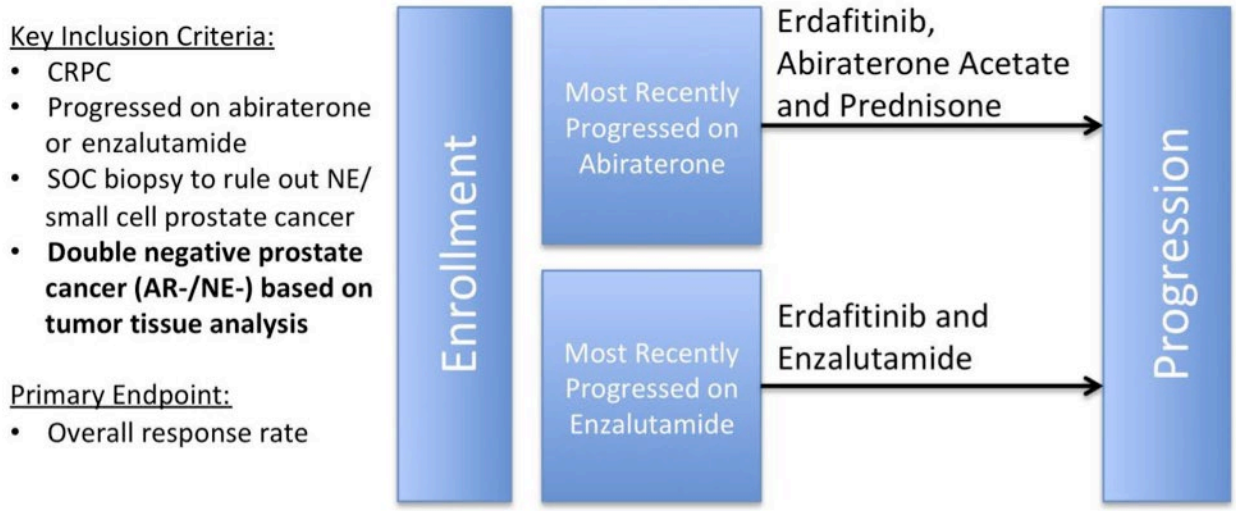


Fig 7. Study schema.

4. Subject Population

Full study screening for eligible subjects will be performed within 30 days before administration of the study drug.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections.

4.1 Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Patients must be ≥ 18 years of age prior to signing informed consent

2. History of histologically diagnosed prostatic adenocarcinoma

3. Participants must have evidence of castration resistant prostate cancer as evidenced by a confirmed rising PSA or radiographic progression (per Prostate Cancer Working Group 3 [PCWG3] criteria) and a castrate serum testosterone level (i.e. ≤ 50 ng/dL)

4. Participants must have previously progressed on abiraterone acetate and/or enzalutamide, with PSA or radiographic progression on the most recent agent per PCWG3 criteria. If the most recent agent received was abiraterone or enzalutamide there should be no washout prior to initiating erdafitinib per protocol

5. Measurable disease as defined per RECIST v1.1 criteria

6. Subjects who have progressed on only one next-generation AR-directed therapy (e.g. abiraterone, enzalutamide) and who have not received taxane chemotherapy will be required to have evidence of double-negative prostate cancer as defined by immunohistochemistry (see Section 9.2.1.1) on biopsy. A fresh metastatic biopsy within 8 weeks is preferred; however, any archival tissue showing a DNPC phenotype will be acceptable for determining eligibility. Patients who have received two

prior lines of AR-directed therapy and at least one prior taxane do not require histologic confirmation of DNPC.
Note: transcript profiling methods for defining DNPC may be accepted per the PI's discretion

7. ECOG performance status score ≤2

8. Clinical and laboratory values and cardiovascular measurements at screening:

Hematology	
Hemoglobin	≥ 8 g/dL (≥5 mmol/L) (must be without red blood cell [RBC] transfusion within 7 days prior to the laboratory test)
Platelets	≥ 75 x 10^9/L
Absolute Neutrophil Count (ANC)	≥ 1.5 x 10^9/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
Chemistry	
AST and ALT	≤ 2.5 x upper limit of normal (ULN) or ≤ 5 x ULN for subjects with liver metastases
Creatinine clearance	≥40 mL/min/1.73 m^2 based upon Modified Diet in Renal Disease formula calculation
Total bilirubin	≤ 1.5 x ULN; except in subjects with congenital bilirubinemia, such as Gilbert's syndrome
Cardiovascular	
Corrected QT interal (QTcF or QTcB)	≤480 msec based on the average of triplicate assessments performed approximately 5 minutes apart
ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; GFR = glomerular filtration rate; QTcB = QT corrected interval by the Bazett's formula; QTcF = QT corrected interval by the Fridericia's formula; ULN = upper limit of normal	
IF Glibert's disease is present, direct bilirubin can be measured	

9. Subjects must agree to use acceptable contraception (see Section 11.3 for requirements)

10. Must sign an informed consent form (ICF) indicated that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study

Exclusion Criteria

1. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 14 days prior to enrollment

2. Active malignancies (i.e. requiring treatment change in the last 24 months) other than malignancy under study (except skin cancers within the last 24 months that are considered completely cured)

3. Evidence of predominant small cell or neuroendocrine variant prostate cancer (see section 9.2.1.1) on most recent standard of care metastatic biopsy

4. Symptomatic central nervous system (CNS) metastases. Treated CNS metastases will be allowed if these are stable for at least 8 weeks prior to enrollment

5. Received prior FGFR inhibitor treatment or if the subject as known allergies, hypersensitivity, or intolerance to erdafitinib or its excipients

6. Current central serous retinopathy (CSR) or retinal pigment epithelial detachment of any grade

7. Has persistent phosphate level >ULN during screening (on 2 consecutive assessments at least 1 week apart, within 14 days of treatment and prior to Cycle 1 Day 1) and despite medical management

8. Has a history of current uncontrolled cardiovascular disease including:

    a. Unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes, cardiac arrest, or known congestive heart failure Class III-V within the preceding 3 months; cerebrovascular accident or transient ischemic attack within the preceding 3 months

    b. Pulmonary embolism or other VTE (venous thromboembolism) within the preceding 2 months

9. Has known active AIDS (human immunodeficiency virus (HIV) infection)

10. Hepatitis B infection as defined according to the American Society of Clinical Oncology guidelines. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status. Hepatitis C (anti-hepatitis C virus [HCV] antibody positive or HCV-RNA quantitation positive) or known to have a history of hepatitis C. If positive, further testing of quantitative levels to rule out positivity is required

11. Has not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are not clinically significant such as alopecia, skin discoloration, hot flashes, Grade 1 neuropathy, Grade 1-2 hearing loss)

12. Has impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions

13. Major surgery within 2 weeks of the first dose, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration (Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate)

14. Any serious underlying medical conditions, such as:
    a. Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection

    b. Active autoimmune or a documented history of autoimmune disease

c. Psychiatric conditions (e.g., alcohol or drug abuse), dementia, or altered mental status

15. Any other issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

16. Patient, who, in the opinion of their treating physician, requires immediate treatment (e.g. those with extensive liver metastases)

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 9.1.2, Screening Phase, describes options for retesting. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

5 TREATMENT ALLOCATION AND BLINDING

6 DOSAGE AND ADMINISTRATION

6.1 Erdafitinib

Erdafitinib will be provided as a tablet for oral administration. Subjects will be instructed to take erdafitinib orally once daily for 21 days on a 21-day cycle. Treatment will be up-titrated to 9 mg, maintained at 8 mg, or withheld, based on phosphate level measured on Cycle 1 Day 14, and taking into account observed toxicity to that day. Erdafitinib is to be taken with approximately 240 mL (8 ounces) of water. The tablets should be swallowed intact and subjects should not attempt to

dissolve them in water. Each dose should be taken at approximately the same time each day. Subjects should avoid consuming grapefruit or Seville orange, due to CYP450 3A4/5 inhibition by such fruits.

Up-titration Guidelines

All subjects will start erdafitinib 8 mg once daily from Day 1 to Day 14. On Day 14, a blood sample will be drawn to determine serum phosphate concentration.

- Subjects with serum phosphate levels higher than 9 mg/dL will withhold erdafitinib treatment, with at least weekly assessment of serum phosphate until it returns to less than 7.0 mg/dL (see Table 4 for detailed guidelines regarding further treatment).
- Subjects with serum phosphate levels between 7.0 to 9.0 mg/dL should increase the erdafitinib dose to 9 mg once daily, while concurrently initiating treatment with a phosphate binder such as sevelamer (see Table 4 for details).
- Subjects with serum phosphate level less than 7.0 mg/dL will increase the erdafitinib dose to 9 mg once daily without concomitant phosphate binder such as sevelamer.

The study drug will be dispensed at the first visit of each cycle. All study drug doses dispensed must be captured in the source documents, including the subject's diary card, and the electronic case report form (eCRF). Unused study drug in the issued bottles and empty bottles must be returned to the site at each study visit. Study drug must be returned to the site when a subject discontinues study treatment. Returned tablets cannot be re-issued in this study or outside the study (follow study drug accountability guidelines per institutional guidelines).

If a dose is missed, it can be taken up to 6 hours after the scheduled time; the subject may return to the normal schedule the following day. If it has been more than 6 hours since the missed dose, then that dose should be skipped and the subject should continue treatment at the scheduled time the next day. Missed doses will not be replaced and the next dose will remain unchanged. If vomiting occurred with drug administration, no replacement dose will be taken and any such event that occurs up to 4 hours following dose administration must be recorded on the subject's diary card and the eCRF.

6.1.1 Dose Modifications and Dose Delays for Erdafitinib

Treatment with erdafitinib should be discontinued or modified based on toxicity as described in Table 1. For eye, skin/nail, dry mouth/mucositis, liver, and phosphate toxicity, specific recommendations in the management guidelines are provided in Sections 6.1.2.2 through 6.1.2.7.

Table 1. Erdafitinib Dose Modification Rules Based on Toxicity

Toxicity Grade	Action	Dose modification after resolution of AE
1	None	Continue same dose
2	None or consider interruption	If interrupted, restart at same dose or 1 dose lower, if necessary.
3	Interrupt drug	Restart at 1 or 2 doses lower if recovery (to ≤Grade 1 or back to baseline for non-hematologic toxicity) is within 28 days. Discontinue drug if unresolved for >28 days.
4	Interrupt drug	Discontinue*

[a] For eye, skin/nail, dry mouth/mucositis, liver, and phosphate toxicity please follow specific recommendations in the management guidelines.

- Subjects with any grade of toxicity (Grade 1 to 4) should be provided symptomatic treatment where applicable.
- If erdafitinib is interrupted consecutively for 1 week or longer due to drug-related toxicity, erdafitinib may be reintroduced at either the same dose level or the first reduced dose level following recovery from the toxicity (see dose reduction levels in Table 2). A second dose reduction may be implemented following a second occurrence of drug-related toxicity.
- If erdafitinib must be withheld for more than 28 days for a drug-related adverse event that fails to resolve to acceptable level (e.g., ≤Grade 1 non-hematologic toxicity or back to baseline), treatment with erdafitinib should be discontinued except when the subject has been deriving benefit from treatment, and the investigator can demonstrate that continued treatment with erdafitinib is in the best interest of the subject. Erdafitinib may be re-started at the same or a lower dose (Table 2) if the Sponsor-Investigator (Dr. Schweizer) concurs with the assessment.
- If erdafitinib was dose-reduced and the adverse event that was the reason for this dose-reduction has completely resolved, the dose may be re-escalated to the next higher dose if the subject was deriving benefit from treatment, and the investigator can demonstrate that dose re-escalation of erdafitinib is in the best interest of the subject and the Sponsor-Investigator concurs with the assessment.
- In all cases of clinically significant impaired wound healing or imminent surgery or potential bleeding complications, it is recommended that dose administration be interrupted, appropriate clinical laboratory data (e.g., coagulation) be carefully monitored, and supportive therapy administered, where applicable. Dose administration may be restarted when it is considered safe and at an appropriate dose, according to the investigator's assessment.

Dose modification rules are provided in Table 2.

Table 2. Erdafitinib Dose Reduction Levels

Category		No up-titration	With up-titration
		Dose	Dose
Starting dose	**6 mg**	**8 mg**	**8 mg**
Up-titration	None	None	9 mg
1st dose reduction	5mg	6 mg	8 mg
2nd dose reduction	4mg	5 mg	6 mg
3rd dose reduction	**stop**	4 mg	5 mg
4th dose reduction		**stop**	4 mg
5th dose reduction			**stop**

6.1.2 Guidance for Specific Erdafitinib Toxicities

6.1.2.1 Grading of Hyperphosphatemia and Nail Disorders

Hyperphosphatemia and adverse events related to nails will be graded as outlined in Table 3.

Table 3: Grading of Hyperphosphatemia and Nails Adverse Events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Nail Changes (onychodystrophy)	Nail discoloration, asymptomatic separation of the nail bed from the nail plate or nail loss	Nail/finger tips pain, symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	Severe nail finger tips pain, symptomatic separation of the nail bed from the nail plate or nail loss; significantly limiting instrumental ADL	Life-threatening consequences, urgent intervention indicated
Hyperphosphatemia	5.5-6.9 mg/dl 1.8-2.2 mmol/L	7.0-8.9 mg/dl 2.3-2.9 mmol/L	9.0-10.0 mg/dl (2.9-3.2 mmol/L), or asymptomatic soft tissue calcification with any phosphate level	>10 mg/dl (>3.2 mmol/L), or symptomatic soft tissue calcification with any phosphate level

6.1.2.2 Guidelines for the Management of Elevated Phosphate Levels

Guidelines for the clinical management of elevated serum phosphate levels are presented in Table 4. Hyperphosphatemia should be graded according to Table 3.

Table 4: Guidelines for Management of Serum Phosphate Elevation

Serum Phosphate Level	Study Drug Management	Symptom Management
<5.5 mg/dL (<1.8 mmol/L)	Continue erdafitinib treatment.	None.
5.5-6.9 mg/dL (1.8-2.2 mmol/L)	Continue erdafitinib treatment.	Restriction of phosphate intake to 600 – 800 mg/day.
7.0-9.0 mg/dL (2.3-2.9 mmol/L)	Continue erdafitinib treatment. A dose reduction will be implemented for persistent[a] hyperphosphatemia defined as serum phosphate ≥7 mg/dL for a period of 2 months) or if clinically necessary (e.g., in the presence of additional adverse events linked to hyperphosphatemia or electrolyte disturbances)	Restriction of phosphate intake to 600 – 800 mg/day. Start sevelamer 800 to 1,600 mg TID with food until phosphate level is <7.0 mg/dL.
>9.0-10 mg/dL (>2.9-3.2 mmol/L)	Withhold[b] erdafitinib treatment until serum phosphate level returns to <7.0 mg/dL (weekly testing recommended). Re-start treatment at the same dose level. A dose reduction will be implemented for persistent[a] hyperphosphatemia (defined as serum phosphate	Restriction of phosphate intake to 600 – 800 mg/day. Sevelamer up to 1,600 mg TID with food until serum phosphate level returns to <7.0 mg/dL.

Table 4: Guidelines for Management of Serum Phosphate Elevation

Serum Phosphate Level	Study Drug Management	Symptom Management
	≥9 mg/dL for a period of 1 month) or if clinically necessary (e.g., in the presence of additional adverse events linked to hyperphosphatemia or electrolyte disturbances)	
>10.0 mg/dL (>3.2 mmol/L)	Withhold[b] erdafitinib treatment until serum phosphate level returns to <7.0 mg/dL (weekly testing recommended). Re-start treatment at the first reduced dose level. If persistent[a] hyperphosphatemia (≥10 mg/dL) for >2 weeks, erdafitinib should be discontinued permanently.	Medical management as clinically appropriate.
Significant alteration in baseline renal function or Grade 3 hypocalcemia	Erdafitinib should be discontinued permanently. (In situations where the subject is having clinical benefit and the investigator and the Sponsor-Investigator agree that continuation of treatment is in the best interest of the subject, the drug may be re-started at 2 dose levels lower if appropriate. Follow other recommendations described above.)	Medical management as clinically appropriate.

Note: These are general guidelines that are based on emerging data and consensus experience of participating investigators or the experts in the field. The treating physicians must use clinical judgment and local standard of care to decide the best way to manage phosphate elevation. If sevelamer hydrochloride (Renagel®) is not available, use of other phosphate binders (non-calcium containing) based on the local standard is recommended, including sevelamer carbonate (Renvela) or lanthanum carbonate (Fosrenol®). These guidelines will be updated based on emerging data. Additional information on phosphorous in foods by class of food can also be found at www.permanente.net/homepage/kaiser/pdf/42025.pdf. Additional information for phosphate management and diet can be found at the National Kidney Foundation website (http://www.kidney.org/atoz/content/phosphorus.cfm)
a. Persistent hyperphosphatemia is considered to be more than 1 sequential phosphate value above the cut-off.
b. Study drug interruptions for hyperphosphatemia suggested to be 7 days duration.

6.1.2.3 Guidelines for the Management of Dry Mouth and Stomatitis

Guidelines for the clinical management of dry mouth (xerostomia) and stomatitis are provided in Table 5 and Table 6, respectively.

- **General Prophylaxis:**
  - Good oral hygiene
  - Use a soft toothbrush
  - Avoidance of spicy, acidic, hard, and hot food and beverages
  - Use of mild-flavored toothpastes
  - Use of saline-peroxide or salt and baking soda mouthwashes 3 or 4 times per day
  - Water soluble lubrication agents like artificial saliva (for xerostomia or dry mouth)

Table 5: Guidelines for the Management of Dry Mouth (Xerostomia)

Grade and Definition	Study Drug Management	Symptom Management
Grade 1: symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 mL/min	Continue erdafitinib at current dose.	Sorbitol lozenges PRN
Grade 2: moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min	Continue erdafitinib at current dose.	Sorbitol lozenges PRN and Cevimiline 30 mg TID or Pilocarpine 5 mg TID
Grade 3: inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva less than 0.1 ml/min	Hold erdafitinib (for up to 28 days), with weekly reassessments of clinical condition. When resolved to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the Sponsor-Investigator.	Sorbitol lozenges PRN and Cevimiline 30 mg TID or Pilocarpine 5 mg TID
Grade 4: life-threatening consequences, urgent intervention indicated	Discontinue erdafitinib.	Evaluation and therapy as clinically indicated

Table 6: Guidelines for the Management of Oral Mucositis

Grade	Study Drug Management	Symptom Management
Grade 1	Continue study drug at current dose.	• Continue general prophylaxis recommendations. • Dexamethasone solution (0.5 mg/5mL solution) swish and spit QID or similar solution that is available in your country and lidocaine 2-5% jelly or solution. • Consider clotrimazole/nystatin if subjects are at risk of developing oral candidiasis.
Grade 2	• Consider holding study drug if the subject has other study-drug related concomitant Grade 2 AEs. • Hold study drug if the subject was already on symptom management (dexamethasone solution swish and spit and lidocaine 2-5% jelly or solution) for more than a week. • If the study drug is withheld, reassess in 1-2 weeks. • If this is the first occurrence of toxicity and resolves to ≤Grade 1 or baseline within 2 weeks, restart at same dose. • If recurrent event or takes >2 weeks to resolve to ≤Grade 1 or baseline, then restart at 1 dose level below.	• Dexamethasone solution (0.5 mg/5mL solution) swish and spit QID or similar solution that is available in your country and lidocaine 2-5% jelly or solution. • Consider concomitant etiologies such as oral candidiasis, oral herpes and recommend appropriate anti-fungal or anti-viral agents.
Grade 3	• Hold study drug, with reassessments of clinical condition in 1-2 weeks. • When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	• Dexamethasone solution (0.5 mg/5mL solution) swish and spit QID or similar solution that is available in your country and lidocaine 2-5% jelly or solution. • Consider pain management strategies. • Consider IV hydration.
Grade 4	Discontinue study drug.	Evaluation and therapy as clinically indicated.
AE=adverse event; QID=quater in die (four times each day).		

6.1.2.4 Guidelines for the Management of Dry Skin and Skin Toxicity

Guidelines for the management of dry skin are provided in Table 7.

- **General prophylaxis:**
  - Avoid unnecessary exposure to sunlight and excessive use of soap.
  - Avoid bathing in excess; use tepid rather than hot water.
  - Use moisturizers regularly; apply thick, alcohol-free and oil-in-water based emollient cream on exposed and dry areas of the body.
  - Avoid perfumed products, bubble bath, perfumed soaps, and take breaks from shaving.
  - Use broad spectrum sunscreen with a skin protection factor (SPF) ≥15.
  - Wear cotton clothes next to skin rather than wool, synthetic fibers, or rough clothing.
  - Use occlusive alcohol-free emollient creams (jar or tub) for treatment of mild/moderate xerosis.
  - For scaly areas, use exfoliants (ammonium lactate 12% or lactic acid cream 12%).

Table 7: Guidelines for Management of Dry Skin

Grade and Definition	Study Drug Management	Symptom Management
Grade 1: Dry skin covering less than 10% body surface area (BSA) and no associated erythema or pruritus	Continue erdafitinib at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles.
Grade 2: Dry skin covering 10 to 30% BSA and associated with erythema or pruritis with limited instrumental activities of daily living (IADL)	Continue erdafitinib at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles. Use zinc oxide 13-40% at night for areas with fissures.
Grade 3: Dry skin covering >30% BSA and associated with pruritis; limiting self-care activities of daily living (ADL)	Hold erdafitinib (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ⩽Grade 1 or baseline, restart at 1 dose level below in consultation with the Sponsor-Investigator.	Use topical steroid ointment or cream* BID and zinc oxide 13-40% at night for areas with fissures.
Grade 4: Dry skin with life-threatening consequences, urgent intervention indicated	Discontinue erdafitinib.	Evaluation and therapy as clinically indicated
*Topical Steroid Ointments: Clobetasol 0.05%, Betamethasone 0.05%, Fluocinonide 0.05%		

6.1.2.5 Guidelines for Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia)

Guidelines for management of nail discoloration/loss/ridging (onycholysis/onychodystrophy) are provided in Table 8. Guidelines for the management of paronychia are provided in Table 9.

- **General Prophylaxis:**
  - Good hygienic practices, keep fingers and toes clean.
  - Keep nails trimmed
  - Use gloves for housecleaning and gardening to minimize damage and prevent infection
  - Nail polish and imitation fingernails should not be worn until the nails have grown out and returned to normal
  - Wearing comfortable shoes (wide sized shoes with room for the toes)
  - Trimming nails but avoiding aggressive manicuring

Table 8: Guidelines for Management of Nail Discoloration/Loss/Ridging (Onycholysis/ Onychodystrophy)

Grade	Study Drug Management	Symptom Management
Grade 1	Continue study drug at current dose.	• Continue general prophylaxis recommendations • Over-the-counter nail strengthener OR poly-urea urethane nail lacquer (Nuvail) OR diethylene glycol monoethylether nail lacquer (Genadur) daily. • Use non-alcohol-containing moisturizing creams.
Grade 2	Consider holding study drug with reassessment in 1-2 weeks. If first occurrence and it resolves to ≤Grade 1 or baseline within 2 weeks, restart at same dose. If recurrent event or takes >2 weeks to resolve to ≤Grade 1 or baseline, then restart at 1 dose level below in consultation with the medical monitor.	• Manage as per Grade 1 • For signs of infection (periungal edema/erythema/ tenderness or discharge), obtain bacterial cultures, and then start the following: o treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim BID) AND o topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily) • Silver nitrate application weekly AND topical antibiotics AND vinegar soaks[a]
Grade 3	Hold study drug, with reassessment in 1-2 weeks. When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Silver nitrate application weekly AND topical antibiotics AND vinegar soaks.[a] For signs of infection (periungal edema/erythema/ tenderness or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/trimethoprim BID). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological or surgical evaluation.
Grade 4	Discontinue study drug.	Evaluation and therapy as clinically indicated.

[a] Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day. Examples of topical antibiotic ointments: Mupirocin 2%, gentamycin, bacitracin zinc/polymixin B.
BID=bis in die (two times each day).

Table 9: Guidelines for Management of Paronychia

Grade and Definition	Study Drug Management	Symptom Management
Grade 1: Nail fold edema or erythema; disruption of the cuticle	Continue erdafitinib at current dose.	Topical antibiotics AND vinegar soaks[a]
Grade 2: Nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Continue erdafitinib at current dose. Consider erdafitinib holding if no improvement in 1 to 2 weeks. When resolves to ≤Grade 1 or baseline, restart at same or 1 dose level below in consultation with the Sponsor-Investigator.	Topical antibiotics AND vinegar soaks[a] AND topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily) For signs of infection (periungal edema/erythema/tenderness and/or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim (Bactrim) DS BID).
Grade 3: Limiting self-care ADLs, surgical intervention, or intravenous antibiotics indicated	Hold erdafitinib (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤ grade 1 or base line, restart at one dose level below in consultation with the Sponsor-Investigator.	Vinegar soaks[a] AND consider nail avulsion For signs of infection (periungal edema/erythema/tenderness and/or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim (Bactrim) DS BID). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological and/or surgical evaluation.
Grade 4: life-threatening consequences, urgent intervention indicated	Discontinue erdafitinib.	Evaluation and therapy as clinically indicated

[a] Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day. Examples of topical antibiotic ointments: Mupirocin 2%, gentamycin, bacitracin zinc/polymixin B

6.1.2.6 Guidelines for Eye Exam and Toxicity Associated With Vision Changes

The baseline ophthalmological examinations must be performed by an ophthalmologist and should include assessment of visual acuity, slit lamp examination, fundoscopy (examination of both central and peripheral zones should be performed) and slit lamp biomicroscopy. An Optical Coherence Tomography (OCT) will also be performed at Screening. The ophthalmological test should be performed once during screening. The Amsler Grid test will also be administered by the treating physician or nurse as screening visit. Additional exams should be performed as clinically necessary based on the findings of the Amsler grid test and clinical assessment at regular intervals as deemed necessary by the screening ophthalmologist.

When CSR/ retinal pigment epithelial detachments (RPED) is suspected then an OCT should be performed. Fluorescein angiography could be considered appropriate in conditions such as suspected

retinal vein occlusion (RVO). It is also recommended that color fundus photos or OCT images be obtained and stored in the patient's file for future reference. In patients with suspected retinal pathology such as CSR or RVO a consultation with a retina specialist should be considered.

Assessment and Evaluation Plan for Subjects in a Study and New Subjects

New subjects enrolling onto this study

- Patients that are yet to be consented should have a baseline ophthalmological exam including fundoscopy as described, prior to the first dose of study medication.
- Additionally, an Amsler grid test should be performed at the beginning of every new cycle, end of treatment, and at follow up visits to identify any new abnormalities (observation of wavy, broken or distorted lines or a blurred or missing area of vision).
- If the subject is asymptomatic and the Amsler grid test is negative, then continue study medication at current dose and schedule.
- If the subject is asymptomatic and the Amsler grid test is positive (observation of wavy, broken or distorted lines or a blurred or missing area of vision) then the subject should have a full ophthalmological exam as described, within 7 days. If this is not possible then the study drug should be withheld until a full ophthalmological exam is performed.
- If the subject has ocular abnormalities, manage as outlined below.

Subjects currently enrolled with no ocular symptoms

- An Amsler grid test should be performed at the beginning of every new cycle, end of treatment and at follow up visits to identify any new abnormalities (observation of wavy, broken or distorted lines or a blurred or missing area of vision).
- If the subject is asymptomatic and the Amsler grid test is negative, then continue study medication at the current dose and schedule.
- If the subject is asymptomatic and the Amsler grid test is positive (observation of wavy, broken or distorted lines or a blurred or missing area of vision) then the subject should have a full ophthalmological exam as described, within 7 days. If this is not possible then the study drug should be withheld until a full ophthalmological exam is performed.

Any subject with ocular symptoms

Subjects that have ocular symptoms at any time should be managed as per the guidelines in Table 10 and as outlined in the current version of the Investigator's Brochure.

Additional modification to the type and or frequency of these exams could be made based on emerging data and/or in consultation with regulatory agencies. If and when such changes are made they will be communicated and incorporated into existing protocols.

Table 10: Guidelines for Management of Eye Toxicity

Definition	Study Drug Management	Symptom Management
Asymptomatic or mild symptoms; clinical or diagnostic observations only Or abnormal Amsler grid test	Refer for an ophthalmologic examination. If an ophthalmologic exam cannot be performed within 7 days, withhold treatment of erdafitinib until an examination can be performed. If there is no evidence of eye toxicity on ophthalmologic examination, continue erdafitinib therapy at the same dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as central serous retinopathy (CSR)/ retinal pigment epithelial detachments (RPED), withhold erdafitinib until signs and symptoms have resolved. If toxicity is reversible (complete resolution or stabilization and asymptomatic) in 4 weeks according to ophthalmologic examination, resume erdafitinib therapy at the next lower dose level after consultation with the medical monitor.[a] Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence then re-escalation can be considered in consultation with the medical monitor.[a]	Refer the subject for an ophthalmologic examination. For retinal pathology perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.
Moderate; minimal, local symptoms Or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Immediately withhold erdafitinib therapy. If there is no evidence of drug-related corneal or retinal pathology on ophthalmologic examination, withhold erdafitinib until signs and symptoms have resolved. Resume erdafitinib therapy at the next lower dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as CSR/RPED, withhold erdafitinib until signs and symptoms have resolved, stabilized, or subject is lost to follow-up or withdraws consent (which ever happens first). If toxicity is reversible (complete resolution or stabilization and asymptomatic) within 4 weeks according to ophthalmologic examination, resume erdafitinib therapy at the next lower dose level after consultation with the medical monitor. Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2-3-week intervals until resolution. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence, then re-escalation can be considered in consultation with the medical monitor.	Refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. For retinal pathology, perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.
Severe or medically significant but not immediate sight-threatening symptoms; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Report as a serious adverse event and immediately withhold erdafitinib therapy. If toxicity is not reversible, permanently discontinue erdafitinib. If however the toxicity is reversible (complete resolution or stabilization and asymptomatic) within 4 weeks and the subject is having clinical benefit, and the investigator and the Sponsor-Investigator agree that re-starting drug is in the best interest of the subject, then erdafitinib therapy may be resumed at 2 dose levels lower if appropriate. Monitor for recurrence using appropriate investigations every 1 to 2 weeks for a month and as clinically appropriate thereafter. For cases of recurrence consider permanent discontinuation.	Refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. For retinal pathology, perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation

Table 10: Guidelines for Management of Eye Toxicity

Definition	Study Drug Management	Symptom Management
Symptoms with sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	Permanently discontinue treatment with erdafitinib . Report as a serious adverse event and monitor resolution of the event until complete resolution, stabilization or the subject is lost to follow-up or withdraws consent (which ever happens first).	Promptly refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. Follow specific treatment per the ophthalmologist's recommendation.
Eye toxicities should be graded according to NCI-CTCAE. ADL=Activities of Daily Living, OCT= Optical Coherence Tomography		

6.1.2.7 Guidelines for the Management of Dry Eye

- **General considerations:** Avoid unnecessary exposure to sunlight, use sunglasses in bright light.
- **Prophylactic management:** Frequent use of artificial tear substitutes is strongly recommended.
- **Reactive management**:
  - Withhold erdafitinib for Grade 3 toxicity
  - Artificial tear substitutes if not started, every 4 to 6 hours
  - Hydrating /lubricating eye gels and ointments
  - Severe treatment-related dry eye should be evaluated by an ophthalmologist

6.2. Enzalutamide

Enzalutamide is administered in capsules containing 40 mg of enzalutamide. It will be administered at the FDA approved dose of 160 mg (4 capsules) by mouth daily. Enzalutamide doses should be taken as close as possible to the same time each day. Subjects will take 4 capsules of enzalutamide once daily.

6.2.1. Dose Modifications

Patients who experience a Grade 3 or greater toxicity deemed at least possibly related to enzalutamide that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a Grade 2 or lower severity. The exception will be non-clinically significant AEs such as hot flashes. Patients may subsequently be re-started on study drug, including at a reduced dose of 120 mg (3 tablets) by mouth daily will be allowed with approval by the sponsor-investigator.

6.3. Abiraterone Acetate

Abiraterone acetate is administered in 250 mg tablets. It will be administered at the FDA approved dose of 1000 mg (4 tablets) by mouth daily. Systemic exposure of abiraterone acetate is increased when administered with food, with an approximate 7- and 5-fold increase in the C_{max} and AUC respectively when given with a low-fat meal. When given with a fatty meal, the C_{max} and AUC increased 17- and 10-fold respectively. Given this variation, no food should be consumed at least 2 hours before and one hour after taking abiraterone acetate. Abiraterone acetate is associated with symptoms of mineralocorticoid excess, and should be taken concurrently with prednisone 5 mg by mouth twice daily to blunt these side effects. Abiraterone

acetate doses should be taken as close as possible to the same time each day. Subjects will take 4 tablets of abiraterone acetate once daily.

6.3.1. Dose Modifications for LFT Abnormalities Attributed to Abiraterone Acetate

Dose modifications are provided as guidance and should not replace the investigator's own clinical judgment.

Toxicity	Dose of abiraterone acetate	Dose of prednisone
Grade 1	No change	No change
Grade 2	Hold until return to Grade 1 or baseline, resume after discussion and agreement with the Sponsor-Investigator *	No change
≥Grade 3	Discontinue	Taper off

*Note: Treatment will be permanently discontinued for Grade 3 toxicity lasting longer than 5 days, or any grade toxicity that has not resolved to Grade 1 or less within 2 weeks

6.3.2. Dose Modifications for Hypokalemia Attributed to Abiraterone Acetate

Dose modifications are provided as guidance and should not replace the investigator's own clinical judgment.

Toxicity	Dose of abiraterone acetate	Dose of prednisone
Grade 1 or 2	Initiate oral potassium supplementation, titrate to ≥3.5 to ≤5.0 mmol/L, maintenance at ≥4.0 mmol/L recommended*	No change
≥Grade 3	Hold and initiate IV potassium and cardiac monitoring, resume only after discussion and approval by the Sponsor-Investigator *	No change
Recurrence ≥Grade 3, or Grade 4	Discontinue	Taper off

*Note: Treatment will be permanently discontinued for Grade 3 toxicity lasting longer than 5 days, or any grade toxicity that has not resolved to Grade 1 or less within 2 weeks. Subjects will

be allowed to resume/continue treatment if serum potassium level is maintained ≥3.5 to ≤5.0 mmol/L with oral potassium supplementation.

6.3.3. Dose Modifications for Hypertension and Edema/Fluid Retention Attributed to Abiraterone Acetate

Dose modifications are provided as guidance and should not replace the investigator's own clinical judgment.

Toxicity	Dose of abiraterone acetate	Dose of prednisone
Grade 1	No change	No change
Grade 2	Hold until return to Grade 1 or baseline, resume at full dose*	No change
≥Grade 3	Hold until Grade 1 or baseline, resume at full dose*	No change
Recurrence ≥Grade 3, or Grade 4	Discontinue	Taper off

*Note: Treatment will be permanently discontinued for Grade 3 toxicity lasting longer than 5 days, or any grade toxicity that has not resolved to Grade 1 or less within 2 weeks.

7 TREATMENT COMPLIANCE

The investigator or designated study personnel will maintain a log of the amount of study drug dispensed and returned. Drug supplies will be inventoried and accounted for throughout the study.

Subjects will receive instructions on compliance with study treatment at the screening visit. A drug diary (Appendix 3) will be given to the subject to record date and time of drug intake at home. During the course of the study, the investigator or designated study research staff will be responsible for providing additional instruction to reeducate any subject who is not compliant with the study drug schedule.

8 CONCOMITANT THERAPY

Concomitant therapies are to be recorded at the time of screening (within 30 days prior to the first dose of study drug), throughout the study, and up to 30 days after the last dose of study drug in the appropriate section of the CRF.

All therapies (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF. Caution should be exerted for subjects taking anti-coagulant therapies. Frequent monitoring for international normalized ratio (INR) is allowed at the treating physician's discretion.

The Sponsor Investigator must be notified in advance, or as soon as possible thereafter, of any instances where prohibited medications are administered.

8.1 Permitted Medications

Throughout the study, investigators may prescribe concomitant medications or treatments (including nutritional support, correction of metabolic disorders, optimal symptom control, and pain management) deemed necessary to provide adequate supportive care. Concurrent use of hormones for non-cancer related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. Permitted medications are to be recorded at the time of screening (within 30 days prior to the first dose of study drug), throughout the study, and up to 30 days after the last dose of study drug in the appropriate section of the eCRF.

In addition, the following medications may be administered during the study:

- Standard supportive care therapies (antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor [H2] antagonists or proton pump inhibitors, and other medications intended to treat symptoms or signs of disease) as clinically indicated, according to institutional standards and as deemed necessary by the investigator.
- Documented infectious complication should be treated with oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Growth factor support for the management of treatment-emergent hematological toxicity as recommended according to National Comprehensive Cancer Network/European Organization for Research and Treatment of Cancer (NCCN/EORTC) guidelines.
- Palliative radiotherapy: Localized radiotherapy for symptomatic control is permitted, but should not include definitive radiation to target lesions.
- Chronic supportive therapies: Ongoing bisphosphonates and denosumab or other supportive therapies are permitted..

8.2 Prohibited Medications

The following concomitant medications are prohibited during the study. The Sponsor-Investigator must be notified in advance, or as soon as possible thereafter, of any instances in which prohibited therapies were administered.

- Concurrent investigational agents
- Medications known to increase serum levels of calcium (thiazide diuretics, vitamin A supplements, vitamin D supplements, calcium dietary supplements, calcium antacids, lithium, estrogens, anti-estrogens). Vitamin D and calcium supplements may be given if clinically indicated (in the setting of low serum vitamin D and calcium levels). Medications known to have calcium as an excipient should be avoided unless no alternatives exist.
- Medications known to increase serum levels of phosphate, such as potassium phosphate supplements (oral or IV), vitamin D supplements, antacids, and phosphate-containing enemas and laxatives (oral/rectal) thought to increase serum phosphate levels. Medications known to have phosphate as an excipient should be avoided unless no alternatives exist.

8.3 Precautions for Concomitant Medications

The following precautions are advised for subjects receiving erdafitinib:

- Based on in vitro data, erdafitinib is metabolized by cytochrome CYP2C9 and CYP3A4. A clinical drug-drug interaction study showed that on average, erdafitinib exposure (Cmax and AUC) was increased 5-34% when co-administered with itraconazole (a strong inhibitor of CYP3A4) and 21-49% when co-administered with fluconazole (a moderate inhibitor of CYP2C9). For this reason, strong CYP3A4 and moderate CYP2C9 inhibitors should be used with caution (see Attachment 5). Consider alternative therapies that are not strong inhibitors of CYP3A4 or moderate inhibitors of CYP2C9 during treatment with erdafitinib. If co administration of these drugs is unavoidable, monitor the subject closely for adverse reactions and consider dose modifications accordingly. If the strong inhibitor of CYP3A or moderate inhibitor of CYP2C9 is discontinued, the erdafitinib dose may be increased in the absence of drug-related toxicity
- The impact of moderate to strong inducers of CYP3A4 and CYP2C9 (such as rifampin) on erdafitinib was not clinically studied. Caution should be exercised for concomitant administration of erdafitinib and CYP inducers (see Attachment 5)
- Erdafitinib was shown to inhibit, in in vitro experiments, human P-glycoprotein (P-gp) at concentrations achieved at therapeutic doses in humans. If the compound is administered with drugs that are substrates of P-gp, there is the potential for observing increased concentrations of the substrate drug. Therefore, caution should be exercised for co administered drugs that are P-gp substrates, such as digoxin, dabigatran, and fexofenadine (https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf); in addition, drugs with a narrow therapeutic index should only be used where the benefit outweighs the potential risk
- For subjects taking erdafitinib: medications known to increase serum levels of phosphate, such as potassium phosphate supplements (oral or IV), vitamin D supplements, antacids, and phosphate-containing enemas and laxatives (oral/rectal) thought to increase serum phosphate levels. Caution should be exercised considering the risk benefit ratio, and more frequent monitoring of phosphate levels during treatment with medications known to increase the serum level of phosphate put in place
- Concomitant use of medications that are known strong inducers of CYP3A4 is to be avoided with erdafitinib

9 STUDY EVALUATIONS

9.1 Study Procedures

9.1.1 Overview

The Time and Events Schedule summarizes the frequency and timing of safety, efficacy, biomarker, and other measurements applicable to this study.

The number of blood samples and volume of blood that will be required from each subject for the various study procedures is outlined in the Laboratory Manual. The number of samples and the blood volume will vary depending on the number of cycles of the study drug that the subject receives. Unscheduled blood samples may be required for safety issues of individual subjects

The maximum research blood volume to be collected from each subject will be approximately 40

mL at any given timepoint.

9.1.2 Screening Phase

The Study Screening Period is 30 days before the first dose of study medication. Subjects must meet all of the inclusion and none of the exclusion criteria in Section 4. All information required for determining eligibility must be available prior to C1D1. Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting will take place during an unscheduled visit in the screening phase.

The following procedures will occur during the Study Screening Period:

1. Comprehensive medical history and physical exam, including height and weight, medications, blood pressure and heart rate
2. ECOG performance status assessment
3. Ophthalmic examination
4. PSA (Prostate-specific antigen)
5. CBC (Complete blood count) with differential
6. CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2)
7. Serum testosterone
8. Phosphate level
9. PT/INR and PTT
10. Radiographic assessments: CT chest/abdomen/pelvis and Bone scan
11. Electrocardiogram (EKG)
12. Pathologic evaluation of tumor tissue acquired at any time to assess for DNPC phenotype in patients who have only progressed on one AR-directed therapy and not previously treated with taxane chemotherapy (see Section 9.2.1.1). Note: metastatic biopsy obtained within 8 weeks of enrollment is preferred.

9.1.3 Treatment Phase

Assessments must be done within ±7 days of the specified time point unless indicated otherwise. All procedures are to be completed on Day 1 of each cycle unless otherwise noted.

1. Comprehensive medical history and physical exam, including weight, medications, blood pressure and heart rate
2. ECOG performance status assessment

3. PSA (Prostate-specific antigen) [to be completed after every 3 cycles (e.g. C4D1, C7D1, C10D1, etc)].

4. CBC (Complete blood count) with differential

5. CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2)

6. Phosphate level [Day 1 of each cycle AND on C1D14 ±2 days]

7. Radiographic assessments: CT chest/abdomen/pelvis and Bone scan [to be completed after every 3 cycles (e.g. C4D1, C7D1, C10D1, etc)].

8. Correlative blood draw [C1D1 and C4D1]

9.1.4 End of Treatment

Assessments must be done within ±14 days of the specified time point unless indicated otherwise. All procedures are to be completed on Day 1 of each cycle unless otherwise noted. Procedures need not be repeated if done within the past 14 days.

1. Comprehensive medical history and physical exam, including weight, medications, blood pressure and heart rate

2. ECOG performance status assessment

3. PSA (Prostate-specific antigen)

4. CBC (Complete blood count) with differential

5. CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2)

6. Phosphate level

7. Radiographic assessments: CT chest/abdomen/pelvis and Bone scan

8. Correlative blood draw

9. Metastatic research biopsy. Will only be obtained if feasible (i.e. safe and amenable metastatic lesion).

9.2 Efficacy Evaluations

Disease assessments will be performed according to the Time and Events Schedule. Assessment of responses for solid tumors will be performed according to RECIST (version 1.1) by

investigators. For subjects who discontinue study drug before disease progression, tumor assessments should continue as described in Section 9.1.3.

More frequent radiological assessments are allowed, if clinically indicated/desirable. Identical methodology should be used for disease assessment at baseline, and throughout the course of the study, to characterize each identified and reported lesion to document disease status. Patients will ideally undergo CT and bone scans to assess for radiographic progression; however, MRI may substitute the CT scan with approval of the sponsor-investigator. Ultrasound, fluorine 18-fluorodeoxyglucose positron emission tomography (FDG-PET), and plain x-rays are not acceptable methods of evaluating disease response in the absence of CT or MRI scans.

If symptomatic deterioration (on the basis of global deterioration of health status) occurs without documentation of radiographic progression, the clinical findings used to make this determination must be specified in the eCRF and documented in the source documents. Every effort should be made to document the objective progression even after discontinuation of treatment for symptomatic deterioration. Tumor response will be reported by the investigator in the eCRF.

9.2.1. Evaluations

9.2.1.1 Pathologic Assessment

It is well recognized that in the late stages of prostate cancer, dependency on AR-signaling is often lost, with ~10% tumors trans-differentiating into small cell/NE variants[36,37]. Recognizing the presence of small cell prostate cancer is imperative, as standard of care for these cases involves platinum-doublet chemotherapy akin to the regimens used to treat small cell lung cancer[37,38]. Clinical criteria to identify these cases, include: visceral metastases only, predominately lytic bone lesions, bulky lymphadenopathy, bulky high-grade prostatic or pelvic mass, low PSA level, neuroendocrine markers in serum and short interval to developing CRPC[36,37]. Given that many of these clinical features are expected to overlap with those of DNPC, it is recommended that the treating physician obtain a standard of care metastatic biopsy prior to enrollment to rule out predominate small cell/NE prostate cancer.

Pathologic assessment during screening will involve IHC for AR or proteins that are regulated by AR-signaling (e.g. PSA, NKX3.1, etc.) and a NE marker (e.g. synaptophysin, INSM1, chromogranin, etc.). We will utilize a composite score for AR/AR regulated proteins and NE marker expression to define DNPC. This composite score will be calculated as follows:

AR/AR regulated protein or NE marker composite expression score = (Percentage of nuclear AR/AR regulated protein or NE marker positive cells) x (Intensity of staining, where 1=low intensity, 2=moderate intensity and 3=high intensity)

We will define AR/AR regulated protein negative as a score <40 and NE marker negative as a score <10. These cutoffs were selected based on prior experience from our rapid autopsy program. Of 73 AR+ cases, only 3 had AR composite expression scores <40. Similarly, 0 of 5 NE/small cell cases had synaptophysin scores <10. These cut offs were selected to avoid being overly stringent in defining the study population given that we have observed heterogeneity across tumors from rapid autopsy patients, with at least one case demonstrating a NE tumor in one location and a DNPC in the other[24]. Patients with evidence of small cell morphology on biopsy will be excluded.

Transcript profiling methods for identifying DNPC may also be accepted for determining trial eligibility at the PI's discretion. This is based on data showing that transcriptional signatures can accurately define the various prostate cancer subtypes, including DNPC[5,39].

Given that intra/inter-tumoral phenotypic heterogeneity is increasingly recognized in late stage prostate cancer, and that FGFR inhibition plays an important role in mediating lineage plasticity in this clinical context, we will not require histologic confirmation of DNPC in late stage prostate cancer[19-22]. Patients who have previously progressed on two next-generation AR-directed therapies (e.g. abiraterone, enzalutamide) AND at least one prior taxane will not be required to undergo histologic assessment to determine eligibility. However, metastatic biopsy should be performed if there is clinical suspicion for a small cell/NE variant as outlined above.

9.2.1.2. RECIST Assessment of Disease

RECIST 1.1 is an accepted methodology by regulatory authorities. RECIST 1.1 will be applied by the investigator as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy).

After screening, imaging will be repeated during the study as indicated in the Time and Events Schedule.

9.2.1.3. Radiographic Images Assessment

Bone scan and Computed tomography (CT) scans of the chest, abdomen, pelvis, and any other location where disease is present will be performed at Screening. During the study, disease response will be assessed using bone scan and CT scans of the locations of known disease. Magnetic resonance imaging may be used to evaluate sites of disease that cannot be adequately imaged using CT (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations or in cases where use of CT scan is clinically contraindicated). For all other sites of disease, MRI studies do not replace the required chest, abdomen, and pelvic CT scans. Brain MRI and lumbar puncture are required, only if clinically indicated.

Imaging should not be delayed due to delays in cycle starts or extension of cycle intervals. After disease progression is documented, subjects will be monitored as outlined in Section 9.1.4.

If the site study team makes an initial assessment of disease progression, and if the subject is clinically stable, treatment may be continued if the investigator and sponsor-investigator agree that continuation of treatment is in the best interest of the subject considering the terminal nature of the underlying disease, he/she may receive study treatments until such time as the treating physician and the sponsor-investigator agree that further continuation of treatment is no longer beneficial to the subject or he has completed two years of treatment total, whichever comes first.

9.3. Correlative research

This study will also include a number of correlative studies aimed at identifying candidate biomarkers for response/resistance to FGFR inhibitor therapy. We will evaluate pre- and post-treatment tissue as well as serial blood samples in order to develop blood-based biomarkers for response/resistance to erdafitinib. Baseline protein and transcript expression, as well as changes in these parameters with treatment will be correlated with clinical outcomes. This information will be used to develop a gene expression *response-signature*, which we will be assessed in

blood samples.

Biospecimen samples (e.g., blood, tumor tissue) will be stored for up to five years following the completion of this study and any unused samples will be destroyed at the end of this time period. Samples will be stored at University of Washington and/or Fred Hutchinson Cancer Research Center, and the Sponsor-Investigator will oversee access to biospecimens. In order to protect the identity of study subjects, all biospecimen samples will be labeled with a subject-specific study ID code. Samples will be analyzed at University of Washington and/or Fred Hutchinson Cancer Research Institute. Biospecimens will used for research pertaining to this clinical study only.

Next-generation sequencing
Patients will undergo next-generation sequencing (NGS) using UW-OncoPlex, a comprehensive whole gene NGS panel that has been validated for use on tumor tissue and cell-free circulating tumor DNA (ctDNA)[40]. A research-based sequencing assay may also be utilized in order to evaluate for mutations in genes not covered by UW-OncoPlex. Sequencing studies will be prioritized for patients that have demonstrated a clinical response to treatment.

Transcript profiling studies

Transcript profiling studies (e.g. RNA-seq, NanoString) will be performed on metastatic biopsies to assess activation of the core AR-, MAPK- and FGF/FGFR-signaling programs, and to identify unknown pathways involved in mediating response/resistance to treatment[41,42]. We may also perform circulating tumor cell (CTC)-based transcript profiling studies using AdnaTest and multiplex qPCR or another blood-based transcript profiling assay.

Protein expression studies

Protein expression studies at baseline and at the time of progression, including IHC for AR, PSA, phospho-FRS2 (a downstream target of the FGF8 cognate receptors: FGFR1IIIc and FGFR2IIIc) and phosphor-FGFR. Additional protein expression studies may be added depending on the results of NGS and transcript profiling studies.

9.4. Safety Evaluations

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, clinical laboratory tests, ECOG performance status, ophthalmic examinations, and other safety evaluations at specified time points as described in the Time and Events Schedule.

Any clinically significant abnormalities or toxicities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint. For adverse events such as skin/nail and mucosal toxicity, upon subject consent, photographs may be taken for assessment and monitoring of the toxicity.

9.4.1. Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. Adverse events will be graded according the NCI-CTCAE, Version 4.0. Adverse events will be

followed by the investigator as specified in Section 11, Adverse Event Reporting.

9.4.2. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected according to the Time and Events Schedule. More frequent clinical laboratory tests may be performed, as indicated by the overall clinical condition of the subject and for abnormalities that warrant more frequent monitoring.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. Laboratory test results completed on Cycle 1 Day 1 should be reviewed prior to dosing and subjects should continue to meet eligibility requirements per the Inclusion/Exclusion criteria.

The following tests will be performed:

Complete Blood Count

-hemoglobin
-platelet count
-white blood cell (WBC) count and differential

Serum Chemistry Panel

-sodium
-blood urea nitrogen
-potassium
-creatinine
-albumin
-alanine aminotransferase (ALT)
-aspartate aminotransferase (AST)
-alkaline phosphatase
-chloride
-glucose
-bicarbonate (CO_2)
-phosphate
-total protein
-direct bilirubin
-total bilirubin

9.4.3. Renal Toxicity Evaluation

Creatinine or creatinine clearance will be determined per institutional standard.

9.4.4. Electrocardiogram

Screening electrocardiograms, to be used to determine subject eligibility, will be performed at the study site. The subject should rest in a supine position for at least 5 minutes before ECG recording, and should refrain from talking or moving arms or legs. Triplicate ECGs should be performed with 5 minute intervals between each assessment. At least 1 printout should be produced and stored in the subject's source documents. The 12-lead ECG recorder device used should have been recently serviced and calibrated. The following variables should be measured: heart rate, RR, QT, PR, QRS, QTc (Fridericia) intervals. QTcF (Fridericia) will be used for assessment of QTc interval. The investigator will comment on the clinical relevance and document this in the eCRF (along with details of clinically significant findings).

9.4.5. Ophthalmic Examination

All subjects should have an ophthalmological examination performed at Screening by an

ophthalmologist, which should include assessment of visual acuity, tonometry, fundoscopy (examination of both central and peripheral zones should be performed) and an Amsler Grid test; where available, an Optical Coherence Tomography (OCT) should be performed. A follow-up examination should be performed as clinically necessary based on the findings of the Amsler grid tests and clinical assessment.

When Central Serous Retinopathy (CSR)/Retinal Pigment Epithelial Detachments (RPED) is suspected, an OCT should be performed. Fluorescein angiography could be considered appropriate in conditions such as suspected Retinal Vein Occlusion (RVO). It is also recommended that color

fundus photos or OCT images be obtained and stored in the subject's records for future reference. In subjects with suspected retinal pathology such as CSR or RVO, a consultation with a retina specialist should be considered.

Amsler grid testing will be administered by the treating physician or nurse at timepoints according to the Time and Events Schedule. Observation of wavy, broken or distorted lines, or a blurred/missing area of vision is equivalent to a positive Amsler grid test. For any positive Amsler grid test, subject should be referred for full ophthalmologic exam within 7 days. However, if the subject has an abnormal Amsler grid test at baseline (during Screening), then a repeat ophthalmic examination would be recommended only if, in the opinion of the investigator, there is a likelihood of significant change from the subject's baseline Amsler Grid test at Screening, or the subject has developed new clinical symptoms.

9.4.6. Vital Signs

Blood pressure (systolic and diastolic), heart rate, and oral or tympanic temperature will be assessed. Abnormalities will be recorded as AEs

9.4.7. Physical Examination

A full physical examination, including height, and weight will be performed at screening. Targeted physical examinations of involved organs, and including weight, will be performed at subsequent visits as listed in the Time and Events Schedule. New abnormalities will be recorded as AEs.

9.4.8. ECOG Performance Status

Eastern Cooperative Oncology Group performance status score will be determined at pre-specified time points listed in the Time and Events Schedule. Eastern Cooperative Oncology Group scoring information is provided in Appendix 1.

9.5. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form/source documentation. Refer to the Time and Events Schedules for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the Laboratory Manual.

10 SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered as having completed the study if he or she has died during the study or has not been withdrawn from the study by the end of the study.

10.2 Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

A subject who discontinues study treatment will continue to participate in the study for follow-up of survival status, resolution of any ongoing AEs, and disease assessments if treatment discontinuation occurs before disease progression.

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (e.g., adverse event) it is in the best interest of the subject to discontinue study treatment
- Disease progression
  - Exception: if the investigator and sponsor-investigator agree that continuation of treatment is in the best interest of the subject considering the terminal nature of the underlying disease, he may receive erdafitinib until such time as the treating physician and the sponsor-investigator agree that further continuation of treatment is no longer beneficial to the subject.
- The subject refuses further treatment with the study drug
- The Sponsor-Investigator terminates the study
- Investigator decision approved by the sponsor

If a subject discontinues treatment, an End-of-Treatment visit should be conducted within 30 days of the subject's last dose of study drug. The primary reason for treatment discontinuation will be clearly documented in the subject's medical record and recorded in the eCRF. Once a subject discontinues treatment with the study drug, the subject will not be permitted to be retreated.

If a subject discontinues study treatment for any reason before the end of the treatment phase, post-treatment assessments should be obtained and scheduled assessments should be continued.

Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

If a subject discontinues study drug and withdraws from the study before the end of the treatment period, all post-treatment assessments should be obtained.

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws consent before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. In addition, subjects who withdraw consent must complete and sign a withdrawal of consent form to specify if they agree to have survival data collected or not. Study drug assigned to the withdrawn subject may not be assigned to another

subject. Subjects may be replaced only if the subject withdrew prior to the study drug administration.

10.3. Withdrawal From the Use of Research Samples

The subject may withdraw consent for use of samples for research. In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11 DATA MONITORING AND ADVERSE EVENT REPORTING

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

Additionally, scheduled meetings will take place weekly and will include the Sponsor Investigator (Michael Schweizer, MD), research nurse, data manager, and, when appropriate, the collaborators, sub-investigators, and biostatistician involved with the conduct of the protocol.

During these meetings the investigators will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for secondary objectives.

If ≥3 out of the first 10 subjects enrolled are removed from the study due to a safety issue, the trial will terminate prematurely. Depending on the number of patients removed from the study due to safety issues, study accrual may have to be put on hold until the 10^{th} subject has completed at least one treatment cycle. For example, if 2 subjects were removed for safety reasons prior to accruing the 10^{th} subject, accrual would not continue until the 10^{th} subject completes the first cycle. Safety issues will be continually monitored and safety oversight will be provided through the weekly meetings between the PI and relevant staff.

11.1 Management of Safety Data

As the Sponsor-Investigator of the Study, Dr. Michael T. Schweizer shall be solely responsible for complying with required timelines, any safety-reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations.

This Study has been designated as an interventional study. As such, all adverse events, special situations including pregnancies and product quality complaints will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until 30 days after the last documented use of the product under study within the study. All subsequent AEs and SAEs will be collected after this period if the Principal Investigator considers the AE/SAE to be causally-related to the use of the study drug.

For the purposes of this study, the J&J medicinal product(s) are: Balversa (erdafitinib (JNJ-42756493) and Zytiga (abiraterone acetate).

11.2 Definitions

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Adverse Events of Special Interest

Adverse events of special interest are events that Janssen Research & Development is actively monitoring as a result of a previously identified signal (even if non-serious).

For erdafitinib, the adverse events of special interest are:

- Central Serous Retinopathy: including PTs of retinal detachment, chorioretinopathy, detachment of retinal pigment epithelium, retinopathy, vitreous detachment, retinal edema, detachment of macular retinal pigment epithelium

There are no adverse events of special interest for abiraterone acetate.

Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting

requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- The name of the investigational product (i.e. erdafitinib, abiraterone acetate and/or enzalutamide)
- an adverse event, outcome, or certain special situations

The minimum information required is:

- date of therapy (start and end date, if available)
- batch or lot number, if available
- Suspected J&J medicinal product (doses, indication)
- subject details (subject ID and country)
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- J&J protocol ID

Adverse Drug Reaction (ADR)

A noxious and unintended response to any dose of the drug (or biological) product for which there is a reasonable possibility that the product cause the response. ''Reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product

- Physical Defect: e.g. abnormal odor, broken or crushed tablets
- Potential Dosing Device Malfunction: e.g., auto-injector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

  *Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)

- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

Life-Threatening Conditions

The cause of death of a subject in a study within 30-days of the last dose of one or more of the Study Drugs, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

For erdafitinib, the expectedness of an adverse event will be determined by whether or not it is listed in Section 6 of the Investigator's Brochure (reference safety information for assessment of expectedness of serious adverse reactions).

For abiraterone acetate, the expectedness of an adverse event will be determined by whether or not it is listed in the FDA prescribing information.

https://www.zytiga.com/

https://www.balversa.com/

For Balversa™ (erdafitinib) and Zytiga™ (abiraterone acetate), the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure

Special Reporting Situations

Safety events of interest for a J&J medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a J&J medicinal product
- Exposure to a J&J medicinal product from breastfeeding
- Suspected abuse/misuse of a J&J medicinal product

- Inadvertent or accidental exposure to a J&J medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a J&J medicinal product
- Medication error (includes potential, intercepted or actual) involving a J&J medicinal product (with or without patient exposure to the J&J medicinal product(s) under study, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product

- Unexpected therapeutic or clinical benefit from use of a J&J medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen Research & Development perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Research & Development **within 24 hours of becoming aware of the event.**

11.3 Pregnancy

Erdafitinib is developed as an anticancer agent. There are no reproductive or developmental toxicology data available for erdafitinib. There may be unforeseeable risks to the embryo or fetus. Subjects (with a partner of child-bearing potential) must use medically acceptable methods of birth control prior to study entry and for the duration of the study, and for at least 3 months after the last intake of study drug. Subjects must use a condom with spermicide when sexually active and must not donate sperm from the first dose of study drug until 3 months after the last dose of study drug. Medically acceptable methods of contraception that may be used by the subject and/or his partner include hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, true sexual abstinence, and surgical sterilization (e.g., confirmed successful vasectomy or tubal ligation). True sexual abstinence is an acceptable method of contraception and is defined as refraining from heterosexual intercourse during the entire period of the study, including up to 3 months after the last dose of study drug is given. Periodic abstinence (calendar, symptothermal, postovulation methods) is not considered an acceptable contraceptive method.

Because the study drug may have an effect on sperm, pregnancies in partners of male subjects included in the study must be reported by the Sponsor-Investigator within 24 hours to of their knowledge of the event using the Serious Adverse Event Form. All pregnancies must be reported from the time of informed consent and 90 days following last dose. Depending on local legislation this may require prior consent of the partner. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

11.4. Adverse Event Monitoring and Reporting

The Sponsor Investigator, Sub-Investigators, and/or the research nurse will monitor each patient closely for the development of adverse events and toxicities and record all such events. Patients

will be evaluated for toxicity if they have received one dose of any of the Study Drugs. The timely reporting of adverse events (including toxic deaths) is required by the Food and Drug Administration (FDA).

In general, the Sponsor-Investigator must immediately report (i.e. within 24 hours) to Janssen Research & Development any serious adverse event and Special Reporting Situations, whether or not considered drug related. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death as a result of anaphylactic reaction or fatal hepatic necrosis). In that case, the investigator must immediately report the event to Janssen Research & Development. The sponsor must record non-serious adverse events and report them to Janssen Research & Development according to the timetable outlined in the Research Funding Agreement section entitled Reporting of Data and to fulfill regulatory reporting requirements.

For each subject, AEs, SAEs, Adverse Events of Special Interest and Special Reporting Situations should be recorded after informed consent is obtained until the subject has completed participation in the study as follows:

A Serious Adverse event must be reported if it occurs during a subject's participation in the Study (whether receiving Study Product or not) and within 30 days of receiving the last dose of Study Product.

Any serious adverse event that is ongoing when a subject completes his/her participation in the Study must be followed until any of the following occurs:

- the event resolves or stabilizes;
- the event returns to baseline condition or value (if a baseline value is available);
- the event can be attributed to agents(s) other than the Study Product, or to factors unrelated to Study conduct.

11.5. Procedures for Reporting Safety and Data and Product Quality Complaints (PQCs) for J&J Medicinal Products to the Company

All adverse events, whether serious or non-serious, related or not related, following exposure to study drugs are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to the study drugs.

All (serious and non-serious) adverse events reported for the study drugs should be followed up- in accordance with clinical practice.

11.5.1. Serious Adverse Events (SAE), Adverse Events of Special Interest, and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study,

must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The Sponsor Investigator will transmit all SAEs, Adverse Events of Special Interest and special situations following exposure to the Study Drugs in a form provided by the Janssen Research & Development **within 24-hours of becoming aware of the event(s).**

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the Sponsor Investigator, **within 24 hours becoming aware**, to Janssen Research & Development using their Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, Adverse Events of Special Interest, serious ADR or special situation is required.

- The Sponsor Investigator is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.
- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Study Drugs, are to be provided to the Janssen Research & Development within **24 hours of such report or correspondence being sent to applicable health authorities.**

11.5.2. Product Quality Complaints Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Research & Development, and are mandated by regulatory agencies worldwide. Janssen Research & Development has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be

quarantined immediately and if possible, take a picture.

All initial PQCs involving J&J medicinal product(s) under study must be reported to Janssen Research & Development by the Sponsor Investigator **within 24 hours after being made aware of the event.** The J&J contact will provide additional information/form to be completed.

If the defect for the Lot and/or Batch of the J&J medicinal product(s) under study is combined with either a serious adverse event or non-serious adverse event, the Sponsor Investigator must report the PQC to Janssen Research & Development according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Research & Development.

For SAEs, special reporting situations and PQCs following exposure to a non-J&J medicinal product under study, the Sponsor Investigator should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

11.6. Evaluating Adverse Events

The grade and severity of the event will be determined using the DCT/NCI Common Terminology Criteria, CTCAE v.5.0 (Appendix 2). All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. Study staff must use one of the CTCAE criteria to define the event. Adverse events not included in the CTCAE v.5.0 should be reported and graded under the "Other" adverse event within the appropriate category and grade 1 to 5 according to the general grade definitions, mild, moderate, severe, life-threatening, fatal or disabling, as provided in the CTCAE.

The event will be determined to be expected or unexpected. The determination of whether an AE is expected is based on agent-specific adverse event information provided in the Investigators Brochure (erdafitinib) or the FDA Prescribing Information (abiraterone acetate and enzalutamide). Unexpected AEs are those not listed in the agent-specific adverse event information.

The event will be evaluated for relationship to the medical treatment or procedure. The Investigator should document his/her opinion of the relationship of the event to study medication as follows:

- *Unrelated*- The adverse event is clearly not related to the investigational agent(s).
- *Unlikely*- The adverse event is doubtfully related to the investigational agent(s).
- *Possible*-The adverse event may be related to the investigational agent(s).

- *Probable*-The adverse event is most likely related to the investigational agent(s).

- *Definite*- The adverse event is clearly related to the investigational agent(s).

Based on this information, a decision will be made whether an adverse event should be reported as an expedited report (Serious Adverse Event) in addition to the routinely reported clinical data. All expedited adverse event reports that meet reporting criteria per institutional requirements should be submitted to the Institutional Review Board (IRB) and to the FDA. Additionally, all SAEs should be submitted to Janssen Research & Development within 24 hours of becoming aware of event and via secure e-mail.

11.6.1. Documenting Adverse Events

Each individual sign or symptom must be documented separately. Worksheets must be signed and dated by person conducting evaluation to be used as source documentation. The attribution of all adverse events must be verified by an investigator. Evaluation of laboratory toxicities may be documented directly on a printed laboratory report or CRF provided it is signed by the investigator. However, if an action was conducted due to this abnormality (e.g. RBC transfusion due to low Hgb) this would be recorded on the AE form also. Recording should be done in a concise manner using standard, acceptable medical terms.

The adverse event recorded should not be a procedure or a clinical measurement (i.e. a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement.
Preexisting conditions that worsen in severity or frequency during the Study should also be recorded (a preexisting condition that does not worsen is not an adverse event).

Further, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring in-patient hospitalization that occurs during the course of a subject's participation in a trial must be reported as an SAE. Hospitalizations that do not meet the criteria for SAE reporting are:

A. Reasons described in the Protocol, e.g. drug administration, Protocol-required testing
B. Surgery or procedure planned prior to entry into the Study.

If, in the Sponsor Investigator's judgment, a clinical significant worsening from baseline is observed in any laboratory or other test parameter (e.g. electrocardiogram (ECG), angiogram), physical exam finding, or vital sign, a corresponding clinical adverse event should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the adverse event, whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis

should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an adverse event, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

11.6.2. Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The Sponsor Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs' request.

11.6.3. SAEs Listing

At a minimum, on a semi-annual basis and at the end of the Study, Janssen Research & Development will provide to the Sponsor Investigator a listing of all SAEs reported to the Janssen Research & Development. The Sponsor Investigator will review this listing and will resolve any discrepancies with the data provided by Janssen Research & Development.

11.7. IRB Reporting

The Sponsor Investigator is responsible to report serious adverse events and protocol problems (e.g. protocol deviations, non-adherence) to the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). Adverse events (AEs) that are unexpected, possibly related to the study drug, and serious or suggest a risk of greater harm from the research than previously known will be reported to the IRB per institutional policy.

In addition, all safety data must be submitted to Janssen Research & Development. The following methods are acceptable for transmission of safety information to Janssen Research & Development.:

- Electronically via J&J SECURE Email service (preferred)
- For business purposes, if SECURE Email is non-functional:
    - Facsimile (fax), receipt of which is evidences in a successful fax transmission report
    - Telephone (if fax is non-functional)

Contact information for Janssen Research & Development is below:

SAE email: IIS-BIO-VIRO-GCO@its.jnj.com
SAE fax: 1-866-651-0219

Follow-up reports must be submitted in a timely fashion as additional information becomes available. The initial SAE report should be updated with the pertinent follow up information.

11.8. Protocol Amendments

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB before implementation. Changes to the protocol or informed consent will be reviewed and approved by Janssen Research & Development prior to submitting to the IRB for approval.

11.9. Informed Consent

Written informed consent will be obtained by a study investigator working on this study. An explanation of the nature of study, its purpose, procedures involved, expected duration, potential risks and benefits will be provided to each participant by the investigator or the research nurse. Each participant will be informed that participation in the study is voluntary and that he may withdraw from the study at any time, and that withdrawal of consent will not affect his subsequent medical treatment. Participants will be allowed time needed to make an informed decision. Participants will be encouraged to ask questions about the study and the consent before signing the consent form. Original signed consent forms will be filed in each patient's research chart, while each patient will receive a copy of the consent document. No patient will enter the study before his informed consent has been obtained.

12 STATISTICAL METHODS

Statistical analysis will be done by the sponsor investigator or under the authority of the Sponsor- Investigator. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below.

The primary objective will be to determine the objective tumor response rate in subjects with measurable lesions as defined by RECIST v1.1 criteria in mCRPC patients with DNPC receiving either enzalutamide or abiraterone acetate. Key secondary objectives will include determining: radiographic progression free survival (PFS) in patients using RECIST 1.1 criteria for soft tissue metastases and Prostate Cancer Working Group 3 (PCWG3) criteria for bone metastases; time to response using RECIST 1.1 criteria; overall survival (OS) defined as the time interval from C1D1 to the date of death; PSA response, defined as >50% reduction in PSA compared with baseline at any point during treatment; and the incidence and severity of adverse events according to National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[2,3].

12.1. Subject Information

12.2. Sample Size Determination

Although there are no published data on ORR among patients with progressive disease on both abiraterone acetate and enzalutamide, several small studies have explored the objective response rates of abiraterone acetate following enzalutamide and *vice versa* in the post-docetaxel setting:

with ORRs ranging from 3-8%.[5,6] Therefore, if we assume a historical-control ORR (H0) of 5% and an alternative hypothesis of a 25% ORR (H1), a sample size of 23 patients gives 86% power to detect a difference in ORR of the hypothesized magnitudes with a type-1 error of 3% based on an exact binomial test. We will therefore plan to enroll up to 25 patients to account for 10% dropout.

12.3. Efficacy Analyses

The primary objective will be to determine the ORR, which will be calculated as the percentage of patients, with 95% confidence intervals, achieving a complete response (CR) or partial response (PR) across the entire study population at any time. On the basis of an exact binomial test, 4 responses are needed to reject the null hypothesized 5% historical control ORR in favor of the alternative at a significance level of p=0.026. If a patient drops out of the study prior to first on-study radiographic assessment, they will be considered a non-responder for the purpose of the primary analysis; however, an additional subject will be accrued to account for early dropouts. We will also present ORR, with 95% confidence intervals, for the patients receiving erdafitinib in combination with abiraterone acetate or enzalutamide separately. Secondary objectives will include determining: radiographic progression free survival (PFS) in patients using RECIST 1.1 criteria for soft tissue metastases and Prostate Cancer Working Group 3 (PCWG3) criteria for bone metastases; time to response using RECIST 1.1 criteria; overall survival (OS) defined as the time interval from C1D1 to the date of death; PSA response, defined as >50% reduction in PSA compared with baseline at any point during treatment; and the incidence and severity of adverse events according to National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[2,3]. Survival endpoints (e.g. PFS, OS) will be presented with Kaplan-Meier curves, and the median survival with 95% CI will be calculated. Rates will be reported as percentages with 95% CI. We will characterize AEs by type and grade. Safety will be summarized as the severity and frequency of a given AE.

12.4. Correlative Research Analyses

Exploratory correlative work will be conducted with the goal to determine if there are biomarkers predictive of response/resistance to erdafitinib in combination with a next-generation AR-signaling inhibitor. Studies to be conducted include the following. Protein expression studies at baseline and at the time of progression, including IHC for AR, PSA, phospho-FRS2 and phosphor-FGFR. Transcript profiling studies (RNA-seq) on metastatic biopsies and blood to assess activation of the core AR-, MAPK- and FGF/FGFR-signaling programs, and to identify unknown pathways involved in mediating response/resistance to treatment. Next-generation sequencing to assess for FGFR mutations. Baseline protein and transcript expression, as well as changes in these parameters with treatment, will be correlated with the primary and secondary endpoints using chi-square tests and logistic regression, or (for PFS and OS) using proportional hazards models, Kaplan-Meier methods and log-rank tests.

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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.

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Appendix 2: 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/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Appendix 3: Pill Diary Templates

PARTICIPANT PILL DIARY **STUDY #**

Participant Study ID: _____

Erdafitinib
Dose (mg) per tablet: _____

		Number of Tablets or Capsules/Time of Day	
			Time
Date	Day	Erdafitinib tablets/day	AM/PM
	1		
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
	11		
	12		
	13		
	14		
	15		
	16		
	17		
	18		
	19		
	20		
	21		

PARTICIPANT PILL DIARY **STUDY #**

Participant Study ID: _____

Enzalutamide

Date	Day	Number of Tablets or Capsules/Time of Day	
			Time
		Enzalutamide 160 mg/day	AM/PM
	1		
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
	11		
	12		
	13		
	14		
	15		
	16		
	17		
	18		
	19		
	20		
	21		

PARTICIPANT PILL DIARY **STUDY #**

Participant Study ID: _____

Abiraterone

Date	Day	Number of Tablets or Capsules/Time of Day	
		Abiraterone 1000 mg/day	Time AM/PM
	1		
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
	11		
	12		
	13		
	14		
	15		
	16		
	17		
	18		
	19		
	20		
	21		